haematologica
the hematology journal

s2

Volume 98, supplement no. 2, October 2013
www.haematologica.org

9th International Symposium on Hodgkin Lymphoma

Cologne, Germany, October 12-15, 2013

Guest Editors
Boris Böll, Andreas Engert, Bastian von Tresckow

ISSN 0390-6078
Journal of the European Hematology Association
Published by the Ferrata-Storti Foundation, Pavia, Italy

www.haematologica.org

Official Organ of the
European Hematology Association

haematologica
the hematology journal

Owned & published by the Ferrata Storti Foundation, Pavia, Italy

Official Organ of the
European Hematology Association

haematologica
the hematology journal

European Hematology Association (EHA)

The European Hematology Association (EHA) aims to promote excellence in clinical practice, research and education in European hematology.
EHA was founded in June 1992 and today – with over 3500 members from 100 countries – is a consolidated representative of European hematologists.

Our aim

- To become the official European representative of hematology and hematologists – especially where research, education and regulatory issues are concerned – and to become a conduit for European harmonization;
- To promote the creation of a highly attractive market for practitioners and researchers in Europe thus fostering the mobility of hematologists in and to Europe;
- To reach out and offer a platform to countries that wish to further develop excellence in hematology;
- To promote education, training and scientific research in hematology in Europe;
- To exchange and disseminate knowledge and scientific information in the field of hematology.

Our activities

- Organizing an annual scientific and educational congress in a major European city;
- Dissemination of medical research, both basic and clinic, through the Haematologica/The Hematology Journal;
- Collaborating with other leading organizations in the field of hematology and oncology;
- Providing postgraduate education through the annual congress, tutorials and workshops;
- Supporting junior basic and clinical researchers in the development of their careers through the EHA Fellowship Program.
- Strengthening the quality and professional status of hematology throughout Europe by accrediting scientific meetings and providing CME accounts.

EHA Membership

Join the European Hematology Association's 3500 members from 100 countries and support programs and project which promote excellence in clinical practice, research and education in European hematology.

Benefits of EHA membership:
- Subscription to Haematologica/ The Hematology Journal, including on-line access
- Reduced registration fee for the EHA Annual Congresses
- Opportunity to apply for fellowships and awards of the EHA Career Development Program
- EHA Newsletter
- EHA E-bulletin
- Access to webcast sessions of the EHA Annual Congress
- Access to online EHA Membership Directory

For information about how to become an EHA Member, contact us at membership@ehaweb.org

www.ehaweb.org

Official Organ of the
European Hematology Association

haematologica
the hematology journal

Information for readers, authors and subscribers

Haematologica/The Hematology Journal (print edition, pISSN 0390-6078, eISSN 1592-8721) publishes peer-reviewed papers on all areas of experimental and clinical hematology. The journal is owned by a non-profit organization, the Ferrata Storti Foundation, and serves the scientific community strictly following the World Association of Medical Editors (WAME) recommendations on publication ethics policies for medical journals (www.wame.org/pubethicrecom.htm).

Haematologica/The Hematology Journal publishes editorials, perspectives, research papers, decision making & problem solving papers, review articles, brief reports and scientific letters. Manuscripts should be prepared according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE) and fully available online (http://www.icmje.org). Additional papers may be considered for the purely online journal (Haematologica/The Hematology Journal on Internet, eISSN 1592-8721). Because there are no space constraints online, Haematologica/The Hematology Journal will publish several items deemed by peer review to be scientifically sound and mainly useful as educational papers. These will include case reports, irreplaceable images, educational material from scientific meetings, meeting abstracts, and letters to the Editor.

Papers should be submitted online at http://www.haematologica.org/.

Conflict of interests. According to the International Committee of Medical Journal Editors (http://www.icmje.org/#conflicts), "Public trust in the peer review process and the credibility of published articles depend in part on how well conflict of interest is handled during writing, peer review, and editorial decision making". The ad hoc journal's policy is reported in detail online (http://www.haematologica.org/misc/about.dtl).

Galley Proofs and Reprints. Galley proofs should be corrected and returned by email, fax or express delivery within 48 hours. Minor corrections or reasonable additions are permitted; however, excessive alterations will require editorial re-evaluation and will be possibly charged to the authors. Papers accepted for publication will be printed without cost. The cost of printing color figures will be communicated upon request. Reprints may be ordered at cost by returning the appropriate form sent by the Publisher.

Transfer of Copyright and Permission to Reproduce Parts of Published Papers. Authors will grant copyright of their articles to the Ferrata Storti Foundation. No formal permission will be required to reproduce parts (tables or illustrations) of published papers, provided the source is quoted appropriately and reproduction has no commercial intent. Reproductions with commercial intent will require written permission and payment of royalties.

Haematologica/The Hematology Journal is published in two printed editions: International (worldwide except Italy, Spain, Portugal and Latin America), and Spanish (Spain, Portugal and Latin America). Detailed information about subscriptions is available online at URL http://www.haematologica.org. While access to the online journal is free, online access to some additional items available on http://www.haematologica.org may require either institutional or personal subscription.

Rates of the International edition for the year 2013 are as following:

	Institutional	*Personal*
Print edition (including full access to the online CME for personal subscribers)	*Euro 500*	*Euro 150*
Full access to the online CME only		*Euro 75*

To subscribe to the International edition, please visit our web site http://www.haematologica.org/misc/subscribe.dtl or contact: Haematologica Office, via Giuseppe Belli 4, 27100 Pavia, Italy (phone +39.0382.27129, fax +39.0382.394705, E-mail: office@haematologica.org).

Advertisements. Contact the Advertising Manager, Haematologica Office, via Giuseppe Belli 4, 27100 Pavia, Italy (phone +39.0382.27129, fax +39.0382.394705, e-mail: info@haematologica.org).

Direttore responsabile: Prof. Edoardo Ascari; Autorizzazione del Tribunale di Pavia n. 63 del 5 marzo 1955.
Printing: Tipografia PI-ME, via Vigentina 136, Pavia, Italy. Printed in September 2013.

EUROPEAN
HEMATOLOGY
ASSOCIATION

Opportunities for Early Career
Clinical & Non-Clinical Hemalogical Scientists

EHA Career Development
Research Fellowships

EHA offers fellowships to conduct research for a three year period. Outstanding clinical and non-clinical scientists are invited to submit a research proposal in the field of hematology.

Clinical Research Fellowships
Award € 80K per year for three years

Non-Clinical Junior Research Fellowships
Award € 50K per year for three years

Non-Clinical Advanced Research Fellowships
Award € 80K per year for three years

Information about eligibility and submission is available at the Career Development section at ehaweb.org

Official Organ of the European Hematology Association

haematologica
the hematology journal

supplement 2 - October 2013

Table of Contents

9th International Symposium on Hodgkin Lymphoma
Cologne, Germany, October 12-15, 2013

Guest Editors
Boris Böll, Andreas Engert, Bastian von Tresckow

Oral and posters

EUROPEAN
HEMATOLOGY
ASSOCIATION

FUTURE CONGRESSES

Vienna

Milan

19th Congress
Milan, Italy
June 12 - 15 2014

20th Congress
Vienna, Austria
June 11 - 14 2015

21st Congress
Venue
to be decided
June 9 - 12 2016

22nd Congress
Venue
to be decided
June 22 - 25 2017

23rd Congress
Venue
to be decided
June 14 - 17 2018

9th International Symposium on Hodgkin Lymphoma
Cologne, Germany, October 12-15, 2013

Advanced Stages

T001

IMPACT OF DOSE REDUCTIONS OF BLEOMYCIN AND VINCRISTINE IN PATIENTS WITH ADVANCED HODGKIN LYMPHOMA TREATED WITH BEACOPP POLYCHEMOTHERAPY: A COMPREHENSIVE ANALYSIS OF THE GERMAN HODGKIN STUDY GROUP (GHSG) HD12 AND HD15 TRIALS

von Tresckow B, Haverkamp H, Böll B, Eichenauer DA, Sasse S, Fuchs M, Borchmann P, Engert A

German Hodgkin Study Group (GHSG), Department of Internal Medicine I, University Hospital of Cologne, Germany

Introduction. BEACOPPescalated is the German Hodgkin Study Group (GHSG) standard for advanced Hodgkin Lymphoma (HL). Bleomycin and vincristine cause significant acute and long-term toxicities and are frequently discontinued during the course of therapy. However, the impact of bleomycin and vincristine dose reductions on outcome and tolerability of BEACOPP chemotherapy has never been systematically assessed. Therefore, we performed a retrospective analysis in patients treated within the GHSG HD12 (8xBEACOPPescalated versus 4xBEACOPPescalated plus 4xBEACOPPbaseline) and HD15 (8xBEACOPPescalated versus 6xBEACOPPescalated versus 8xBEACOPP14) trials for advanced stages. Methods. Characteristics and outcomes of patients with the full number of chemotherapy cycles from the intention-to-treat sets of the final analyses of HD12 and HD15 were analyzed with respect to bleomycin and vincristine dose reductions. Progression-free survival (PFS) and overall survival (OS) from end of chemotherapy were estimated according to the Kaplan-Meier method and compared between groups using the log-rank test. Results. 3309 (89.4%) of patients received the full number of planned cycles and had complete chemotherapy documentation available. Bleomycin was discontinued in 10.5%, vincristine in 21.7% of cases. All other substances had discontinuation rates not exceeding 1.5%. 157 (4.7%) of patients received ≤4 cycles of bleomycin and 218 (6.6%) of patients received ≤3 cycles of vincristine, these were deemed sufficient numbers for comparisons to patients with >4 cycles of bleomycin (3152 patients [95.3%]) and >3 cycles of vincristine (3091 patients [93.4%]). After a median follow-up of 59 months, there was no significant PFS or OS difference in patients with ≤4 or >4 cycles of bleomycin (6-year PFS-difference 0.3% [95%CI -5.7 to 6.2%]; 6-year OS-difference 0.4% [95%CI -3.7 to 4.5%]; Figure 1A). Similarly, there was no significant PFS or OS difference in patients with ≤3 or >3 cycles of vincristine (6-year PFS-difference -1.6% [95%CI -6.4 to 3.2%]; 6-year OS-difference 1.9% [95%CI -2.5% to 6.3%]; Figure 1B). Detailed analyses and comparisons of patient characteristics, dose delivery of chemotherapy and toxicity will be presented. Conclusion. Bleomycin and vincristine may have a limited role in the BEACOPP regimen and discontinuation in the event of drug-specific side effects seems to be safe.

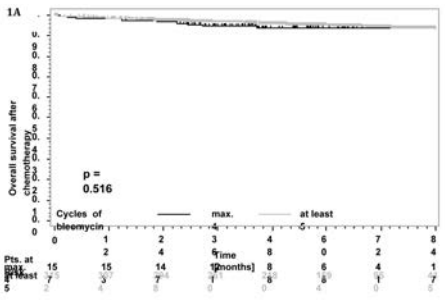

Figure 1.A.

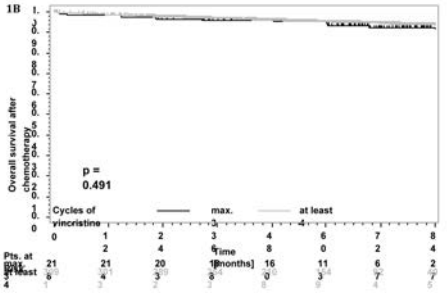

Figure 1.B.

T002

STANDARD ABVD *vs* ESCALATED BEACOPP IN STAGE III-IV LOW RISK HODGKIN LYMPHOMA (IPS 0-2): THE LYMPHOMA STUDY ASSOCIATION (LYSA) H34 TRIAL.

Mounier N, Brice P, Bologna S, Briere J, Gaillard I, Voillat L, Gabarre J, Casasnovas O, Jaubert J, Colin P, Devidas A, Coiffier B, Aoudjhane A, Audhuy B, Carde P, Andre M

Lymphoma Study Association, Lyon Sud Hospital, Pierre Benite, France

Introduction. Escalated BEACOPP achieved superior time to treatment to failure over ABVD in patients with disseminated Hodgkin lymphoma. However, given the higher treatment related morbidity, whether or not BEACOPP should be given to low risk patients is still matter of debate. Methods. Eligibility criteria: clinical stage III/IV HL, International prognostic score (IPS) ranging 0-2; age<60. Patients with IPS >2 were included in the EORTC Intergroup 20012 study (P. Carde, ASCO 2012). We compared ABVD (8 cycles) *vs* BEACOPP (escalated 4 cycles => baseline 4), without irradiation. Primary endpoint was EFS, defined as treatment discontinuation, no complete remission after 8 cycles, progression, relapse or death. Results. From February 2003 to august 2008, 150 pts were randomized (ABVD 80, BEACOPP 70): IPS was 0-1 for 64% of pts. There was no toxic death. Early discontinuation (prior to cycle 5) occurred in 10 & 9 pts, respectively (13%). Main reasons were treatment failure (3 & 2), patient refusal (3 & 2) and toxity (1 & 3). There were 1 crossover to BEACOPP and 3 to ABVD. CR was 85% for ABVD and 90% for BEACOPP. Relapses were more frequent in ABVD (14 *vs* 3 patients). Among them 9/14 and 3/3 received stem cell transplantation. Second cancer occurred in 5 ABVD and 1 BEACOPP pts (NHL 2 & 1, lung 1 & 0, other 2 & 0). Among the 5 ABVD pts, 3 received second line HL treatment. With a median follow-up of 5.5 yrs, 7 patients died : 6 in ABVD and 1 in BEACOPP (HL 3 & 0, 2nd cancer 2 & 1, other 1&0). EFS at 5 yrs was estimated at 62% *vs* 77%, respectively (HR = 0.6, p=0.07). PFS at 5 yrs was 75% *vs* 93% (HR = 0.3, p=0.007). OS at 5 yrs was 92 *vs* 99% (HR = 0.18, p=0.06). Conclusion. EFS and OS were not different between treatment arms. However, more progressions/relapses were observed with ABVD. As in high risk group, additional considerations as late morbidity due to salvage treatment may help decisions making toward ABVD or BEACOPP for low risk patients.

T003
RESPONSE RATES AND TOXICITY OF RESPONSE-ADAPTED THERAPY IN ADVANCED HODGKIN LYMPHOMA: INITIAL RESULTS. FROM THE INTERNATIONAL RATHL STUDY

Johnson P, Federico M, Fossa A, Barrington S, Kirkwood A, Roberts T, Trotman J, Berkahn L, Enblad G, d'Amore F, Smith P, Radford J

NCRI Lymphoma Clinical Studies Group, UK; Dipartimento di Oncologia ed Ematologia, Modena, Italy; Norwegian Radium Hospital, Oslo, Norway; Australasian Leukaemia and Lymphoma Group; Uppsala University Hospital, Uppsala, Sweden; Aarhus University Hospital, Aarhus, Denmark; UCL/CR UK Trials Office, London, UK

This randomised trial used interim FDG PET-CT scanning to assess early chemotherapy response and guide treatment. Adults with newly diagnosed advanced HL (stages IIB-IV, IIA with bulk or ≥3 involved sites) underwent interim PET-CT scans after 2 ABVD (PET2). Quality control for PET-CT was supervised by core labs using common methods of scan acquisition and interpretation. Images were scored on a 5-point scale, as negative (score 1-3) or positive (score 4,5). Patients with -ve scans were randomised to ABVD or AVD for 4 more cycles. Patients with +ve scans were escalated to either BEACOPP-14 or escalated BEACOPP for 8-9 weeks before a third PET-CT scan (PET3). Patients with -ve PET3 completed a further 2 BEACOPP-14 or 1 eBEACOPP; patients with positive PET3 received off-study salvage. Radiotherapy was not advised for patients with -ve scans. 1214 patients were registered over 54 months. Median age was 33, with 34% IPS Score 0-1; 48% 2-3; 17% ≥4. PET2 Results. were available from 1136 patients and were -ve in 84%. Only 2.4% of PET2-ve patients received consolidation radiotherapy. Outcomes at 1 year were assessable in 680 patients. 9% of PET2-ve patients experienced a PFS event (progression/death), with no difference according to PET2 score, compared to 22% of PET2+ve patients. Comparing toxicity between patients continuing ABVD or receiving AVD showed no difference in haematologic toxicity, but worse non-haematologic toxicity with ABVD (29% *vs* 19% patients grade III/IV toxicity, p=0.001), especially thromboembolic events (4.9% *vs* 2.0%, p=0.018). Among 587 patients with end of treatment lung function, mean change in diffusion capacity after ABVD was reduction by 11.15% of normal (95% CI 9.48-12.81) *vs* 4.31% (2.56-6.06) with AVD (p<0.001). Among PET2+ve patients, further PET-CT scans were analysed after BEACOPP in 156, with 76% PET3-ve. PET3 scores did not differ according to the BEACOPP schedule chosen. Good Results. can be obtained using intemediate PET-CT to modulate therapy, and escalation after a positive scan yields substantial response rates. There is a reduction in toxicity after stopping bleomycin after favourable PET2 results. , but longer follow up is required to rule out any loss of efficacy.

P004
FIRST-LINE TREATMENT OF ADVANCED STAGE HODGKIN LYMPHOMA. FINAL RESULTS OF A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Borchmann P,[1] Rancea M,[2] Skoetz N,[2] Trelle S,[3] Haverkamp H,[1] Engert A[1]

[1]Department I of Internal Medicine, Center of Integrated Oncology Köln Bonn, University Hospital of Cologne, Cologne, Germany; [2]Cochrane Haematological Malignancies Group, Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany; [3]CTU Bern, University of Bern, Switzerland

Background. Hodgkin lymphoma (HL) in advanced stages can nowadays be cured with different combined-modality approaches, but the debate whether BEACOPPescalated (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) or ABVD (doxorubicin, bleomycin, vincristine, dacarbazine) is superior is still ongoing. With regard to the most important outcome overall survival (OS) no high-level evidence supporting one or the other strategy exists. Aim of this study is, to assess the efficacy (OS) of different first-line treatment strategies compared to standard ABVD. Methods. We developed sensitive search strategies for CENTRAL, MEDLINE, and conference proceedings from 01.1980 to 09.2012, additionally, we obtained missing data from investigators. Two authors independently screened search results. , extracted data, and assessed quality of trials. We pooled data using network meta-analysis and combined direct with indirect comparisons with Bayesian random-effects model. Results. were reported relative to ABVD, indicating superiority of ABVD if hazard ratio (HR) >1. Results. The search resulted in 2,229 relevant references, of which 74 publications with 14 randomized controlled trials evaluating eleven different regimens were included. Overall, we judged the methodological quality of trials as high. Six cycles BEACOPPescalated (HR = 0.38, 95% credible intervals (CrI) 0.20 to 0.75) and eight cycles BEACOPP-14 (HR = 0.43, 95% CrI 0.22 to 0.86) were associated with the lowest risk of mortality and showed a 98% probability to be the best treatment regimens for patients with advanced HL. Additional standard meta-regression estimated a 89% five-year survival rate for ABVD, resulting in a five-year survival benefit of 7% for both regimens: six cycles BEACOPPescalated (95% CrI 3% to 10%) and eight cycles BEACOPP-14 (95% CrI 2% to 9%) as compared to ABVD. These Results. were confirmed by the reconstructed digitized individual patient analysis that included 10,042 patients and 1,189 deaths over 47,033 patient-years of follow-up. OS as increased by 10% (95% CI 3% to 15%) at five years with six cycles BEACOPPescalated. Conclusions. This network analysis of different first-line treatment strategies for patients has shown a meaningful benefit OS for first-line treatment with six cycles BEACOPPescalated over standard ABVD. Thus, BEACOPPescalated represents the gold standard of care for advanced stage HL patients.

P005
FRONTLINE THERAPY WITH BRENTUXIMAB VEDOTIN COMBINED WITH ABVD OR AVD IN PATIENTS WITH NEWLY DIAGNOSED ADVANCED STAGE HODGKIN LYMPHOMA

Ansell SM,[1] Connors JM,[2] Park SI,[3] O'Meara M,[4] Younes A[5]

[1]Mayo Clinic, Rochester, MN, USA; [2]BC Cancer Agency Centre for Lymphoid Cancer, Vancouver, Canada; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [4]Seattle Genetics, Inc., Bothell, WA, USA; [5]University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background. The regimen containing doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is a common standard of care for the frontline treatment of Hodgkin lymphoma (HL). A phase 1, open-label, multicenter study evaluating the safety of brentuximab vedotin (ADCETRIS®) administered in combination with standard therapy (ABVD) or a modified standard (AVD) in patients with advanced stage HL has been completed (ClinicalTrials.gov NCT01060904). Methods. Twenty-five patients received doses of 0.6 (N=6), 0.9 (N=13), or 1.2 mg/kg (N=6) brentuximab vedotin with ABVD and 26 patients received 1.2 mg/kg brentuximab vedotin with AVD on Days 1 and 15 of each 28-day cycle for up to 6 cycles. Response was assessed by investigator per Cheson 2007. Results. Overall, 37/51 patients were male (73%) and median age was 33 years (range, 18-59). At baseline, 45% of all patients had Stage IV HL, 25% had an IPS score ≥4, and 33% presented with bulky disease. No DLT (any Cycle 1 toxicity requiring a delay of ≥7 days) was observed up to 1.2 mg/kg, the maximum planned dose, in either regimen. Across both regimens, AEs occurring in ≥30% of patients overall were alopecia, constipation, diarrhea, fatigue, insomnia, nausea, neutropenia, peripheral sensory neuropathy, pyrexia, and vomiting. Pulmonary toxicity symptoms were noted in 11/25 patients (44%) in the ABVD cohorts only and resolved in 9/11 patients; 2 patient deaths were associated with pulmonary toxicity. No pulmonary toxicity was observed in the AVD cohort. Of 51 patients treated, 4 withdrew consent or were lost to follow-up prior to completing frontline therapy. The remaining 47 had a 96% CR rate at the end of frontline therapy: 21/22 ABVD patients (95%) and 24/25 AVD patients (96%). Conclusions. The safety profile confirmed that brentuximab vedotin may be safely combined with AVD; however, combination with a bleomycin-containing regimen is contraindicated due to the incidence of pulmonary toxicity. Brentuximab vedotin 1.2 mg/kg every 2 weeks combined with AVD resulted in CR rates at the end of frontline therapy that compare favorably with historically-reported Results. with ABVD alone among advanced-stage HL patients. A phase 3 study comparing brentuximab vedotin plus AVD versus ABVD alone is ongoing.

P006

EARLY TREATMENT INTENSIFICATION IN ADVANCED-STAGE HIGH-RISK HODGKIN LYMPHOMA (HL) PATIENTS, WITH A POSITIVE FDG-PET SCAN AFTER TWO ABVD COURSES–SECOND INTERIM ANALYSIS OF THE GITIL/FIL HD0607 CLINICAL TRIAL

Gallamini A,[1] Rossi A,[2] Patti C,[3] Picardi M,[4] Di Raimondo F,[5] Cantonetti M,[6] La Nasa G,[7] Viviani S,[8] Bolis S,[9] Trentin L,[10] Olivieri A,[11] Zoli V,[12] Biggi A,[13] Chauvie S,[14] Fiore F,[1] Borra A,[1] Prosperini G,[15] Cavazzina R,[15] Marchioli R,[15] Parvis G,[16] Zanotti R,[17] Gavarotti P,[18] Dodero A,[19] Schiavotto C,[20] Ciceri F,[21] Avigdor A,[22] Mulè A,[23] Tarella C,[24] Gianni AM,[25] Rambaldi A[2]

[1]Hematology, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy; [2]Hematology, Ospedali Riuniti di Bergamo, Bergamo, Italy; [3]Hematology, Ospedale V. Cervello, Palermo, Italy; [4]Hematology, Az. Ospedaliera Policlinico Federico II, Napoli, Italy; [5]Hematology, Ospedale Ferrarotto, Catania, Italy; [6]Hematology, Policlinico Universitario Tor Vergata, Roma, Italy; [7]Department of Internal Medicine, Ospedale R. Binaghi, Cagliari, Italy; [8]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy; [9]Hematology, Ospedale San Gerardo, Monza, Italy; [10]Hematology, Internal Medicine, Università di Padova, Padova, Italy; [11]Hematology, Ospedale San Carlo, Potenza, Italy; [12]Hematology, Az. Ospedaliera S. Camillo Forlanini, Roma, Italy; [13] Nuclear Medicine S. Croce Hospital, Cuneo, Italy; [14]Medical Physics Unit, S. Croce e Carle, Cuneo, Italy; [15]Laboratory of Clinical Epidemiology, Mario Negri Sud Institute, Santa Maria Imbaro, Italy; [16]Hematology, S. Luigi Hospital, Orbassano, Torino, Italy; [17]Hematology, Policlinico B.G. Rossi, Verona, Italy; [18]Hematology, S. Giovanni Battista Hospital, Torino, Italy; [19]Hematology, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy; [20]Hematology, S. Bortolo Hospital, Vicenza, Italy; [21]Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milano, Italy; [22]Hematology, Tel-Ashomer Hospital, Tel-Avis, Israel; [23]Azienda Ospedali Riuniti Villa Sofia Cervello, Palermo, Italy; [24]Hematology, Mauriziano-Umberto I Hospital, Torino, Italy; [25]Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori Milano, Milan, Italy

Background. Despite its prognostic role in advanced-stage HL (aHL), in still unproven whether early therapy intensification in patients (p.) with a positive interim PET after 2 ABVD (PET-2) improves overall treatment efficacy for all aHL pts compared to standard ABVD Patients and Methods. In the HD 0607 clinical trial aHL p. are treated with 2 ABVD courses and a PET-2 performed afterwards. PET-2+p. are randomized to either BEACOPP escalated (Be) plus BEACOPP baseline (Bb) (4+4 courses) or Be+Bb (4+4) and Rituximab (R). PET-2- p. are treated with 4 additional ABVD and, upon CR achievement, randomized to either consolidation radiotherapy (Rxt) on the sites of initial bulky disease or no further treatment. Scans are interpreted by an expert panel of reviewers in a Blinded Independent Central Review (BICR) according to the Deauville 5-point scale (5PS). Results. 627 aHL pts were consecutively enrolled and 590 scanned with PET-2. 287/590 (49%) PET-2 underwent review: 117 were adjudged as positive (80 score 4, 37 score 5) and 170 as negative (score 1-3). Altogether, of 590 PET-2, 117 (20%) resulted positive and 473 (80%) negative. Treatment efficacy could be assessed in a cohort of 330 pts. with a minimum follow-up of 24 months from enrolment: 59 (17,9%) with a positive and 271 (82.1%) with a negative PET-2. The median follow-up was 952 days (736-1181). Among 59 PET-2+ p., CCR (Continuous CR) was recorded in 40 (68%), Pro/Rel in 9 (15%), SD in 2 p. (3%) and death in 8 pt (13%), 2 of them for progressive disease. Among 271 PET-2- p. CCR was recorded in 240 (89%), Pro/Rel in 19 (7%), SD in 2 (0.7%), death in 8 (3%), 4 of them for disease progression. The 2-y PFS was 67.8%, 88.6% and 84.6% for PET-2+p., PET-2-p., and for all p., respectively (p<.001). Conclusions. These preliminary findings suggest that 1) an early switch from ABVD to escalated BEACOPP can induce PET negativity and sustained CR achievement in most cases; 2) BICR is feasible and allows a real time decision making process in a prospective multicentre clinical trial.

P007

RELAPSE ANALYSIS OF IRRADIATED PATIENTS WITHIN THE HD15 TRIAL OF THE GERMAN HODGKIN STUDY GROUP

Kriz J,[1] Reinartz G,[1] Kobe C,[2] Kuhnert G,[2] Haverkamp H,[3] Haverkamp U,[1] Hegerfeld K,[1] Baues C,[4] Engert A,[3] Eich HT[1]

1Department of Radiation Oncology, University Muenster; 2Department of Nuclear Medicine, University of Cologne, Germany; 3First Department of Internal Medicine, University of Cologne; 4Department of Radiation Oncology, University of Cologne, Germany

Introduction. The role of consolidation radiotherapy (RT) after effective chemotherapy (CTX) in advanced stages Hodgkin Lymphoma (HL) is unclear. In the HD15 trial of the German Hodgkin Study Group therefore patients having residual disease of ≥2.5 cm after 6-8 cycles BEACOPP were evaluated using Fluorodesoxyglucose positron emission tomography (PET). PET-positive patients were subsequently irradiated. The aim of the present study was to determine whether sites of relapses were within the irradiated area and to analyse whether the definition of the RT volume was correct. In addition, the correlation between quality of RT and the pattern of relapse was assessed. Methods. After completion of CTX, all patients with residual disease ≥2.5 cm were evaluated using PET and in case of a PET-positive result, these patients were irradiated with 30 Gy local RT to the site of residual disease. For all patients receiving RT who had a documented relapse, we analysed sites of disease before and after chemotherapy and especially the PET positive sites that were irradiated. Documentation of RT, treatment planning and portal images were carefully analysed and compared to the centrally recommended RT prescription. The irradiated sites were compared to sites of relapse using follow-up CT scans. Results. Of all patients in this trial, 191 (26%) had PET-positive residues after CTX and 175 of these patients (92%) were irradiated with 30 Gy to the PET-positive site. 28 irradiated patients relapsed. RT radiation plans and follow-up CT scans of these patients were analysed. Overall, 12 patients (42%) had an in-field relapse, 8 (29%) patients relapsed outside the irradiated site and an additional 8 patients (29%) had in- and outfield relapse. In these relapsing patients, RT was not performed according to the radiation plan in 19/28 (68%) and in additional 7 patients (32%), the RT was not realized correctly. Conclusion. The pattern of relapse suggests that local RT is sufficient for patients in advanced stages HL. There was no correlation between quality of RT and occurrence of relapse.

P008

CHARACTERISTICS AND OUTCOME OF HIV ASSOCIATED HODGKIN LYMPHOMA AMONG 59 PATIENTS INCLUDED IN THE FRENCH ANRS CO16 LYMPHOVIR COHORT STUDY

Besson C,[1] Prevot S,[2] Hendel-Chavez H,[1] Lancar R,[3] Génin M,[3] Trabelsi S,[3] Marchand L,[4] Meyohas MC,[5] Marchou B,[6] Gabarre J,[7] Bonnet F,[8] Goujard C,[1] Boué F,[2] Mounier N,[9] Partisani M,[10] Raffi M,[11] Costello R,[12] Raphael M,[1] Taoufik Y,[1] Costagliola D[7]

[1]Université Paris Sud, Le Kremlin-Bicetre, France; [2]Université Paris Sud, Clamart, France; [3]INSERM u943, France; [4]ANRS, France, [5]CHU Saint-Antoine, Paris, France; [6]CHU Toulouse, France; [7]CHU Pitié-Salpétrière, Paris, France; [8]CHU Bordeaux, France; [9]CHU Nice, Nice, France; [10]CHU Strasbourg, France; [11]CHU Nantes, Nantes, France; [12] CHU Marseille, France

Background. Human Immunodeficiency Virus (HIV) infection is associated with an increased risk of Hodgkin (HL) and non Hodgkin lymphoma (NHL). The widespread use of combined antiretroviral therapy (cART) has reduced the incidence of NHL but not the incidence of HL. Methods. The national prospective Cohort of HIV-related lymphomas (ANRS CO16 Lymphovir cohort sponsored by Inserm-ANRS) enrolled 138 adult patients at diagnosis of lymphoma in 32 centres between July 2008 and April 2012. Investigations were performed after approval of the ethic committee and competent autority. Pathological materials of 40 patients were centralized and reviewed. Diagnoses were based on World Health Organization criteria. Patients are followed every 6 months during 5 years. Results. Among the 138 patients, 43% (59) were diagnosed with HL. Median age was 44 years (ranging from 20 to 61), male/female ratio was 6.4 (51/8). HIV infection had been diagnosed for a median of 156 months (0 to 312) and all patients except one were treated with cART at HL diagnosis. Median CD4 T-cell count was 368/mm3 (range 37-1518) and HIV RNA was <50 in 78% (46/59) of the patients. HL mixed cellularity subtype was noticed in 37 out of 40 reviewed cases, nodular sclerosing in 2 cases and nodular lymphocyte predominant (NLP) in one case. All the 40 tested cases for in situ EBV hybridization were positive except the NLP HL. Advanced clinical stage (III/IV) was noticed in 77% of the cases. The median interval between lymphoma occurrence and last follow-up was 26 months. During follow-up, all patients were treated with cART. 50 out of 54 were treated with ABVD, the patient with NLP received Rituximab. At 24 months, overall survival was 96% [95%CI 92, 100] and progression free survival was 91% [83, 99]. All the

5 events occurred among the patients with stage III and IV.. There were 2 deaths from disease progression (1) and sepsis (1). Summary / Conclusion. The present study points out the high proportion of HL among HIV infection with lymphoma in the cART era. Although these patients have advanced stage at diagnosis, their prognosis has largely improved.

P009
PROGNOSTIC IMPACT OF CD20 EXPRESSION IN ADVANCED STAGE CLASSICAL HODGKIN'S LYMPHOMA (CHL) TREATED WITH ABVD CHEMOTHERAPY: A RETROSPECTIVE ANALYSIS

Sengar M,[1] Sridhar E,[2] Menon H,[1] Dangi U,[1] Shet T,[2] Gujral S,[2] Jain H,[1] Laskar S,[3] Khanna N[3]

[1]Department of Medical Oncology; [2]Department of Pathology; [3]Department of Radiation Oncology Tata Memorial Centre, Mumbai, India

Background. CD20 expression on Hodgkin and Reed-Sternberg (HRS) cells is seen in approximately 5-58% of CHLs. The prognostic relevance of CD20 expression in CHL remains conflicting. Given the efficacy of rituximab in CHLs in a few studies, we felt it relevant to further investigate its prognostic role. Herein we report the prognostic impact of CD20 expression in patients with advanced stage CHL treated at our centre with ABVD chemotherapy. Methods. The electronic medical records of newly diagnosed advanced stage (stage IIB, III and IV) CHL patients (14 years or more) registered at our centre from January 2008 to December 2010 were reviewed for baseline disease characteristics, international prognostic score (IPS), treatment, response, death , progression or relapse. CD20 expression (focal or diffuse membrane positivity in HRS cells) was noted. Patients receiving more than 2 cycles with evaluable response were analysed for overall survival (OS) and progression free survival (PFS). Results. A total of 143 patients (males-112) were analysed. Median age was 28 years (range 14-70 years). 73% of patients had stage III/IV disease. B symptoms, bulky disease, IPS ≥4 and bone marrow involvement was seen in 75%, 38%, 22% and 15%, respectively. Post 6 cycles of ABVD 88% achieved complete response whereas 8% experienced disease progression. CD20 positivity was noted in 22% (evaluable in 112 patients). CD15 was positive in 31/92 patients. Baseline disease characteristics were similar in the CD20+ and negative subset. The 3-year PFS and OS were 80% and 95% respectively. 3-year PFS was 65.5% and 87% (p=0.035) respectively in CD20+ and negative subset, while OS was 88% and 97% respectively (p=0.06). CD20+, IPS≥4 was associated with inferior PFS both in the univariate and multivariate analysis. Absolute lymphocyte and monocyte ratio and CD15 expression did not impact PFS or OS. Conclusion. In our study CD20 expression did affect progression free survival. However there was no impact on overall survival which may be explained by short follow up and availability of effective salvage therapies.

P010
PROSPECTIVE EVALUATION OF THE UTILITY OF THE INTERNATIONAL PROGNOSTIC SCORE (IPS) FOR PATIENTS WITH ADVANCED HODGKIN LYMPHOMA (HL) TREATED WITH CONTEMPORARY THERAPY: RESULTS FROM US INTERGROUP TRIAL E2496

Diefenbach CS, Li H, Hong F, Gordon LI, Fisher RI, Bartlett NL, Crump M, Gascoyne RD, Wagner H, Stiff PJ, Cheson BD, Stewart D, Kahl BS, Friedberg JW, Blum KA, Habermann TM, Tuscano JM, Hoppe RT, Horning SJ, Advani RH

New York University School of Medicine/NYU; Cancer Institute; Dana Farber Cancer Institute; Northwestern University; Fox Chase Cancer Center-Temple Health; Washington University Sch. of Med. Siteman Cancer Center; Princess Margaret Hospital; BC Cancer Agency; Penn State Milton S Hershey Medical Center; Loyola University Medical Center; Georgetown University Hospital Lomabardi Cancer Center; Tom Baker Cancer Center University of Calgary; University of Wisconsin Hospital and Clinics; James P Wilmot Cancer Center University of Rochester; Ohio State University Comprehensive Cancer Center; Mayo Clinic; UC Davis Cancer Center; Stanford University; Genentech Inc.; Stanford University, USA

Background. The International Prognostic Score (Hasenclever, NEJM 1988) built from a retrospective analysis of patients treated before 1992 continues to be the most commonly used risk stratification index for advanced HL and predicts for 5 year freedom from progression (FFP) of 42%-84% and overall survival (OS) of 56%-89%. A retrospective analysis from British Columbia (Moccia JCO 2012) suggests that more recently the predictive range of the IPS has narrowed. To prospectively confirm the latter findings in the context of changes in staging and treatment paradigms in the modern era, we assessed the ability of the IPS to predict outcome in patients enrolled on the US Intergroup trial E2496. Methods. The seven IPS variables were recorded at study entry. FFP and OS were correlated with the IPS and compared to the published Hasenclever and Moccia reports. For FFP, all deaths from unrelated causes were censored. Results. From 1996-2006, 854 patients were randomized to treatment with ABVD or Stanford V, with no differences in outcome (Gordon et al JCO 2013). On multivariate analysis, only hemoglobin and stage remained significant for FFP, while hemoglobin<10.5, stage IV, and age>45yrs were significant for OS. The IPS remained prognostic for both FFP (p=0.011) and OS (p<0.001). Five year FFP rates of 81%, 74% and 63%, and 5-year OS rates of 92%, 85% and 60% respectively were found for low (0-2), intermediate (3-4), and high risk (>4) patients when grouped according to number of risk factors. Table 1 lists our Results. as well as those of the 2 retrospective analyses. Conclusion. The IPS remained prognostic for FFP and OS in our recently treated patients, however we found superior clinical outcomes than were originally reported, particularly for intermediate and high risk groups, and the predictive range has narrowed for all patient groups. Improved tools for risk assessment are needed to further stratify low and intermediate risk patients, and inform therapeutic decision-making. For the highest risk patients, there is an ongoing need for novel therapeutic strategies.

Table 1. Outcome comparison.

	% Patients			5 yr %FFP			5 yr %OS		
# Risk factors	E2496	Moccia	Hasenclever	E2496	Moccia	Hasenclever	E2496	Moccia	Hasenclever
0-2	67	60	58	81	80-88	67-84	92	91-98	81-90
3-4	27	33	35	74	67-74	51-60	85	85-88	61-78
≥5	6	7	7	63	62	42	60	67	56

P011
A PILOT STUDY OF A REDUCED THERAPY DRIVEN BY EARLY PET RESPONSE IN 64 PATIENTS TREATED WITH 2 CYCLES OF BEACOPPESC FOR ADVANCED HODGKIN LYMPHOMA

Deau B,[1] Franchi P,[2] Briere J,[3] Ohana J,[4] Thieblemont C,[2] Brice P[2]

[1]Hematology department, Hôpital Cochin, Paris, France; [2]Hematology department, Hôpital Saint Louis, Paris, France; [3]Histopathology department, Hôpital Saint Louis, Paris, France; [4]Nuclear Medicine department, Hôpital Saint Louis, Paris, France

The better efficiency of BEACOPPesc against advanced Hodgkin lymphoma is associated to an increase of toxicities. PET performed after 2 courses of chemotherapy (PET2) was shown to predict outcome. In this setting, a pilot study was designed to test in advanced HL patients, a reduced treatment strategy driven by PET after 2 cycles of BEACOPPesc. This is a monocentric prospective study, from 2008 to 2012. Patients with a stage IIB (according to the GHSG criteria), III, and IV, were included at diagnosis. A baseline PET scan was performed. BEACOPPesc was slightly modified for ambulatory administration, including Etoposide 200 mg/m2 with orally administration for days 2 and 3 and prednisone from day 1 to 8. In case of PET2 negative, the treatment was completed by 4 cycles of ABVD with a CT scan after 2 and 4 courses. In case of PET2 positive, the treatment was completed by 2 cycles of BEACOPPesc, then the response was assessed on a PET (PET4), with decisional value for the following treatment. 64 patients were included, 58% female, median age at 25 years (range 15 to 57 years). 11 patients had high risk stage IIB, 9 and 44 patients had stage III and IV disease respectively. 55 patients (86%) obtained a negative PET2, whereas 9 patients (14%) did not. After a median follow up of 28,7 months (range : 7-60), the PFS was 85%. The overall relapse rate was 15% at a median of 8 months after the end of treatment (range : 4-14 months), no deaths. In the PET2 negative arm, all patients were in complete remission after ABVD. Six relapses (11%) occurred, treated with high dose therapy. In the PET2 positive arm : 4 patients relapsed (44%). The 2 years PFS for the PET2 negative and positive arm was 87% and 47% respectively (p

=0,0059). This pilot study confirm that the substitution of oral etoposide is feasible and effective. Therefore, a therapy strategy driven by early PET negative with a reduced treatment is effective. Nevertheless, this Results. have to be confirmed : the randomized trial AHL11 is ongoing in France.

P012
HIGH INCIDENCE OF ASEPTIC HIP NECROSIS IN HODGKIN LYMPHOMA PATIENTS TREATED WITH ESCALATED BEACOPP WITH METHYL-PREDNISOLONE

Basic-Kinda S, Durakovic N, Karlak I, Lubina ZI, Radman I, Dotlic S, Hude I, Aurer I

Division of Hematology; Department of Internal Medicine; University Hospital Centre Zagreb Department of Traumatology; University Hospital Centre Sisters of Mercy Department of Radiology; University Hospital Merkur Department of Pathology; University Hospital Centre Zagreb, Croatia

Escalated BEACOPP (eBEACOPP) is a very effective but toxic regimen for treatment of Hodgkin lymphoma (HL). Hematologic toxicity is almost universal and infections are frequent. Other prominent side-effects include thrombosis, pulmonary toxicity and neuropathy. Aseptic hip necrosis (AHN) was not frequently observed in Germany, where eBEACOPP originated and where more than 2000 patients were treated with this regimen but occurred frequently in Czech and Norwegian series. After observing an unusually high incidence of AHN in our patients treated with eBEACOPP we decided to perform this study. We identified 25 patients with HL treated at our centre who were scheduled to receive at least 4 cycles of eBEACOPP for newly diagnosed high-risk advanced stage HL (Hasenclever index >2) or who were PET+ after 2 ABVD cycles. One patient died of neutropenic sepsis during treatment, all other responded. With a median follow-up of 24 months all surviving patients are in continuous remission. Two-year overall and progression-free survival rates are 96%. Toxicity was largely as expected (grade 3&4 hematological toxicity 96%, infections 36%, DVT/PE 12%), except for the fact that 5 patients developed clinically significant hip problems and two needed hip replacement. We therefore invited all patients to undergo hip MRI and orthopedic evaluation, 17 responded (71%). Six, four symptomatic and two asymptomatic, had radiological signs of AHN (35% of the examined and 25% of the total cohort). AHN did not correlate with the total dose of steroids administered (calculated as the prednisone-equivalent glucocorticoid dose), neither absolute nor relative to weight or body surface. However, there was a strong correlation with the use of methyl-prednisolone in comparison to prednisone (5 out of 7 *vs* 1 out of 10, p=0.0345 2-sided Fisher's exact test). On reviewing the literature, we found two papers describing increased AHN in rabbits and chicken treated with methyl-prednisolone in comparison to prednisolone in glucocorticoid-equivalent doses. We could not find any such report in humans. eBEACOPP is a very effective regimen for treatment of HL but the steroid used in it should not be methyl-prednisolone due to a very high risk of AHN.

P013
TREATMENT RESULTS OF SIX CYCLES EACOPP-14 ±RT IN ADVANCED STAGE HODGKIN LYMPHOMA. MULTICENTERS STUDY IN RUSSIA

Demina EA,[1]Tumyan GS,[1] Stroyakovskiy DL,[2] Ryabukhina YE,[1] Kuliev RG,[2] Leontyeva AA,[1] Profatilo IV,[2] Ovchinnikova EG,[3] Minenko SV,[4] Biyachuev ER,[4] Strelnikova TB,[2] Nyashin VE,[2] Yurchenkov AN,[2] Larina YV,[4] Trofimova OP,[1] Sotnikov VM,[5] Larioniva VB,[1] Osmanov EA[1]

[1]N.N.Blokhin Russian Cancer Research Center RANS, Moscow, Russia; [2] Moscow City Oncology Hospital 62, Moscow, Russia; [3]Regional oncology dispensary 1, Nizhny Novgorod, Russia; [4]Moscow State Medical Institution Municipal Clinical Hospital n.a. S.P. Botkin, Moscow, Russia; [5]Russian Scientific Center of Radiology, Moscow, Russia

Purpose. Intensified chemotherapy (CT) with eight cycles of BEACOPPescalated + RT in advanced stage Hodgkin lymphoma (HL) is highly effective but also associated with relevant treatment related toxicity. To reduce toxicity without losing efficacy we used -14 where bleomycin was excluded, dose of adriblastin was up to 50 mg/m^2 and number of cycles reduced to 6. This modification was named EACOPP-14. Methods. Between June 2008 and December 2013, 129 patients (pts) with newly diagnosed HL aged 17-51 years in Ann-Arbor stage II with large mediastinal mass or extranodal lesions and in stage III or IV were included, male/female were 68/61. After completion of chemotherapy pts in partial response (PR) with a persistent mass 2.5cm and more received additional radiotherapy (RT) with 30-36Gy. All pts who included have follow-up at least 3 months after the end of treatment. Results. All 6 cycles EACOPP-14 reseived 116pts (89,9%), 13pts CT was reduced due to toxicity or progression. RT reseived 88pts (68,2%). Complete response (CR) with or without residual abnormalities were achieved in 92,8%. PR was achieved in 1, progression disease in 6 pts and 1pt had relapse after a year. After a median follow-up of 23 months, there were 3 deaths (2.3%): one from acute myeloid leukemia, one from pneumonia in CR and one from progression. Acute toxicity (WHO grade 3 or 4) were leucopenia 80% pts, anemia 67,3%, thrombocytopenia 16,4%, infections 30,7%, noncontrolled hyperglikemia in 1 and cardiotioxicity in 2 (heart attack in zone of previously stenotic right coronary artery in one and myocardiodistrophia in another). There were lung fibrosis according the RT field in 7pts and clinically mean pulmonitis in 2 (1,8%). Three years rate of freedom from treatment failure (FFTF) was 89%, overall survival (OS) 96.3% and progression-free survival (PFS) 89%. After the treatment 5 women became pregnant, three of them delivered healthy children and two pregnancies continued. One of these women has second pregnancy after treatment. Conclusion. This preliminary results show that six cycles of EACOPP-14 followed by RT is an effective and low toxic program for advanced stage HL. Disclosures: No relevant conflicts of interest to declare.

P014
PERIPHERAL BLOOD LYMPHOCYTE/MONOCYTE RATIO IN ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA: PROGNOSTIC VALUE AND CORRELATION WITH IPS AND TUMOR ASSOCIATED MACROPHAGES

Jakovic LR,[1] Andjelic BM,[1] Bogdanovic AD,[1,2] Perunicic Jovanovic MD,[3] Babic D,[4] Bumbasirevic VZ,[5] Mihaljevic BS[1,2]

[1]Clinic for Hematology, Clinical Center of Serbia; [2]Faculty of Medicine, University of Belgrade; [3]Department for Histopathology, Clinical Center of Serbia; [4]Institute for Medical statistics and Informatics, Faculty of Medicine University of Belgrade; [5]Institute of Histology and Embryology, Faculty of Medicine University of Belgrade, Serbia

Background. High content of tumor associated macrophages (TAM), originated from circulating monocytes, is negative prognostic factor in advanced stage Hodgkin's lymphoma (HL). The aim of the study was to determine whether peripheral blood absolute lymphocyte/monocyte count ratio (ALC/AMC) at diagnosis, a simple biomarker combining surrogates of host immune homeostasis and tumor microenvironment, could add prognostic value to International Prognostic Score (IPS) and contribute to better risk stratification of HL. Material and Methods. We examined the prognostic impact of the ALC/AMC ratio in 303 advanced classical HL (cHL) patients treated from 1997-2008 using receiver operating characteristic curve analysis for optimal cutoff values, survival analysis with Cox proportional hazard regression model and compared these findings with TAM content (Leuk Lymphoma 2011, Onkologie 2012). Results. The median follow-up was 90 months. The absolute lymphocyte/absolute monocyte count ratio at diagnosis of 2.2 or more had the best cut-off value for survival (CI 1.9-2.4). Univariate analysis revealed that the following factors were associated with lower OS: low ALC/AMC ratio (<2.2) (OS5yrs with/without risk factor 64% *vs* 85%, respectively; log rank p=0.0001) and high IPS (>2) score (OS5yrs 62% *vs* 85%, respectively, log rank p<0.001). Similarly, these factors also had significant impact on EFS: low ALC/AMC ratio (<2.2) (EFS5yrs 47% *vs* 74%, respectively; log rank p=0.00001); high IPS (>2) score (EFS5yrs 50% *vs* 70%, respectively, log rank p=0.0001). Multivariate analysis identified both low ALC/AMC ratio (<2.2) and high IPS (>2) to be independent variables for OS (p=0.0003, p=0.0002, respectively). Furthermore, low ALC/AMC ratio (<2.2) and high IPS (>2) affected EFS (p=0.0001 p=0.004, respectively). A Spearman correlation test with TAM content showed a negative correlation with the ALC/AMC ratio (p 0.05). Also, 50% of patients with low ALC/AMC ratio had more than 25% of TAM, while only 28% of those with high ALC/AMC ratio had >25% TAM (Chi square and Fisher test p=0.03 and p=0.04). Conclusion. Our findings suggest that the ALC/AMC ratio might be a simple, independent prognostic factor for survival in patients with advanced cHL and may contribute to their better stratification in addition to the IPS and TAM content.

P015
BEVACIZUMAB ADDED TO ABVD FOR THE TREATMENT OF ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA

Barnes JA, Hochberg EP, Takvorian T, Feng Y, Sohani A, Neuberg D, Abramson JS

Massachusetts General Hospital Cancer Center, Dana-Farber Cancer Institute; Harvard Medical School, Boston MA, USA

Background. In classical Hodgkin Lymphoma (cHL), increased angiogenesis as measured by increased microvessel density and elevations in serum vascular endothelial growth factor (VEGF) are associated with inferior overall survival. We designed a phase II study to assess the efficacy of incorporating the anti-VEGF monoclonal antibody bevacizumab with standard ABVD for advanced stage cHL. Methods. This is a phase II single institution study with a primary end point of 2-year failure free survival (FFS). Patients with advanced stage cHL were treated with bevacizumab 10 mg/kg and standard ABVD on days 1 and 15 every 28-day cycle for a total of 6 cycles. Correlative studies include evaluation of microvessel density, serum and tissue levels of VEGF isoforms, and correlating with outcome. Results. Twenty-five subjects were enrolled and are available for analysis. Median age was 29 years (range 18-52), 60% of patients were male, 60% stage IV, 48% with B symptoms and a median international prognostic score of 3 (range 1-5). The overall response rate was 96% with complete response rate of 52%. The two year FFS was 67% (90% CI [50-84%]). At a median follow-up of 18 months, the progression free survival was 73%. Seven subjects relapsed less than 12 months after the completion of therapy and one additional subject relapsed at 24 months. Seven subjects with relapse underwent salvage therapy with high dose chemotherapy and autologous stem cell transplant. One subject relapsed after autologous transplant and underwent allogeneic transplant. One subject with relapse is still under active treatment awaiting auto transplant. All subjects remain alive at last follow-up. The most common grade 3-4 adverse events were neutropenia (22 patients), and febrile neutropenia (4). Three subjects experienced hypertension with only 1 grade 3 and no grade 4. There were 2 incidents of grade 3 thrombosis requiring anticoagulation. No patients experienced proteinuria. Two subjects discontinued treatment due to toxicity. Conclusions. In this non-comparative study, bevacizumab combined with ABVD does not appear to offer improvement over ABVD alone in advanced stage cHL, and does add additional toxicity. Correlative studies investigating biomarkers of angiogenesis and response are ongoing.

P016
EARLY SALVAGE WITH HIGH-DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANTATION IN ADVANCED STAGE HODGKIN'S LYMPHOMA PATIENTS WITH POSITIVE POSITRON EMISSION TOMOGRAPHY AFTER TWO COURSES OF CHEMOTHERAPY: PRELIMINARY RESULTS OF THE IIL-HD0801 STUDY

Zinzani PL,[1] Bonfichi M,[2] Rossi G,[3] Zaja F,[4] Vitolo U,[5] Pavone V,[6] Pulsoni A,[7] Rigacci L,[8] Gaidano G,[9] Santoro A,[10] Stelitano C,[11] Rusconi C,[12] Castagna L,[10] Zaccaria A,[13] Fattori PP,[14] Liberati AM,[15] Freilone R,[16] Petti MC,[17] Molinari A,[18] Spina M,[19] Latte G,[20] Gioia D,[21] Ferranti A,[21] Ciccone G,[22] Evangelista A,[22] Castagnoli A,[23] Riccardi U,[24] Levis A[25]

[1]University of Bologna, Institute of Haematology , Bologna, Italy; [2]Haematology, Policlinico San Matteo Foundation, Pavia, Italy; [3]Haematology, Spedali Civili Hospital, Brescia, Italy; [4]Haematology, S.Maria della Misericordia University and Hospital, Udine, Italy; [5]Haematology, Città della Salute e della Scienza Hospital, Torino, Italy; [6]Haematology, Cardinale Panico Hospital, Tricase, Italy; [7]Haematology, La Sapienza University, Roma, Italy; [8]Haematology, Careggi University and Hospital, Firenze, Italy; [9]Haematology, A Avogadro University, Novara, Italy; [10]Haematology, IRCCS Humanitas, Rozzano, Italy; [11]Haematology, Bianchi Melacrino Morelli Hospital, Reggio Calabria, Italy; [12]Haematology, Niguarda Hospital, Milano, Italy; [13]Haematology, S. Maria dell Croci Hospital, Ravenna, Italy; [14]IRST of Meldola, Meldola, Italy; [15]Onco-Haematology Department, S.Maria Hospital, Terni, Italy; [16]SC Medicina Trasfusionale ed Ematologia-ASL TO4, Ivrea, Ciriè e Chivasso, Italy; [17]Haematology, Regina Elena Institute, IFO, Roma, Italy; [18]Haematology, Ospedale degli Infermi, Rimini, Italy; [19]Division of Medical Oncology A, National Cancer Institute, Aviano, Italy; [20]Ematologia e Centro Trapianti, San Francesco Hospital, Nuoro, Italy; [21]Haematology, Italian Lymphoma Foundation Onlus, Alessandria, Italy; [22]Oncology Epidemiology, Città della Salute e della Scienza Hospital, Torino, Italy; [23]Nuclear Medicine, AUSL4 Hospital, Prato, Italy; [24]Radiotherapy, Città della Salute e della Scienza Hospital, Torino, Italy; [25]Haematology, SS Antonio e Biagio Hospital, Alessandria, Italy

IIL-HD0801 is an ongoing prospective multicenter clinical trial aiming to assess the early salvage with high-dose chemotherapy and autologous stem cell transplantation (ASCT) in advanced stage Hodgkin's lymphoma (HL) patients with positive positron emission tomography (PET-2 positive) after two courses of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). The study focuses also on comparison of radiotherapy versus no radiotherapy in PET-2 negative patients in complete remission after 4 additional ABVD courses. At the time of this present interim analysis, focusing on PET-2 positive patients and on their outcome after salvage approach, 417 subjects were deemed evaluable. PET-2 positive patients were scheduled for 4 courses of ifosfamide, gemcitabine, vinorelbine and prednisolone (IGEV) chemotherapy. After IGEV, a second PET evaluation was carried out: PET-IGEV negative patients received high-dose BEAM chemotherapy followed by ASCT, PET-IGEV positive patients received high-dose chemotherapy followed by two ASCT or one ASCT and one allogeneic stem cell transplant according to donor availability. Baseline characteristics of PET-2 positive patients (n=81) were: 42 (52%) males, median age was 31 years, 73% (n=59) nodular sclerosis HL, 42 (52%) stage IV and 36% (n=29) bulky. 55/81 PET-2 positive patients were evaluable after 4-IGEV courses: 32 (58.2%) obtained a negative PET and underwent ASCT. 26 patients were also restaged after ASCT: 24 (92.3%) had a final negative PET, while only two had a positive PET. 23/55 (41.8%) patients were PET positive after IGEV: 6 went out of therapy and the others are ongoing. At a median time of follow up of 19 months, preliminary results showed that patients judged resistant due to residual PET-positive masses after the first two course of ABVD can be salvaged by early shift to high-dose chemotherapy supported by stem cell rescue. Further updated results will be presented at the meeting as the enrollment was just closed.

P017
PHASE 3 STUDY OF BRENTUXIMAB VEDOTIN PLUS DOXORUBICIN, VINBLASTINE AND DACARBAZINE (A+AVD) *VS* DOXORUBICIN, BLEOMYCIN, VINBLASTINE AND DACARBAZINE (ABVD) AS FRONT-LINE TREATMENT FOR ADVANCED CLASSICAL HODGKIN LYMPHOMA (HL): THE ECHELON-1 STUDY

Radford J,[1] Younes A,[2] Ansell SM,[3] Gallamini A,[4] Kim WS,[5] Feldman TA,[6] Hamadani M,[7] Chung J,[8] Wang J,[8] Huebner D,[9] Connors JM[1]

[1]University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom; [2]Memorial Sloan-Kettering Cancer Center, New York NY, USA; [3]Mayo Clinic, Rochester, MN, USA; [4]Nice University, Nice, France; [5]Samsung Medical Center, Seoul, South Korea; [6]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [7]West Virginia University, Morgantown, WV, USA; [8]Millennium: The Takeda Oncology Company, Cambridge, MA, USA; [9]Centre for Lymphoid Cancer, British Columbia Cancer Agency and the University of British Columbia, Vancouver BC, Canada

Brentuximab vedotin (ADCETRIS®), a CD30-targeted antibody-drug conjugate, has conditional approval in Europe for adult relapsed/refractory CD30-positive HL following autologous stem cell transplant (ASCT) or following ≥2 prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. ABVD, a common front-line regimen for advanced HL, achieves complete response (CR) rates of 70–80%. However, 10–20% of patients have diseases refractory to front-line treatment and up to 35% relapse after front-line multi-modality therapy. In patients with relapsed HL post-ASCT, objective response rate to single-agent brentuximab vedotin is 75% (CR, 33%; Chen, ASH 2012). In a phase 1, dose-escalation study (SG035-009; NCT01060904), 51 patients (median 33 years; range, 18–59) with treatment-naïve HL stage IIA bulky or stage IIB-IV disease were enrolled to evaluate safety, maximum tolerated dose, and antitumor activity of brentuximab vedotin in combination with either ABVD (A+ABVD) or AVD (A+AVD) (Ansell, ASH 2012). Brentuximab vedotin was administered on Days 1 and 15 of 28-day cycles (≤6 cycles). 3 A+ABVD cohorts received brentuximab vedotin 0.6, 0.9, or 1.2 mg/kg, respectively; 1 A+AVD cohort received brentuximab vedotin 1.2 mg/kg. A+AVD was associated with manageable toxicity and a CR rate of 96%, whereas A+ABVD induced unac-

ceptable pulmonary toxicity. We hypothesize that substituting bleomycin with brentuximab vedotin may improve progression-free survival (PFS) compared to standard ABVD while simultaneously eliminating bleomycin-associated pulmonary toxicity. ECHELON-1, an ongoing, open-label, randomized, multicenter study (C25003; NCT01712490) will compare A+AVD *vs* ABVD in 1040 patients with advanced stage classical HL. Key inclusion criteria: histologically-confirmed previously untreated stage III or IV classical HL. Patients will receive A+AVD (brentuximab vedotin 1.2 mg/kg with each dose of AVD) or ABVD administered intravenously on Days 1 and 15 of 28-day cycles (≤6 cycles). Primary endpoint: modified (m) PFS (death, progression, and receipt of chemotherapy or radiotherapy by patients not in CR after completing front-line therapy count as progression events). A total of 260 mPFS events will provide 90% power to detect a hazard ratio of 0.67 at a 1-sided significance level of 0.025. Key secondary endpoint: overall survival. Disease status, patient reported outcomes and adverse events will also be assessed.

P018
RESULTS OF TREATMENT OF HODGKIN LYMPHOMA IN PREGNANT WOMEN

Sharkunov NN,[1] Moiseeva TN,[1] Al-Radi LS,[1] Zybunova EE,[1] Shmakov RG,[2] Kravchenko SK[1]

[1]Hematology Research Center, Moscow, Russia; [2]V.I. Kulakov Center of Obstetrics, Gynecology and Perinatology, Moscow, Russia

Introduction. Hematologic tumors during pregnancy are rare, but represent a significant risk to the life of mother and fetus. One of the most common hematological tumors in young women is Hodgkin lymphoma (HL). Patients and methods. From 1993 to 2013 we observed 37 pregnant or just delivered women with newly diagnosed HL, median age was 28 years (range 17-37). Among them 32 (86%) patients had advanced-stage HL (IIB-IV), 78% histology was nodular sclerosis. There were 14 patients in 2nd–3rd trimester of pregnancy and 23 patients were after childbirth. Results. Chemotherapy during pregnancy was started in 6 patients because of clinical indications to the urgent treatment (1–4 courses COPP-ABVD, or BEACOPP, or ABVD). One patient had radiotherapy. Another 7 pregnant women were observed without treatment until delivery. In 3 weeks after delivery they underwent chemotherapy BEACOPPesc/BEACOPP-14 or ABVD. The same treatment was performed to 23 HL patients diagnosed in the postpartum period. Consolidating radiotherapy was performed in 27 (73%) patients in a total dose of 30 to 40 Gy. All women gave birth on 36-40 weeks of pregnansy healthy children without signs of hypoxia. Six women (86%) treated during pregnancy achieved complete remissions (CR), lasting 18-240 months (median follow up-51 months). In 30 HL patients treated after delivery CR were achieved in 29 (97%) patients, and a partial response in 1 patient (then achieved CR after second-line chemotherapy), follow up is 1-110 months (median–18 months). One patient relapsed in 3.5 months. Conclusions. Starting treatment in HL pregnant women depends on the period of pregnancy, tumor size, the presence of mediastinal compression, B-symptoms, tumor growth. Early pregnancy in HL patient should be terminated (except local forms with non-aggressive course of disease). HL women in the 2nd–3rd trimester of pregnancy need careful observation to administrate chemotherapy before delivery in cases of advanced-stage HL and/or unfavorable course of the disease, using non-intensive programs us ABVD, BEACOPP. After birth, chemotherapy may be started as necessary, optimally in 3 weeks.

P019
SUBSTITUTION OF CYCLOPHOSPHAMIDE FOR NITROGEN MUSTARD IN THE STANFORD V (SV) REGIMEN DOES NOT COMPROMISE OUTCOME IN ADULTS WITH HODGKIN LYMPHOMA

Advani RH,[1] Varma G,[1] Horning SJ,[1] Allen J,[1] Rosenberg SA,[1] Hoppe RT[2]

[1]Medical Oncology, Stanford University Medical Center; [2]Radiation Oncology, Stanford University Medical Center, USA

Background. Stanford V is an effective combined modality regimen for treating Hodgkin Lymphoma (HL). In 2010, a national shortage of mechlorethamine (M) led to modification of the Stanford V chemotherapy in which cyclophosphamide (650 mg/m2) was substituted for M (6 mg/m2) (SV-Cy). A pediatric group recently reported significantly inferior 2-year event free survival with SV-Cy compared to SV-M, 75% versus 88%, respectively, p=0.01 in patients with intermediate and high risk disease (Metzger et al. NEJM 2012). Of note, the pediatric regimen used a radiotherapy (RT) dose of 15-25 Gy to the involved field compared to 36 Gy to sites ≥5 cm used in adults. The aim of this analysis was to assess outcomes in adult patients treated with SV-Cy at Stanford. Methods. Patients treated with SV-Cy were identified retrospectively from the Stanford HL database. Two year freedom from progression (FFP) and disease specific survival (DSS) were estimated using the Kaplan-Meier method, and compared to those treated with SV-M using the log-rank test. The proportion of relapses and deaths were compared using a Chi-square test. Results. Between 1989 and 2012, 291 patients with stage I-II bulky mediastinal or stage III-IV HL were treated with 12 weeks of chemotherapy and 36 Gy RT to initial sites of bulky disease. Median age was 29 (16-82 years). 265 patients received SV-M and 26 SV-Cy. Table 1 compares the outcome in the two groups. For SV-M versus SV-Cy, there is no significant difference in a) the proportion of patients who relapsed or died from disease b) 2-year FFP or 2-year DSS. Conclusions. In adult patients with HL, substitution of cyclophosphamide for mechlorethamine did not impact outcome. The inferior results reported in the pediatric literature may relate to the lower doses of RT used and underscore the importance of adhering to all components of the original published protocol.

Table 1.

	SV-M (n=265)	SV-Cy (n=26)	p-value
Median followup, yr	10.35 (0.13-22.61)	1.81 (0.64-3.07)	
Relapsed, %	9.3	7.0	0.63
Died from disease, %	5.2	0	0.23
2y FFP, %	87.9 [95% CI, 83.3-91.3]	84.9 [95% CI, 58.3-95.1]	0.91
2y DSS, %	96.2 [95% CI, 93.4-97.9]	100	0.38

P020
BEACOPP-14 IN 299 PATIENTS WITH ADVANCED-STAGE HODGKIN LYMPHOMA: A SINGLE CENTER RESULTS.

Moiseeva TN, Sharkunov NN, Al-Radi LS, Zybunova EE, Chernova NG, Margolin OV, Maryin DS, Julakyan UL, Melikyan AL, Mangasarova YK, Skidan NI, Tseytlina MA, Shitareva IV, Tsyba NN, Kravchenko SK

Hematology Research Center, Moscow, Russia

Purpose. To evaluate the effectiveness of chemotherapy regimen BEACOPP-14 in primary patients with advanced stages of Hodgkin lymphoma (HL). Materials and methods. From March 2006 to March 2012 we observed 299 patients (median age 27 years, range 16-66) with primary HL stage III-IV or stage II with poor prognostic factors (bulky-disease, syncytial-cell variant of nodular sclerosis and lymphoid depletion variant, tumor invasion into the surrounding tissue). All patients underwent 6-8 cycles chemotherapy BEACOPP-14. Residual lymph nodes larger than 2 cm were irradiated with a dose 30 Gy in 191 patients (including mediastinal irradiation in 162 patients). Results. Two patients died before the ending of the treatment after the 5th and the 6th courses of chemotherapy becouse of resistant pneumocystic pneumonia. One patient died in complete remission (CR) of unrelated to HL reasons. CR were reached In 297 patients, overall survival rate was 98.7%. 285 patients are still in CR with median follow-up 54 months (range 11-84), disease-free survival rate was 96%. Relapses developed in 11 (3.7%) patients (9 early relapses and 2 late relapses). The relapsed patients were treated with second line high-dose chemotherapy (DHAP, Dexa-BEAM). 7 patients who achieved remissions after second line treatment were subjected to autologous stem cell transplantation (autoHCT). Patients with late relapses achieved complete remissions with follow-up for 21 and 19 months. Only 3 (33%) patients with early relapses had complete remissions, maintained for 46, 27 and 4 months. Conclusions. BEACOPP-14 is a highly effective course of chemotherapy in primary patients with advanced-stage HL. The relapses rate was 3.7%, most of them (82%) are early relapses.

P021
NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA WITH BONE MARROW INVOLVEMENT

Khlavno AB, Moiseeva TN, Kovrigina AM, Al-Radi LS, Sharkunov NN, Kravchenko SK

Hematology Research Center, Moscow, Russia

Introduction. Bone marrow involvement in nodular lymphocyte predominant Hodgkin Lymphoma (NLPHL) is considered as a very rare event. Approximate incidence of bone marrow involvement in this case is around 1% (V. Diehl et al , 1999). Materials and methods. From 2003 to 2013 we revealed 28 patients with NLPHL. Median age was 39 years (range 17- 63 years), M:F=3:1. Most of the patients had advanced stage disease (17(61%) patients with stages III-IV), without -symptoms (21 (75%) patients). Results. Bone marrow involvement was found histologically and immunohistochemically in 8 (29%) patients (7 males and 1 female). All patients with bone marrow involvement had multiple lesions, 5 (62,5%) of them had extranodal involvement of bones and soft tissues. -symptoms were absent in 7 (87,5%) patients. In 4 patients we revealed NLPHL transformation to T cell rich B cell lymphoma (TCRBCL) in bone marrow, 2 of them with concordant transformation in peripheral lymph node biopsy. Bone marrow involvement was predominantly found in older age group (median age 44 years, range 33-63 years). History of prolonged asymptomatic lymphadenopathy was registered in three patients (lasting for 3, 5 and 11 years). Patients underwent following treatment: ABVD -1 patient,-2 patients, esc- 1 patient, P-14 +/- Rituximab–4 patients. In two cases involved field radiotherapy was administered in combination with chemotherapy. One patient underwent salvage chemotherapy followed by autologous stem cell transplant. All patients are alive, treatment is completed in 6 patients, 4 of them are in complete remission with median follow up 19 months (range 8-87 months). Two patients are still being treated. Two patients had early relapses. Conclusion. In our patients bone marrow involvement in advanced stages of NLPHL is more frequent event in comparison with published data. The evidence of possibility of transformation of NLPHL to TCRBCL in cases with bone marrow involvement needs further investigation.

P022
LONG-TERM RESULTS. OF RISK- ADAPTED THERAPY FOR ADVANCED HODGKIN'S LYMPHOMA: ONE-CENTER EXPERIENCE (1998-2012)

Bogatyreva TI, Pavlov VV

Medical Radiological Research Centre, Obninsk, Russia

Introduction. This prospective MRRC trial was aimed to investigate possibilities: 1) to minimize over-treatment in advanced Hodgkin's lymphoma (HL) by prescribing first-line chemotherapy (ABVD or BEACOPPbas) according to the proposed risk factors (RF), and 2) to reduce cumulative cardiopulmonary toxicity both by change for COPP in 1-2 cycles which preceded mediastinal irradiation and by treating residual tumor with low dose radiotherapy (RT) 20-22 Gy in accelerated hyperfractionated regimen. Patients and Methods. Between 1998 and 2012, the adult patients with advanced (stage III-IV) HL were allocated BEACOPPbas if they had one or more RF, associated with early progression: a) lymphoid depletion or NSII histology, b) pericardial effusion, c) bones or bone marrow involvement plus splenic lesions. Patients without RF received ABVD. Total six cycles were planned for supradiaphragmatic disease and 8 cycles-for involvement on both sides of the diaphragm (including 1-2 COPP), with involved-field RT to residual lesions. Overall survival (OS) and progression-free survival (PFS) were evaluated with regard to IPI scores 0-1, 2-3 or ≥4 (subgroups a,b,c). Results. With a median follow-up of 7 years, total 383 patients were eligible for analysis; 250 patients allocated BEACOPPbas (gr.1) and 133 patients started ABVD (gr.2);% pts with IPI score≥4 was higher in gr.1 (23% *vs* 3%). The % receiving 1-2 COPP at the end of chemotherapy course was 72% in gr.1 and 49% in gr.2. For all pts of gr.1, OS and PFS at 10 years were 85% and 71%; for pts of gr.2, 96% and 87%, respectively. In subgroups a/b/c of IPI score, 10-year OS was 93%/87%/71% for gr.1 and 100%/93%/100% for gr.2; PFS was, respectively, 88%/71%/55% for gr.1 and 93%/82%/75% for gr.2. There were no statistically significant differences in the outcome of 179 pts after 4 to 6 BEACOPPbas+2 COPP (OS 92%, PFS 86%) as compared to 35 pts after 6-8 BEACOPP (OS 73%, PFS 73%). Similarly, the outcome of 65 pts after 5-7 ABVD+ COPP (OS 96%, PFS 93%) did not differ from that in 40 pts after 6-8 ABVD (OS 100%, PFS 90%). Conclusion. Our data show that tailoring of induction chemotherapy to the risk factors (RF) helps to discriminate a proportion of patients with advanced stage for less toxic treatment.

P023
INTENSIFIED BEACOPP THERAPY FOR NEWLY DIAGNOSED PATIENT WITH ADVANCED STAGES CLASSICAL HODGKIN'S LYMPHOMA

Kriachok I, Novosad O, Titorenko I, Filonenko K, Aleksik E, Kadnikova T, Gubareva A, Kushchevoy E, Martynchyk A, Pastushenko Y, Ulyanchenko K, Stepanishyna I

Department of Oncohematology, National Cancer Institute, Kiev, Ukraine

Background. According to insufficient treatment results in high risk patients with Hodgkin's Lymphoma (HL) and possible improvement of the efficiency by intensification in this group of patients, we initiated the prospective randomized multicenter study, in order to compare the efficacy and toxicity -14 and -esc.in high risk group patients with HL. Methods. 111 patients (from September 2009 until December 2012) from 18 to 65 years old (median–30.6), 40.5% male and female 59.4%, with stage III-IV, were treated with -14 (n=47) and -esc (n=64). The treatment efficacy in both groups was evaluated after 4, 6, 8 cycles by heson criteria (1999, 2007). All patients received supporting therapy (erythropoietin, G-CSF). Results. Overall response rate of -14 and -esc were 97.7% and 96.5%, respectively (>0.05); Complete response rate was also equal (60.8% and 67.24%, respectively) (>0.05). Maximal observation period is 38 months. The 3-year progression-free (PFS) and overal survival (OS) in the whole group (n=111) were 94.0% and 94.7%, respectively. OS in BEACOPP-esc group was 91.9% and 85.9% in BEACOPP-14 group (p>0.05). 5 patients relapsed, among them 2 pts in BEACOPP-14 group and 3 pts–in BEACOPP-esc group, in term 1.2 to 30.5 months after treatment completed. Toxicity profile was represented mainly by hematological toxicity in 91.9% of cases (Grade 3/4 toxicities -30%). Anemia (62.8% *vs* 50.9%, >0.05) and thrombocytopenia (20.3% *vs* 11.6%, p>0.05) predominated in BEACOPP-esc group, while neutropenia rate was slightly higher in BEACOPP-14 group (71.3% *vs* 60.0%, > 0.05). Conclusion. Treatment of patients with advanced stages of HL with -14 and -esc is highly effective. Toxicity rate is acceptable provided that supportive therapy is used.

P024
BONE MARROW INVOLVEMENT IN CLASSICAL AND NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA–INDIAN TERTIARY CANCER CENTRE EXPERIENCE

Epari S,[1] Sengar M[2], Gujral S, Menon H,[2] Laskar S,[1] Shet T[2]

[1]Departments of Pathology, Radiation Oncology and Medical Oncology; [2]Tata Memorial Centre, Mumbai, India

Introduction. Hodgkin lymphoma, both classical (CHL) and Nodular lymphocyte predominant (NLPHL) types have lesser a propensity for involvement of bone marrow. This study compares the frequency of involvement of bone marrow in CHL and NLPHL. Material and Methods. All the consecutive cases from the years 2010 to 2012 of both CHL and NLPHL, where there is available bone marrow biopsies were included. The bone marrow involvement in these cases was also evaluated and compiled. Results. A total of 56 and 521 diagnosed cases of NLPHL and CHL with presence of bone marrow biopsies were included in the study. Age range was 6-68 (<18yrs: 11, 19-30yrs:21, 31-50yrs:18 &>50yrs: 18) with M:F ratio of 2.5:1 for NLPHL and for CHL was 3-78yrs (<18yrs:162,19-30yrs:150, 31-50yrs:140 &>50yrs: 69) with M:F ratio of 2.84:1. Of these cases, 3 (5.4%) and 32 (6.1%) cases of NLPHL and CHL cases showed bone marrow involvement at presentation. Cases presenting at stage IV but no histological documentation of bone marrow involvement have excluded. The pattern of involvement was predominantly focal in both types (though some cases of CHL showed diffuse marrow replacement). But the fibrosis and the presence of admixed eosinophils was seen in CHL but no case NLPHL showed fibrosis and eosinophils. Conclusion. Bone marrow involvement at presentation in Hodgkin lymphoma (both NLPHL and HL) is rare and as noted in the present study, there does not appear to be any significant difference in their frequency.

P025

COMPARISON OF DEMOGRAPHIC CHARACTERISTICS OF HODGKIN'S LYMPHOMA FROM TWO PROSPECTIVE REGISTRIES IN BRAZIL AND ITALY

Biasoli I,[1] Luminari S,[2] Castro N,[3] Delamain M,[4] Bellei M,[2] Gaiolla R,[5] Cesaretti M,[2] Simões B,[6] Iachetta F,[2] Solza C,[7] Praxedes M,[8] Bonamin Sola C,[9] Baiocchi O,[10] Chiattone C,[11] de Souza C,[4] Spector N,[1] Federico M[2]

[1]Universidade Federal do Rio de Janeiro, Brazil; [2]Oncology unit, Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy; [3]Hospital de Cancer de Barretos; [4]Center of Hematology and Hemotherapy, State University of Campinas; [5]UNESP, Botucatu, [6]USP-Ribeirão Preto; [7]Universidade do Estado do Rio de Janeiro; [8]Universidade Federal Fluminense; [9]Universidade Federal do o Paraná; [10]UNIFESP; [11]São Paulo Santa Casa Medical School, Brazil

Background. The outcome of Hodgkin's lymphoma (HL) has markedly improved over the past few decades. However, data about HL in developing countries are scarce. It is well established that patients in underprivileged societies present with malignancies in more advanced stages. In studies of HL patients treated in Brazil during the 80's, most patients presented with advanced disease. However, in a recent retrospective analysis a distribution similar to that reported in developed countries was found. Whether this represents a shift towards earlier diagnosis, it remains to be confirmed. In order to verify possible differences in the epidemiology of HL, we compared the characteristics of HL patients identified in a Brazilian Prospective Registry (BPR) to that from Modena Cancer Registry (MCR). Methods. The BPR was implemented in 2010 and 17 institutions take part in the registry. All HL patients from the MCR diagnosed between 1997-2010 were identified. Socio-economic status information (SES) was collected in the BPR according to previously published criteria. Results. A total of 372 patients were identified in BPR and 290 in MCR. The median age was 30 years (3-80) in Brazil, and 38 years (8-91) in Modena (P<0.001). Patients in Brazil presented more frequently with poor clinical prognostic factors when compared to Italian patients: poor performance status (13% x 5.5%, p=0.017), B symptoms (68% x 37%, p<0.0001), advanced stage IIB-IV (76% x 55%, p<0.001), albumin <4 g/dL (63% x 42%, p<0.001), hemoglobin < 10.5 g/dL(30% x 13%, p<0.001), ESR≥45 (54% x 41%, P<0.003) and high risk IPS score (66% x 49%, p<0.001). Among Brazilian patients, high and low SES patients were not different in regard of the proportion of poor clinical features. Also, when compared to Italian patients, Brazilian patients with a higher SES still presented poorer clinical features. Conclusion. The organization of a national registry of HL provides a reliable portrait of this disease in Brazil. The comparison of two databases confirmed the diagnosis of HL in more advanced stages in Brazil and also more frequently associated with poor prognostic factors. Survival data are currently being collected.

P026

EXTRANODAL DISSEMINATION IN CLASSICAL HODGKIN LYMPHOMA. REAL UNFAVOURABLE DISEASE

Jakovic LR,[1] Andjelic BM,[1] Bogdanovic AD,[1,2] Perunicic Jovanovic MD,[3] Bumbasirevic VZ,[4] Mihaljevic BS[1,2]

[1]Clinic for Hematology, Clinical Center of Serbia; [2]Faculty of Medicine, University of Belgrade; [3]Department for Histopathology, Clinical Center of Serbia; [4]Institute of Histology and Embryology, Faculty of Medicine University of Belgrade, Serbia

Background. Extranodal (EN) dissemination in classical Hodgkin lymphoma (cHL) is rare event and has prognostic value in advanced disease. It is still controversial whether specific organ involvement or number of EN sites is of prognostic relevance. AIM: We analyzed the prognostic value of specific organ involvement and number of involved EN sites in advanced cHL pts. Material and Methods. In a group of 95 cHL pts with EN disease treated with ABVD (1997-2008), prognostic relevance of bone marrow, lungs, liver involvement, as well as two or more involved extranodal localizations (EN2) was analyzed. The median follow up was 90 months. Their significance was tested according to response rate an overall survival (OS). Results. EN disease was present as 38 pts with bone marrow infiltration, lungs were involved in 24 pts, the liver in 8 pts and other sites in 5 pts. EN2 localizations were found in 20 pts. The most common dual involvement was bone marrow and liver 13 (56%), then bone marrow and lungs in 7 pts (21%). Complete remission was much higher in pts with single EN localization compared to those with two or more (79% *vs* 52%, p=0.010). There was no significant difference in CR between single specific extranodal involvement site. Overall survival (OS5y) in whole group was 65%. Patients with EN2 had significantlly shorter OS comapared to those with single site involvement (31% *vs* 73%, p=0.0009). Futhermore pts with double involvement, bone marrow and liver or bone marrow and lungs, had significantlly lower OS rate comparing to patients with single EN involvement (31% *vs* 67% p=0.010; 14% *vs* 68% p=0.02, respectively). Between these two groups with dual EN, we have not found any difference in OS. Conclusion. Advanced cHL patients with EN2 are at higher risk of treatment failure and might be eligible for different treatment approach.

P027

HODGKIN'S LYMPHOMA PRESENTING WITH PULMONARY CAVITATIONS

Lusis MKP,[1] Nucci FM,[2] Lusis LKP,[3] Mercante DR,[2] Orlando EP,[2] Aide MA,[4] Carvalho JEM,[4] Figueira CFN,[5] Monnerat AC,[6] Teixeira GHC,[6] Pires ARC,[6] Dias LVB[7]

[1]Professor of Haematology of the Medicine School; [2]Haematologist of the University Hospital; [3]Haematology resident doctor; [4]Professor of Pneumology of the Medicine School; [5]Pneumology resident doctor; [6]Professor of Pathology of the Medicine School; [7]Pathology resident doctor. Universidade Federal Fluminense. Hospital Universitario Antonio Pedro. Rio de Janeiro, Brazil

Case Report. A 35-year-old white woman, with bronchial asthma history, was admitted to Antonio Pedro University Hospital for investigation of weight loss, fever, night sweats, cough and dyspnoea, that had been progressing in the last 6 months, despite the use of antibiotics and bronchodilators. The main physical findings were pallor and bilateral supraclavicular lymphadenopathy. No visceromegaly was found. Computated tomography (CT) of the chest showed bilateral hilar adenomegaly and multiple parenchimal nodules with diffuse pulmonary cavitating lesions. There was no evidence of intra-abdominal disease. A bronchoscopy detected no lesions. Specimens for cultures for fungi, bacteria and tuberculosis were negative. Malignant cells were not found. The patient, whose HIV test was negative, underwent a lymph node biopsy which revealed Hodgkin lymphoma (HL) nodular sclerosis grade 2. Although the negative results for infectious agents supported the diagnosis of cancer, because of the very unusual pattern, exhibiting pulmonary cavitation, a lung biopsy was performed, which proved the neoplastic origin of the lesions.

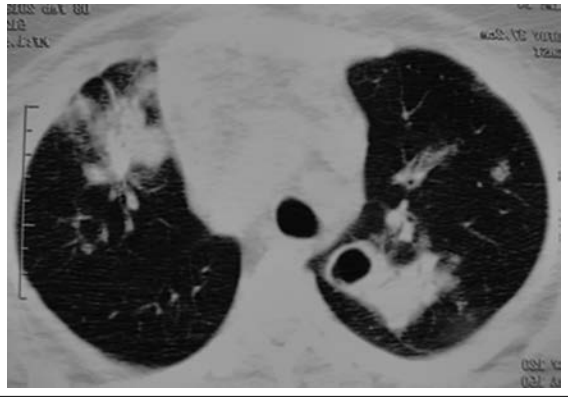

Figure 1.

A bone marrow biopsy was not done, as the patient had intense dyspnoea and the presence of diffuse lung lesions had already defined the stage as IVB. The patient showed regression of the pulmonary and constitutional symptoms after the first cycle of chemotherapy. Due to the extension of the parenchimal lung lesions, she was treated with Doxorubicin, Vimblastine and Dacarbazine, without Bleomycin. Discussion. Isolated pulmonary lesions of HL are very rare. However, secondary involvement is not uncommon, at initial diagnosis, during the clinical course or after the relapse, through hematogenous dissemination or direct invasion from hilar and/or mediastinal lymph nodes. In HL the infiltration of the parenchyma is almost always associated with intrathoracic adenopathy with contiguous spread from the lymph nodes. The most common finding at CT are pulmonary nodules or masses, usu-

ally multiple and bilateral, but cavitation is extremely rare. This patient's unusual presentation required histological confirmation in order to establish a differential diagnosis with tuberculosis, fungal infection, bronchoalveolar carcinoma, bronchiolitis obliterans organizing pneumonia, lymphomatoid granulomatosis, collagen vascular disorders and vasculitis as Wegener's granulomatosis.

P028
THERAPEUTIC RESPONSE OF TUNISIAN NATIONAL PROTOCOL: EXPERIENCE OF TWO CENTERS

Kacem K,[1] Zriba S,[2] Ghédira H,[2] Yahyaoui Y,[1] Mansouri R,[1] Dridi M,[1] Hadj Mansour M,[1] Manai Z,[1] Zarrouk M,[1] Ben Neji H,[1] Ben Abdennebi Y,[1] Jeddi R,[1] Aissaoui L,[1] Belhadj Ali Z,[1] Ben Abid H,[1] M'Sadek F,[2] Ben Lakhal R,[1] Meddeb B[1]

[1]Clinical Hematology Department of Aziza Othmana Hospital of Tunis; [2]Clinical Hematology Department of Military Hospital of Tunis, Tunisia

Purpose. Assessment of therapeutic response of Hodgkin lymphoma (HL) treated according the national protocol HL-2008. Patients and Methods. Between 2008 and 2011, 173 patients from 2 departments were enrolled in HL-2008 protocol (a third version of prospective trial). Results. Median age was 30 years (15-82) with a sex ratio 0.99. HL-2008 defined 5 groups: G1: favorable early stage, G2: unfavorable early stage, G3: advanced stage and localized stage with mediastinal bulk (MTI>0.35), G4: early stage in elderly patients, G5: advanced stage in elderly group. We recommend 2 cycles ABVD + radiotherapy (IFRT) for G1, 4 cycles of ABVD + IFRT for G2, 8 cycles of BEACOPP (4 escalated +4 baseline) for G3. Elderly groups received 6 and 8 cycles of ABVD for G4 and G5 respectively. Early assessment of response was recommended after 2 cycles in each group and an escalation to BEACOPP-R took place if response was less than 75%. 66.5% of patients were treated in G3, 19.5% in G2, 7% in G1, 6% in G5 and 1% in G4. 82% of patients were in complete response after the first line therapy. 12% were refractory. Median follow-up was of 32 months at 3 years, OS, EFS and RFS were respectively of 90, 75 and 95%. IFRT at 36 Gy was done in 48 patients with a median delay of 2 months (1-4). 5 patients received RT for residual disease. Conclusion. Comparatively to the second version, intensive chemotherapy for unfavorable HL (advanced stage and bulky mediastinal disease with stage II), RFS and OS are better.

P029
THE DIFFERENCES IN RISK PROFILE OF MALE AND FEMALE PATIENTS WITH ADVANCED HODGKIN'S LYMPHOMA

Andjelic B,[1] Jakovic Lj,[1] Antic D,[1,2] Todorovic M,[1,2] Bila J,[1,2] Sretenovic A,[1] Djurasinovic V,[1] Mihaljevic B[1,2]

[1]Clinic for Hematology, Clinical Center of Serbia, Belgrade, Serbia; [2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Background. Male gender is considered as an unfavorable prognostic factor for Hodgkin's lymphoma (HL). Modern studies are having the aim to define risk adopted treatment approach. Currently, the HL treatment for both genders is uniform. Aim. The aim of this study is to identify risk factors for poor outcome according to the gender in patients with advanced HL. Patients and Methods. A retrospective study was performed on 163 female and 151 male patients with advanced HL diagnosed in the period June 1997-December 2008. The initial treatment was 6-8 cycles of ABVD followed by radiotherapy. Prognostic relevance of histological subtype, presence of B symptoms, large mediastinal tumor, "bulky" disease, extranodal disease (EN), erythrocyte sedimentation rate (ESR) ≥50 mm/h and risk factors included in IPS score (except gender) was examined. Results. The median age of female patients was 31 (range 16-69) and for males 35 (range 17-80). Complete response rate was higher in females (86.5% *vs* 80.7%), but not statistically significant (p>0.05). There was a trend toward better both 5 yrs overall survival (79.8% *vs* 71.5%; p=0.074) and 5 yrs event free survival (66.3% *vs* 57.6%; p=0.06) in females. In univariate analysis, bulky disease and histological subtype influenced overall survival (OS) in females (p=0.045; p=0.011, respectively) and there was a trend towards worse event free survival (EFS) in patients with EN and clinical stage IV (p=0.083; p=0.051, respectively). The presence of B symptoms, EN, ESR≥50 mm/h, anemia and lymphopenia influenced in males both OS (p=0.015; p=0.002; p=0.015; p=0.005; p=0.004, respectively) and EFS (p=0.045; p=0.043; p=0.043; p=0.010; p=0.006, respectively) in univariate analysis. Males with CS IV and age>45 years had worse OS (p=0.021; p=0.03, respectively) and there was a trend towards worse EFS in males with CS IV (p=0.054). The multivariate analysis identified bulky disease in females as the independent prognostic factor for OS, while in males these are EN and anemia. Furthermore, lymphopenia is independent prognostic factor for EFS in males. Conclusion. ABVD is reasonable solution in females without large tumor, especially if planning pregnancy in future. Males having EN, anemia or lymphopenia require more effective initial treatment.

P030
THE IDENTIFICATION OF HIGH RISK ABVD TREATED ADVANCED HODGKIN'S LYMPHOMA PATIENTS-IPS REMAINS THE MOST APPROPRIATE PROGNOSTIC TOOL

Andjelic B,[1] Antic D,[1,2] Jakovic Lj,[1] Todorovic M,[1,2] Bogdanovic A,[1,2] Bila J,[1,2] Mihaljevic B[1,2]

[1]Clinic for Hematology, Clinical Center of Serbia, Belgrade, Serbia; [2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Background. International prognostic score (IPS) was derived from large cohort of Hodgkin's lymphoma (HL) patients, who were partially treated with historical regimens. Nowadays, the improvement in treatment results with modern strategies lead to question whether IPS is still an appropriate prognostic tool in HL. Aim: The aim of this study was to assess prognostic value of IPS in patients with advanced HL. Also, we tried to identify other risk factors who could additionally contribute in risk stratification. Patients and Methods. A retrospective study was performed on 314 advanced classical HL patients, diagnosed in the period June 1997-December 2008. The standard of initial care was 6-8 cycles of ABVD followed by radiotherapy. Prognostic relevance of IPS≥3, IPS≥4, histological subtype, presence of B symptoms, large mediastinal tumor, "bulky" disease, extranodal involvement of more than 1 site (EN2) and erythrocyte sedimentation rate (ESR) ≥50 mm/h was examined. Results. The median age of the patients was 32 (range 16-80). The median follow up was 90 months. For the whole group 5 years event free survival (EFS) was 62.1% and 5 years overall survival (OS) was 75.8%. In univariate analysis, worse OS was found in patients with IPS≥3, IPS≥4, bulky disease, EN2 and ESR≥50 mm/h (log rank; p=0.000, p=0.000, p=0.042, p=0.000, p=0.006, respectively). The patients with IPS≥3, IPS ≥4 and and EN2 had also significantly worse EFS (log rank; p=0.000, p=0.007, p=0.000, respectively). The multivariate Cox regression analysis identified IPS≥3, EN2 and bulky disease as the independent prognostic factors for OS (p=0.000; p=0.000; p=0.023, respectively). Furthermore, IPS≥3 (p=0.001) and EN2 (p=0.001) are also independent prognostic factors for EFS. Conclusion. IPS can effectively identify advanced HL patients at high risk for poor outcome if treated with ABVD. Patients with IPS 3 or higher should be considered as high risk. More effective treatment is needed for patients with high IPS and/or EN2 and/or bulky disease.

P031
LOWER DOSE INTENSITY CHEMOTHERAPY; IMPACT ON TREATMENT OUTCOME AND SURVIVAL OF PATIENTS WITH ADVANCED HODGKIN LYMPHOMA: SINGLE INSTITUTION EXPERIENCE

Tomasevic Z, Tomasevic Z

Institute for Oncology and Radiology, Belgrade, Serbia

Background. Combined chemotherapy regimen, although highly effective, still fail to cure about one third of patients with advanced Hodgkin lymphoma (aHL). On the other hand, similar proportions of patients are probably over treated and cure might be obtained with less intensive doses. The aim of this retrospective analysis is to evaluate chemotherapy dose intensity and cumulative dose in aHL, in the context of treatment outcome and survival. Methods. At the Institute for Oncology and Radiology of Serbia, during 1991-1993 all consecutive aHL patients have been treated with MOPP (M; 41 pts) and afterwards (1994-1996) with MOPP/ABVD (M/A; 40 pts). In accordance to previous local practice, chemotherapy was given in projected, absolute doses, calculated on average body surface area of 1.7 m^2. Characteristics of patients in both regimens were well balanced for age, gender, PS, B symptoms, histology, stage, laboratory prognostic parameters (International Prognostic Score- IPS). Approximately 50% pts in both groups

were in high/intermediate risk IPS. Relative dose intensity (RDI), defined as given/scheduled dose ratio per week and relative cumulative dose (RCD), defined as given/projected dose ratio, were retrospectively analyzed whether there is potential negative impact on response, time to relapse and survival. Results. The average RCD and RDI for both regimens were 85% and 58%. Complete remission (CR) was achieved in 60% (M/A 67% *vs* M 54%) (p=NS); 90% of pts with CR in both groups had no relapse during follow up. Different cumulative doses and dose intensity had no significant impact on time to relapse and overall survival. However, trend for better overall survival for patients receiving RDI over 60% was observed (p=0.09). Hemoglobin level ≤10.5 g/dl had significant adverse effect on outcome regardless of treatment dosage (p=0.02). No second malignancy has been registered during follow up. Conclusions. Although this retrospective analysis does not pretend to recommend lower chemotherapy dose regimen for routine treatment, it seems that selected aHL patients could still be effectively treated with less chemotherapy dose intensity, because 90% of pts with CR are cured.

P032
DIAGNOSTICAL CHALLENGES IN OUR ADOLESCENT PATIENT WITH LYMPHOMA

Magyari F,[1] Rajnai H,[3] Barna S,[2] Miltényi Z,[1] Váróczy L,[1] Csomor J,[3] Illés A[1]

[1]Institute for Internal Medicine, Medical and Health Science Center, University of Debrecen; [2]Scanomed LTD; [3]1st Dept. of Pathology an Experimental Cancer Research, University of Semmelweis, Hungary

Objectives. The B-cell lymphoma, unclassifiable, showing intermediate features typical for both diffuse largeB-celllymphoma (DLBCL) and classical Hodgkinlymphoma (HL) is a novel category of diffuse large B-cell lymphomas (DLBCL/HL), which has been described by the WHO classification in 2008. This rare type of lymphomas presents peculiar clinical, morphological and immunophenotypical patterns, previously called as gray zone lymphomas. Case Report. In December 2011 a 17-year old male was diagnosed with mixed cellularity subtype of classical HL The staging18FDG-PET/CT scan showed a disseminated, abdominal bulky disease. His clinical stage was IV/BXS with unfavourable prognosis. After an incomplete course of ABVD chemotherapy the patient's symptoms disappeared and the sizes of the involved lymph nodes decreased as well. Because of the unusally extended disease (nodal-extranodal-bulky) a histological revision was performed. The diagnosis changed into DLBCL/HL, so the treatment was modified to R-CHOP-14 regimen. After 3 cycles of R-CHOP-14 he achieved a complete metabolic remission (CMR), which was confirmed by a 18FDG-PET/CT scan. Receiving further 3 cycles of R-CHOP-14 therapy the patient was still in CMR, but a PET negative large mass (7x3 centimeter) still remained visible in the abdominal region. Cosidering this residual tumor and the agressive subtype of lymphoma he was referred for an autologous hemopoietic stem cell transplantation (AHSCT). After 2 cycles of R-DHAP regimen, successful CD34 positive stem cell collection was performed in August 2012. In September of 2012, he underwent a R-BEAM conditioning followed by AHSCT. The next18FDG-PET/CT scan performed was 100 days after the AHSCT and it still showed CMR. Conclusions. Upon this case, it should be underlined that the diagnosis may need revision if a patient represents atypical clinical signs and behavior, and the importance of cooperation between clinicians and pathologistsis also strongly emphasized.

Early Stages

T033
IMPACT OF BLEOMYCIN AND DACARBAZINE WITHIN THE ABVD REGIMEN IN THE TREATMENT OF EARLY-STAGE FAVORABLE HODGKIN LYMPHOMA: FINAL RESULTS OF THE GHSG HD13 TRIAL

Behringer K,[1] Goergen H,[1] Borchmann P,[1] Diehl V,[1] Fuchs M,[1] Hitz F,[2] Zijlstra JM,[3] Greil R,[4] Markova J,[5] Topp MS,[6] Soekler M,[7] Mathas S,[8] Meissner J,[9] von Tresckow B,[1] Böll B,[1] Engert A[1]

[1]German Hodgkin Study Group (GHSG), Department of Internal Medicine I, University Hospital of Cologne, Germany; [2]Onkologie-Hämatologie Kantonsspital St.Gallen, St.Gallen, Switzerland; [3]Vrije Universiteit University Medical Centre Amsterdam, Amsterdam, The Netherlands; [4]University of Salzburg, Salzburg, Austria; [5]University Hospital Kralovske Vinohrady, Charles University Prague, Prague, Czech Republic; [6]University of Wuerzburg, Wuerzburg, Germany; [7]University of Tuebingen, Tuebingen, Germany; [8]Campus Virchow Klinikum, Berlin, Germany; [9]University of Heidelberg, Heidelberg, Germany

Background. Combined modality treatment consisting of two cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) followed by involved-field radiotherapy (IFRT) is regarded as standard of care for early-stage favorable Hodgkin Lymphoma (HL). However, the impact of bleomycin and dacarbazine in this combination has been questioned for years. Patients and Methods. The GHSG HD13 study compared two cycles of ABVD with a dacarbazine-deleted variant (ABV), a bleomycin-deleted variant (AVB), and a variant in which both, dacarbazine and bleomycin were deleted (AV). In each treatment arm, chemotherapy was followed by IFRT of 30 Gy. Primary objective was to demonstrate non-inferiority of the three experimental variants compared to ABVD regarding the primary endpoint freedom from treatment failure (FFTF) by excluding a difference of 6% after 5 years. Between 01/2003 and 09/2009, 1710 patients were enrolled into the study; 72 were excluded from all analyses due to revision of HL diagnosis, revision of staging and participation in another GHSG trial, or loss to follow-up before start of treatment. Due to higher event rates during a continuous safety analysis, the AV and ABV arms were closed early in 09/2005 and 02/2006 after recruitment of 186 and 209 patients, respectively. Inferiority of these arms regarding FFTF could be confirmed in an interim analysis in 09/2009; results will be updated in this final analysis. For the comparison of ABVD and AVD, 1243 patients were analyzed for therapy adherence, toxicity, and efficacy. Results. Patient characteristics were well balanced between the four treatment arms: Median age was 39 years, 68% had stage II disease, and there were more male patients included (59%). The most frequent histologic subtypes were nodular sclerosis and mixed cellularity (38% each). Inclusion criteria were violated in 136 patients (8%), who were excluded from analyses of protocol adherence and toxicity. Most qualified patients received chemo- and radiotherapy as per protocol; protocol deviations are reported in 3%. Results. Regarding acute toxicity and efficacy will be presented. Conclusion. Dacarbazine cannot be deleted from the ABVD regimen without a significant loss of efficacy. Whether bleomycin can be safely omitted will be discussed in view of the final analysis presented.

T034
DEFINITION OF BULKY DISEASE IN EARLY STAGE HODGKIN LYMPHOMA IN COMPUTED TOMOGRAPHY ERA: PROGNOSTIC SIGNIFICANCE OF MEASUREMENTS IN THE CORONAL AND TRANSVERSE PLANES

Kumar A,[1] Burger IA,[2] Zhang Z,[3] Maragulia J,[1] Yahalom J,4 Moskowitz CH,1 Zelenetz AD[1]

[1]Lymphoma Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center; [2]Department Medical Radiology, University Hospital Zurich, Switzerland; [3]Biostatistics and Epidemiology, Memorial Sloan-Kettering Cancer Center; [4]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Purpose. To investigate the prognostic significance of bulky disease measured in the transverse and coronal planes on computed tomography (CT) imaging in early stage Hodgkin lymphoma (HL). Patients and Methods. This single-center retrospective study included 195 pediatric and adult patients with early stage classical HL treated with doxoru-

bicin-containing chemotherapy with or without radiotherapy from 2000 to 2010. The longest diameter of the largest lymph node mass was measured in the transverse and coronal axes on pre-treatment CT scan. Results. By analyzing impact on progression-free survival (PFS), the optimal cutoff for defining bulky disease was found to be a maximal diameter of greater than 7 cm measured in either the transverse or coronal plane of section. Thirty patients with maximal transverse diameter ≤7 cm were found to have bulk based on coronal measurements. At a median follow up of 4.3 years, overall survival (OS) was 96.8% and PFS was 87.8% for the entire group. PFS, at 4.3 years, for patients with a transverse or coronal maximal diameter of >7cm was 81.1% compared to 95.8%, p=0.001. PFS was not impacted in patients with bulky disease treated with combined modality therapy; however, PFS was significantly inferior when treated with chemotherapy alone. Conclusion. Presence of bulky disease, defined as a mass >7 cm in the transverse or coronal plane on CT imaging, is a significant prognostic factor in early stage HL. The use of coronal reformations on CT examinations should be considered for routine staging evaluation of early stage HL patients.

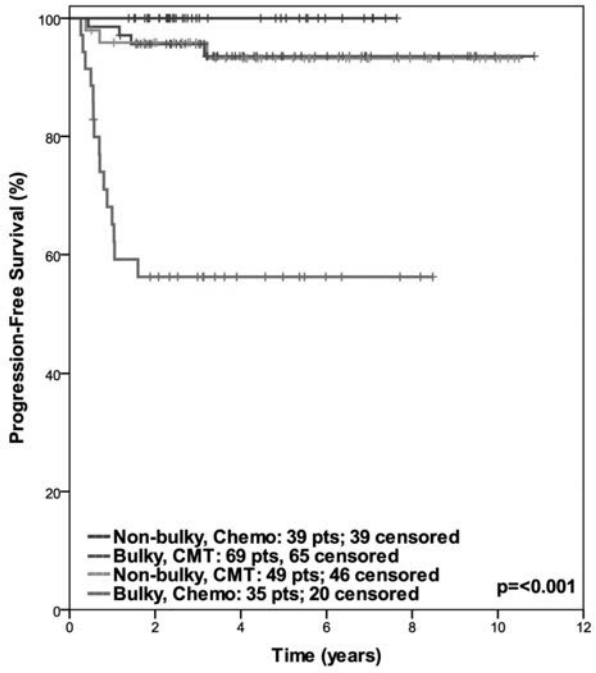

Figure 1.

T035
BRENTUXIMAB VEDOTIN PLUS AVD AS INITIAL THERAPY OF NON-BULKY LIMITED STAGE CLASSICAL HODGKIN LYMPHOMA: INTERIM ANALYSIS OF AN ONGOING PHASE II TRIAL

Abramson JS, Hochberg EP, Joyce R, Avigan D, Bello CM, LaCasce AS, Feng Y, Neuberg D, Takvorian T, Barnes JA, Arnason JE

Massachusetts General Hospital Cancer Center, Boston MA; Beth-Israel Deaconess Medical Center, Boston MA; Moffitt Cancer Center, Tampa FL; Dana-Farber Cancer Institute, Boston, MA, USA

Background. Limited-stage Hodgkin lymphoma has a high cure rate with standard chemoradiotherapy, but treatment carries long-term risks including bleomycin-lung injury and radiation toxicities. We designed a phase II study assessing whether adding brentuximab vedotin to AVD without radiation would preserve a high cure rate while decreasing the risk of late toxicities. Methods. This is an ongoing phase II multicenter study. Patients with non-bulky limited HL receive a lead-in cycle of brentuximab monotherapy 1.2 mg/kg on days 1 and 15, followed by an exploratory PET scan. Patients without progressive disease then receive 2 cycles of combination therapy with brentuximab 1.2 mg/kg and standard dose AVD on days 1 and 15 of each 28-day cycle, followed by interim PET/CT. Patients in complete response receive 2 additional cycles; patients in partial response receive 4 additional cycles. Response is per the 2007 Revised Response Criteria. Primary endpoint is complete response rate. Secondary endpoints include rate of grade 3-4 adverse events, response to the brentuximab lead-in cycle, and overall response rate to combination therapy. Results. The initial 12 patients are evaluable. Median age is 47 (range 24–71). Stage is IIA (8) and IA (4). Nine cases are early favorable, and 3 early unfavorable per GHSG criteria. The most common grade 1-2 adverse events have been nausea/vomiting (9 patients), fatigue (7), peripheral neuropathy (6), abdominal pain (6), hepatic transaminitis (5), constipation (5), diarrhea (5), and arthralgias (4). The most common grade 3-4 events have been neutropenia (7), febrile neutropenia (6) including one case of grade 5 sepsis, and peripheral neuropathy (5). Due to the high rate of neutropenic fever observed among the first 9 subjects, the protocol was amended to require growth factor support during combination chemotherapy cycles, with no subsequent events to date. Peripheral neuropathy prompted dose-reduction of brentuximab and vinblastine in 4 patients. Conclusions. In this preliminary analysis, brentuximab-AVD appears to be associated with a unique toxicity profile including a higher rate of neutropenic fever and peripheral neuropathy than expected with AVD alone. Updated results will be presented and preliminary efficacy data will be discussed.

P036
INFRADIAPHRAGMATIC HODGKIN LYMPHOMA IN PATIENTS TREATED WITH STATE-OF-THE-ART THERAPIES: A RISK FACTOR ANALYSIS FROM THE GERMAN HODGKIN STUDY GROUP (GHSG) HD13 AND HD14 TRIALS

von Tresckow B, Görgen H, Plütschow A, Böll B, Eichenauer DA, Sasse S, Rothe A, Fuchs M, Behringer K, Engert A, Borchmann P

German Hodgkin Study Group (GHSG), Department of Internal Medicine I, University Hospital of Cologne, Cologne, Germany

Introduction. The prognostic impact of isolated infradiaphragmatic Hodgkin Lymphoma (HL) is controversial and no large risk factor analysis in patients treated with state-of-the-art therapies exists. Therefore, we performed a risk factor analysis focusing on isolated infradiaphragmatic nodal disease in patients treated within the German Hodgkin Study Group (GHSG) HD13 and HD14 trials. Methods. The characteristics and outcomes of patients with isolated infradiaphragmatic nodal disease qualified for and treated within the HD13 and HD14 trials were compared to patients with supradiaphragmatic nodal disease. Patients with extranodal disease were excluded from the analyses. Progression-free survival (PFS) and overall survival (OS) were estimated according to the Kaplan-Meier method and compared between groups using the log-rank test. The Cox proportional hazards regression model was applied for multivariate analyses. Results. 1494 and 1403 patients with fully documented nodal disease from the HD13 and HD 14 trials, respectively, qualified for the analysis. Of those, 139 patients from HD13 (9.3%) and 84 patients from HD14 (6.0%) had isolated infradiaphragmatic disease. Compared to patients with supradiaphragmatic disease, patients with infradiaphragmatic HL were older (median age 47 versus 35 years, p<0.001), had a WHO index > 0 more frequently (22.4 versus 15.1%, p<0.01), and had the subtype of nodular sclerosis less frequently (29.9 versus 55.4%, p<0.001).

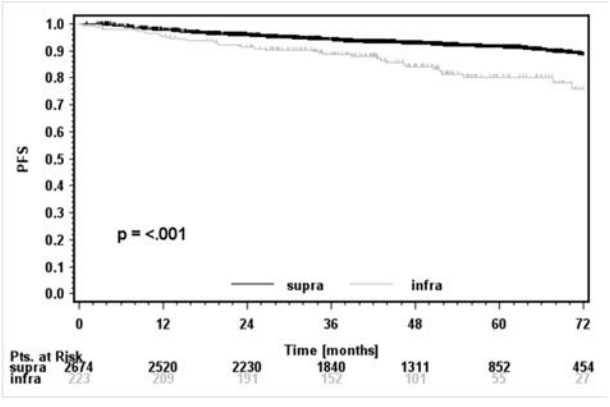

Figure 1.

More patients with infradiaphragmatic disease were male (69.1 versus 51.9%, p<0.001). After a median follow-up of 50 months, PFS was significantly worse in the patients with infradiaphragmatic disease (5-year PFS 80.2 versus 91.3% in patients with infradiaphragmatic versus supradiaphragmatic disease, respectively, p<0.001, Figure 1). In a multivariate model adjusted for age and sex, infradiaphragmatic HL remained a significant risk factor in terms of PFS (HR 1.7 [1.2-2.4], p<0.01). Moreover, infradiaphragmatic disease was a significant risk factor for OS when analyzed univariately (5-year OS 91.7 versus 97.7%, p<0.001) and in a multivariate model adjusted for age, trial and WHO index (HR 2.3 [1.4-4.0], p<0.01). Multivariate analyses including chemotherapy intensity will be presented. Conclusion. Isolated infradiaphragmatic disease is a risk factor for PFS and OS in HL patients treated with up-to-date therapies.

P037
IMPACT OF DOSE INTENSIFICATION ON THE OUTCOME IN EARLY-STAGE UNFAVORABLE HL: 7-YEAR FOLLOW-UP ANALYSIS OF THE GHSG HD14 TRIAL

Sasse S,[1], von Tresckow B,[1], Plütschow A,[1] Fuchs M,[1] Klimm B,[1] Markova J,[2] Hitz F,[3] Kral Z,[4] Greil R,[5] Topp MS,[6] Meissner J,[7] Zijlstra JM,[8] Soekler M,[9] Eich HT,[10] Borchmann P,[1] Engert A[1]

[1]German Hodgkin Study Group (GHSG), Department of Internal Medicine I, University Hospital of Cologne, Germany; [2]University Hospital Kralovske Vinohrady, Charles University Prague, Prague, Czech Republic; [3]Onkologie-Hämatologie Kantonsspital St.Gallen,St.Gallen, Switzerland; [4]University Hospital of Brno, Brno, Czech Republic; [5]University of Salzburg, Salzburg, Austria; [6]University of Wuerzburg, Wuerzburg, Germany; [7]University of Heidelberg, Heidelberg, Germany; [8]Vrije Universiteit University Medical Centre Amsterdam, Amsterdam, The Netherlands; [9]University of Tuebingen, Tuebingen, Germany; [10]University Hospital of Münster, Münster, Germany

Background. In patients with early unfavorable HL, four courses of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) followed by 30 Gy involved-field radiotherapy (IF-RT) are still widely regarded as standard treatment leading to a long-term remission rate of approximately 80%. In the HD14 trial of the German Hodgkin Study Group (GHSG), an intensified chemotherapy regimen consisting of two courses of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) and two courses of ABVD ("2+2") followed by 30 Gy IF-RT resulted in significantly improved 5-year freedom from treatment failure (FFTF) and progression free survival (PFS) rates. However, it has been frequently questioned if the significant PFS and FFTF difference persists with longer follow-up and if the improved tumor control translates in an overall survival (OS) benefit. Patients and Methods. Between January 2003 and Juli 2008, 1655 patients with histologically confirmed early-stage unfavorable HL were randomized to treatment with either four courses of ABVD or "2+2", each followed by 30 Gy IF-RT. Primary objective was to demonstrate superiority of the experimental arm regarding the primary endpoint FFTF. Results. As previously described in detail, the patient characteristics were well balanced between the treatment arms (von Tresckow et al., 2012). The median observation time was about 70 months in the current follow-up analysis. So far, the number of PFS failure events has increased by about 25%, and there are more than 50% more deaths than in the 5-year analysis. The current analysis confirms the significant PFS- and FFTF-difference between the treatment arms. Further details of the survival analysis and the analysis of secondary malignancies will be presented. Conclusion. The current analysis confirms that "2+2" followed by 30 Gy IF-RT results in a significantly improved tumor control in early unfavorable HL.

P038
PROGNOSTIC PERFORMANCE OF PRE-TREATMENT EORTC, GHSG AND IPI RISK FACTORS AND POST-CHEMOTHERAPY PET RESPONSE IN THE UK NCRI RAPID TRIAL IN EARLY STAGE HODGKIN LYMPHOMA (HL)

Radford J,[1] Barrington S,[2] Counsell N,[3] Pettengell R,[4] Johnson P,[5] Wimperis J,[6] Coltart S,[7] Culligan D,[8] Lister A,[9] Bessell E,[10] Kruger A,[11] Hancock B,[12] Hoskin P,[13] O'Doherty M,[14] Illidge T[15]

[1]The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [2]PET Imaging Centre, St Thomas' Hospital, London, UK; [3]Cancer Research and UCL Cancer Trials Centre, London UK; [4]St George's, University of London, London, UK; [5]University of Southampton, Southampton, UK; [6]Norfolk and Norwich University NHS Foundation Trust, Norwich UK; [7]Kent and Canterbury Hospital, Canterbury UK; [8]Aberdeen Royal Infirmary, Aberdeen, UK; [9]Barts and the London School of Medicine, London, UK; [10]Nottingham City Hospital, Nottingham, UK; [11]Royal Cornwall Hospital, Truro, UK; [12]University of Sheffield, Sheffield, UK; [13]Mount Vernon Cancer Centre, Northwood, UK; [14]PET Imaging Centre, St Thomas' Hospital, London, UK; [15]The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK

Introduction. The performance of pre-treatment risk stratification and PET after 3 cycles ABVD have been compared in patients taking part in the RAPID trial. Methods 602 patients, median age 34 years, with stages IA/IIA HL and no mediastinal bulk were registered into RAPID 2003-2010. Although not used as selection factors for trial entry, 61.7% and 67.8% patients were in the favourable category using EORTC/GHSG risk stratifications respectively. Using the IPI for HL, 21.8% patients had a score of 0, 47.7% scored 1, 24.3% scored 2 and 6.3% scored >2. Following 3 cycles ABVD, 571 patients had a PET scan reported as "negative" (score 1 or 2 on a 5-point scale) in 426 (74.6%) patients or "positive" (score 3, 4 or 5) in 145 (25.4%) patients. 420 of 426 PET negative patients were randomised between involved field radiotherapy (IFRT, n=209) and no further treatment (NFT, n=211); 145 PET positive patients received a 4th cycle ABVD and IFRT. At median follow-up of 48 months, 3-year progression-free survival (PFS) was 94.5% in the IFRT arm, 90.8% in the NFT arm and 86.2% in the non-randomised PET positive patients. Results. There was no evidence of association between EORTC, GHSG and IPI risk stratifications and PFS (p's >0.1) but PET score after 3 cycles ABVD was highly significant (p <0.01). In both univariate and full multivariate models, none of the individual factors contributing to risk stratifications were significantly associated with PFS. Using a stepwise selection approach the model comprising PET score alone was selected. Increasing PET score was associated with an increased risk of progression or death (see figure). Patients with a PET score of 5 had a significantly higher risk than all other PET scores (HR=6.6, 95% CI: 3.2 to 13.7, versus PET score 1; HR=6.6, 95% CI: 2.7 to 15.9, versus PET score 2; HR=9.4, 95% CI: 3.2 to 27.8, versus PET score 3; HR=3.3, 95% CI: 1.1 to 9.8, versus PET score 4). Conclusion For patients treated in RAPID, the PET score after 3 cycles ABVD was superior to pre-treatment risk stratification in predicting PFS.

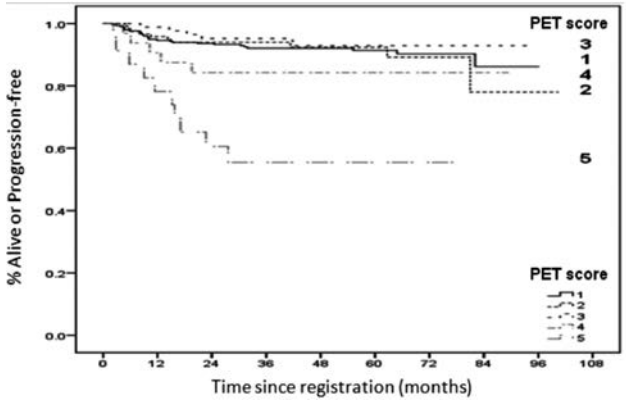

Figure 1.

P039

IMAGE-GUIDED INTENSITY MODULATED RADIOTHERAPY *VS* STANDARD 3D-CONFORMAL RADIOTHERAPY IN EARLY STAGE HODGKIN'S LYMPHOMA.

Filippi AR,[1] Ciammella P,[2] Piva C,[1] Ragona R,[1] Botto B,[3] Gavarotti P,[4] Merli F,[5] Vitolo U,[3] Iotti C,[2] Ricardi U[1]

[1]Radiation Oncology, Department of Oncology, University of Torino, Torino, Italy; [2]Radiation Therapy Unit, Department of Oncology and Advanced Technology, ASMN Hospital-IRCCS, Reggio Emilia, Italy; [3]Hematology, Città della Salute e della Scienza, Torino, Italy; [4]Hematology, University of Torino and Città della Salute e della Scienza, Torino, Italy; [5]Hematology Unit, ASMN Hospital-IRCCS, Reggio Emilia, Italy

Aims and Background. Image-Guided Intensity-Modulated Radiotherapy (IGRT-IMRT) allows for margins reduction and highly conformal dose distribution in Hodgkin's Lymphoma (HL), with consistent dosimetric advantages on healthy tissues. Very few data are available on clinical outcomes and toxicity profiles. Purpose of this multi-institutional study is to retrospectively compare IGRT-IMRT with standard 3D-CRT in early stages HL. Material and Methods. We collected 105 stage I-IIA HL patients with mediastinal involvement, either treated with 3D-CRT or IGRT-IMRT (Volumetric Modulated Arc Therapy or Helical Tomotherapy) between 2005 and 2012. Inclusion criteria were: favorable or unfavorable disease (EORTC criteria), 3-4 ABVD cycles, 30 Gy Involved Field Radiotherapy. Exclusion criteria were: chemotherapy other than ABVD, RT dose different from 30 Gy, presence of B symptoms, extra-nodal presentations. Margins between CTV and PTV were 10 mm for 3D-CRT and 5 mm for IGRT-IMRT.

Table 1.

	3D-CRT	IGRT/IMRT	Total
N° patients	59 (56.2%)	46 (43.8%)	105
Follow-up (months)			
Median	55	22	46
Age (y)			
Range	16-84	15-77	15-84
Median	31	27	29
Sex			
Male	26 (44.1%)	26 (56.5%)	52 (49.5%)
Female	33 (55.9%)	20 (43.5%)	53 (50.5%)
Ann Arbor Stage			
I	0	0	0
II	59 (100%)	46 (100%)	105 (100%)
Bulky	9 (15.2%)	11 (23.9%)	20 (19%)
Involved sites			
< 4	55 (93.2%)	43 (93.5%)	98 (93.3%)
≥ 4	4 (6.8%)	3 (6.5%)	7 (6.7%)
Favorable	46 (78%)	29 (63%)	75 (71.4%)
Unfavorable	13 (22%)	17 (37%)	30 (28.6%)
Toxicity			
G0	26 (44.1%)	27 (58.7%)	53 (50.5%)
G1	19 (32.2%)	14 (30.4%)	33 (31.4%)
Lung	2	0	2
Heart	0	0	0
Skin	1	0	1
Esophagus	16	14	30
G2	14 (23.7%)	5 (10.9%)	19 (18.1%)
Lung	1	0	1
Heart	0	1	1
Skin	1	0	1
Esophagus	12	4	16

Relapse rate and acute toxicities (RTOG score) were analyzed according to treatment technique. Other investigated factors in multivariate analysis were: age, stage (I *vs* II), number of involved sites, gender. Results. Fifty-nine patients were treated with 3D-CRT (56.2%) and 46 with IGRT-IMRT (43.8%). Median follow-up interval was 55 months for 3D-CRT and 22 months for IGRT-IMRT. Patients' characteristics are summarized in the table. There were only 2 relapses, one in each group. Among 3D-CRT group, G1-G2 toxicity was recorded in 19 (32.2%) and 14 (23.7%) patients, respectively. In IGRT-IMRT group, G1 was recorded in 14 patients (30.4%) and G2 in 5 (10.9%). The difference in G2 incidence was statistically significant in favor of IMRT-IGRT (p=0.05). Age >30 years old was significantly associated to a higher rate of G2 toxicity (p=0.03). Conclusions. No differences in recurrences were observed between IGRT-IMRT and 3D-CRT. Grade 2 toxicity, mainly dysphagia, was significantly lower for IGRT-IMRT. Relapse rate was extremely low in both groups, regardless of CTV-PTV margin reduction. These results support the clinical safety of advanced radiotherapy planning and delivery techniques for patients with early stage HL.

P040

LOCAL CONTROL IN STAGE I-II HODGKIN LYMPHOMA: PATTERNS OF FAILURE ANALYSIS IN COHORT TREATED WITH MODERN TECHNIQUE

Skliarenko J,[1] Lao L,[1] Gospodarowicz M,[1] Pintilie M,[2] Hodgson D,[1] Sun A,[1] Kukreti V,[3] Kuruvill J,[3] Crump M,[3] Tsang R[1]

[1]Radiation Medicine Program, Princess Margaret Hospital; [2]Department of Biostatistics, Princess Margaret Hospital; [3]Department of Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada

Purpose. Over the past 20 years there has been a trend towards reduction in RT fields when treating stage I-II HL. Involved field radiation therapy (IFRT) has evolved from whole nodal region coverage to involved nodal coverage. We examined the outcomes in our patients to assess if the reduced RT coverage compromised disease in stage I-II HL patients treated with ABVD+RT. Materials/Methods. Retrospective review of 187 stage I-II HL patients treated with curative intent between 2004 and 2008. 160 adults were analyzed (what happened to the other 27pts?): 154 treated with CMT and 6 RT. Median age-32 (range: 18-85), 53% were male. Stage distribution was: IA- 28%, IIA- 54% and IB/IIB- 18%. Histology was: NS: 75%, MC: 6%, LR: 2%, NLPHL in 8%, NOS: 9%. Bulky disease (10 cm) was present in 24%. ABVD ≤4 cycles were given to 59% of patients and 6 cycles to 33%. Median RT dose was 30Gy (range: 20–40Gy); most patients (give%) received 30 or 35Gy. 126 pts were treated with IFRT: 39-involved region alone; 87-additional adjacent uninvolved nodal, while 30 were treated with partial nodal region or involved node coverage. Sites of initial disease involvement and RT treatment fields were coded for each patient. The neck and the mediastinum were subdivided into upper and lower subsites. Relapse pattern was classified as in-field, adjacent, or distant. Results. Median follow-up was 4.3 years (range: 0.5–8 years). Analysis was limited to 156 pts with CR/CRu and adequate follow-up to determine failure pattern. Four patients were excluded: 2were lost to follow up immediately after treatment, 1 with PR ,1 with PD). The 5 year OS was 95%, 5 year DFS-90%. Amongst 156 pts, 11(7%) relapsed (Table). Only 2 pts had isolated adjacent nodal relapse. Conclusions. For stage I-II HL treated with CMT, reduction of the RT volume did not result in significant adjacent nodal region failure.

Table 1.

Sites of Relapse	Number of patients
Isolated infield	1
Isolated adjacent	2
Isolated distant	4
Infield + distant	2
Adjacent + distant	1
Infield + adjacent + distant	1
Total:	**11**

P041
DOSES TO HEAD AND NECK NORMAL TISSUES AFTER RADIOTHERAPY FOR EARLY STAGE HODGKIN LYMPHOMA

Maraldo MV,[1] Brodin NP,[1] Aznar MC,[1] Vogelius IR,[1] Munck af Rosenschöld P,[1] Petersen PM,[1,2,3] Specht L[1,2,3]

[1]Department of Radiation Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [3]Department of Hematology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Introduction. Patients with supradiaphragmatic early stage Hodgkin lymphoma (HL) regularly present with cervical lymph node involvement, alone or in combination with mediastinal disease. For these patients, head and neck normal tissues will invariably be irradiated. In this study, we evaluate the dosimetric effects of Involved Node Radiotherapy (INRT) delivered as 3D conformal radiotherapy (3DCRT), volumetric modulated arc therapy (VMAT), and proton therapy (PT) for HL patients with cervical involvement, and we compare these techniques with the extended Mantle Field (MF) of the past. Materials and Methods. We included 37 patients with cervical involvement treated with INRT for clinical stage I-II classical HL. All patients were treated with chemotherapy followed by 3DCRT (30.6 Gy). Head and neck risk organs were contoured (the thyroid, neck muscles, pharynx, larynx, submandibular and parotid glands) and, in addition to the clinical 3DCRT-INRT plan, a VMAT-INRT, PT-INRT (both 30.6 Gy) and a MF plan (36 Gy) were simulated for each patient. Doses to risk organs were evaluated by cumulative dose-volume histograms and repeated measures ANOVA with post hoc pair-wise comparison analyses. Results. The estimated median mean dose to the thyroid gland, the larynx, the pharynx, the neck muscles, and the parotid and submandibular glands with 3DCRT, VMAT, PT, and MF treatment are shown in table 1. Conclusion. INRT significantly lowers the estimated radiation dose to the head and neck normal tissues for HL patients with cervical involvement, compared to the extensive MF of the past, which should result in a reduced risk of late effects. The low-dose bath with VMAT appears unacceptable with the low radiation doses used in HL compared to 3DCRT. For some patients, the use of PT could offer an additional gain.

Table 1. Mean dose to the head and neck risk organs with 3DCRT, VMAT, Proton, or Mantle Field treatment

	3DCRT		VMAT		PT		MF		p-value			
										pair wise comparisons		
	Median	Range	Median	Range	Median	Range	Median	Range	all†	3DCRT vs. VMAT	3DCRT vs. PT	VMAT vs. PT
Mean Dose (Gy)												
Thyroid	15.3	(0.2-32.0)	19.3	(0.4-29.7)	15.4	(0-30.6)	37.3	(32.7-41.8)	<0.0001	0.05	0.14	<0.0001
Larynx	2.3	(0.3-31.7)	11.1	(0.6-28.7)	1.8	(0-26.3)	37.1	(30.5-40.8)	<0.0001	<0.0001	0.01	<0.0001
Pharynx	1.7	(0.1-18.2)	5.1	(0.1-26.0)	1.3	(0-16.9)	23.8	(14.1-32.0)	<0.0001	<0.0001	0.02	<0.0001
Neck muscles	10.9	(1.6-24.4)	12.0	(2.5-23.1)	7.9	(0.3-18.3)	34.5	(28.4-38.6)	<0.0001	0.17	<0.0001	<0.0001
Ipsilateral parotid gland*	0.5	(0-27.2)	0.8	(0-22.9)	0.01	(0-22.8)	32.3	(0-37.8)	<0.0001	0.75	0.02	0.003
Contralateral parotid gland*	0.1	(0-5.2)	0.2	(0-6.0)	0	(0-3.7)	27.4	(0-37.2)	<0.0001	0.02	0.56	0.004
Ipsilateral submandibular gland	2.4	(0.1-31.8)	3.8	(0.1-30.9)	0.7	(0-30.7)	34.7	(22.2-39.7)	<0.0001	0.009	<0.0001	0.02
Contralateral submandibular gland	0.1	(0-29.6)	0.4	(0-27.7)	0	(0-29.7)	30.3	(0-37.8)	<0.0001	0.002	0.22	0.0004

3DCRT - 3D conformal radiotherapy, VMAT - volumetric modulated arc therapy, PT - proton therapy, MF - mantle field.
Ipsilateral defined as side with lymph node involvement, patients with bilateral involvement have 2 ipsilateral glands and no contralateral.
* repeated measures ANOVA with Greenhouse-Geisser corrections.
† only 35 patients in the analysis.

P042
DEEP INSPIRATION BREATHHOLD RADIATION THERAPY REDUCES RADIATION DOSE TO CARDIAC STRUCTURES IN PATIENTS TREATED FOR MEDIASTINAL HODGKIN LYMPHOMA

Meidahl Petersen P,[1,2] Aznar MC,[1,3] Kiil Berthelsen A,[1] Loft A,[4] Schut DA,[1] Maraldo M,[1] Levin Klausen T,[4] Andersen F,[4] Specht L[1,2]

[1]Department of Radiation Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]Department of Haematology, Rigshospitalet, Copenhagen, Denmark; [3]Niels Bohr Institute, Faculty of Sciences, University of Copenhagen, Denmark; [4]Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Copenhagen, Denmark

Introduction. In this study we investigated whether a precise target definition using PET-CT combined with accurate radiation delivery using deep inspiration breath hold (DIBH) technique can reduce the dose to cardiac structures without compromising the dose to the target in patients with early Hodgkin Lymphoma (HL). Patients and Methods. 19 patients with mediastinal HL had chemotherapy followed by involved node radiation therapy (RT). All had pre-chemo- FDG-PET/CT in free breathing (FB) and in DIBH. Involved nodes were contoured independently on both scans. After chemotherapy all patients had a planning CT in both FB and DIBH. Two radiotherapy treatment plans were made for all patients using fused images from pre-and post-chemo DIBH and FB scans, respectively. The optimal plan using conventional 3D radiotherapy or intensity modulated treatment (IMRT) was chosen. Planning target volume (PTV) coverage (% of PTV receiving 95% dose level) (V95%), heart, mean dose as well as mean dose to aortic-, mitral-, tricuspid- and pulmonic valves was calculated for each patient in both DIBH and FB. Wilcoxon's signed rank test for paired data was used for statistical analysis. The patients were treated with the plan determined to be the best in terms of clinical target volume/PTV coverage and sparing organs at risk. Results. Dose characteristics and cardiac structures are shown in the table. Conclusions. RT in DIBH compared to RT in FB substantially reduces dose to cardiac structures without compromising the dose to the target in selected patients with mediastinal Hodgkin lymphoma.

Table 1. Doses to cardiac structures for radiation planned in deep inspiration breathhold and free breathing respectively.

Parameter	FB (median,range)	DIBH (median,range)	P value (Wilcoxons signed rank test)
PTV V95%	94 (61-97)%	93(78–96)%	0.40
Mean heart dose	7.3(0.12-23)Gy	4.4(0.10–17)Gy	<0.01
Mean aortic valves dose	26(0.23–31)Gy	16(0.22–32)Gy	<0.01
Mean mitral valve dose	12(0.12–29)Gy	1.6(0.10–29)Gy	<0.01
Mean tricuspid valves dose	3.1(0.20–32)Gy	1.5(0.10-29.6)Gy	0.02
Mean pulmonic valves dose	24(0.26–31)Gy	13(0.17–33)Gy	<0.01

P043
THE ROLE OF HIF SIGNALING IN THE REPROGRAMMING OF HODGKIN AND REED/STERNBERG CELLS

Wein F, Otto T, Fandrey J, Küppers R

Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, Medical School, Essen, Germany

Hodgkin and Reed/Sternberg (HRS) cells are the tumour cells in classical Hodgkin lymphoma (HL). Although HRS cells are derived from germinal center (GC) B cells, they lack expression of most B cell-specific genes and aberrantly express numerous genes whose expression is normally restricted to other hematopoietic lineages and transcription factors that are characteristic for progenitor cells, *e.g.* ID2 and NOTCH1. These factors are known to induce tumour cell dedifferentiation. Notably, they have also been shown to be inducible upon hypoxia and HIF1a activation. Global gene expression analyses revealed that public gene sets of HIF dependent genes were enriched in primary HRS cells if compared with GC B cells or non-Hodgkin lymphoma cells. Therefore, we investigated the possibility whether hypoxia-induced HIF signaling contributes to the reprogramming of HRS cells. Exposing peripheral blood B cells and a GCB DLBCL line to acute hypoxia led to stable HIF1a protein expression and up regulation of VEGF, ID2, MYC, DTX1 and HES1. Additionally, the surface expression of the B cell markers CD19 and CD79b were reduced in two DLBCL lines (SUDHL6, SUDHL4) whereas no significant reduction was observed for primary B cells. The consistent up regulation of ID2 upon hypoxia is particularly relevant, because ID2 is aberrantly expressed in HRS cells and by inhibiting E2A, a key regulator of B cell development, likely plays a key role in the lost B cell phenotype of HRS cells. In conclusion, inducing HIF signaling in primary B cells and GCB DLBCL lines shifted their phenotype closer to HRS cells. This observation may indicate that hypoxia plays a role in the initial stages of HL development.

P044

PHASE II STUDY OF INVOLVED NODE PROTON THERAPY FOR STAGE I-III HODGKIN LYMPHOMA

Hoppe BS,[1] Flampouri S,[1] Su Z,[1] Zaiden R,[2] Ozdemir S,[2] Slayton W,[3] Sandler E,[4] Dang N,[3] Lynch J,[3] Li Z,[1] Mendenhall N[2]

[1]University of Florida Proton Therapy Insitute Jacksonville, FL; [2]University of Florida Jacksonville, FL; [3]University of Florida Gainesville, FL; [4]Division of Hematology/Oncology, Nemours Children's Clinic and Wolfson Children's Hospital, Jacksonville, FL, USA

Background. Late effects from radiotherapy continue to be a problem decades following treatment adversely effecting overall survival. The present study investigates the benefits of involved node proton therapy (INPT) and patient outcomes. Method: Between 8/2009 and 6/2013, 20 patients with stage IA-IIIB (bulky/non-bulky) classical Hodgkin lymphoma involving the mediastinum enrolled in the study following a complete or partial response to standard chemotherapy. Patients underwent radiation treatment planning per EORTC INRT guidelines and had 3 separate plans created: 1)3D conformal (3DCRT), 2) IMRT, 3) PT. Pediatric patients were treated to15-25.5Gy at 1.5Gy/fraction (n=6), while adults were treated to 30-39.6Gy at 1.8Gy/fraction(n=14). The following organ at risk (OAR) prioritization was used: heart>lung>breast (women)>esophagus>thyroid>total body. Results. In all 20 patients, the PT plan was the best of the 3 treatment plans and offered to the patients. Fifteen patients received the planned INPT, one patient received a combination IMRT/PT involved node plan because the largest proton nozzle was still under commissioning, three patients chose treatment closer to home with photon radiation, and one patient progressed prior to starting INPT and received involved field PT. The average dose to the OARs among the 20 patients with 3DCRT, IMRT, and PT were: heart (16.4Gy, 12.2Gy, 8.8Gy), lungs (11.5Gy, 9.7Gy, 6.9Gy), breast (6.4Gy, 6Gy, 4.3Gy), esophagus (20.5Gy, 16.5Gy, 13.2Gy), thyroid (19.7Gy, 18Gy, 16.1Gy), integral dose (124J, 104J, 53J). Three events have occurred among the 16 patients treated with involved node treatment with a median follow-up of 30 months (range 14-45). Relapses occurred in 2 pediatric patients <6 months posttreatment, including a bulky stage IIB and stage IIIA HL. A 20-year-old female developed a primary mediastinal B-cell lymphoma (in-field) 6 months after receiving 39.6 Gy following partial response to chemotherapy. The 2-year-relapse-free survival and event-free survival are 88% and 81%. No Grade 3 acute or late toxicities have occurred. Conclusions. Early Results. using INPT are promising; however, long term benefits won't be realized for decades. Consequently, PT should be strongly considered as an alternative to photon radiation to reduce the radiation dose to the OARs.

P045

ABVD WITHOUT CONSOLIDATION RADIOTHERAPY (RT) AFTER COMPLETE REMISSION (CR) IN PEDIATRIC HODGKIN LYMPHOMA (HL): PRELIMINAY RESULTS OF A PILOT STUDY

Terenziani M,[1] Schiavello E,[1] Crippa F,[2] Cefalo G,[3] Gandola L,[4] Pecori E,[4] Casanova M,[1] Ferrari A,[1] Luksch R,[1] Meazza C,[1] Polastri D,[1] Spreafico F,[1] Catania S,[1] Biassoni V,[1] Podda M,[1] Chiaravalli S,[1] Vajna de Pava M,[1] Massimino M[1]

[1]Department of Pediatrics, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]Department of Nuclear Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Department of Pediatrics, Ospedale San Paolo, Milan, Italy; [4]Radiotherapy, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background. Children with HL have a good survival but treatments bring on appreciable morbidity. To minimize sequelae, we designed a study with ABVD, for stages 1-3, including B symptoms, without RT in CR patients and reduced volumes and doses of RT in PR patients. Patients and Methods. From 1998 onwards 62 consecutive children with HL (median-age 13 yrs; stage I/11 ; II/35 , III/16 ; M/F ratio1.5; B symptoms 30%) were treated. Chemotherapy consisted of 4-6 courses of ABVD followed by RT for patients in PR (25 Gy on PR sites only). CR was defined on the basis of clinical and imaging (CT/MRI+/-PET). After 2008, to assess early response after 2nd ABVD, we regularly performed PET2 . Results. 43/62 pts achieved CR after CT (11 stage I, 23 stage II, 9 stage III). The number of patient irradiated do not differ between stage I-II and stage III (p= ns). 18 (29%) children were irradiated, only one after regular Introduction. of PET2 . 53/62 patients are in CCR at a median follow up of 7 years. Seven patients relapsed (median time 12 months): 2 after CT only (1 in previously uninvolved and 1 in involved nodes), 5 after CT+RT (3 within RT field, 2 outside). Two primary refractory were intensified with high-dose CT+RT+ autologous PBSC-rescue). 6/9 relapsing-refractory patients are in CR (5 in 2nd , 1 in 3rd); two pts died, 1 is alive with disease. We observed two second malignancies: one osteosarcoma outside RT-field and one lung synovial-sarcoma adjacent to the radiation field, at 81 and 89 months after diagnosis. With a median follow-up of 7 years PFS, EFS and OS were 84%, 80, 96% respectively. Conclusions. This series suggests that a significant number of pts (69%) could be cured without RT in any stage. Those poor responders may deserve an intensified treatment. The systematic use of PET has improved response evaluation and reduced the number of irradiated patients.

P046

A RESPONSE-BASED ABVD REGIMEN WITH OR WITHOUT RADIOTHERAPY FOR PEDIATRIC LOW AND INTERMEDIATE RISK HODGKIN LYMPHOMA IN CENTRAL AMERICA AND DOMINICAN REPUBLIC A REPORT FROM AHOPCA

Castellanos M, Metzger M, Fulgencio Baez L, Gamboa Y, Peña Hernandez A, Alabi S, Luna-Fineman S, Nieves R, de Alarcon P

AHOPCA; Euronet Associate member

Objective. In 2004 AHOPCA designed a treatment regimen for low-risk (LR) (stage IA, IIA without bulky disease, less than 4 nodal regions) and intermediate-risk (IR) (stage IA or IIA bulky disease, IB, IIA with more than 4 nodal regions, or stage IIIA). The purpose of the protocol was to provide proven effective therapy to improve survival of children with HL in Central America while decreasing the amount of radiation therapy required based on response to chemotherapy. Design/Method. LR patients received 4 cycles of ABVD (adriamicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine 375mg/m^2 on days 1 and 14 of every 28-day cycle). Involved field radiotherapy (IFRT) (2500 cGy) was prescribed only to patients that did not achieve a complete response (CR) after the second cycle of ABVD. IR patients received 6 cycles of ABVD and IFRT (2000 or 2500 cGy) at the end of all chemotherapy, according to response status after 4 cycles of ABVD (CR=20Gys and PR>50% 25Gys). Results. From 1/2004 to 12/2011, 242 evaluable (162 IR and 80 LR) patients with a median age of 7.8 years were treated with this regimen. (87%) of the LR patients were rapid early responder (RER) did not require IFRT, and 73% of IR patients were RER and only required 2000 cGy,. With a median follow-up time of 4 years we had 3 relapses in LR (91% EFS and100% OS), and 4 relapse, 2 progresion with 18 patients abandoned (85% EFS and 94% OS) in IR subjets, taking abandonment as a event . There were no grade 4/5 toxicities. Conclusions. This regimen was well tolerated and produced excellent results for our setting. Abandonment among the intermediate risk group is still a problem and earlier and more aggressive interventions are needed to target this group.

P047

INFLUENCE OF INTERPLAY EFFECTS DUE TO BREATHING MOTION FOR PROTON SPOT SCANNING TREATMENT OF MEDIASTINAL HODGKIN LYMPHOMA

Norrlid O,[1] Nilsson K,[2] Bäck A,[3] Sooaru M,[3] Raunert I,[3] Goldkuhl C,[4] Molin D[2]

[1]Department of Radiology, Oncology and Radiation Science, section of Radiation Physics, Uppsala University, Uppsala, Sweden; [2]Department of Radiology, Oncology and Radiation science, section of Oncology, Uppsala University, Uppsala, Sweden; [3]Department of Therapeutic Radiation Physics, Sahlgrenska University Hospital, Götebborg, Sweden; [4]Department of Oncology, Sahlgrenska University Hospital, Göteborg, Sweden

Proton radiotherapy can reduce absorbed dose outside the target volume and decrease late side effects compared to photon radiotherapy of Hodgkin Lymphoma (HL). Current experiences in proton therapy of HL are based on double scattering delivery technique. A Swedish proton facility for spot scanning therapy is under construction. Important for spot scanning is the interplay effects from relative motion of the patient and proton beam. In order to create a feasible protocol for spot scanning therapy of mediastinal HL, we studied the influence of interplay effects

due to breathing motions. Free breathing 4D-CT scans and deformable image registration were used to assess 3D proton therapy plans with simulated interplay effects. Three patients in stage IIA planned for 29.75Gy(RBE) (17 fractions) were included. From the 4D-CT an ITV was created and then a PTV with 7mm margin to the ITV. Treatment plans were created in RayStation (RaySearch Laboratories) planning system with 0.5cm energy layer separation. Interplay effects of 10 breathing phases of the 4D-CT and the dynamic delivery of energy layers for a 1 second energy switching time were simulated for four fractions, i.e. for four different starting phases of the breathing cycle. One field proton plans with 22-25 energy layers were studied. Respiratory motion in points in vicinity of the target was less than 5 mm between extreme points for patient 1 and 2 but up to 8mm for patient 3. The simulated interplay effects in the ITV were small for patient 1 and 2 where the effect in mean dose, D98% and D2% were <1%/fraction and 0,5% summed over 4 fractions. The effect in ITV was larger for patient 3 where the effect in D98% was 8-13%/fraction. We found that the interplay effects due to breathing motions for proton spot scanning treatment of mediastinal HL differ from patient to patient. More patients are needed to make general conclusions. The difference between patients could be due to the different magnitude of breathing motions, but also other factors, like the patient geometry, and the beam direction. The interplay effects will be diminished by the effect of fractionation.

P048
COMPARATIVE CHARACTERISTICS OF RADIOTHERAPY (RT) METHODS IN TREATMENT OF HODGKIN'S LYMPHOMA (HL) WITH MEDIASTINAL LYMPH NODES INVOLVEMENT

Larinov DV

Russian Research Center for Radiology and Surgical Technologies (RRCRST)

Aim. To evaluate the direct results after combined treatment in patients with HL stage II AB after applying different methods of mediastinal irradiation. From March 2010 to December 2012 RRCRST consistently 52 patients there were observed with HL stage II AB with lymph mass involvement above the diaphragm, including mediastinal lymph nodes treated with chemoradiotherapy (2-4 cycles of chemotherapy ABVD + RT). RT was performed by impact irradiation from two opposed fields. Group A consisted of 14 patients who received three-dimensional conformal radiotherapy (3D-RT) to the mediastinum through a linear electron accelerator (LEA) Elekta Axesse by usual fractionation (UF) to a total dose 30-36 Gy; Group B consisted of 23 patients who received it by two-dimensional planning (2D-RT) RT through LEA Elekta Precise with UF up to a total dose 30-36 Gy and Group C consisted of 15 patients who received 2D-RT by the LEA SL-75-5 Philips through upper complex shaped figure fields in multi-fractionation (MF), dose per fraction-1.2 Gy, irradiation rhythm-2 fractions per day with an interval of 4 hours, to a total dose 30-36 Gy. All 52 patients achieved remission. 12 out of 14 patients in Group A obtained a complete remission (CR) 85.7%, 2 patients were in an unconfirmed complete remission (CRu)-14.3%; 7 out of 23 patients in Group B were stated as a partial remission (PR)-30.4%, 9 patients were stated CRu (39.2%) and 7 patients achieved CR (30.4%); 7 out of 15 patients in Group C achieved PR (46.7%), 5 patients achieved CRu (33.3%) and 2 patients achieved CR 20.0%. Thus, the total CR + CRu set 100% in Group A, and 80% in Group B and Group C. Differences between groups are significant (p <0,01). Conclusions. 1. Rate the PR + CRu in Group A (100%) was significantly higher than in other groups. 2. Frequency of RP emergence was the lowest in groups B and C, and frequency of RE emergence was the least in groups A and C. Thus, an immediate effect of the treatment is higher in conformal radiotherapy planning.

Biology and Microenvironment

T049
PLASMA MICRORNA ARE DISEASE RESPONSE BIOMARKERS IN CLASSICAL HODGKIN LYMPHOMA

Jones K,[1,2] Nourse JP,[1] Keane C,[1,2,3] Bhatnagar A,[1] Seymour L,[2,3] Gandhi MK[1,2,3]

[1]Clinical Immunohaematology Laboratory, Queensland Institute of Medical Research, Brisbane, Australia; [2]Experimental Haematology Laboratory, School of Medicine, University of Queensland, Translational Research Institute, Brisbane, Australia; [3]Department of Haematology, Princess Alexandra Hospital, Brisbane, Australia

In classical Hodgkin lymphoma (cHL), Hodgkin-Reed-Sternberg (HRS) cells are sparse, embedded within a benign tumour microenvironment (TME) that has a distinct composition from healthy lymph nodes. We previously demonstrated that informative circulating disease response protein biomarkers might arise from HRS cells or the TME, exhibiting different kinetics during chemotherapy. MicroRNA show considerable potential as tissue biomarkers in cHL. However, the role of microRNA as circulating cell-free disease response biomarkers remains untested. Studies to date have focused on identifying tumour-specific microRNA, i.e. derived from HRS cells, including miR-21, miR-155 and miR-16. We rationalized that identification of microRNA over-expressed within the whole node ('diseased node associated microRNA') might be more informative in identifying candidate disease response blood biomarkers. Agilent array profiling of >1000 human microRNA was performed on a discovery cohort of 14 cHL primary tissues and 8 healthy lymph nodes. Following quantile normalization, the top four over-expressed microRNA were selected, and expression correlated by qRT-PCR (all r>0.6). None of these microRNA had been previously identified in HRS-cell specific microRNA studies. Differential expression was confirmed by qRT-PCR in a second discovery cohort of 26 cHL tissues (all P<0.004). We prospectively tested these, as well as miR-21, miR-155 and miR-16, as disease response biomarkers in a cohort of 42 early and advanced stage disease cHL patients undergoing induction chemotherapy, versus 20 healthy participants by qRT-PCR. Plasma samples were taken in conjunction with radiological imaging at fixed time-points prior to, during and after therapy, and standard curves were generated to enable absolute quantification. Levels of miR-494, miR-1973 and miR-21 were higher in patients than control plasma (P=0.004, P=0.008, P<0.0001, respectively). MiR-494 and miR-21 associated with Hasenclever scores ≥3. All three microRNA returned to normal at remission (P=0.0006, P=0.0002, P<0.0001). However, only miR-494 and miR-1973 reflected interim therapy response with reduction being more pronounced in patients achieving complete versus partial responses (P=0.043, P=0.0012, respectively). Our results indicate that circulating cell-free microRNA can reflect disease response once therapy has commenced. The combination of microRNA and protein biomarkers should be tested in large prospective cohorts as disease response biomarkers during first-line therapy for cHL.

T050
CD57+ T CELLS IN NODULAR LYMPHOCYTE PREDOMINANT HODGKIN'S LYMPHOMA ARE T-FOLLICULAR HELPER CELLS

Sattarzadeh A, Rutgers B, Diepstra A, van den Berg A, Visser L

Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Background. Nodular lymphocyte predominant Hodgkin lymphoma accounts for 5% of all cases. The neoplastic lymphocyte-predominant (LP) cells, compose less than 1% of the total cell population. The LP cells are localized in a background. of CD4+CD57+ T cells reported to have a T helper 2 phenotype. The cells rosetting the LP cells are described to be PD-1 and BCL6 positive, which are markers of T follicular helper (Tfh) cells. Tfh cells play a critical role in maturation of B-cells in the germinal center reaction. This study was designed to establish if the CD57+ T cells in NLPHL are Tfh cells. Material and methods Double staining of CD57 and PD-1 was performed using immunofluorescent labeled antibodies. Scoring was performed by determining the number of single and double positive CD57 and PD-1 cells in tonsil and NLPHL tissues. For tonsil, the number of positive cells per germinal center were counted and

for NLPHL, the number of cells in the LP cell area were counted with a magnification of 40x. In addition, the number and phenotype of the rosetting cells were determined for CD57, PD-1 and BCL6. To assess whether CD57+ cells are BCL6+, triple immunohistochemical staining was performed with a combination of CD57, BCL6 and CD20 antibodies on tonsil and NLPHL tissue sections. CD20 was used to discriminate between BCL6 positive B and T cells. Results. In both tonsil and NLPHL more than 90% of the CD57+ T cells are PD-1 positive and 50% of the total PD-1+ cell population are CD57+. These double positive cells form 20%-60% of the LP rosetting cells in NLPHL. The remaining LP rosetting cells are single PD-1+. The CD57+ rosetting and not rosetting cells co-express BCL6 in NLPHL. In addition, we observed BCL6+CD57- rosetting T cells, which based on the PD-1 staining must be PD-1 positive cells. Conclusion. We conclude that the CD57+ T cell population present in tonsil and NLPHL tissue are Tfh and form a subpopulation of the total Tfh cell population.

T051
ANALYSIS OF MYELOID SUPPRESSOR MARKER ARGINASE IDENTIFIES CD68+/ARGINASE+ MYELOID/MONOCYTIC SUBSETS AND EXERTS STRONGER PROGNOSTIC INFLUENCE THAN MACROPHAGE QUANTIFICATION IN CLASSICAL HODGKIN LYMPHOMA

Gallamini A,[1] Agostinelli C,[2] Tripodo C,[3] Starcqualursi L,[4] Fuligni F,[2] Fiore F,[1] Rigacci L,[7] d'Amore F,[6] Merli F,[7] Vitolo U,[7] Patti C,[7] Stelitano C,[7] Di Raimondo F,[7] Levis A,[7] Trentin L,[7] Kamper P,[6] Piccaluga PP,[2] Broccoli A,[5] Zinzani PL,[5] Pileri SA,[2]

[1]Hematology Department, S. Croce Hospital, Cuneo, Italy; [2]Hemopathology Unit, Bologna University, Bologna, Italy; [3]Tumor Immunology Unit, Human Pathology Section, University of Palermo, Italy; [4]Statistics Department, University of Bologna; [5]Institute of Haematology and Medical Oncology L & A Seràgnoli, University of Bologna, Bologna, Italy; [6]Danish Lymphoma Group; [7]Intergruppo Italiano Linfomi

Early-interim PET-scan(IP) after two ABVD-courses represents the most effective predictor of the treatment outcome.Our aim was to build a discriminative model that was predictive of progression/recurrence of lymphoma, investigating a set of biological markers,representative of diverse key aspects of cHL neoplastic and bystander cell biology, in 209 patients and challenging their prognostic/predictive power versus IP. We focused on cell-cycle regulatory proteins (TOP2A/RRM2/ MAD2L1/ CDC2/PCNA), B-cell ontogeny-related proteins (BCL11a/ CD20), cell damage and apoptosis markers(P53/BCL2), EBV-status, and on macrophages related markers(CD68/CD163/ALDH1A1/STAT1) and T-cell cytotoxicity(TIA1/Perforin/GranzymeB), regulation/suppression markers(FOXP3/PD1/SAP). Moreover, we analyzed the expression of functional markers of myeloid suppressor cells/MSC (Arginase).In univariate analysis, the factors related to OS were BCL2 on HRSC and IP. BCL2, P53 on HRSC, PD1, FOXP3 on microenvironment(MC), stage and IP were significantly related to a worse PFS. In multivariate analysis, IP maintained its prognostic value on OS and P53, FOXP3, stage and IP on PFS. By restricting the analysis to IP-negative cases,CART-analysis produced an accurate data partitioning scheme which allowed to distinguish possible high-risk patients from low-risk patients: low-risk class included patients with low values of CD68KP1 percentage<25% and patients that, despite CD68KP1≥25%, had jointly scattered PD1 in MC and positive STAT1 on HRSC; high-risk class consisted of patients that were characterised by CD68KP1≥25% and diffuse or rosetting PD1 pattern and subjects that had jointly CD68KP1≥25%, scattered PD1 pattern and STAT1 on HRSC.Finally we showed that high number of Arginase+ MSC on MC, but not CD68KP1+ cells content, was significantly associated to shorter PFS in stage I/II cHL patients and was related to a worse OS; notably, immunoflurescence revealed that a fraction of CD68KP1+ elements do also express Arginase.We demonstrated that the development of a clinical-pathological algorithm based on the combination of IP with some of the investigated biological markers, allowed the identification of poor prognosis patients that were misclassified by IP alone. Moreover, the expression of functional markers of MSC suggests a new perspective of monocytic/macrophagic elements populating cHL microenvironment

P052
THE CD30 / CD16A BISPECIFIC ANTIBODY TANDAB AFM13 ACTIVATES NK CELLS FROM HODGKIN LYMPHOMA PATIENTS RESULTING IN SPECIFIC TUMOR CELL KILLING

Reiners KS,[1] Kessler J,[1] Sauer M,[1] Rothe A,[1] Hansen HP,[1] Reusch U,[2] Hucke C,[2] Köhl U,[3] Dürkop H,[4] Engert A,[1] Pogge von Strandmann E[1]

[1]Department I of Internal Medicine, Laboratory of Immunotherapy, University Clinic of Cologne, Cologne, Germany; [2]Affimed Therapeutics AG, Heidelberg, Germany; [3]GMP Development Unit/ Cellular Therapy Centre, Hannover Medical School (MHH), Hannover, Germany; [4]Pathodiagnostik, Berlin, Germany

It is a hallmark of Hodgkin lymphoma (HL) that the malignant cells in affected lymph nodes are surrounded by immune effector cells including lymphocytes, that are unable to recognize and kill the tumor cells. Here, we demonstrate that the recognition and killing of the HL-derived target cell line L428 was impaired in NK cells isolated from patients with HL, although this cell line was efficiently lyzed by NK cells from healthy donors. Impaired NK cell function correlated with elevated serum levels of soluble ligands for the NK cell receptors NKp30 (BAG6/BAT3) and NKG2D (MICA), factors known to constrict NK cell function. In vitro, NK cell cytotoxicity could be restored by an NKG2D/NKp30-independent antibody construct (CD30xCD16A, AFM13). This antibody construct targets CD16A on NK cells and the surface receptor CD30, which is overexpressed on malignant HL cells. In vitro assays demonstrated that AFM13 binds with high affinity to both CD30 and CD16A antigens and enhanced specific killing of CD30+ target cells. AFM13 activated CD16A only in the presence of tumor cells and no systemic activation of NK-cells in the absence of target cells was observed. The drug was investigated in an open-label single-arm phase I dose escalation trial in heavily pre-treated patients with relapsed/refractory HL. Each patient received 4 weekly doses of AFM13. Seven dose levels from 0.01 to 7.0 mg/kg were escalated in cohorts of 3 patients. In addition, one cohort of 4 patients received AFM13 twice a week at 4.5 mg/kg for 4 weeks. All dose levels of AFM13 proved to be well tolerated and safe and clear signs of anti-tumor activity were demonstrated. Interestingly, we observed that NK cells from patients treated with this construct were generally activated and revealed an enhanced expression of the activation marker CD69. They moreover displayed restored cytotoxicity against a HL derived target cell line. These data suggest that suppression of NK cell activity contributes to immune evasion in HL and can be antagonized therapeutically. AFM13 has demonstrated encouraging biologic activity and represents a new targeted therapy for heavily pretreated patients with HL.

P053
HLA ASSOCIATED SUSCEPTIBILITY TO EBV+ HODGKIN LYMPHOMA: NO CORRELATION WITH INFECTIOUS MONONUCLEOSIS OR NUMBER OF CIRCULATING EBV+ B CELLS

Diepstra A,[1,2] Leese AM,[2] Pachnio A,[2] Bell AI,2 Hepkema B,[3] van den Berg A,[1] Moss P,[2] Lee SP,[2] Rickinson AB[2]

[1]Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, the Netherlands; [2]School of Cancer Sciences, College of Medicine and Dental Sciences, University of Birmingham, United Kingdom; [3]Laboratory Medicine, University of Groningen. University Medical Center Groningen, the Netherlands

In the western European population, HLA-A2 protects against the development of EBV+ Hodgkin lymphoma (HL), while both HLA-A1 and infectious mononucleosis (IM) are risk factors. In this study we tested 2 hypotheses: 1. HLA-A type is associated with IM risk and 2. HLA-A type determines EBV+HL risk by influencing the number of circulating EBV+B cells (EBV+HL precursors). To test the first hypothesis, HLA class I typing was performed in 158 clinically diagnosed Caucasian IM patients. Allele frequencies were compared to 12,762 regional Blood Bank volunteers. The HLA-A1 type was clearly under represented in IM patients (12.3%) compared to controls (19.3%, OR 0.59; 95%CI 0.42-0.83), in sharp contrast to the situation in EBV+ HL. These data indicate that the known association of HLA-A1 and HLA-A2 with EBV+ HL is not paralleled by a similar association with IM. The unexpected negative correlation between HLA-A1 and IM may be caused by an association with less severe IM symptoms, if individuals with less severe IM symptoms did not seek medical attention. To answer the second hypothesis, EBV viral load was measured by Q-PCR using PBMC DNA from 270 first year medical students with positive EBV serology and no

recent IM symptoms. Viral load was considered indicative for number of circulating EBV+B cells. For each HLA type (A1, A2, B7, B8 and B35) EBV loads were compared between HLA type carriers and non-carriers. Results with medians and percentage of individuals with detectable EBV loads indicated under the x-axis are shown below. Of the individuals with HLA types previously shown to be involved in cytotoxic immune responses to latent EBV (A2, B7, B8 and B35), only HLA-B7 positive individuals had a significantly lower viral load than HLA-B7 negative individuals (p=0.038, median: 0 *vs* 44). In conclusion, the risk effect of HLA-A1 and the protective effect of HLA-A2 in the development of EBV+HL are unlikely to be explained by differences occurring during primary EBV infection or differences in the lifelong virus-host balance. Instead, these effects probably relate to immune surveillance of EBV infected Hodgkin (precursor) cells at later stages of disease pathogenesis.

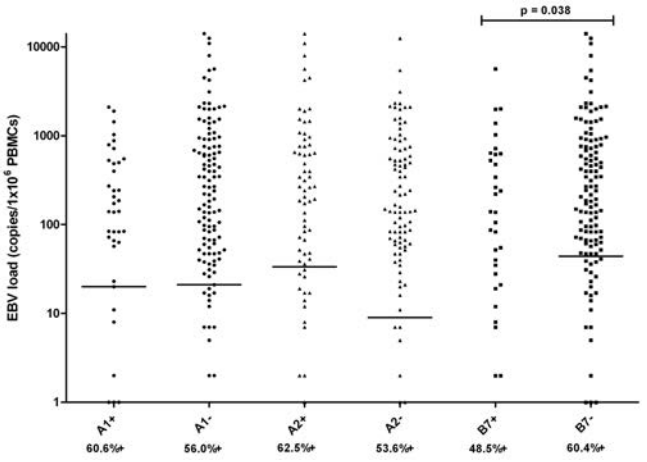

Figure 1. EBV load in peripheral blood of healthy individuals

P054
PROMYELOCYTIC LEUKEMIA NUCLEAR BODIES AND SPECIAL AT RICH BINDING PROTEIN 1 ARE RELATED TO HLA CLASS I AND II EXPRESSION IN HODGKIN REED-STERNBERG CELLS

Liu Y,[1] van den Berg A,[1] Veenstra R,[1] Rutgers B,[1] van Imhoff G,[2] Visser L,[1] Diepstra A[1]

[1]Departments of Pathology & Medical Biology; [2]Department of Hematology, University of Groningen, University Medical Center Groningen, The Netherlands

Hodgkin Reed-Sternberg cells in classical Hodgkin lymphoma (cHL) are characterized by a general loss of B cell phenotype, whereas antigen presenting properties are commonly retained. HLA class I and class II are expressed in most EBV+cHL cases, and often their level of expression is even enhanced. This is remarkable since EBV+cHL patients do have anti-EBV immune responses. Promyelocytic leukemia protein (PML) and special AT-rich region binding protein 1 (SATB1) are two global chromatin organizing proteins that have been shown to regulate HLA class I expression whereas PML also influences HLA class II expression by upregulating the class II transactivator (CIITA). We analyzed HLA class I, HLA class II, SATB1, PML and the number of PML nuclear bodies (NBs) expression in cHL cell lines and in tumor cells in cHL cases. At the mRNA level, significant positive correlations were found between PML-I and HLA-DOB, PML-III and HLA-C, PML-III and 2M, and between PML-V and HLA-DMA in cHL cell lines. There were no significant correlations between SATB1 and the HLA class I or II genes. In cHL cases, strong membrane HLA class I protein expression was observed in approximately 40% of EBV+ cHL and not in EBV- cHL patients. The number of PML-NBs was positively correlated to the level of HLA class I expression ($p<0.01$). The percentage of SATB1 positive cells was inversely correlated with the level of HLA class I expression ($p<0.05$). Multivariate analysis indicated that the number of PML-NBs and the percentage of SATB1+ tumor cells are independent factors affecting HLA class I expression in EBV+ cHL. The number of PML NBs, SATB1, patient characteristics and tumor cell EBV status were not correlated with HLA class II (DP/DQ/DR) expression in cHL cases. In conclusion, the mRNA levels of specific PML isoforms are associated with the mRNA levels of multiple HLA class I and II genes in cHL cell lines. Both PML and SATB1 appear to play a role in the regulation of HLA class I protein expression in EBV+cHL.

P055
LONG NON-CODING RNAS IN HODGKIN LYMPHOMA

Tayari M,[1] Kok K,[2] Kortman G,[1] Sietzema J,[1] de Jong D,[1] Terpstra M,[2] Visser L,[1] Diepstra A,[1] Kluiver J,[1] van den Berg A[1]

[1]Department of Pathology & Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [2]Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Long non-coding RNAs (lncRNAs) are deregulated in a number of cancers and have diverse roles in transcriptional, posttranscriptional and epigenetic mechanisms. A number of lncRNAs have been linked to cancer development based on differential expression patterns and functional studies. To what extent lncRNAs are involved in the pathogenesis of Hodgkin lymphoma (HL) is yet unclear. To analyze lncRNA expression we designed a custom made microarray based on a recently published lncRNA catalog of 10,509 lncRNA loci (Cabili et al., 2011). Our microarray contains probes for 10,229 lncRNA loci (97,3%) with 3 probes per locus on average. It also includes probes for all protein coding genes, allowing simultaneous detection of the lncRNA and mRNA expression pattern in each individual sample. We analyzed 6 cHL cell lines and three samples of purified GC B-cells. For qRT-PCR validation, we used a targeted primer design based on the expression pattern of individual probes within a lncRNA gene locus. A significant differential expression pattern between HL and normal GC B-cells was obtained for 717 out of 11,842 lncRNA probes. To determine the cellular location of the lncRNAs we isolated nuclear and cytoplasmic fractions of 2 cHL cell lines. We observed that 27% of all expressed lncRNAs are enriched in the nuclear fraction and 17% were predominantly enriched in the cytoplasmic fraction. 42 of the differentially expressed lncRNAs were enriched in the nucleus and 6 in the cytoplasm. Using qRT-PCR we confirmed differential expression for four up- and two downregulated lncRNAs in the same set of cell lines and purified B cell subsets. RNA-FISH experiments to confirm subcellular localization and expression in HRS cells of primary HL cases are ongoing. Also loss-of-function experiments will be performed to identify lncRNAs that affect HL tumor cell growth. In conclusion, a substantial number of lncRNAs are differentially expressed between HL and normal GC B-cells. Several of these lncRNAs are enriched in the nucleus or in the cytoplasm.

P056
IMMUNOSUPPRESSIVE PROPERTIES OF MYELOID CELLS IN HODGKIN`S LYMPHOMA

Romano A, Parrinello NL, Vetro C, La Cava P, Forte S, Chiarenza A, Motta G, Triolo A, Palumbo GA, Consoli U, Di Raimondo F

University of Catania, Italy

Background. In Hodgkin Lymphoma (HL) elevated neutrophil count is a well recognized negative prognostic factor but its biological meaning is not elucidated. Material and Methods. in neutrophils (N) obtained from 15 HL patients we tested phagocytic activity, enzymatic activity of arginase (ARG-1), expression of ARG-1 and pro-angiogenic factor PROK-2, and suppression of healthy T-lymphocytes activation in co-culture experiments. Amount of ARG+ cells was also evaluated in HL lymphonodes. Results. We observed an increase of ARG-1 expression in N-HL up to 100 folds and of PROK-2 up to 36 folds compared to healthy subjects matched for age and sex ($p=0.001$), independently from tumor load and other well-known prognostic factors, including sex, anemia, stage, bulky disease and IPS. In the lymphonodes, ARG-1 evaluated in immunohistochemistry showed a granular pattern distribution in lack of overlapping with CD68+ staining. N-HL exhibited a reduced phagocytosis (93.2 ±1.9% *vs* 73.1 ± 3.7, $p=0.0008$) and an increased arginase activity up to 15 times compared to healthy subjects matched for age and sex. Finally, we co-cultured lymphocytes isolated from healthy subjects (h-Ly) with neutrophils isolated from fresh peripheral blood of HL patients (HL-N) or healthy subjects (h-Ne) and we evaluated markers of activation after stimulation with PHA-P at different time-points. After PHA-P

stimulation, CD69 and CD25 were increased in h-Ly from 6 to 24 hours with peak at 24 hours and declining thereafter. CD71 increased slowly from 6 to 24, 48 and 72 hours, while HLA-DR maintained low expression with increase at 72 hours. Expression of these activation markers was down-regulated by co-culture of h-Ly with HL-N at ratio 1:4 and 1:8 at all tested time-points. Conclusion Taken together our findings confirm the impact of dysfunctional myeloid arm in HL with a promising prognostic meaning, to confirm prospectively in a larger series.

P057
MACROPHAGES IN T CELL/HISTIOCYTE RICH LARGE B CELL LYMPHOMA STRONGLY EXPRESS METAL-BINDING PROTEINS AND SHOW A BI-ACTIVATED PHENOTYPE

Hartmann S,[1] Tousseyn T,[2] Döring C,[1] Flüchter P,[1] Hackstein H,[3] Herreman A,[2] Ponzoni M,[4] de Wolf-Peeters C,[2] Facchetti F,[5] Gascoyne RD,[6] Küppers R,[7] Steidl C,[6] Hansmann ML[1]

[1]Dr. Senckenberg Institute of Pathology, Goethe University, Frankfurt am Main, Germany; [2]Department of Pathology, University Hospitals K.U.Leuven, Leuven, Belgium; [3]Immunology, Gießen University Hospital, Gießen, Germany; [4]Unit of lymphoid malignancies, Department of Pathology, Scientific Institute San Raffaele, Milan, Italy; [5]Department of Pathology, University of Brescia, Brescia, Italy; [6]Department of Pathology and Laboratory Medicine and the Centre for Lymphoid Cancer, British Columbia Cancer Agency, University of British Columbia, Vancouver, Canada; [7]Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, Medical School, Essen, Germany

Abundant macrophage infiltration in tumors often correlates with a poor prognosis. T cell/histiocyte rich large B cell lymphoma (THRLBCL) is a distinct aggressive B cell lymphoma entity showing a high macrophage content. To further elucidate the role of tumor-associated macrophages in THRLBCL, we performed gene expression profiling of microdissected histiocyte subsets of THRLBCL, nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), Piringer lymphadenitis, sarcoidosis, nonspecific lymphadenitis, and monocytes from peripheral blood. In a supervised principal component analysis, histiocytes from THRLBCL were most closely related to epithelioid cells from NLPHL, with both types of cells expressing genes related to proinflammatory and regulatory macrophage activity. Moreover, histiocytes from THRLBCL strongly expressed metal-binding proteins like MT2A, by which histiocytes of THRLBCL can be distinguished from the other histiocyte subsets investigated. Interestingly, the validation at the protein level showed a strong expression of TXN, CXCL9, MT2A and SOD2 not only in macrophages of THRLBCL but also in the tumor cells of NLPHL and classical Hodgkin lymphoma (cHL). Overall, the present findings indicate that macrophages in the microenvironment of THRLBCL have acquired a distinct gene expression pattern, that is characterized by a mixed M1/M2 phenotype and a strong expression of several metal binding proteins. The microenvironments in NLPHL and THRLBCL appear to have a similar influence on the macrophage phenotype. The high expression of metal binding proteins in histiocytes of THRLBCL may be diagnostically useful, but a potential pathophysiological role remains to be identified.

P058
CIRCULATING CELL-FREE DNA AS PROGNOSTIC BIOMARKER IN HODGKIN LYMPHOMA: QUANTITATIVE AND QUALITATIVE EVALUATIONS

Giachelia M, Cupelli E, Cuccaro A, Massini G, Bartolomei F, Tisi MC, D'Alò F, Voso MT, Leone G, Hohaus S

Catholic University of Sacred Heart, Institute of Hematology, Rome, Italy

Introduction. Cell-free DNA (cfDNA) is significantly higher and more fragmented in plasma of cancer patients and levels have been reported to associate with prognosis. The aim of our study was to evaluate levels and fragmentation of cfDNA in plasma of patients at HL diagnosis and during follow-up. Methods cfDNA levels were studied in pre-treatment plasma samples of 163 consecutive HL patients diagnosed at our Institution and 64 healthy volunteers. 70 patients were also evaluated after two cycles of chemotherapy. cfDNA fragmentation was evaluated in 31 patients and 19 controls. cfDNA has been analyzed by Q-PCR for the beta-globin gene amplifying fragments of different length and integrity indices were calculated (Mouliere et al, PLoS One 2011). Patients were treated with ABVD (101 patients), BEACOPP (42 patients) or other types of chemotherapy (17 patients). Results. cfDNA at diagnosis was significantly increased (median, 21.83 *vs* 12.18 ng/ml; p<0.0001) in patients with HL when compared to controls. At diagnosis, cfDNA was also more fragmented than controls with a lower integrity index (II, median: 0.15 *vs* 0.22; p=0.016). However, II resulted higher when compared to aggressive tumors like Burkitt lymphoma or solid tumors, suggesting that most of the increase of cfDNA in HL is probably due to the tumor microenvironment rather than to the neoplastic cells. cfDNA levels were elevated in 62 (38%) patients and significantly decreased after 2 cycles of chemotherapy in patients with increased pre-treatment levels, while they remained in the normal range in patients with low cfDNA at diagnosis (ratio 0.32 and 1.44, respectively; p<0.0001). Increased cfDNA at diagnosis was associated to parameters indicating an unfavorable prognosis as an IPS score>2 (p=0.0008). Patients with elevated cfDNA levels at diagnosis had an inferior outcome compared to patients with levels within the normal range both in univariate and in a multivariate analysis including IPS and adjusted for the type of chemotherapy (EFS, p<0.03). Conclusions. Our data suggest that cfDNA could become a potential biomarker for HL, that it is frequently elevated at diagnosis of HL, shows a lower integrity index, tend to normalize during treatment and are associated to a inferior outcome.

P059
PROGNOSTIC VALUE OF CD68 COUNT IN THE TREATMENT OF HODGKIN LYMPHOMA IN THE "PET ERA"

Cuccaro A, Calcagni ML, Rufini V, Massini G, Bartolomei F, Giachelia M, Cenci T, Martini M, D'Alò F, Balducci M, Leone G, Larocca LM, Hohaus S

Institute of Hematology, Catholic University, Rome, Italy

Introduction. Despite recent advances in Hodgkin Lymphoma treatment, about 20% of the patients still die from progressive disease. Interim PET imaging has proved to be a useful prognostic tool when included in a response-adapted therapy setting (Gallamini, Blood 2012). Different studies showed that an increased number of tumor associated macrophages strongly correlates with a poorer prognosis in patients with cHL, thus providing a new biomarker (Steidl, NEJM 2010). The aim of this study was to evaluate the role of CD68 count as a prognostic factor in its relation to early response evaluated by PET. Methods We studied 104 patients with HL (median age 38.5 years; 52 females, 52 males), diagnosed at our Institution between 2004 and 2013 and treated with ABVD (70 patients), BEACOPP (25 patients) or other types of chemotherapy (9 patients). CD68+ cells were assessed by staining with the PGM-1 antibody. In 50 patients, the CD68 count was <5% and in 54 patients >5%. PET was performed after 2 cycles of chemotherapy in 91 patients: 70 patients were PET-negative, 21 PET-positive. Primary endpoint was progression-free survival, defined as time from date of diagnosis to date of first relapse, disease progression, subsequent anticancer therapy for residual disease after conclusion of planned frontline therapy, or death from any cause.

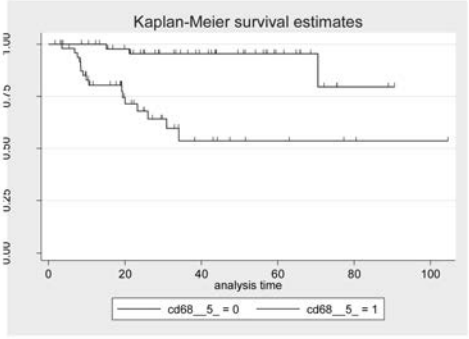

Figure 1. Progression-free survival in 102 pts

Results. No association was found between CD68 count and patient characteristics, as stage, bulky disease, monocyte and lymphocyte count, or IPS score. CD68 >5% was associated to age ≥45 (p<0.001). Patients with a higher CD68+ count had a higher risk being interim PET positive (p<0.05). In univariate analyses, that was adjusted for the type of chemotherapy, high CD68 count and interim PET positivity were independent predictors for reduced PFS (p=0.002 and p=0.004 respectively). Moreover, in a multivariate analysis adjusted for the type of chemotherapy, including age, CD68 count, and interim PET, both CD68 count and interim PET retained their prognostic significance (p=0.003 and p=0.004). Conclusions. CD68 count was an independent prognostic marker, also when considering interim PET response. This may potentially allow for a risk stratification at diagnosis with further treatment adaptation according to interim PET result.

P060
CLINICAL SIGNIFICANCE OF TUMOR-ASSOCIATED MACROPHAGES IN EARLY-STAGE HODGKIN'S LYMPHOMA

Gotti M,[1] Nicola M,[2] Fiaccadori V,[1] Bono E,[1] Lucioni M,[2] Bonfichi M,[1] Varettoni M,[1] Pascutto C,[1] Arcaini L,[1] Paulli M,[2] Cazzola M[1]

[1]Dept of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo & University of Pavia, Pavia, Italy; [2]Dept of Human Pathology, Fondazione IRCCS Policlinico San Matteo & University of Pavia, Pavia, Italy

Although patients with early-stage Hodgkin's lymphoma (HL) have a high rate of cure, a portion of them is resistant to or relapse after standard treatment and current clinical prognostic criteria do not allow an accurate identification of patients with less favourable clinical outcome. In a recent study an increased number of tumor-associated macrophages was found to have a strong correlation with shortened survival in patients with classic HL [N Engl J Med. 2010 Mar 11;362(10):875-85]. The aim of this study was to evaluate the clinical significance of the proportion of CD68-positive infiltrating macrophages in patients with early-stage HL. We performed immunohistochemistry analysis on diagnostic biopsies of 83 patients followed at our institution between 2002 and 2010, and uniformly treated with ABVD±RT. Forty-eight (58%) patients were males and 35 (42%) were females; median age at diagnosis was 31 years (range 17-85). Seventy-eight patients had supradiaphragmatic localizations and sixty-two of them were classified in the EORTC unfavorable subset. Fifty-one out of 78 (65%) patients received radiotherapy as a consolidation treatment after chemotherapy. After completion of the therapeutic program, 71 out of 83 (86%) patients obtained complete remission, while 12 (14%) had refractory disease; 7 out of 71 (10%) patients in complete remission relapsed during follow up. Diagnostic biopsies were classified into 3 groups according to the intensity of CD68 expression: lower than 5% in 17 patients (group A), between 5 and 25% in 59 patients (group B), and greater than 25% in 7 patients (group C). The 2-year OS and PFS in the entire cohort were 96% and 81%, respectively. There was a difference in the 2-year PFS according to the EORTC risk criteria (100% *vs* 79%, P=.0314) and CD68 expression (88%, 85% and 57% in group A, B and C, respectively; P=.002). Within those with unfavorable EORTC criteria, patients with CD68 expression greater than 25% had a worse 2-year PFS (43% *vs* 78%, P=.0002). In conclusion, our findings suggest that a proportion of CD68-positive infiltrating macrophages greater than 25% is associated with unfavourable clinical outcome in patients with early-stage Hodgkin's lymphoma.

P061
REGULATORY T-CELLS DETECTABLE IN PERIPHERAL BLOOD IN HODGKIN`S LYMPHOMA INCREASE DURING ABVD CHEMOTHERAPY, EXCEPT FOR PATIENTS WITH POSITIVE INTERIM PET

Romano A, Parrinello NL, Vetro C, La Cava P, Chiarenza A, Motta G, Triolo A, Palumbo GA, Di Raimondo F

University of Catania, Italy

Background. Recent observations suggest a prognostic role for regulatory T cells (Treg) in classical Hodgkin lymphoma (HL) tissues, correlate with poor overall survival both at diagnosis and in relapsed/refractory cases. Currently, no data have been published in the era of interim positive emission tomography PET (PET-2)- risk adapted strategy. Objective: To investigate whether the frequency of peripheral blood (PB) regulatory T cells (Treg) correlates with the clinical disease activity of HL. Methods. PB Treg cells, defined as the CD4+CD25(high)CD127(low/-) population, were examined by flow cytometry in a prospective study involving 20 healthy donors and 25 patients with newly diagnosed HL, including 15 in early stage and 10 with advanced disease at different timepoints (T0= baseline, T2 after two courses of ABVD chemotherapy, T4, after two months from the last course of chemotherapy). The association of C-reactive protein (CRP), fibrinogen level or erythrocyte sedimentation rate (ESR) with the frequency of PB Treg cells was examined. Baseline levels were correlated to the ability to predict patients with a positive PET-2. Results. The frequency of PB Treg cells in patients with HL was significantly low compared with that of healthy controls in terms of percentage (mean ±DS, 5.9%±2.1 *vs* 8.5%±2.1, p=0.0004) and absolute numbers (mean ±DS, 30.3±16.4 cells/uL *vs* 75.5±25.6 cells/uL, p<0.0001). Among the 3 timepoints tested, Treg cell frequency was lowest in patients at diagnosis with a progressive increase during chemotherapy (p=0.0028). Patients with positive PET-2 exhibited lower count of Treg compared to patients with a negative PET-2 (mean ±DS, 12.5±7.2 cells/uL *vs* 33.1±16.1 cells/uL, p=0.0013), but no differences were due to presence of bulky disease or stage at diagnosis. The absolute count of CD4+CD25(high)CD127(low/-) Treg cells weakly negatively correlated with CRP and ESR, but not with fibrinogen. Conclusion. Taken together our data suggest that Treg cells, defined as the CD4+CD25(high)CD127(low/-) population, may contribute to the pathogenesis of HL and be an indicator of disease activity. easily detectable in PB, to confirm prospectively in a larger series.

P062
SPECIFIC DEGRADATION PATTERN OF PEROXIREDOXIN 1 CORRELATES WITH ADVERSE OUTCOME IN CLASSICAL HODGKIN LYMPHOMA PATIENTS

Ludvigsen M,[1] Kamper P,[2] Singers Soerensen B,[3] Hamilton-Dutoit SJ,[4] Bendix K,[4] Boe Møller M,[5] Alsner J,[3] d'Amore F,[2] Honoré B[1]

[1]Department of Biomedicine, Aarhus University, Denmark; [2]Department of Hematology, Aarhus University Hospital, Denmark; [3]Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark; [4]Institute of Pathology, Aarhus University Hospital, Denmark; [5]Department of Pathology, Odense University Hospital, Denmark

Background. The treatment results in patients with relapsed/refractory classical Hodgkin lymphoma (cHL) are often still unfavorable. Thus, there is a need to identify prognostic markers that can identify cHL patients, who may benefit from an improved upfront approach. Several reports have indicated a role of peroxiredoxin 1 (prdx1) in various malignancies[1]. Our group has previously shown a correlation between low pre-therapeutic prdx1 expression and unfavorable outcome in patients with classical Hodgkin lymphoma (cHL)[2]. Prdx1 is an antioxidant protein which plays a role in the cellular defense against reactive oxygen species by reducing peroxides. Interestingly, prdx1 knock-out mice develop hemolytic anemia, but also a variety of malignancies including lymphomas[3]. In this study, we observed a specific proteolytic degradation pattern of prdx1that correlates with an adverse outcome following first line treatment in cHL patients. Methods. Frozen tissue samples from 11 patients with advanced stage cHL were identified from archives and clinical data were obtained from a review of clinical records. Of the 11 identified patients, 6 had chemosensitive disease with favorable outcome following first line therapy and 5 displayed relapsed/refractory disease upon first line treatment. Since many studies have indicated the prognostic relevance of the tumor microenvironment, i.e. not only the tumor cells, in cHL, we investigated prdx1 expression in total lymph node extracts from our cohort of cHL patients. Protein expressions were visualized by western blotting and mRNA levels were examined by qPCR. Results. Tumor tissue from cHL patients with unfavorable treatment response showed low to undetectable levels of full-length prdx1 protein compared to tissue from cHL patients with favorable treatment response (p=0.005). In contrast, a lower molecular mass protein reacting with the same prdx1 antibody was observed in the unfavorable samples with low to undetectable expression levels in favorable samples (p=0.03). Both groups showed similar levels of full-length prdx1 transcripts. Conclusions. This observation may suggest a specific proteolytic degradation of prdx1 in patients with unfavorable outcome. A validation of this finding in a larger cHL cohort is warranted. References: 1 Zang *et al.*, Cancer Lett. 2009;286(2):154-60 2 Kamper *et al.*, Blood. 2011;117(24):6638-49. 3 Neumann *et al.*, Nature 2003;424(6948):561-565

P063
EFFECT OF THE EBV+CHL RISK ALLELE HLA-A*01:01 UPON EBV INFECTED B-CELL FREQUENCY AND THE EBV-SPECIFIC IMMUNE RESPONSE

McAulay KA, Farrell K, Lake A, Jarrett RF

MRC-University of Glasgow Centre for Virus Research, Glasgow, UK

Class I HLA alleles are associated with risk of developing EBV-positive classical Hodgkin Lymphoma (EBV+cHL); HLA-A*01:01 and HLA-A*02:01 alleles are associated with increased and decreased risk, respectively. Since class I genes influence cytotoxic T-cell (CTL) responses, HLA associations with EBV+cHL suggest that EBV-specific immune responses play a key role in disease pathogenesis. Such responses could be important at several stages in disease development: initial infection; during persistent latent infection; or during oncogenesis. To further understand the biology underlying these associations, we investigated whether the presence of HLA-A*01:01 alleles modifies EBV-specific CTL responses and the frequency of circulating EBV-infected cells in healthy donors. HLA-A*01:01 homozygotes (n=11), A*01:01/02:01 heterozygotes (n=15) and HLA-A*02:02 homozygotes (n=12) were selected from a cohort of healthy individuals. The number of EBV-infected B-cells was determined by limiting dilution analysis of B-cells enriched from peripheral blood mononuclear-cells (PBMC). Un-stimulated and lymphoblastoid cell line (LCL)-stimulated B-cell depleted PBMC were investigated in an ELISPOT assay using a panel of predicted HLA-A*01:01 or known HLA-A*02:01-restricted peptides to identify EBV-specific T-cell responses. Levels of cytokines in culture supernatants were measured following EBV stimulation. EBV-infected B-cell number was comparable across all three genotypes. The median frequency/million cells was 8.13 for HLA-A*01:01 homozygotes, 2.22 for HLA-A*01:01/02:01 heterozygotes, and 6.39 for HLA-A*02:01 homozygotes (p = 0.62). No HLA-A*01:01-restricted EBV-specific T-cell responses were detected in ELISPOT assays with or without stimulation. No difference in response to HLA-A*02:01-restricted EBV-specific epitopes was observed between HLA-A*02:01 homozygotes and HLA-A*01:01/02:01 heterozygotes. IL-6 levels were significantly higher in HLA-A*01:01 homozygotes than HLA-A*01:01/02:01 heterozygotes following LCL-stimulation (3519 versus 395 pg/ml, p=0.001). The lack of a HLA-A*01:01-restricted EBV-specific CTL response may partially explain the elevated disease risk associated with this allele. HLA-A*01:01 homozygotes do not have increased numbers of EBV-infected circulating B-cells, suggesting that the lack of HLA-A*01:01-restricted responses does not influence the set point of persistent EBV infection. Taken together, these data favour the idea that the critical T-cell responses are directed against EBV antigens expressed during disease pathogenesis rather than early time-points. Different patterns of cytokine response elicited by different HLA alleles may play a role and warrant further investigation.

P064
INFLAMMATORY MONOCYTES ARE INCREASED IN PERIPHERAL BLOOD IN HODGKIN`S LYMPHOMA

Parrinello NL, Romano A, Vetro C, Triolo A, Di Raimondo F

University of Catania, Italy

Background. In Hodgkin Lymphoma (HL) microenvironment has a prominent pathological role. Inflammatory CD14+/CD16+ monocytes (IM) have a wide range of chemokine pathways for recruitment into tumour microenvironment, in which they differentiate into macrophages or alternatively in dendritic cells and as shown exclusively in mouse model they might enhance oxidative stress and endothelial dysfunction. Objective. To investigate whether the frequency of peripheral blood (PB) inflammatory monocytes (IM) correlates with the clinical disease activity of HL. Methods. PB IM cells, defined as the CD14+CD16+population, were examined by flow cytometry in a prospective study involving 20 healthy donors and 40 patients with newly diagnosed HL, including 26 in early stage and 14 with advanced disease at different timepoints (T0= baseline, T2 after two courses of ABVD chemotherapy, T4, after two months from the last course of chemotherapy). The association of C-reactive protein (CRP), fibrinogen level or erythrocyte sedimentation rate (ESR) with the frequency of PB IM cells was examined. Baseline levels were correlated to the ability to predict patients with a positive PET-2. Results. The frequency of PB IM cells in patients with HL was significantly high compared with that of healthy controls (mean ±DS, 81.2 ± 9.2 cells/uL *vs* 52.7 ± 7.2 cells/uL, p=0.0069). Patients affected by HL in advanced stage exhibited higher count of IM compared to patients early stage (mean ±DS, 129.9 ± 18.5 cells/uL *vs* 54.9±5.1 cells/uL, p=0.0003). No significant differences were due to presence of bulky disease or PET-2 status. Again, among the 3 timepoints tested, MI frequency was stable, with no significant differences. Similarly, the absolute count of IM was independent from levels of CRP, ESR, and fibrinogen. Conclusion Taken together our data suggest that IM, defined as CD14+CD16+ population, may contribute to the pathogenesis of HL and be an indicator of disease activity. IM are easily detectable in PB, and further studies are needed to address their role in HL.

P065
THE NUMBER OF TUMOR-INFILTRATING MAST CELLS CORRELATES WITH ADVERSE PROGNOSIS IN MIXED CELLULARITY, BUT NOT NODULAR SCLEROSIS TYPE, CLASSICAL HODGKIN LYMPHOMA

Andersen MD,[1] Kamper P,[1] Nielsen P,[2] Bendix K,[2] Riber-Hansen R,[2] Steinicke T,[2] Hamilton-Dutoit S,[2] Clausen M,[1] d'Amore F[1]

[1]Department of Hematology, Aarhus University Hospital, Aarhus C, Denmark; [2]Instutute of Pathology, Aarhus University Hospital, Aarhus, Denmark

Background. In classical Hodgkin lymphoma (cHL) a minority of neoplastic cells is surrounded by a heterogeneous cellular Background. including mast cells (MC). A possible adverse prognostic impact of tumor-infiltrating MC in cHL has been suggested. The aim of the present study was to evaluate the prognostic impact of tumor-infiltrating MC in a cohort of homogeneously treated patients with cHL previously described by our group with regard to tumor-microenvironmental parameters. Methods. In the present study, the analysis was restricted to cases aged over 15 yrs. Tumor-infiltrating MC were stained immunohistochemically with an antibody recognizing mast-cell derived tryptase. The number of tryptase-positive cells was determined using automated quantification. MC-scores were subdivided in "low" (lower quartile) and "high" (upper three quartiles). Clinical data, were obtained from clinical records. Overall- and event-free survival (OS and EFS), were analyzed by the Kaplan-Meier method and compared using log-rank-test. Results. 276 patients with a median age of 38.5 yrs (range: 16-86 yrs) were analyzed. The M:F ratio was 1:2. A total of 92 patients (33%) had disseminated disease. B-symptoms were present in almost half of the cohort (48%). Extranodal disease and bulky lesions were present in 20% and 28% of the patients, respectively. Almost a third of all patients (34%) had a high IPS-score and 32% were EBV-positive (EBER, LMP-1). The number of tumor-infiltrating MC did not impact OS or EFS in patients with nodular sclerosis type cHL, 5-yr OS "low" *vs* "high": 89% and 86% (p=0.95), 5-yr EFS "low" *vs* "high": 78% and 67% (p=0.71). Interestingly, when mixed cellularity type cHL patients were analyzed separately, high MC counts strongly influenced both 5-yr OS and EFS values, OS "low" *vs* "high": 100% and 76% (p=0.04), EFS "low" *vs* "high": 90% and 55% (p=0.01). Conclusion. In the present study, high intratumoral MC-counts showed marked adverse prognostic impact on cHL, mixed cellularity subtype while the same was not the case for nodular sclerosis histology. If validated, this observation warrants further investigations on the underlying biological mechanisms and their possible implications for future treatment strategies.

P066
CELL CYCLE DYNAMICS OF HODGKIN AND REED-STERNBERG CELLS OF CLASSICAL HODGKIN LYMPHOMA AT PRIMARY DIAGNOSIS AND RELAPSE ASSESSED *IN VIVO*

Gontarewicz A, Vogt N, Klapper W

Institute of Pathology, Haematopathology Section and Lymph Node Registry, University Hospital Schleswig-Holstein, Campus Kiel, Germany

Although therapy targeting specific pathways or surface molecules has become available for classical Hodgkin Lymphoma (cHL) treatment very recently, most cytotoxic drugs of current standard therapy primarily target proliferating cells. Though cHL cell lines are highly proliferative in vitro, proliferation of Hodgkin and Reed-Sternberg cells (HRSC) in vivo has been described to be characterized by a low number of mitosis. To gain further insight into the pathogenetic development of cHL relapses, we analyzed the cell cycle dynamics of HRSC in biopsies at diagnosis and relapse (n=7). In contrast to previous published studies we

applied immunohistochemical multi-staining for CD30 in combination with Ki67, survivin or phosphorylated Histone 3 (pH3) to generate a quantitative measure for the cell cycle dynamics of HRSC. The comparison to normal lymphatic tissue from germinal centers and to other lymphomas like mantle cell lymphoma suggests that HRSC have a relative prolonged G2 and probably also S phase of the cell cycle. The number of cHL cells in or close to the mitosis as identified by pH3 expression was variable but interestingly there was no change in the cell cycle dynamics and proliferative index between HRSC before treatment and at relapse. In conclusion, HRSC of cHL seem to have an extended S and G2 phase of the cell cycle. Therefore, real proliferation/duplication of HRSC can only be assessed by detection of mitotic markers like pH3. Further studies will have to assess, whether expression of pH3 in cHL is of prognostic relevance. In our cohort, there seems to be no selection for a highly proliferative clone at relapse.

P067
SPINDLE SHAPED CD163+ROSETTING MACROPHAGES REPLACE CD4+ T CELLS IN HIV-RELATED CLASSICAL HODGKIN LYMPHOMA

Hartmann S,[1] Jakobus C,[1] Rengstl B,[1] Döring C,[1] Newrzela S,[1] Brodt HR,[2] Wolf T,[2] Hansmann ML[1]

[1]Dr. Senckenberg Institute of Pathology; [2]Department of Internal Medicine 2-Infectious Diseases, Hospital of the J. W. Goethe University, Frankfurt am Main, Germany

Combination antiretroviral therapy is highly effective in HIV-infection, leading to decreased incidences of AIDS-defining neoplasms. However, HIV-patients still have a 10-fold increased risk of developing classical Hodgkin lymphoma compared with the general population. As Hodgkin-and Reed-Sternberg cells represent only a minority in the tumor infiltrate, the aim of the present study was to characterize the microenvironment of HIV-related classical Hodgkin lymphoma and compare it with classical Hodgkin lymphoma cases of immunocompetent individuals. The major morphologic differences were the presence of necrotic foci and the absence of epithelioid cell formation in HIV-related Hodgkin lymphoma. We observed a significantly decreased number of CD4+ T cells and a significantly increased number of CD163+ macrophages in HIV-related Hodgkin lymphoma. Cases exhibiting a "sarcomatoid" pattern of the reactive infiltrate exhibited significantly greater numbers of macrophages, associating the "sarcomatoid" pattern to the presence of spindle shaped macrophages. Whereas rosetting of CD4+ T cells around Hodgkin- and Reed-Sternberg cells was frequently observed in classical Hodgkin lymphoma in immunocompetent persons, rosetting in a subset of HIV-related Hodgkin lymphoma cases appeared to involve cytoplasmic protrusions of spindle shaped macrophages. HIV-related Hodgkin lymphoma, therefore, is characterized by unique morphologic features, which should be recognized by pathologists.

P068
HODGKIN LYMPHOMA SUBTYPES AND PERIPHERAL LYMPHOPENIA ARE ASSOCIATED WITH EBV STATUS IN CHILDREN AND ADOLESCENTS IN FRANCE: A PRELIMINARY REPORT OF THE EURONET LH EPI PROJECT

Besson C, Boudjema S, Hamdi L, Creidy R, Leblanc T, Lambilliote A, Dainese L, Doukoure B, Krzysiek R, Coulomb A, Landman-Parker J

Immunological and Haematology Department, Kremlin Bicêtre Hospital, Le Kremlin Bicêtre; Department of Pathology, Armand Trousseau Hospital, Paris; Paediatric Immunology-Haematology Department, Robert Debré Hospital, Paris; Peadiatric Oncology Department, CHRU Lille, Lille; Haematology-Immunology-Oncology Department, Armand Trousseau Hospital, Paris, France

Background. Hodgkin's lymphoma (HL) microenvironment is enriched in soluble factors and direct cellular interactions known to be strong modifiers of lymphocyte homeostasis. Yet, HL tumor microenvironment differs between EBV negative and EBV positive tumors. The impact of this milieu on the peripheral lymphocytic compartments in HL patients remains to be defined. Methods. Morphological data of 153 children with HL included in EuroNet-PHL-C1 protocol were prospectively reviewed. 84 patients were also analyzed for plasmatic EBV load and peripheral lymphocytic counts. Results. Median age was 13.5 years, ranging from 5 to 18. Male to female ratio was 1.2 with a larger male predominance below the age of 10 (M/F ratio: 2.5). Histological subtypes were: Nodular Sclerosis (NS):86%, Mixed Cellularity (MC):7%, unspecified (mainly because of small biopsies):6%. MC subtype was highly predominant in males (90%) and associated with a younger age (median 11.5 yr). EBV RNA was detected in situ in 23% of cases and was associated with male sex and MC subtype. Plasma EBV load was positive in 38% of patients and strongly correlated with in situ EBV expression ($p<0.01$). A decrease in B-lymphocyte counts was observed in 31 out of 84 patients (37%). Mixed T- and B-cell lymphopenia was present in 18/31 (58%) of cases. Peripheral B-cell lymphopenia was associated with the following adverse prognostic factors: advanced stages ($p<0.04$), hemoglobin<10.5 g/dL ($p<0.06$) and B symptoms ($p<0.01$). B-cell lymphopenia was not statistically correlated with tumor morphology (histological subtype, extent of tumor cells infiltration and necrosis). Remarkably, B-lymphocytic counts were significantly higher in patients with in situ EBV (<0.05). Discussion. Our findings corroborate the known epidemiological data of HL in children and adolescents with a predominance of NS subtype and more frequent EBV-positive HL in younger age and in MC cases. We show that peripheral B cell lymphopenia in paediatric and adolescent HL patients is frequent and associated with adverse prognosis factors. Our findings support the notion that HL tumor-associated factors interfere with peripheral distribution of lymphocytes. Further analyses are ongoing to define the impact of HL tumor-associated microenvironment on lymphocyte homeostasis in HL patients.

P069
SERUM TARC LEVELS IN A COHORT OF PEDIATRIC PATIENTS WITH HODGKIN LYMPHOMA (HL): A PROMISING BIOMARKER?

Schiavello E,[1] Terenziani M,[1] Mazzocchi A,[2] Casanova M,[1] Ferrari A,[1] Luksch R,[1] Meazza C,[1] Polastri D,[1] Spreafico F,[1] Catania S,[1] Biasson V,[1] Podda M,[1] Chiaravalli S,[1] Vajna de Pava M,[1] Massimino M[1]

[1]Department of Pediatrics, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]Unit of Transfusion Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background. TARC (thymus and activation-regulated chemokine) is a protein expressed by Hodgkin Reed-Sternberg cells detectable in serum TARC seems to have a role correlated with prognosis in adult HL patients but there aren't data published in pediatrics. METHODS We tested TARC serum level prospectively in 17 consecutive patients, considering pathological level >500 pg/ml, as already reported on healthy controls: 14 naïve (Group 1); 2 at relapse after autologous stem cell transplantation (autoSCT) and 1 primary refractory (Group 2). In group1 TARC samples were collected at diagnosis, after the 2nd cycle, and at the end of treatment. In the group2 every 2 cycles, after auto-alloSCT, and during follow-up. The 17 patients' characteristics were: median age 13 years, stage III-IV 8; B symptoms 7; bulky disease 10; extranodal involvement 4. Results. Basal TARC level (median 42315 pg/ml) was high in 16/17 pts (range 344-129462) and significant higher with B symptoms ($p=0.05$); higher but not significant in bulky and stage III-IV disease. In Group1, 1 patient had normal value, 13 had a significant ($p= 0.0004$) decline after the 2nd cycle , with normalization that persisted during follow-up, 1 had a significant decrease without reaching normalization. None of these 14 patients did relapse so far. In Group2, two pts were monitored for TARC during reinduction: one had a progressive disease with concomitant increasing TARC, the other had a normalization of TARC while in partial remission before subsequent alloSCT. After transplantation, TARC increased before radiological detection of relapse. The primary refractory patient had TARC decrease correlated with good radiological response. Conclusions. This preliminary study shows a correlation between TARC and some clinical risk factors and radiological response. Our first pediatric series needs to be validated in a larger cohort to confirm if TARC could be useful in clinical practice.

P070
PROGNOSTIC SIGNIFICANCE OF CD68, CD20, FOXP3 EXPRESSION; PRESENCE OF EPSTEIN-BARR VIRUS AND MAST CELL INFILTRATION IN CLASSICAL HODGKIN LYMPHOMA PATIENTS

Salihoglu A,[1] Ozbalak M,[2] Demiroz AS,[3] Tuzuner N,[4] Elverdi T,[1] Gulturk E,[1]Eskazan AE,[1] Ar MC,[1] Ongoren S,[1] Baslar Z,[1] Soysal T,[1]Aydin Y,[1] Ferhanoglu B[1]

[1]Istanbul University Cerrahpasa Medical Faculty, Hematology Department; [2]Istanbul University Cerrahpasa Medical Faculty, Internal Medicine; [3]Istanbul University Cerrahpasa Medical Faculty, Pathology, Turkey

Background. Classical Hodgkin Lymphoma (cHL) is a highly curable B cell lymphoid malignancy characterized by the presence of Reed-Sternberg(RS) cells in a Background. of mixed inflammatory cells constituting only the minority of the total tumor mass. Recently, emphasis is given to the contribution of the non-tumoral cells to disease outcome. Aims: The aim of this study was to find out if there is a relationship between the composition of the immune infiltrate and clinical outcome in our cases with cHL. Patients and Methods. Patients were retrospectively collected from 2000 to 2010 in one center(Cerrahpasa Medical Faculty, Istanbul, Turkey). From 250 adult cHL patients diagnosed at our center during this time period, tissue and data regarding clinical outcome (with a follow up time of at least 24 months) were available for 83 patients (49 males, 34 females, median age 38(13-77) years). Analysis was performed on sections from previously untreated patients' biopsies in 76 patients(91.6%), in 7 (8.4%) biopsies during disease relapse were evaluated. The slides were stained for CD68, CD20, FOXP3, LMP-1 and tryptase. Clinical and laboratory data available on presentation and follow up were recorded. Median follow up was 56 (range 6-156) months. Two patients included in the study had a follow up time less than 24 months (6 and 9 mo). The patients died because of infection at the 6th and 9th month of the follow up. Statistical analysis was made with STATA software (version 11). The study was approved by the institutional ethics committee. Results. Bulky disease and advanced stage were associated with poor prognosis. Mast cell infiltration was not significantly associated with B symptoms. CD68 expression was not associated with mortality and did not predict advanced stage disease. Decreased FOXP3 expression was associated with poor prognosis but its impact on OS was not statistically significant (p=0.063). Decrease of lymphoid follicles was a poor prognostic factor. CD20 expression of small B lymphocytes was significantly decreased in advanced stage (p=0.048). Summary/Conclusion. In our conclusion microenvironment composition is of prognostic value in cHL patients. For obtaining more accurate and reliable results we are intending to study a larger group of patients.

P071
MULTIOMYXTM: NOVEL CHEMISTRY AND VISUALIZATION TOOLS TO AID RESOLUTION OF DISCREPANT HODGKIN LYMPHOMA CASES

Adams A,[1] Bordwell A,[1] Bouman D,[1] Fisher D,[1] Hollman D,[1], Lazare M,[1] Li M,[1] Ross AS,[1] Weiss LM[2]

[1]Clarient Diagnostic Services, Inc., a GE Healthcare company, Aliso Viejo, CA, USA; [2]Clarient Pathology Services, Inc., Aliso Viejo, CA, USA

Background/Introduction. The diagnosis of classical Hodgkin lymphoma is often difficult to establish due to the rarity of the neoplastic component and the necessity to perform immunostains on serial sections. We have developed a multiplexed methodology in formalin-fixed, paraffin-embedded sections which enables assessment of multiple antigens on a single tissue section and allows evaluation of specific cells within specific fields (MultiOmyx). In this clinical application, we assessed CD30-positive cells with eight additional antibodies as an aid to diagnosis for Hodgkin lymphoma. Methods. Directly conjugated fluorescent antibodies were applied to a slide, followed by whole slide imaging. The dye was chemically inactivated, enabling a second round of staining with another fluorescent antibody. This process was performed multiple times on that single slide. The gray scale fluorescent images were transformed into virtual bright-field images which closely resembled conventional images, and also enabled direct comparison of antibodies within the same field. The antibodies used included CD30, CD15, PAX-5, CD45, CD20, CD79a, OCT-2, BOB.1, and CD3 (Fig.1). Results. This novel approach has similar staining characteristics as standard immunohistochemical stains, and has the added advantage that it may be performed on a single section. MultiOmyx allowed improved assessment of Hodgkin cells for antigens expressed on other cell types (*e.g.*, B-cell antigens on reactive immunoblasts, or CD15 on reactive histiocytes), as well as antigens expressed on directly adjacent cells (*e.g.*, CD45 and CD3). Using the unique MultiOmyx viewer, we could distinguish cases of classical Hodgkin lymphoma from other differential diagnosis entities, including nodular lymphocyte predominance Hodgkin, T-cell rich B-cell, peripheral T-cell, including anaplastic large cell lymphoma, and reactive immunoblastic proliferations. Illustrative cases in which this technology allowed improvement in diagnosis will be presented. Discussion: MultiOmyx allows for better correlation of results between stains in a given case, particularly in cases with rare Hodgkin cells, since it allows direct comparison of stains within the same field of view. MultiOmyx may be also advantageous in small samples, in which full immunohistochemical profiles may not be possible. This novel methodology is practical for routine diagnosis, and will likely be an aid to the improved diagnosis of Hodgkin lymphoma.

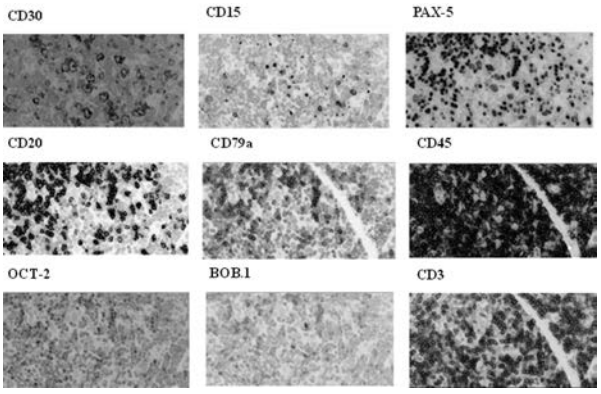

Figure 1. Representative virtual bright-field images of the nine biomarkers from the same field of view in a Hodgkin Lymphoma sample

P072
EFFECTS OF THE NF-KB INHIBITORS BORTEZOMIB AND DHMEQ ON THE EXPRESSION OF MOLECULES INVOLVED IN MICROENVIRONMENTAL INTERACTIONS AND SYNERGY WITH CHEMOTHERAPY AGENTS

Celegato M,[1] Borghese C,[1] Casagrande N,[1] Umezawa K,[2] Colombatti A,[1] Carbone A,[3] Aldinucci D[1]

[1]Experimental Oncology 2, Centro di Riferimento Oncologico, IRCCS-National Cancer Institute, Aviano, PN, Italy; [2]Molecular Target Medicine Screening, Aichi Medical University, Nagakute, Japan; [3]Division of Pathology, Centro di Riferimento Oncologico, IRCCS-National Cancer Institute, Aviano, PN, Italy

The malignant classical Hodgkin lymphoma (cHL) cells constitutively express high levels of activated nuclear factor kappaB (NF-kB). Both the proteasome inhibitor bortezomib and Dehydroxymethylepoxyquinomicin (DHMEQ) affect NF-kB activity: bortezomib by inhibiting the degradation of the cytoplasmic inhibitor of nuclear factor-B (I B) and DHMEQ by inhibiting nuclear translocation of NF-kB. Bortezomib, active in cHL cell lines, has low clinical activity when used as single agent, suggesting that micro-environmental interactions could protect from drug efficacy. Therefore, we investigated bortezomib activity in the presence of HL-associated fibroblasts (HL-AFs) and sCD40L. We found that co-cultivation with human HL-AFs or addition of sCD40L during treatment protected cHL-cells from apoptosis and cytotoxicity and rescued the down-regulation of the survival factor Interferon Regulatory Factor 4 (IRF4). On the contrary, bortezomib treatment before co-cultivation with HL-AFs, inhibited cHL cells adhesion to HL-AFs and overcame HL-AFs protection against drug activity. Consistently, bortezomib down-regulated CD49d and CD44 that mediate the adhesion of cHL cells to HL-AFs and CD54 and CD40 that mediate the adhesion to CD40L+ rosetting T-cells. DHMEQ decreased both Bcl-2 and Bcl-xL lev-

els causing apoptosis and down-regulated CD40 and IRF4. sCD40L did not affect drug activity. DHMEQ decreased CD30, increased Reactive Oxigen Species (ROS) production and the ROS scavenger NAC rescued both growth inhibition and CD30 down-regulation, suggesting that the NF-kB inhibitor could induce antitumor activity by a direct antiproliferative/apoptotic activity and also by reducing the positive effects of the microenvironment. DHMEQ reduced the secretion of the chemokines CCL5/RANTES, TARC/CCL17 and IL-6, involved in the formation of an immunosuppressive microenvironment, and exerted synergistic activity with doxorubicin, gemcitabine and cisplatin. Collectively, these data suggest that the inclusion of bortezomib in cHL drug regimen, by reducing IRF4 expression and the interactions with the microenvironment, could increase the efficacy of current chemotherapeutic treatment of relapsed/refractory cHL and that DHMEQ could have potential usefulness in future therapeutic strategies.

P073
RELATIONSHIP BETWEEN EPSTEIN-BARR VIRUS LATENCY IN PEDIATRIC HODGKIN LYMPHOMA AND IMMUNOLOGICAL STATUS OF THE HOST

Klekawka T, Balwierz W

Department of Pediatric Oncology and Hematology, Polish-American Institute of Pediatrics, Jagiellonian University Medical College in Krakow, Poland

Pediatric Hodgkin lymphoma (HL) is connected with latent Epstein-Barr virus (EBV) infection which is the major environmental factor associated with this disease. HL has the unique ability to cause immunodeficiency. Scanty data on host immunological status are available for pediatric patients in respect to EBV status of Hodgkin and Reed-Sternberg cells. To assess the impact of latent EBV infection on immunological status of the patient analysis of 61 HL cases (2.6-18.0; median: 14,2 years) treated in Department of Pediatric Oncology and Hematology, P-A Institute of Pediatrics, JUMC in Krakow, Poland was performed. HIV infection and inherited immune deficiency syndroms were excluded. EBV status of neoplastic cells was determined by EBER-specific in situ hybridization and by immonohistochemical LMP-1 protein detection (respectively 14 and 27 cases were positive). Serum IgA, IgM and IgG concentration data were collected for 59 cases. Lymphocyte subpopulation studies were available in 47 cases and lymphocyte transformation tests were performed in 16 cases only. Immunological tests Results. were compared both for LMP-1 expression status and EBER status as well. No differences between both groups of patients were found for IgA and IgG serum concentration. IgM serum concentration was significantly lower (p=0.03) in LMP-1 positive than in LMP-1 negative group (median: 1.06 and 1.57 g/L respectively). In LMP-1-negative (n=47) group there were 2, 1 and 1 patients with lower than normal IgG, IgA and IgM concentration respectively. In LMP-positive group all patients had IgG, IgA and IgM concentration above the lower normal level. Differences were not statistically significant. Also a trend towards slightly lower IgM concentration in EBER-positive than in EBER-negative cases (p=0.06) was observed. No difference in CD3, CD4, CD8 and CD19 lymphocyte subpopulations in respect to LMP-1 or EBER status was found. Only a trend towards higher mitogen response index to PWM was observed (p=0.07) in an EBER-positive group. No other differences in lymphocyte transformation tests were found respective to EBER or LMP-1 status. No relation to EBV status was found except for IgM concentration. Larger group is to be analyzed to identify differences between host immunological status and EBV latency in HL.

P074
INTERLEUKIN IL-12B IN PEDIATRIC PATIENTS WITH HODGKIN'S LYMPHOMA IN THE STATE OF PERNAMBUCO, BRAZIL

Morais A,[3] Ferreira de Barros T,[2] Silva Ferreira F,[2] Vieira Gomes A,[2] Ortolan M,[3] Cartaxo Muniz MT,[1,2,3] de Mendonça Cavalcanti MdoS[1]

[1]Instituto de Ciências Biológicas/Universidade de Pernambuco; [2]Faculdade de Ciências Médicas/Universidade de Pernambuco; [3]Hospital Universitário Oswaldo Cruz /Universidade de Pernambuco, Brasil

Hodgkin's Lymphoma (HL) is a neoplasm arising from lymphatic system and endothelial reticulum, with clinical and anatomopathological distinct characteristics of non-Hodgkin Lymphomas. The challenge in treating HL in childhood consists in reducing acute and late toxicity without affecting the prognosis. The interleukin 12 features an antiviral and antitumor action through the activation of the immune system, and the determination of polymorphisms of interleukin will help to understand the molecular biology and clarify some mechanisms involved in the development of HL. In this way, the aim of this study was to verify the possible association between the clinical risk group of the disease and the polymorphism of IL-12B in pediatric patients with HL. Eighty three pediatric patients with HL were evaluated. Clinical and biological characteristics were analysed in 70 of them and compared with 167 healthy children. The determination of polymorphism was performed using DNA extracted from peripheral blood and tissues included in paraffin blocks. Boys (62,86%) were more affected than girls and 57.15% were older than 10. In eighty percent of the cases stages II and III were observed while nodular sclerosis subtype was more frequent (40%). The alleles A and C were the most frequent in controls (68.86%) and patients (35.54%), respectively. The AA genotype showed higher frequency (49.10%) in controls, while the AC genotype was more frequent in patients (54.81%). This study did not find a significant association between gene polymorphism IL-12B and the clinical risk group of HL, however the AC genotype showed an intention of association with the HL (OR=1.8035, IC=1.0295 -3.1596, p=0.0536). These results suggest that further studies are needed to investigate the association of polymorphism of IL-12B in HL to clarify its antitumor mechanisms. Key words: Hodgkin's lymphoma, Genetic polymorphism, IL-12B.

P075
INTERLEUKIN IL-28B POLYMORPHISM IN PEDIATRIC PATIENTS WITH HODGKIN'S LYMPHOMA IN THE STATE OF PERNAMBUCO, BRAZIL

Cartaxo Muniz MT,[1,2,3] Ferreira de Barros T,[2] Silva Ferreira F,[2] Vieira Gomes A,[2] Morais A,[3] de Mendonça Cavalcanti MdoS[1]

[1]Instituto de Ciências Biológicas/Universidade de Pernambuco; [2]Faculdade de Ciências Médicas/Universidade de Pernambuco; [3]Hospital Universitário Oswaldo Cruz /Universidade de Pernambuco, Brasil

Hodgkin's lymphoma (HL) is a cancer originated in lymphatic and reticuloendothelial system, with clinical characteristics and distinct full of non-Hodgkin Lymphomas. The challenge in treating HL during childhood is the reduction of acute and late toxicity, but it does not affect the therapeutic prognostic. The interleukin 28 have antiviral and antitumor action through the activation of the immune system, and the determination of polymorphisms of interleukin will help to understand the molecular biology and clarify some mechanisms involved in the development of HL. In this way, the aim of this study was to verify the possible association between the clinical risk group of disease and polymorphism of interleukin 28B in pediatric patients with Hodgkin's lymphoma. 83 pediatric patients with HL were evaluated, in which 70 had their clinical and biological characteristics evaluated and 167 healthy children aged 0-18 years. Identification of the polymorphisms was performed using DNA extracted from peripheral blood and paraffin imbibed tissue. These patients had above ten years old (57,15%) and males are more affected by the disease (62.86%). The stages of the disease more common were the II and III in 80% of cases, while the nodular sclerosis subtype was more frequent with 40%.The C allele was more frequent in controls (66.47%) and the T allele had the same percentage in patients and controls (46%). The CT genotype presented higher frequency (46.71%) in controls, while the TT genotype was more frequent in patients (24,1%). The TT genotype of the IL-28B gene showed an increase of 3.3 at risk for developing of HL (OR=3,3882, 95% IC= 1,5368-7,4702, p=0,0038). These results. suggest that the IL-28B gene polymorphism is associated with the development of HL. New studies are needed to investigate the association of polymorphisms of IL-28B in HL to clarify the mechanisms of antitumor interleukin.

Hodgkin Lymphoma in Older Patients

T076
GHSH PHASE I/II TRIAL OF AVD-REV (ADRIAMYCIN, VINBLASTIN, DACARBACIN AND LENALIDOMIDE) FOR OLDER HODGKIN LYMPHOMA PATIENTS

Böll B, Plütschow A, Fuchs M, Thielen I, Eichenauer DA, von Tresckow B, Behringer K, Engert A, Borchmann P

German Hodgkin Study Group, Cologne, Germany Internal Medicine I University Hospital Cologne, Germany

Patients ≥60 years account for up to 1/3 of all Hodgkin Lymphoma (HL) patients and the prognosis for these patients remains poor, mainly due to excessive toxicity and insufficient efficacy of current regimens . We developed a novel regimen (AVD-Rev) for older HL patients, introducing lenalidomide combined to AVD (adriamycin, vinblastin, dacarbacin), a truncated ABVD omitting bleomycin. We initiated the GHSG AVD-Rev phase I/II trial (NCT01569204) for patients with first diagnosis of early unfavorable- or advanced stage HL. Inclusion criteria were an age between 60 and 76 years, good general performance status (ECOG/WHO ≤2) and the absence of severe organ dysfunction. ASA or heparin and a contraception agreement were mandatory. Depending on stage and response at interim staging, patients received 4-8 cycles of AVD-Rev (standard-dose AVD on days 1 and 15 of a 28 day cycle and lenalidomide daily from day 1 to 21) followed by radiotherapy (figure 1). The daily lenalidomide dose for the first patient was 5 mg, and there were 7 possible dose levels ranging from 5 mg to 35 mg. Subsequently, all incoming information on dose limiting toxicities (DLT) during the first 4 cycles of therapy was used for dose level determination for the next patient using the EWOC (Escalation with Overdose Control) method. Critical adverse events as thromboembolism, haematological toxicity such as severe cytopenia (ANC<500/µl and thrombocytopenia below 25.000/µl ≥1 day) and resulting complications as neutropenic fever and prolonged therapy delay were considered as dose limiting toxicities. 25 patients (median age 67y) were recruited; male patients were slightly more common (15 male, 10 female patients). 68% had advanced stage disease according to the GHSG definition and 80% had B-symptoms. According to the protocol, a phase II dose of 25 mg could be recommended after 20 patients had been assessed for DLT within the first 4 cycles of therapy. The final decision will depend on a comprehensive analysis of all toxicity and efficacy data from all 25 patients recruited into the phase I part of the trial. First results including detailed data on toxicity and efficacy will be presented.

T077
SEQUENTIAL BRENTUXIMAB VEDOTIN (BV) AND ADRIAMYCIN, VINBLASTINE, AND DACARBAZINE (AVD) FOR OLDER PATIENTS WITH UNTREATED HODGKIN LYMPHOMA (HL): PRELIMINARY TOXICITY FINDINGS FROM A PHASE II WINDOW STUDY

Evens AM,[1] Hamlin PA,[2] Advani RH,[3] Fanale M,[4] Smith SM,[5] Bociek G,[6] Fenske TS,[7] Petrich A,[8] Winter J,[8] Gordon L[8]

[1]Tufts University School of Medicine, Boston, MA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [4]Stanford University Medical Center, Stanford, CA, USA; [5]University of Chicago, Chicago, IL, USA; [6]University of Nebraska, Omaha, NE, USA; [7]Medical College of Wisconsin, Milwaukee, WI, USA; [8]Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Background. HL in older patients is a disease entity in which survival rates remain significantly inferior compared with younger patients. Further, a standard treatment paradigm does not exist for older patients. We initiated a multi-center study examining BV given sequentially with chemotherapy (NCT01476410). We report here preliminary toxicity findings including examination of related occurrences in the MedWatch FDA Adverse Event Reporting System (FAERS). Methods. Older patients (ages ≥60 years) with stage II-IV untreated HL were eligible. Patients received 2 lead-in cycles of single-agent BV 1.8 mg/kg q 3 weeks, followed by 6 cycles of standard AVD chemotherapy. Responding patients then proceed to consolidation with 4 cycles of BV. Results. Seven patients have enrolled with a median age of 73 years (range, 61-88), median ECOG PS of 1 (range, 0-2), and 86% have stage III/IV disease. During the 2 lead-in cycles of BV, 6 of 7 patients had ≥ grade 3 serious adverse events (SAE) including diarrhea (n=3), pancreatitis (n=2), and infection (n=2) (Table). The grade 3 pancreatitis SAE occurred 10 days after the second lead-in dose of BV; this patient had evidence of cholelithiasis and choledocholithiasis. The second pancreatitis case was a grade 5 event that occurred in a 65-year-old female 9 days following the second BV lead-in dose; the patient died 6 days later. Notably, there were no conventional pancreatitis risk factors present in this case (*e.g.*, gallstones, alcohol, other inciting medications, etc). The latter event led to study suspension for safety analysis and protocol modification. Within FAERS (data-capture through 8/2012), there are 3 additional cases of BV-related pancreatitis documented, which includes a case of "recurrent pancreatitis" on BV re-exposure. Finally, there is an ongoing pharmacovigilance effort to more accurately delineate this potential association including assessment of absolute risk. Conclusions. Unexpected toxicity, including a grade 5 SAE due to pancreatitis, was seen during the initial enrollment of our phase II window study that incorporates lead-in BV for untreated older HL patients. The current study will re-open with exclusion criteria for prior history of pancreatitis and close monitoring including amylase testing prior to each cycle of BV.

Table 1. Severe AEs (grades 3-5) during BV lead-in dosing

Age/sex	Description	Relationship
81/F	Diarrhea, Grade 3; Pneumonia, Grade 3	Expected, related
69/F	Diarrhea, Grade 3	Expected, related
65/F	Pancreatitis, Grade 5	Unexpected, related
65/F	Diarrhea, Grade 3	Expected, related
69/F	Hypoglycemia, Grade 4	Unexpected, unlikely related
61/M	Abdominal pain/gallstone pancreatitis, Grade 3	Unexpected, unlikely related
83/F	None	None
88/F	Urinary tract infection, Grade 3	Expected, possibly related

T078
TREATMENT OUTCOME IN 111 ELDERLY PATIENTS WITH HODGKIN LYMPHOMA: A RETROSPECTIVE ANALYSIS

Stamatoullas A, Bertrand P, Cassuto O, Chamseddine A, Groza L, Lenain P, Lepretre S, Lanic H, Lemasle E, Jardin F, Contentin N, Picquenot JM, Bastard C, Tilly H

Inserm U918, Centre Henri Becquerel, Rouen, France

Background. Twenty percent of classical Hodgkin's Lymphoma (cHl) patients are over 60 years of age. Their survival is inferior to that of younger patients. Reasons for this disappointing outcome are mainly lower delivery of classical chemotherapy, and excess of toxicity. The international prognostic score fails to predict survival in older patients and there is no "standard of care" in this population. Some risk factors have been reported and are predictive for inferior overall survival. Material and method: We retrospectively analyzed 111 patients aged over 60 years referred to the Centre Henri Becquerel between 1992 and 2012 for HL at diagnosis. Thirty three patients were excluded (8 no data or follow up, 5 NLPHL, 18 concomitant tumor, 1 HIV infection, 1 on therapy). Results. Clinical characteristics of the remaining 78 patients were: median age 74 years (61-90), sex ratio 35F/43M, stage I for 10 patients, II for 22, III for 24, stage IV for 22. ECOG was 0 in 30 patients, 1 in 23, 2 in 15, and >2 in 10. B symptoms were presents in 50 patients. All patients were treated: 2 with corticosteroids, 8 with radiotherapy (rt) only, 32 with ABVD (+rt in 9), 6 with EBVP (+rt in 5), 14 with MOPP, 6 with MOPP/ABVD (+rt in 4) and 10 with the association of natulan and vinblastine. Reasons for treatment modification (n: 32) were: progression (14), death (3) and toxicity (15). Among these latter patients all but 4 died. Regarding the whole group 47 patients died, 20 from HL, 2 from other tumors including 1 AML, 18 from toxicities (10 pulmonary, 1 SNC

hemorrhage, 1 cardiac failure, 6 infections) and 7 from unknown cause. Thirty one patients are alive in CR. Overall survival was significantly poorer for age >70 (91.7 versus 25.2 months). Lower ECOG (0,1,2 versus 3,4), and initial response also influenced survival. Discussion: Our data confirm the poor survival of elderly patients even with conventional treatments. Mortality is mainly related to HL and toxicities. Comorbidities and geriatric evaluation have to be well evaluated before specific treatment.

P079
PULMONARY LETHALITY ASSOCIATED WITH BLEOMYCIN IN ABVD CHEMOTHERAPY FOR FIRST-LINE HODGKIN LYMPHOMA(HL) TREATMENT

Arar A,[1] Malphettes M,[2] Bergeron A,[2] Azoulay E,[2] Brice P[2]

[1]Unit of Cell Biology, [2]Department of Hematology, Saint Louis Hospital Paris France

Bleomycin is known to have a 1% mortality rate related to pulmonary toxicity and fibrosis as side effects. We aimed to study the impact of Bleomycine treatment on HL mortality in patients treated with ABVD. From 1987 to 2012, among 950 patients treated with ABVD, for newly diagnosed HL, in our department, three cases of early pulmonary deaths were analyzed. Ages at diagnosis were 66, 67 and 80 years; initial stages for the 3 patients were: IA, IIA, IIIA and there was 2 men and 1 woman. One patient was a heavy smoker and none had previous pulmonary disease. Patients received ABVD with a fixed dose of Bleomycin at 15 mg. Pulmonary event occurred early without dyspnea in 2 cases after two cycles and later after episodes of dyspnea and fatigue after the sixth course for the third, but in these three patients a fever without clinical point of call was observed. The episode is marked by onset of fever, dyspnea, and desaturation requiring hospitalization and a bi-broad-spectrum antibiotic and Bactrim. The CTscan show images in frosted glass with an interstitial syndrome. The appearance of a rapid respiratory status' deterioration necessitated a transfer to resuscitation unit with intubation and use of amines. Bronchial washing looking for a PCP returns positive in one of three patients. The three patients died between D 13 and D 16 of intensive care unit . Bleomycin, seems to be the most likely responsible of these deaths. Mortality attributed to Bleomycin is very rare but should be avoided in this curable disease, It may be an early event at the beginning of chemotherapy, patients with unexplained fever with or not dyspnea should be followed with caution and bleomycine should be stopped in any suspicion of toxicity even with a normal chest X ray. Since 2009 in our department the maximal number of courses of ABVD is at 6 and further, we decided since the last case in 2012 to limited the dose of Bleomycin at 10 mg instead of 15 mg for patients with HL older than 60.

P080
ABVD THERAPY IN OLDER PATIENTS WITH HODGKIN LYMPHOMA: RESPONSE AND COMPLICATIONS

Johnston PB,[1] Yin J,[2] Micallef INM[1]

[1]Mayo Clinic, Rochester, MN, USA; [2]Yangzhou, China

There is no consensus as to the optimal treatment for elderly patients diagnosed with Hodgkin lymphoma. We conducted an IRB approved review of the medical records of all patients diagnosed with Hodgkin lymphoma age 60 and over between 1996 and 2007 at the Mayo Clinic in Rochester, Minnesota. Fifty patients were identified; the baseline characteristics, treatment plan, toxicity and response were examined. Thirty-five of these patients were treated with ABVD +/ involved-field radiotherapy. The median age of these patients was 69 (range 60-84). Sixty-nine percent of patients were stage III/IV. Complete and partial remission rates in patients treated with ABVD-based regimens were 69% and 17%, respectively. Three-year OS and PFS were 66% and 64% respectively. Lung toxicity was the most common toxicity and mortality due to presumed bleomycin-induced lung injury was up to 20%. Neutropenia grade 3/4, infection and neuropathy were also frequent complications (51%, 26% and 21% respectively). Cardiac toxicity only occurred in 11% of the ABVD treated patients. We conclude that elderly HL patients can have high response rates to ABVD-based regimens, but have a high incidence of pulmonary complications; therefore the selection of treatment should be individualized based on comorbidities.

P081
HODGKIN LYMPHOMA IN PATIENT WITH ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

Chernova NG, Sidorova JV, Margolin OV, Mariyin DS, Al-Radi LS, Moiseeva TN, Kovrigina AM, Kremenetskaya AM, Vorobiev AI, Kravchenko SK

Haematology Research Center, Moscow, Russia

Introduction. Patients with lymph id neoplasms have an increased risk of second tumors, including those of lymphoid origin. We present a case of Hodgkin lymphoma (HL) which developed in patient with angioimmunoblastic T-cell lymphoma (AITL). Case report. Female 63 years old was diagnosed with AITL IV stage Bb lymphoma in February 2008. She had enlarged lymph nodes, disseminate lung tumor lesions, hepatomegaly, splenomegaly, diffuse bone marrow involvement. The diagnosis of AITL was confirmed by lymph node biopsy where proliferation of small and middle-size lymphoid cells CD3+, D4+, CD5+, D43+, PD1+, CD10+, CD30- was found, with Ki-67 15-20%. There was a big amount of B-lymphocytes in the tumor microenvironment, expressing CD30+, EBV+, with marked proliferation of blood vessels. T-cells clonality due to the rearrangement of gamma-chain gene of T-cell receptor was detected in lymph node, blood and bone marrow. Chemotherapy with the addition of epigenetic agents has led to the disease stabilization–the symptoms of intoxication and lymph nodes enlargement have disappeared as well as lung's foci of tumor lesions, T-cell clonality in blood and bone marrow was not detected more. Nevertheless moderate splenomegaly up to 14-17 cm and lymphadenopathy sometimes was seen. Five years later B-symptoms have appeared again, and CT-scan detected multiple separate lesions in lungs with thoracic lymph node enlargement. Lung and lymph node biopsy in February 2013 revealed HL II type nodular sclerosis with a lot of Ridd-Stenberg cells showing CD15, CD30, CD20, PAX5, EBV. Both of T-clonality and B-clonality in lymph node and bone marrow were negative. The primary biopsys were revised and first diagnosis of AITL was confirmed by histomorphology and T-cell clonality, with no signs of HL. The patient successfully underwent ABVD chemotherapy with evidence of regression of tumor lesions in all area involved. Conclusion. In the case of detecting new tumor lesions the additional biopsies are required to avoid misdiagnosis, and sometimes to identify the second tumor. In this report the appearance of HL may be caused after the persistence of Epstein-Barr virus in lymphoid B-cells inf the microenvironment of the primary T-cell tumor.

Pathways

T082
DISRUPTION OF B CELL DIFFERENTIATION BY CONDITIONAL ACTIVATION OF THE HODGKIN LYMPHOMA-ASSOCIATED E2A ANTAGONISTS ID2 AND ABF1 *IN VIVO*

Janz M,[1,2] Li S,[1,2] Calado DP,[1] Mathas S,[1,2] Dörken B,[1,2] Rajewsky K[1]

[1]Hematology, Oncology and Tumorimmunology, Charité, University Hospital Berlin, Campus Virchow-Klinikum, Berlin, Germany; [2]Max Delbrück Center for Molecular Medicine, Berlin, Germany

Oncogenic transformation is not only characterized by enhanced proliferation and higher apoptosis resistance of malignant cells, but also by disruption of physiological differentiation. Among human lymphoid malignancies, classical Hodgkin lymphoma (cHL) constitutes one of the most prominent examples for this aspect of tumor biology. In contrast to their origin from germinal center (GC) or post-GC B cells, the malignant Hodgkin/Reed-Sternberg (HRS) cells of cHL have lost a considerable part of the B cell-specific gene expression program and show an upregulation of genes that are usually considered to be associated with other hematopoietic lineages. In previous work, we have shown that this phenotype is linked to an aberrant activity of the transcription factor E2A, which is functionally inhibited in HRS cells by overexpression of the helix-loop-helix (HLH) proteins ID2 and ABF1. To enable a detailed analysis of Id2- or Abf1-dependent effects on growth and differentiation of lymphoid cells in vivo, we have generated transgenic mice that allow for conditional activation of Id2 or Abf1 from the Rosa26 locus in a lineage- and stage-specific manner via cre-mediated recombination. Induction of Id2 and Abf1 in mb1-cre mice, which express cre in early stages of B cell differentiation, revealed a pronounced block of B cell development in the bone marrow. Analysis of C 1-cre; Rosa26 Id2stopFL and C 1-cre; Rosa26 Abf1stopFL mice, in which cre becomes active when B cells enter the GC reaction, demonstrated that both factors inhibit the GC response as well as the terminal differentiation towards plasma cells. Our experiments show that induction of Id2 and Abf1 results in disruption of the differentiation process of B cells, a feature which reflects a key aspect of cHL biology. These data support our hypothesis that the functional inhibition of E2A activity is a critical step in cHL pathogenesis.

T083
INTEGRATED GENOMIC ANALYSIS OF FLOW SORTED HODGKIN AND REED-STERNBERG CELL IN PRIMARY CALSSICAL HODGKIN LYMPHOMA

Reichel J,[1] Cesarman E,[1] Radaban R,[2] Elemento O,[3] Shaknovich R,[1] Roshal M[1]

[1]Department of Pathology and Laboratory Medicine, Weill-Cornell Medical College; [2]Department of Biomedical Informatics Center for Computational Biology and Bioinformatics Columbia University College of Physicians and Surgeons; [3]Department of Physiology and Biophysics Institute for Computational Biomedicine Weill Cornell Medical College, new York, NY, USA

Genomic studies of classical Hodgkin lymphoma (CHL) have been hampered by the difficulty of isolating purified Hodgkin and Reed-Sternberg (HRS) cell populations. Recent Introduction. of flow cytometric cell isolation has greatly eased the process allowing rapid isolation of thousands of viable HRS cells from primary CHL tumors. We have utilized the technique to produce what is to our knowledge the first integrated study of the whole exome, methylome and transcriptome sequencing of primary cases of Hodgkin Lymphoma. For exome sequencing we have developed a modified low input library generation procedure to obtain an average of approximately 30X sequence coverage of HRS, as well as tumor-infiltrating T cells (used as somatic control) from as low as 1000 sorted HRS cells. Using this techniques we perfomed whole exome sequencing of nine primary cases of CHL. We identified recurrent mutations in genes involved in mitotic checkpoint regulation, epigenetic regulation and immune evasion. In addition we performed high-resolution copy number variation analysis of the exome sequencing data and identified recurrent losses and gains of genes involved in B-cell maturation, transcriptional control, epigenetic regulation and immune evasion. We also performed whole transcriptome analysis of the HRS cells as well as tumor infiltrating B cells to confirm RNA expression level alteration of the genes affected by somatic mutations and copy number variations in HRS. These analyses also confirmed numerous reported transcription-level alterations obtained from previous studies using laser capture microdissected cells. Finally we utilized enhanced form of reduced representation bisulfite sequencing technology to obtain promoter methylation status of 14764 genes. The analysis revealed global promoter hypermethylation within isolated HRS cells compared to naïve, memory and centroblast B cell subsets suggesting key role of epigenetic regulation in CHL pathogenesis. The simultaneous analysis of exome, transcriptome and methylome on the flow-sorted HRS cells allows for expanded study of CHL pathogenesis, new target identification and potentially individualized approaches to CHL therapy.

T084
TCF3/E2A (19P13.3) IS A NOVEL HODGKIN LYMPHOMA SUSCEPTIBILITY LOCUS; A META-GWAS STUDY FROM THE INTERLYMPH HODGKIN LYMPHOMA CONSORTIUM

Van den Berg A[1] Cozen W*, Li D*, Timofeeva M*, Diepstra A*, Hazelet D*, Delahaye-Sourdeix M*, Edlund CK*, Rostgaard K, Van Den Berg DJ, Glaser SL, Robison LL, Mack TM, Ghesquieres H, Salle G, Bhatia S, Strong LC, Hwang AE, Nieters A, Smedby K, de Sanjose S, Cortessis VK, Lightfoot T, Roman E, Becker N, Foretova L, Benavente Y, Maynadie M, Visser L, Veenstra RN, Staines A, Cocco PL, Boffetta P, Kiemeney L, Lake A, Montgomery D, Slager SL, Cerhan JR, Gallagher A, Taylor GM, Brennan P, Conti DV[&] , Coetzee GA[&], Onel K[&], Jarrett RF[&], Hjalgrim H[&], McKay JD[&]

**Co-first authors, [&]Co-Last authors. Presented on behalf of the Hodgkin lymphoma working group of the InterLymph consortium. [1]Department of Pathology and Medical Biology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands*

Hodgkin lymphoma (HL) is known to have a strong genetic susceptibility component, with a highly increased risk in co-twins of patients. Currently reported GWAS's identified several HLA and non-HLA risk loci. In order to identify additional variants associated with HL, we performed a meta-analysis of three HL GWAS studies followed by a validation study. 1,810 cases and 7,879 controls, all of European descent, were included in the meta analysis. Promising variants were tested in an independent set of 1,163 cases and 2,580 controls. We noted strong associations in HLA, with 564 genetic variants presenting with P<10-4, and in non-HLA loci, *i.e.* REL, PVT1 and GATA3, consistent with previous publications. In addition, we identified a novel variant at 19p13.3 that was associated with risk of HL(rs1860661; odds ratio [OR]= 0.81, 95% confidence interval [95% CI]= 0.76-0.86, Pcombined = 3.5x10-10). This SNP is located in intron 2 of the TCF3/E2A gene, a key regulator of B-cell lineage commitment. In silico analysis indicates that rs1860661 is located in a genomic region with an open chromatin structure, active histone marks and a ZBTB7A/LRF transcription factor binding motif. The protective minor G allele maps to a ZBTB7A binding motif, which is disrupted by the major A allele. Two additional variants highly correlated with rs1860661, rs10413888 (r2=0.90) and rs8103453 (r2=0.89), are within an E2F1 and another ZBTB7A/LRF binding motif, respectively. Analysis of TCF3 expression levels in LCL cell lines of 31 genotyped individuals revealed a trend towards lower levels of expression for AA individuals, intermediate levels for AG individuals and the highest levels for GG individuals. This supports a direct functional and protective effect of the rs1860661 SNP by enhancing binding of ZBTB7A and as a result increasing TCF3/E2A expression levels. Thus, this meta-analysis identified a novel association with TCF3/E2A and supports previously reported susceptibility associations with SNPs in other HLA and non-HLA genes. Because the allele predicted to have enhanced TCF3/E2A expression is protective for HL, we suggest that TCF3/E2A functions as a tumor suppressor gene for HL, probably via promotion and/or maintenance of the B-cell phenotype.

T085
HODGKIN-REED-STERNBERG CELLS IN CLASSICAL HODGKIN LYMPHOMA SHOW ALTERATIONS OF GENES ENCODING THE NADPH OXIDASE COMPLEX AND IMPAIRED REACTIVE OXYGEN SPECIES SYNTHESIS CAPACITY

Giefing M,[1,7] Winoto-Morbach S,[2] Sosna J,[2] Döring C,[3] Klapper W,[4] Küppers R,[5] Böttcher S,[6] Adam D,[2] Siebert R,[1] Schütze S[2]

[1]Institute of Human Genetics, Christian-Albrechts University Kiel & Universi-

ty Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; [2]Institute of Immunology, Christian-Albrechts University Kiel & University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; [3]Senckenberg Institute of Pathology, University of Frankefurt, Medical School, Frankefurt, Germany; [4] Department of Pathology, Hematopathology Section and Lymph Node Registry, Kiel, Germany; [5]Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, Medical School, Essen, Germany; [6]Second Department of Medicine, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; [7]Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland

The membrane bound NADPH oxidase involved in the synthesis of reactive oxygen species (ROS) is a multi-protein enzyme encoded by CYBA, CYBB, NCF1, NCF2 and NCF4 genes. Besides its microbicidal function in phagocytes, growing evidence suggests a role of ROS in the modulation of signaling pathways of non-phagocytic cells, including differentiation and proliferation of B-cell progenitors. We have recently reported recurrent transcriptional downregulation of the CYBB gene in cell lines of the B-cell derived classical Hodgkin lymphoma (cHL). Thus, here we explored functional consequences of CYBB downregulation on the NADPH complex. To trigger superoxide anion production we stimulated the CD30 receptor in cHL and non-cHL cell lines. Using flow cytometry we quantified the superoxide anion synthesis and identified recurrent loss of superoxide anion production in all stimulated cHL cell lines in contrast to stimulated non-Hodgkin lymphoma cell lines. As CYBB loss proved to exert a deleterious effect on the NADPH oxidase complex in cHL cell lines, we analyzed the CYBB locus in Hodgkin and Reed-Sternberg (HRS) cells of primary cHL biopsies by in situ hybridisation and identified recurrent deletions of the gene in 8/18 cases. Moreover, by microarray profiling of cHL cell lines we identified additional alterations of NADPH oxidase genes including CYBA copy number loss in 3/7 cell lines and a significant loss of the NCF1 gene on mRNA level ($p=0.006$) compared to normal B-cell subsets. Besides, the NCF1 protein was significantly downregulated ($p<0.005$) in cHL compared to other lymphoma cell lines. Together these findings show recurrent alterations of the NADPH oxidase encoding genes that result in functional inactivation of the enzyme and loss of superoxide anion in cHL. In light of the induction of ROS by CD30 signaling in the CD30+cHL cell lines and the strong and constitutive CD30 expression in primary HRS cells, one may speculate that the inactivation of NADPH oxidase represents a strategy to escape from an overwhelming and toxic ROS production, that could otherwise impair HRS cell survival. Moreover, the loss of ROS signaling may potentially deregulate B-cell lineage development and contribute to the loss of B-cell phenotype of HRS cells.

P086
DOWNREGULATION OF FOXO1 PREVENTS INDUCTION OF THE TUMOR SUPPRESSOR PRDM1 IN CHL

Vogel MJ,[1] Xie L,[2] Guan H,[3] Kick A,[1] Brüderlein S,[4] Melo JV,[5] Tooze RM,[6] Ushmorov A,[1] Wirth T[1]

[1]Institute of Physiological Chemistry, University of Ulm, Ulm, Germany; [2]Cancer Center of Union Hospital, Tongji Medical College, HuaZhong University of Science and Technology, Wuhan, China; [3]Department of Orthopaedic Surgery, Tongji Hospital, Tongji Medical College, HuaZhong University of Science and Technology, Wuhan, China; [4]Institute of Pathology, University Medical Center Ulm, Ulm, Germany; [5]Department of Haematology, Centre for Cancer Biology, SA Pathology University of Adelaide, Adelaide, South Australia, Australia; [6]Section of Experimental Haematology, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom

In contrast to other B-cell lymphomas, Hodgkin and Reed-Sternberg (HRS) cells, the malignant cells of classical Hodgkin lymphoma (cHL), have mainly lost their B cell identity. Of note, HRS cells do not undergo plasma cell differentiation despite constitutive expression of NF- B, IRF4, and STAT3, which are known to induce the master regulator of plasma cell differentiation PRDM1. Still, PRDM1 levels remain low in HRS cells, yet for unknown reasons, thereby preventing terminal differentiation. Recently, we reported that the transcription factor FOXO1, indispensable for B cell development and differentiation, is downregulated in HRS cells whereas reactivation of FOXO1 results in growth arrest and apoptosis. In the present work we show that overexpression of FOXO1 reactivated expression of germinal center-specific genes including BCL6, BACH2, and AICDA in cHL cell lines. Surprisingly, FOXO1 induced also PRDM1, which has been shown to be a tumor suppressor in activated B-cell-like diffuse large B cell lymphoma. Overexpression of PRDM1 , the active isoform of PRDM1, strongly inhibited growth of cHL cell lines, whereas PRDM1 , the truncated isoform with impaired transrepressing activity, demonstrated weak or no growth-inhibitory activity. Antitumor effects of PRDM1 might at least partially be explained by repression of the protooncogene MYC. Searching for other mechanisms of PRDM1 down-regulation we found that its promoter was hypermethylated in two cHL cell lines. Further, our data indicate that constitutive expression of MYC might also contribute to PRDM1 repression in cHL. Interestingly, we found that the dominant-negative variant, PRDM1 , which is normally not detected in B cells, was upregulated in cHL cell lines. This might reduce DNA binding and decrease function of residual PRDM1 in cHL. Taken together, our data indicate that FOXO1 in cHL is essential for PRDM1 induction. In addition, we identified PRDM1 as a tumor suppressor in cHL.

P087
DEVELOPMENT OF AN ORIGINAL XENOGRAFT MODEL OF HUMAN HODGKIN LYMPHOMA: TOWARD A BETTER UNDERSTANDING OF THE PATHOLOGY AND THE DESIGN OF NEW THERAPIES

M'kacher R,[1] Frenzel M,[1] Corina C,[1] Bauchet A,[2] Leunen A,[1] Hempel W,[1] Jinckel S,[3] Girinsky T,[4] Carde P,[5] Boisgard R,[6] Plumio FF,[7] Sabatier L[1]

[1]Radiobiology and Oncology laboratory, CEA, iRCM; [2]Head of Platform for experimental pathology PathEX / CRC MIRCen / CEA-INSERM Fontenay aux roses France; [3]Institute of Human Genetics, University of Aarhus, Aarhus C, Denmark; [4]Department of Radiation Oncology, Institut Gustave Roussy,Villejuif, France; [5]Department of Medicine; Institut Gustave Roussy; Villejuif, France; [6]Laboratoire d'Imagerie Moléculaire Expérimentale Groupe d'Imagerie du petit animal CEA / DSV / I2BM / SHFJ / U1023 Orsay France; [7]Laboratoire des Cellules Souches Hématopoïétiques et Leucémiques, UMR967 INSERM, Universités Paris 7 et Paris 11, IRCM/CEA, Fontenay-aux-Roses, France

Hodgkin lymphoma (HL) is a malignancy of the immune system, characterized by poor growth in vitro and the lack of reliable animal models. Recently, the presence of clonotypic B cells in HL has been documented. However, the low frequency of these cells has precluded the generation of the disease when transplanted into immunodeficient mice. In this study, we have successfully determined the conditions for the in vitro amplification and characterisation of such cells and their transplantation into immunodeficient NOD-SCID-gammac-/- (NSG) mice. Using the Hodgkin cell lines L428 and KMH2, clonotypic B cells were isolated and amplified in semi-solid cultures. Such clones showed a very high cloning efficiency in comparison to the original total cell population (50% *vs* 2%) and increased proliferation. Higher signal intensity of CD15 and CD14 was observed in the clones compared to the cell lines. In addition, CD30 expression was observed in both the clones and HL cell lines. Cytogenetic characterization by M-FISH revealed a complex karyotype and the presence of small metaphases. This enrichment allowed the transplantation of these cells by the intravenous route (retro orbital sinus) into immune-deficient NSG mice. Four to eleven weeks later, regardless of the number of cells injected (106 to 103), an infiltration of tumor cells was observed, essentially in the lymph nodes, liver, bone marrow, and spleen. The tumor cells were identified based on the cell surface expression of CD30, CD15, CD14 and CD68 and DNA probes of alfa-satellite of human chromosomes. Significant infiltration of tumor cells (CD30+, CD15+, CD14+, CD68+ and alfa-satellite probes) resulting in major tumor masses was observed in the liver. Cell lines were re-established from xenografted tumors: they were of B-lymphoid origin and showed numerical and structural chromosomal aberrations similar to those of the original L428 cell line and small metaphases as observed. 2-[18F]-fluoro-2-deoxyglucose (FDG)-PET was used to monitor the reproducibility of the model. The establishment of this animal model of HL is a major advance, not only for understanding the pathology of this enigmatic disease, but also for the development of novel therapeutic strategies.

P088
SPECIFIC BIOENERGETIC ADAPTATION OF DISTINCT B-CELL LYMPHOMAS

Birkenmeier K,[1] Dröse S,[2] Wittig I,[2] Winkelmann R,[1] Barrera M,[3] Hartmann S,[1] Döring C,[1] Völkl L,[1] Wenz T,[4] Reichert AS,[3] Bereiter-Hahn J,[5] Brandt U,[2] Hansmann ML[1]

[1]Senckenberg Institute of Pathology, University Hospital of Frankfurt, Frankfurt am Main, Germany; [2]Centre of Biological Chemistry, and Centre for Membrane Proteomics, Molecular Bioenergetics Group, Medical School, Goethe-University, Frankfurt am Main, Germany; [3]Mitochondrial Biology, Frankfurt Institute for Molecular Life Sciences, and Mitochondrial Biology, Medical School, Goethe-University, Frankfurt am Main, Germany; [4]Institute for Genetics, University of Cologne, Germany; [5]Institute of Cellular Biology and Neuroscience, Goethe-University, Frankfurt am Main, Germany

While energy supply of solid tumors is believed to rely on anaerobic glycolysis (Warburg phenotype), the bioenergetic profile of lymphomas is poorly understood. B-cell lymphomas exhibit differences in invasiveness, cellular growth and the composition of the microenvironment. To gain insight into the adaptations associated with these fundamental differences we analyzed the bioenergetic profile of less invasive classical Hodgkin's lymphoma (cHL) usually representing rare tumor cells and Burkitt lymphoma (BL) characterized by rapid proliferation. We determined key metabolic genes by microarray, Western Blot and immunohistochemistry. We analyzed glycolysis (lactic acid production rate, glucose consumption, glycolytic flux), function and maximal capacity of the respiratory chain by oxygraphy and 2D gel electrophoresis, mitochondrial biogenesis and mitochondrial membrane potential by fluorescence microscopy. Both lymphomas were found, as compared to their precursor cells, to exhibit an energy metabolism dominated by oxidative phosphorylation (OXPHOS). Expression of numerous proteins involved in this pathway, respiration rates and respiratory control ratios were markedly increased in cHL and BL cells as compared to germinal centre B cells (10-15-fold increase). This phenotype was most prominent in cHL cells that in contrast to BL cells produced hardly any lactate that originates from glucose indicating suppression of anaerobic glycolysis. Functional studies even revealed that these cells in contrast to BL cells depend on OXPHOS for cell survival and proliferation. To establish the mechanism linking transforming events to metabolic phenotypes, we investigated how oncogenes contribute to the described phenotypes. Inhibition of Myc, which plays a pivotal role in BL, reduced lactate production and mitochondrial biogenesis in these cells, but did not significantly change these parameters in cHL. NFkappaB is probably an important driver in regulating energy conversion in cHL by promoting OXPHOS because its inhibition reduced respiration rates and led to an increase in lactate production rates. NFkappaB therefore seems to inhibit development of the Warburg phenotype promoting a switch towards a more oxidative metabolism in cHL. We propose that the specific adaptation of both lymphomas is directly linked to the microenvironment and characteristic growth behavior of the tumor cells. This may provide important clues to tailor optimal treatment strategies.

P089
GENOMIC ANALYSIS OF SERIAL HODGKIN LYMPHOMA SAMPLES REVEALS DRIVER MUTATED GENES

Martin-Moreno AM,[1] Mata E,[1] Montalban C,[1] Piris AM,[2] Garcia JF[1]

[1]MD Anderson Cancer Center Madrid, Spain; [2]Hospital Universitario Marques de Valdecilla, Santander, Spain.

Background. Classical Hodgkin s lymphoma (cHL) is the most common type of lymphoma in young people, it s a clonal proliferation of the characteristic Hodgkin Reed Sternberg cells (HRS), diluted in a reactive inflammatory background. (made up of a predominant TH2 microenvironment) with a defective B cell immunophenotype. Few studies have been conducted in order to identify which are the driver mutations in this disease, and only occasional mutations in members of the NF-kappaB and JAK/STAT pathways have been described. Material and Methods. we present the genomic clonal evolution of a single cHL tumor using massive parallel sequencing. A 25 years old male diagnosed of a nodular sclerosis cHL, stage IIB, reached complete remission after ABVD treatment, but developed several relapses that were treated with different savage regimens, including SGN-35 and autologous bone marrow transplant. We used Sureselect Target Enrichment system (including 519 selected genes) and Illumina sequencing using germline DNA (from oral mucosa) and tumor samples (frozen tissue) at diagnosis and after the third relapse. To increase coverage we perform a tumor cell enrichment process using anti-CD30 linked magnetic beads. Data analysis, comparison with germline sequences, and SNPs filtering, were performed using the RAMSES algorithm. Results. We found about 120 gene mutations in each sample, most of them (~60%) missense type, reflecting a high level of genomic instability in the neoplasm. In the original lesion we identified 50% transitions and transversions, in contrast the relapsed samples in which transitions represents about 90%. Mutations in some genes previously described in large B-cell lymphomas were consistently found (CARD11, STAT6, CSF3R, MAP3K6 and BCL6), probably representing driver mutations, as well as in other not previously described new genes. Some identified mutations at diagnosis were not present at relapse, and viceversa, probably related with microclonal dynamics. Conclusions. cHL is characterized by high genomic instability, including numerous mutations in genes related with B-cell differentiation. Driver as well as passenger mutations can be associated with clonal evolution and selected by therapy.

P090
THE NOVEL SECOND GENERATION PROTEASOME INHIBITOR MLN9708 IN HODGKIN LYMPHOMA (HL) AND T-CELL LYMPHOMA (TCL): INDUCTION OF POTENT CELL DEATH THROUGH REDOX, MAPK, AND AUTOPHAGIC-DEPENDENT MECHANISMS IN CELL LINES AND HUMAN LYMPHOMA XENOGRAFT MODELS

Dashnamoorthy R,[1]Kandela I,[2] Bhalla S,[3] Zaretsky I,[4] Galloway J,[4] Mazar A,[5] Evens AM[1]

[1]Tufts University School of Medicine, Boston, MA, USA; [2]Northwestern University, Evanston, IL, USA; [3]Northwestern University Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA; [4]The University of Massachusetts Medical School, Worcester, MA, USA; [5] Chemistry of Life Processes Institute, Northwestern University, Evanston, IL, USA

Background. MLN9708 is a novel second generation proteasome inhibitor with significant anti-neoplastic activity. Methods. We investigated the preclinical therapeutic efficacy of MLN9708 in HL and TCL cells through in vitro and in vivo xenograft tumor models and examined the associated cellular and molecular mechanisms of action. Results. MLN9708 resulted in time- and dose-dependent cytotoxicity in all cell lines (MTT), with IC(50) values of 38nM, 52nM, and 41nM for Jurkat, Hut78, and HH respectively, and 117nM and 39nM for L428 and L540, respectively.

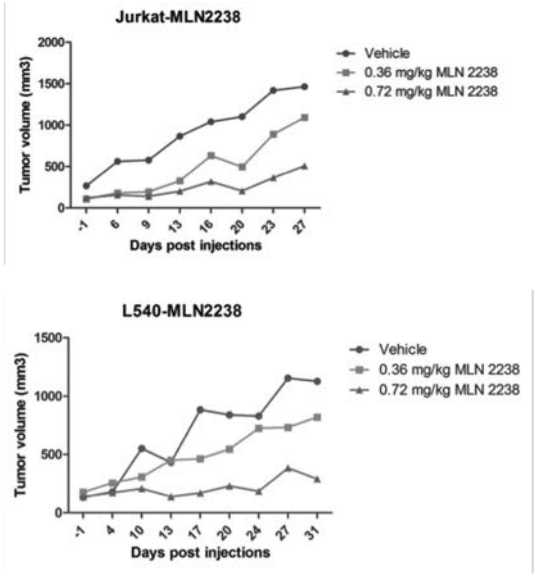

Figure 1.

Treatment with MLN9708 resulted in dose-dependent increases in apoptosis by Annexin-V/PI, PARP cleavage, and activation of caspases 3, 8, 9 in all cell lines. Furthermore, these effects were superior compared with bortezomib treatment.Using CellROX-Red FACS analysis, MLN9708 resulted in increased intracellular oxidative stress. Moreover, MLN9708 resulted in increased p21 expression, degradation of MYC protein, and accumulation of LC3A (autophagy). Apoptosis, oxidative stress, and MYC degradation were abrogated in the presence of N-acetylcysteine, however LC3A accumulation occurred in a redox-independent manner. Further, spautin (a potent inhibitor of autophagy) significantly reduced MLN9708-related cell death. Examination of MAPK signaling showed that p-ERK and p-p38 were downreglated and p-JNK unregulated in HL cells with MLN9708; these findings were opposite in TCL lines. In TCL, shRNA knock-down of ERK and p38 had minimal effect on MLN9708-induced apoptosis, while there was additive cell death with JNK shRNA. In HL, ERK and JNK shRNA knock-outs abrogated the effect of MLN9708, while the cytotoxic effect was potentiated with p38 shRNA knock-out. Finally, MLN9708 resulted in significant tumor/growth inhibition (P<0.001) and improvement in survival (P<0.001) compared with controls in Jurkat and L540-derived SCID xenograft models (Figure). Conclusions. Altogether, the novel proteasome inhibitor, MLN9708, induced potent cell death at clinically achievable concentrations in HL and TCL cell lines and in SCID xenograft models. MLN9708 down-regulated MYC and induced redox-dependent cell death through autophagy in HL and TCL. Further, the cytotoxic effect of MLN9708 was potentiated through JNK in TCL and p38 in HL. Continued examination of this novel agent alone and in rational combinations in HL and TCL is warranted.

P091
GENOME-WIDE ASSOCIATION STUDY IDENTIFIES GERMLINE POLYMORPHISMS ASSOCIATED WITH AGGRESSIVE DISEASE AND TREATMENT RESPONSE OF HODGKIN LYMPHOMA

Yang JJ, Lim J, Shi L, Pounds S, Wu J, Hudson MM, Metzger ML

St Jude Children's Research Hospital, Memphis, TN, USA

Background. and Aim. Although Hodgkin lymphoma (HL) is highly curable, its pathogenesis is poorly understood and biological determinants of treatment response are largely uncharacterized. Tumor microenvironment strongly influences HL prognosis, suggesting a critical role of inherited (germline) genetic variations in anti-tumor drug sensitivity. We performed a pharmacogenomic study to identify germline genetic polymorphisms associated with treatment failure and/or aggressive HL, with the aim to discover genetic markers for individualized therapy to minimize toxicity and to further improve survival. Methods. Germline DNA was extracted from 224 patients with newly-diagnosed HL treated on frontline protocols (or according to guidelines) between 2000 and 2010 at St. Jude Children's Research Hospital. Genotyping was performed using Illumina HumanExome Beadchip for 247,870 polymorphisms. We evaluated the associations of germline polymorphisms with previous exposure to Epstein-Barr virus (EBV), tumor EBV status, B-symptoms at diagnosis, early response to therapy and relapse. Results. Complete response by PET/CT after 2 cycles was achived by 28% of patients, and 20% (44 out of 224) relapsed. In the genome-wide association study, we identified 509 SNPs associated with risk of relapse (P<0.01) and 648 SNPs related to early treatment response (P<0.01), 9 of which were concordantly significant for both phenotypes. Genetic variants influencing treatment response were particularly enriched in the D-glutamine/glutamate metabolism and focal adhesion pathways (P<0.01), including direct molecular targets of chemotherapeutic agents commonly used in HL therapy. Genotype at 579 SNPs were significantly different between patients with B-symptoms *vs* without, and the strongest association was observed in genes involved in cell adhesion. Finally, within 142 patients with prior EBV exposure, 613 SNPs were associated with tumor EBV status (P<0.01). Conclusion. Taking a genome-wide approach, we have identified germline genetic variants associated with aggressive disease and/or treatment outcome of HL. These findings revealed novel biology of HL and potential novel prognostic markers, warranting further validation and functional studies.

P092
THE IMPACT OF THE GSTP1 A313G POLYMORPHISM ON CLINICAL OUTCOME IN HODGKIN'S LYMPHOMA PATIENTS

Kryachok I, Khranovska N, Svergun N, Novosad O, Titorenko I

National Cancer Institute, Kiev, Ukraine

Introduction. Hodgkin lymphoma (HL) is a highly curable malignancy, but treatment outcome might be influenced by inherited gene polymorphisms determining anticancer agent metabolism.We assessed the impact of the GSTP1 A313G polymorphism on clinical outcome in patients with HL. Material and Methods. The case group comprised 202 patients with HL (stages: IA-IIA–68, IIB–43, III-IV–91; median age: 32 years, range: 17-66) treated at National Cancer Institute from 2008 to 2012. Anthracycline-based chemotherapy: ABVD or BEACOPP (14/esc) were administered as a first-line therapy. Radiotherapy was used to treat residual masses of bulky disease for III–IV and all involved areas for IIA–IIBstages. The treatment efficacy was estimated according to the Cheson criteria. The polymorphicvariants of GSTP1 gene were analyzed by Allelic Discrimination Real-Time PCR using TaqMan MGB probes. Results. The distribution of GSTP1 genotypes was consistent with Hardy-Weinberg equilibrium in the control cohort (2=0.59, p=0.44) as well as in the HL patients' cohort (2=0.05, p=0.82).For 202 patients the OR rate after the first-line therapy was 94.6% with a CR of 75.7% and a PR– 17.8%. Response rate didn't differ significantly among GSTP1 genotypes. Disease progression during the therapy was observed in 6.5% of the patients with GSTP1AA genotype and 5.7% of AG genotype, while it wasn't noticed for the GG genotype. Among the patients who achieved CR, during the followup period 33(21.6%) had relapses: 26.1% of patients with AA genotype, 19.4%–AG; 11.8%–GG (p<0.05). Median time to relapse was 14.2 months for AA genotype, 17.4–for AG, 22–for GG (p<0.05). 3-year OS for patients with GG genotype of GSTP1 geneis 100%, for patients with AG genotype –92.2%, and for patients with AA genotype–88.2% (p<0.05). The Cox multivariate analysis showed that GSTP1 A313G polymorphism was an independent prognostic factor. Conclusions.The GSTP1 A313G polymorphismcanpredict clinical outcome in patientswith HL and seems to be promising for the future studies.

P093
DRUG RE-PROFILING IN HODGKIN'S LYMPHOMA IDENTIFIES MONOAMINE OXIDASE OVER-EXPRESSION AS A POTENTIAL THERAPEUTIC TARGET

Fairbanks JY, Nagy E, Khanim F, Wei W, Lu X, Bunce C, Drayson M, Murray PG

University of Birmingham, UK

Drug re-profiling, which is quicker and less expensive than traditional drug development, has already proved to be successful, for example, in the redeployment of thalidomide for the treatment of patients with multiple myeloma. We have investigated the influence on the viability of Hodgkin's lymphoma cell lines, of 97 approved off-patent drugs when used at their clinically relevant peak serum concentrations. Seven drugs; colchicine, zinc acetate, selegiline hydrochloride, methotrexate, mebendazole, desferrioxamine mesilate and niclosamide significantly decreased the viability of HL cell lines. We focused on selegiline hydrochloride, which inhibits monoamine oxidase A (MAOA) at concentrations used to treat depression. MAOA is a mitochondrial membrane enzyme that catalyses the oxidative deamination of biogenic amines. MAOA may contribute to cancer as the deaminated products of MAOA activity have been shown to promote cellular proliferation and to inhibit apoptosis. Re-analysis of two published microarray datasets revealed that MAOA is over-expressed in micro-dissected primary Hodgkin Reed Sternberg cells, but not in Burkitt's lymphoma, follicular lymphoma or diffuse large B cell lymphomas. These observations identify a potentially important novel pathway contributing to HL survival. We are currently investigating how the over-expression of MAOA confers sensitivity to selegiline hydrochloride induced cell death in HL cells.

P094
MECHANISMS OF THE "DEDIFFERENTIATION" OF THE HRS CELLS IN CLASSICAL HODGKIN LYMPHOMA

Schneider M,[1] Bräuninger A,[2] Hansmann ML,[3] Küppers R[1]

[1]Institute of Cell Biology (Cancer Research), Faculty of Medicine, University of Duisburg-Essen, Essen, Germany; [2]University of Giessen, Institute of Pathology, Giessen, Germany; [3]Senckenberg Institute of Pathology, University of Frankfurt, Frankfurt am Main, Germany

Although Hodgkin and Reed-Sternberg (HRS) cells in classical Hodgkin lymphoma (cHL) are derived from preapoptotic germinal center (GC) B cells, they have lost their B cell phenotype and aberrantly express markers and transcription regulators normally restricted to other hematopoietic lineages. This "dedifferentiation" or "reprogramming" of HRS cells is likely of key importance for cHL pathogenesis. In recent years several factors contributing to the dramatic dedifferentiation of HRS cells have been identified, including NOTCH1, which is involved in T cell fate, and MSC and ID2, which both inhibit B cell differentiation. We used gene expression profiles from HRS and GC B cells to identify aberrantly expressed transcription factors that might further contribute to the cellular "dedifferentiation" of HRS cells. Compared with GC B cells CEBPB expression was elevated in HRS cells. CEBPB is a transcription factor involved in the differentiation of myeloid cells. After confirming CEBPB expression in primary cases and cHL cell lines either via immunohistochemistry or Western blot, lentiviral-mediated knockdown of CEBPB was performed in cHL cell lines. Analyses of the consequences of this knockdown are ongoing. A second transcription factor we are interested in is MYC, a well-known oncogene with diverse functions. In the gene expression profiles MYC was found to be elevated in a subset of primary cases but MYC signatures, defined by elevated levels of MYC target genes, were found in all primary cHL cases. Western blot and real-time PCRs showed MYC expression in cHL cell lines and therefore we now plan to perform lentiviral-mediated knockdown of MYC in cHL cell lines and subsequent analysis of cell phenotype, cell survival and proliferation.

P095
MODELLING OF HLA ASSOCIATIONS IN EBV-POSITIVE AND -NEGATIVE CLASSICAL HODGKIN LYMPHOMA SUGGESTS DISTINCT MECHANISMS IN DISEASE PATHOGENESIS

Johnson PCD,[1] McAulay KA,[2] Montgomery D,[2] Lake A,[2] Gallagher A,[2] Taylor GM,[3] Jarrett RF[2]

[1]Institute of Biodiversity, Animal Health and Comparative Medicine, University of Glasgow, Glasgow, UK; [2]MRC-University of Glasgow Centre for Virus Research, Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK; [3]School of Cancer Sciences, University of Manchester, St Mary's Hospital, Manchester, UK

HLA genotyping and genome wide association studies provide evidence for associations between HLA alleles and risk of classical Hodgkin lymphoma (cHL). Increased and decreased risks of EBV-positive cHL (EBV+veHL) are associated with HLA-A*01:01 and HLA-A*02:01, respectively, and risk of EBV-negative cHL (EBV-veHL) is associated with HLA-DR alleles. To further study these associations, we typed HLA-A, B, C and DR genes in 469 cHL cases and 311 controls, and DQA1, DQB1 and DPB1 genes in 246 cases and 305 controls; 31% of cases had EBV+veHL. SNP genotyping Results. for rs6903608 (associated with EBV-veHL) and rs2248462 and rs2395185 (associated with both EBV+veHL and EBV-veHL) were available for all subjects. To identify the HLA alleles that best predict outcome in analyses of cases versus controls, EBV+veHL versus controls and EBV-veHL versus controls, a Bayesian variable selection approach was used. In case versus control analyses, increased risk was associated with HLA-DRB1*03:01 and HLA-DRB1*15:01 whereas HLA-DRB1*07:01, HLA-DRB1*04:01 and HLA-DPB1*01:01 were associated with protection. Following inclusion of SNPs, rs6903608, HLA-DRB1*03:01, HLA-DPB1*01:01 and HLA-DQB1*03:03 were selected in the model. In analyses of EBV+veHL versus controls, HLA-A*01:01, HLA-B*37:01, and HLA-DRB1*03:01 were associated with increased risk and HLA-DRB1*15:01 and HLA-DPB1*01:01 with protection; none of the SNPs was selected in this model. In analyses of EBV-veHL versus controls, HLA-DRB1*07:01 was associated with decreased risk and HLA-DQB1*06:02 (in linkage disequilibrium with HLA-DRB1*15:01) with increased risk. Following inclusion of SNPs, rs6903608 was selected in the model and neither HLA-DRB1*15:01 nor HLA-DQB1*06:02 was included; HLA-DRB1*03:01, HLA-DQB1*03:03 and HLA-B*15:01 were associated with increased disease risk. These analyses confirm that HLA associations with EBV-veHL and EBV+veHL are largely distinct but identify HLA-DRB1*03:01 as a risk allele for both disease subgroups. HLA-DRB1*15:01 and HLA-DPB1*01:01 are identified as alleles associated with protection from EBV+veHL. In EBV-veHL, the HLA class II SNP rs6903608 is the strongest predictor of outcome, strongly suggesting that additional HLA genes, not included in this analysis, play a critical role in modifying risk of this disease.

P096
STUDIES ON THE SIGNAL TRANSDUCTION PATHWAY INVOLVED IN LEUKOTRIENE D4-INDUCED RELEASE OF CYTOKINES FROM THE HODGKIN LYMPHOMA CELL LINE L1236

Han H,[1] Xue-Franzén Y,[2] Nagy E,[3] Xu D,[1] Sjöberg J,[1] Björkholm M,[1] Claesson HE[1]

[1]Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm; [2]Department of Laboratory Medicine, Karolinska Institutet, Stockholm; [3]Department of Medicine, KI, Department of Cardiology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden

Classical Hodgkin lymphoma (cHL) is characterized by a minority of malignant Hodgkin Reed-Sternberg (H-RS) cells interspersed among an abundant infiltrate of inflammatory cells. Our previous study demonstrated that leukotriene (LT) C4 and its metabolite LTD4, produced by infiltrating eosinophils, macrophages and mast cells, can induce the release of TNF-α, IL-6 and IL-8 from the HL derived cell line L1236. To delineate the LTD4-induced pathways, which mediate the cytokine induction, we stimulated L1236 cells with LTD4 and determined the expression of early regulated genes by microarray analysis. Stringent filters yielded 17 induced and 19 down-regulated genes (≥2-fold). We focused our study on five top up-regulated genes: early growth response 1, EGR; NGFI-A binding proteins member 2, NAB2; steroid-thyroid hormone-retinoid receptor Nuclear Receptor Subfamily 4 Group A Member 3, NR4A3; FOS protein B, FOSB and Tribbles homolog 1, TRIB1. These five genes were stimulated by LTD4 treatment in a time- and dose-dependent manner. The effect of LTD4 on the expression of early genes was blocked by zafirlukast, which is a specific cysteinyl-leukotriene receptor type1 antagonist. Furthermore, the inhibitory action of zafirlukast on LTD4-induced expression of EGR1 was also confirmed at the protein level. In essence, this study indicates that EGR1 and certain other early genes are involved in the signal transduction pathway leading to LTD4-induced release of TNF-α, IL-6, and IL-8 in L1236 cells. In summary, this presentation describes novel biochemical signal transduction pathways operating in H-RS cells and reveals the potential clinical effect of zafirlukast in the treatment of HL.

P097
HLA CLASS II ALLELES ARE ASSOCIATED WITH TUMOR CELL HLA CLASS II EXPRESSION IN CLASSICAL HODGKIN LYMPHOMA

Kushekhar K[1] Nolte I,[2] Hepkema B,[3] Veenstra R,[1] Poppema S,[1] Visser L,[1] Diepstra A,[1] van den Berg A[1]

[1]Department of Pathology and Medical Biology; [2]Department of Epidemiology; [3]Department of Laboratory Medicine, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands

Introduction. Hodgkin tumor cells adopt several mechanisms to evade an effective anti-tumor immune response, including downregulation of membranous HLA class I and II expression. In a previous study we showed that downregulation of HLA class II is an independent adverse prognostic factor in cHL. The aim of this study is to determine whether retention or downregulation of HLA class II expression is associated with certain HLA alleles. Methods. Immunohistochemistry for HLA class II using a mouse anti-HLA-DR, DP, DQ antibody was performed on 239 cHL cases. Clear membrane staining on the majority of tumor cells was scored as positive and no staining or cytoplasmic staining was scored negative. Infiltrating cells served as internal positive controls. A PCR-SSOP approach was used to define the HLA genotype. Control HLA typing data (HLA-A, B, DRB1) was obtained from >5,000 healthy

blood donors. HLA allele frequencies were compared between HLA class II positive, negative cHL patients and controls using Chi-square tests and p<0.001 (to correct for multiple testing) was considered significant. In addition, 1394 HLA SNPs were compared between HLA class II positive and negative cases using Chi-square tests at p<0.0001. Results. Downregulation of HLA class II was observed in 40% of the cHL cases and was independent of EBV status. The HLA-DRB1*07 allele frequency was significantly decreased in HLA class II positive cHL compared to controls (3.5% *vs* 10.1%, p=0.00027). HLA-DRB1*02 (23% *vs* 16.4%, p=0.002), HLA-A*11 (9.1% *vs* 4.9%, p=0.001) and HLA-A*28 (7.7% *vs* 4.1%, p=0.002) allele frequencies were borderline significantly increased in HLA class II positive cHL compared to controls. No significant differences were found between HLA class II negative and controls and between HLA class II positive and negative groups. Frequencies of the T-allele of rs2517448 (OR=2.3, p=0.00009) and the A-allele of rs6457327 (OR=2.3, p=0.00009) were significantly increased in the HLA class II positive compared to HLA class II negative group. Conclusion The decreased frequency of HLA-DRB1*07 in HLA class II positive cases indicates that HLA-DR*07 reduces the risk of HLA class II positive cHL, and hence suggests that presence of HLA-DRB1*07 is unfavorable for tumor cell survival.

P098
PROCALCITONIN (PCT) LEVELS IN NEWLY DIAGNOSED PATIENTS WITH HODGKIN LYMPHOMA (HL) PRESENTING WITH FEVER AND/OR ELEVATED C-REACTIVE PROTEIN (CRP)

Vassilakopoulos TP,[1] Zografos E,[1] Petevi K,[1] Boutsikas G,[1] Kanellopoulos A,[1] Hillas G,[1] Dimou M,[2] Gainaru G,[1] Papageorgiou L,[1] Sinni E,[1] Kyrtsonis MC,[2] Pappi V,[1] Tsopra O,[1] Tzenou T,[2] Efthymiou A,[2] Vardounioti I,[2] Pessach E,[2] Flevari P,[1] Telonis V,[1] Koutsi K,[1] Zannou A,[1] Papakostas V,[1] Tsaftaridis P,[1] Plata E,[1] Panayiotidis P,[2] Beris PH,[1] Angelopoulou MK,[1] Meletis J[1]

[1]Department of Haematology, National and Kapodistrian University of Athens; [2]1st Propedeutic Department of Internal Medicine, National and Kapodistrian University of Athens, Greece

Background. CRP is elevated in 70-75% of HL patients. It is usually increased in patients with fever and/or other B-symptoms, in which the presence of infection must be ruled out. PCT levels, potentially useful for this purpose, have not been studied in HL. Aims: To assess PCT levels in patients with HL at diagnosis in correlation with inflammatory biomarkers. Methods. PCT levels were determined in 77 patients with "inflammatory activity" at diagnosis (fever and/or elevated CRP >5 mg/L). PCT >0.5 ng/ml was considered to be abnormal. Patients with normal PCT were divided into those with undetectable PCT (<0.1ng/ml) and those with measurable PCT (0.1-0.5 ng/ml). Results. 5/77 patients had abnormal or measurable PCT levels in the setting of bacteriemia or infection respectively. Thus, the analysis was restricted to the 72 patients with no evidence of infection [median age 32 years (16-82), 53% males, 47% stage III/IV, median CRP 46.9 mg/L (5.46-305.0), CRP ≥100 mg/L in 22%]: Elevated PCT was found in 1/72 patients and returned to normal one week after start of chemotherapy. 53/72 patients (74%) had undetectable PCT and 18/72 (25%) exhibited measurable but normal PCT. An association between PCT and CRP was observed: The median CRP of patients with undetectable PCT was 36.2 mg/L versus 105.0 mg/L in those with measurable but normal PCT (p=0.001). CRP correlated with ESR, ferritin, haptoglobin and a2-globulins (cc=0.653-0.804, p<0.001), platelets (cc=0.388, p=0.001) and gamma-globulins (cc=0.363, p=0.003). Instead, PCT levels correlated only with ESR (cc=0.429, p<0.001), a2-globulins (cc=0.339, p=0.006), haptoglobin (cc=0.349, p=0.005) and ferritin (cc=0.294, p=0.02). Prognosis did not differ according to PCT levels: The 2-year Tumor Control was 80% versus 83% for patients with undetectable and measurable levels respectively (p=0.84). Conclusions. PCT is normal in ~99% of patients with newly diagnosed HL with elevated CRP and/or fever without demonstrable infection. The association between PCT and CRP suggests a common cytokine-regulated pathway for their production. However, the development of abnormal PCT levels occurs only in the case of infection. These observations support the use of PCT as a marker for the exclusion of infection in newly diagnosed patients with HL.

P099
CLASSICAL HODGKIN LYMPHOMA AND HHV-6: A REINVESTIGATION OF A CAUSAL ASSOCIATION

Bell AJ, Gallagher A, Gatherer D, Jarrett RF

MRC-University of Glasgow Centre for Virus Research, College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow, UK

A proportion of cases of classical Hodgkin lymphoma (cHL) are causally associated with the Epstein-Barr virus (EBV) but the aetiology of EBV-negative cHL cases is poorly understood. Epidemiological studies suggest that delayed exposure to a common infectious agent(s) may be involved in these cases. We have previously shown that HHV-6 antibody titres are higher in cHL cases compared to controls, particularly in EBV-negative cases. Studies investigating HHV-6 in biopsy material have produced conflicting results but two recent studies have suggested that HRS cells harbour HHV-6. In complete transcriptome analysis of enriched HRS cells from three cases of cHL, we detected HHV-6 transcripts in one EBV-negative case. Analysis of sequence reads suggested a lytic rather than latent infection. We therefore initiated a further analysis of the association between HHV-6 and cHL to determine the frequency of HHV-6 detection in cHL and the cellular localisation of the HHV-6 sequences. HHV-6B, but not A, pol gene sequences were detected in 39/67 (58.2%) of cHL biopsies but in only 1/21 reactive nodes. EBV-negative cHL cases were more likely to be HHV-6B-positive than EBV-positive cases but differences were not statistically significant (p=0.11). Viral loads in biopsies were generally low. Immunohistochemistry using the HHV-6 p41 antibody revealed only non-specific staining. HHV-6 is able to integrate into chromosomal DNA and is present n the germ-line of 0.5-2% of the general UK population. To determine whether germ-line transmitted HHV-6 (gtHHV-6) is associated with cHL we screened 955 cHL cases and 631 controls with a duplex TaqMan® assay. We identified 16 (1.7%) cases of gtHHV-6 in the cHL group and 10 (1.6%) in the control group (p = 0.889) suggesting that gtHHV-6 is not associated with the development of cHL. In conclusion, this study suggests that HHV-6 is unlikely to have a direct role in the pathogenesis of cHL, but the association requires further detailed investigation.

P100
METABOLITES OF ARACHIDONIC ACID ARE INVOLVED IN THE PATHOPHYSIOLOGY OF HODGKIN LYMPHOMA

Sjöberg J, Han H, Liu C, Xu D, Björkholm M, Claesson HE

Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden

Arachidonic acid can be metabolized to prostaglandins, leukotrienes and other related biological mediators. The metabolites formed in the arachidonic acid cascade are all more or less proinflammatory mediators and these metabolites play an important role in various signal transduction pathways. We have identified the enzyme 15-lipoxygenase (15-LO) in both the Hodgkin lymphoma (HL) derived cell line L1236 and in Hodgkin and Reed/Sternberg (H-RS) cells in 85% of the biopsies from HL patients. The enzyme 15-LO can catalyze the conversion of arachidonic acid to 15-hydroxy-eicosatetraenoic acid (15-HETE) and eoxins (see figure below) which are all proinflammatory mediators.

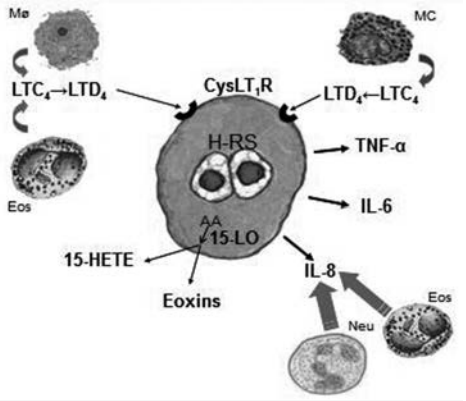

Figure 1.

Thus, the 15-LO pathway may contribute to the characteristic inflammatory features of HL. H-RS cells express also the high-affinity receptor for cysteinyl-containing leukotrienes, named CysLT1. Both HL cell lines and primary biopsies from HL patients express this receptor. Leukotriene D4 stimulated the release of tumor necrosis factor- , interleukin-6 and interleukin-8 from the HL cell line L1236 (see figure). Furthermore, the HL microenvironment contains eosinophils, mast cells and macrophages. All these cells can both produce and respond to cysteinyl-containing leukotrienes. Thus, blocking the CysLT1 receptor might have an impact on the function of H-RS cells and cells in the microenvironment. Montelukast is a potent CysLT1 antagonist which is used for treatment of asthma. In summary, this presentation describes novel biochemical signal transduction pathways operating in H-RS cells and reveals the potential clinical effect of montelukast in the treatment of HL. AA, arachidonic acid; LT, leukotriene; CysLT1R, receptor for LTC4 and LTD4; 15-LO, 15-lipoxygenase

P101
THE ROLE OF MICRORNA IN HODGKIN LYMPHOMA

Schmidt A,[1] Döring C,[2] Hansmann ML,[2] Küppers R[1]

[1]Institute of Cell Biology, Medical School Essen, Dpt. of Molecular Genetics; [2] Senckenberg Institute of Pathology, Medical School, Frankfurt/Main, Germany

Hodgkin lymphoma (HL) is characterized by the rare occurrence of malignant Hodgkin/Reed-Sternberg (HRS) cells in an inflammatory tumor microenvironment. The scarcity of HRS cells has hampered their molecular analysis. In this study, a protocol for microRNA (miRNA) profiling of HRS cells microdissected from paraffin-embedded lymph node biopsies was established. We investigated 22 patient samples from different HL subtypes, among them CD20- nodular sclerosis (NS), CD20+ nodular sclerosis (NS CD20+), mixed cellularity (MC) and nodular lymphocyte predominant (LP) HL. Expression of 360 miRNAs was determined and compared to that of germinal center (GC) B cells purified from human tonsils. Unsupervised clustering analyses revealed significantly different miRNA expression patterns not only of HL and GC B cell samples but also of different HL subtypes. An HL-specific 5-miRNA-signature could be identified, with 3 miRNAs being up- and 2 miRNAs being downregulated in all HL samples and cell lines compared to GC B cells. Functional analyses in HL cell lines with two promising miRNA candidates being upregulated in HRS cells versus normal GC B cells are currently underway. Preliminary data indicate that downregulation of these miRNAs indeed influences activity of signaling pathways and survival in HL.

P102
TREATMENT PATHWAYS AND RESOURCE USE ASSOCIATED WITH THE MANAGEMENT OF RECURRENT HODGKIN LYMPHOMA AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION

Radford J,[1] Johnson R,[2] Mckay P,[3] Malladi R,[4] Peggs K,[5] Sureda A,[6] Bloor A,[7] Kerrigan M,[8] Ralston S,[9] Cooper S,[10] Uden R,[11] Christensen K[12]

[1]The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [2]The Leeds Teaching Hospitals NHS Trust, Leeds, UK; [3]The Beatson West of Scotland Cancer Centre, Glasgow, UK; [4].University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [5]University College London Hospitals, London, UK; [6]Addenbrookes Hospital, Cambridge, UK; [7]The Christie NHS Foundation Trust, Manchester, UK, [8]PHMR Associates, London, UK; [9]PHMR Associates, London, UK; [10]pH Associates, Marlow, UK; [11]pH Associates, Marlow, UK; [12]Takeda Pharmaceuticals International GmbH

Introduction. Recurrence of Hodgkin lymphoma (HL) occurs in approximately 50% of patients after autologous stem cell transplantation (ASCT). This retrospective, observational study describes treatment pathways and resource use at 5 UK Centres in patients with HL who relapse after ASCT. Methods Patients aged ≥16 years with HL who received ASCT January 2005 to December 2009 and subsequently developed recurrence were identified from hospital records at the 5 Centres. Summary data pre-ASCT and detailed data post-ASCT were collected from recurrence to death or until end December 2012. Incomplete medical records were not excluded. Costs were taken from nationally published sources and applied to the resource use data to derive estimates of overall financial costs of treatment. Results. 40 patients (22 males, 18 females; mean age at ASCT 33, range 17-71) were included. Median time to recurrence post-ASCT was 6 months (range 0.23–65 months). Following recurrence, 19 patients (47.5%) received palliative chemotherapy, 14(35%) received chemotherapy followed by allogeneic transplant (allo), 6(15%) received best supportive care (BSC); 1(2.5%) received chemotherapy followed by a 2nd ASCT. Of the 34(85%) patients who received chemotherapy (including allo and 2nd ASCT patients), 12(30%) patients went on to have a 2ndregimen, 6(15%) a 3rd and 2(5%) a 4th. A summary of resource use and mean cost per patient post-ASCT recurrence are detailed in Table 1. Allo was associated with the fewest outpatient visits (mean 10.81/patient/year) and shortest duration of hospital stay (mean 25.27 days/patient/year) but was the most costly in financial terms (mean £110,374/patient). At April 2012, 10(67%) allo/2ndASCT patients and 3(16%) palliative chemotherapy-only patients were alive but all BSC patients had died. Conclusions. Treatment for recurrent HL after ASCT is highly variable in terms of intensity, outcome and resource use. 62.5% of patients in this study received palliative or supportive treatment and 37.5% received chemotherapy followed by a transplant (mainly allo). Chemotherapy followed by allo was the most expensive treatment pathway but also the most successful and represents a cost effective option for appropriately selected patients. Less intensive approaches are associated with a dismal outcome.

Table 1.Resource use and costs of treatment pathways for recurrent Hodgkin Lymphoma after ASCT.

Post ASCT relapse	No. patients (n=40)	Outpatient visits (Mean/patient/year) (Range)	Day case visits (Mean/patient/year) (Range)	Inpatient stays (Mean/patient/year) (Range)	Length of stay (Mean/patient/year) (Range)	Scans (Mean/patient/year) (Range)	Cost of resources and treatments (Mean cost/patient)* (Range)
Palliative chemotherapy only	19 (47.5%)	17.79 (0.48 – 49.54	4.30 (0.00 – 21.84)	3.42 (0.00 – 15.54)	26.34 (0.00 – 121.75)	5.66 (0.00 – 15.54)	£32,264 (£2,686-£119,820)
Chemotherapy followed by allogeneic-transplant	14 (35.0%)	10.81 (0.81 – 28.34)	3.94 (0.00 – 47.90)	1.37 (0.00 – 5.07)	25.27 (0.00 – 131.73)	6.47 (0.57 – 53.89)	£110,374 (£69,289 - £191,670)
Best supportive care only (No HL directed therapy)	6 (15.0%)	12.88 (2.91 – 24.51)	0.23 (0.00 – 1.36)	3.18 (0.29 – 10.90)	39.64 (0.68 – 136.29)	2.99 (0.29 – 5.66)	£13,288 (£8,485 – £23,295)
Chemotherapy followed by 2nd ASCT	1 (2.5%)	17.33 (17.33 – 17.33)	8.00 (8.00 – 8.00)	2.67 (2.67 – 2.67)	31.99 (31.99 – 31.99)	4.00 (4.00 – 4.00)	£21,612 (£21,612-£21,612)

*Cost of resources and treatments is calculated from date of relapse after ASCT to date of death or to most recent follow up within the study period

P103
THE NOVEL SIRTUIN INHIBITOR, AS4.064 IS ACTIVE AGAINST HODGKIN LYMPHOMA LINES AS SINGLE AGENT AND IN COMBINATION WITH OTHER HISTONE DEACETYLASE INHIBITORS.

Kirschbaum MH, Scata K, Sharma A, Desai D, Amin S

Penn State Hershey Medical Center, PA, USA

HDAC inhibitors (HDACi) have proven preclinical and clinical activity against Hodgkin Lymphoma. HDACs are grouped into four categories with classes I, II, and IV, constituting the zinc-dependent family members and class III comprising the NAD+ dependent members (also known as sirtuins). The agents that have been studied thus far clinically have been against the zinc based enzymes, but have no activity against the NAD+ sirtuins. SelSA-1 is a novel selenium-containing hydroxamic acid derivative HDACi and AS4.064 is a novel selenium analog of thiobarbituric acid made in our lab. We have shown that AS4.064 inhibits sirtuins 1-3 in enzymatic studies. Hodgkin Lymphoma lines, along with other lymphoid lines, show decreased proliferation and increased apoptosis when treated with SelSA-1 and/or with AS4.064 by viability studies and annexin V studies. Increased acetylation at H3K9 and H4K8 is seen with SelSA-1 and enhanced by combination with AS4.064. We have previously demonstrated an important role for c-Myc inhibition in the activity of HDACi in lymphoid malignancies. The combination of AS4.064 and SelSA-1 showed enhanced inhibition of c-Myc protein levels in L540 cells. The acetylation of p53 at various lysines is differentially enhanced by single agent versus the combination of the two agents. DNA damage response elements such as GADD45 and FOXO3A, which we have previously published as being a critical com-

ponent of the activity of HDACi, are increased differentially by the two classes of agents, results of telomerase, a variety of related miRNAs and other metabolic pathway studies that may be uniquely linked to sirtuin inhibition will be shown. In summary, both the novel SIRT1 inhibitor, AS-64, and the novel HDACi, SelSa-1, show growth inhibitory and pro-apoptotic activity in Hodgkin Lymphoma lines, alone and in combination. Inhibition of all HDAC classes, including the NAD+ catalyzed deacetylases, may enhance the activity seen with the classic zinc based HDACi. Clinical development of these agents is warranted.

P104
THE EPHRIN AND EPHRIN-RECEPTOR FAMILIES ARE WIDELY EXPRESSED IN HODGKIN LYMPHOMA

Veenstra R, de Jager W, van den Berg A, Diepstra A, Visser L

Department of Pathology & Medical Biology, University of Groningen, University Medical Center Groningen, The Netherlands

Ephrin (Eph) receptors are the largest family of receptor tyrosine kinases and are activated by protein ligands, known as Ephrins (Efn). Hodgkin lymphoma (HL) has a unique cellular composition and consists of less than 1% of tumor cells that are surrounded by a reactive infiltrate consisting mainly of T-cells. In HL tissue, expression of one Eph-receptor, EphB1, together with a high affinity ligand, EfnB1 has been observed. Expression of 21 Eph-receptors and Efn was analyzed in eight Hodgkin lymphoma cell lines using quantitative RT-PCR. Protein expression of 3 Eph-receptors (EphA1, EphA3 and EphB1) and 3 Efn (EfnA3, EfnA4 and EfnB1) was evaluated in 5 nodular lymphocyte predominant (NLP)-HL and 25 classical HL (cHL) tissue samples. EfnA3, EfnA4 and EfnB1 mRNA expression was detected in almost all HL cell lines. Expression of EphA1, EphA3, EfnA5, EphB1, EphB4 and EfnB3 was found in approximately 50% of the HL cell lines, while EphA4 was present in 2/8 HL cell lines. Protein expression was observed in the tumor cells of all NLP-HL cases for EfnA4 and EfnB1, in 3/5 NLP-HL cases for EphA1 and in 4/5 cases for EphA3. EfnA3 was not detectable in NLP-HL. Protein expression for EphA3, EfnA3 EfnA4 and EfnB1 was found in 50% of the cHL patients. EphA1 was not detectable in the cHL cases and EphB1 staining was inconclusive. The main difference between NLP-HL and cHL was expression of EphA1 in NLP-HL and not in cHL and expression of EfnA3 in cHL and not in NLP-HL. In conclusion, we show that the Eph-family is widely expressed in HL tumor cells, with marked differences for EphA1 and EfnA3 between NLP and cHL.

P105
TELOMERASE DEPENDENT AND TELOMERASE INDEPENDENT TELOMERE MAINTENANCE MECHANISMS IN HODGKIN LYMPHOMA

Cuceu C,[1] Morat L,[1] Lemain A,[1] Shim G,[1] Frenzel M,[1] Ricoul M,[1] Henpel W,[1] Guileto E,[2] Junker S,[3] Girinsky T,[4] Carde P,[5] Delhem N,[6] Sabatier L,[1] M'kacher R[1]

[1]Laboratoire de Radiobiologie et d'Oncologie, IRCM/DSV/CEA Fontenay aux roses, France; [2]Laboratory of Cellular and Molecular biology, University Di Pavia, Italy; [3]Institute of Human Genetics University of Aarhus Hospital, Denmark; [4]Departement of Radiation Therapy, Gustave Roussy Institut , Villejuif France; [5]Departement of Medicine, Gustave Roussy Institut , Villejuif France; [6]Immunoregulation of Viro-induit Cancers, Institut of Biology, Lille France

Background. Telomere dysfunction in Hodgkin Lymphoma (HL) requires that the cells activate a telomere maintenance mechanism (TMM) to support immortalization. Most tumor cells activate expression of the enzyme telomerase. Some cells elongate telomeres using telomerase-independent mechanisms, known as alternative lengthening of telomeres (ALT). A telomerase-independent mechanism for TMM in HL has been proposed in the absence of detectable telomerase activity (TA) in some cases. In this study, we have analyzed the TMM in HL cell lines, lymph nodes and peripheral blood lymphocytes of HL patients. Our studies demonstrate that TMMs are not mutually exclusive in Hodgkin lymphoma and, indeed, reveal the presence of multiple TMM. Materials and Methods. Spectral Karyotype, FISH painting, telomere length (TL), TA measurement, immunofluorescence and western blot of different proteins were performed on 50 frozen samples obtained from patients with classic Hodgkin lymphoma during diagnostic lymph node biopsy, blood samples and 7 HL cell lines (L428, KMH2, L540, L591, HD-LM2, L1236, SUP-HD). Results. The major finding of this study is the presence of both telomerase and ALT in selected lymph nodes of HL patients. This TMM heterogeneity was revealed in circulating lymphocytes and in HL cell lines. We have identified a subset of tumors with some cells containing ALT-associated PML bodies, , and separate cells expressing telomerase in the same tumor. In 50 lymph node tumors, 3 contained only ALT-positive cells, 6 contained only telomerase positive cells and 41 contained a mixed population of ALT and telomerase-positive cells. Similarly, in HL cell lines, a high level of TA was detected in L428 and SUP-HD. L1236 presented an ALT profile. In circulating lymphocytes, Telomerase activity was detected in 18 from 50. A significant correlation was observed between telomere length and the TMM. Interestingly, Jak2 amplification and complex chromosomal rearrangements including dicentrics were observed in patients and cell lines with an ALT profile. Conclusion. The presence of both TMMs (TA and ALT) in Lymph nodes, peripheral blood lymphocytes and cell lines cells is unique. Further investigation could establish the relationship between TMMs and the clinical outcome of patients.

P106
PRELIMINARY CHARACTERIZATION OF MHC POLYMORPHISMS AS RISK FACTORS FOR PEDIATRIC AND ADULT CLASSICAL HODGKIN LYMPHOMA IN A REGION WITH EARLY EBV SEROCONVERSION

Hassan R,[1] Garcia A,[1] Cohen M,[2] Vera-Lozada G,[1] Oliveira-Silva M,[1] Segges P,[1] Gantuz M,[2] De Matteo E,[2] Barros MH,[3] Preciado MV,[2] Chabay P[2]

[1]Oncovirology Laboratory, Instituto Nacional do Câncer-INCA, Rio de Janeiro, Brazil; [2]Molecular Biology Laboratory, Pathology Division, Ricardo Gutiérrez Children Hospital, Ciudad de Buenos Aires, Argentina; [3]Institute for Pathology, Unfallkrankenhaus Berlin, Berlin, Germany

Genetic factors linked to the Major Histocompatibility Complex (MHC) have been associated to the risk of classical Hodgkin lymphoma (cHL) in distinct epidemiological frameworks (i.e. developed countries, EBV late seroconversion, adults). This is a pilot study aiming to explore the role of MHC genetic variants in the risk of cHL in developing countries where early EBV seronversion is the rule. A group of 84 children and adolescents (3-18 years, median 11; M:F 2.45) and 67 adults (19-82 years, median 32; M:F 1.7) with cHL, and 67 reactive hyperplasia (2-48 years, M:F 1.2) were included, from cases diagnosed in Brazil and Argentina public Hospitals. EBV was detected by EBER-ISH and PCR. In 147 cases, HLAs A/B/DRB were genotyped using the LabType®SSO typing test (Luminex). HLA-linked SNPs (rs6457110, rs2530388, rs6903608, and rs2523969) were genotyped using TaqMan® probes. NS subtype was detected in 46% children and 68% adults, followed by MC (41% *vs* 14%). EBV was detected in 64% of pediatric cHL, 54.5% of adult cHL and 39% controls. The more frequent HLA alleles were HLA-A*02 (43%), HLA-B*44 (14%) e HLA-DRB*13 (28%), without differences between cases and controls, regardless of EBV status. DR3 and DR8 alleles were preferentially associated with EBV+ cHL females (38.5% *vs* 6.4% males; p=0.017; p=0.003). Case-control comparison for rs6457110 disclosed no significant associations. When compared EBV+ and EBV- cHL stratified by sex, the A allele/AA genotype were more frequent in male EBV+ cases (27% *vs* 5% female, p=0.02). For SNP rs2330388, no differences were found between cases and controls. A allele/AA genotype were associated with EBV+ cHL male children (p=0.018). For SNP rs6903608, genotypic frequencies were significantly different in cases and controls (CC 20% *vs* 6%; p= 0.016), more marked in the EBV-negative cases. In sum, no direct associations were demonstrated between HLA-A*01 or HLA-A*02 and risk of cHL in this region. However, a complex interaction was found among specific alleles of HLA and SNPs in respect of sex, age, and EBV, which demands, besides in=creasing sample size, specific experimental designs to disclose age- and sex-associated risks in this region with early EBV seroconversion. Financial Support: CAPES (Brazil)/MinCyT (Argentina).

P107
CLASSICAL HODGKIN LYMPHOMA: EVALUATION FOR B-CELL CLONALITY FROM FORMALIN FIXED PARAFFIN EMBEDDED TISSUES

Epari S,[1] Sengar M,[2] Basak R,[1] Gujral S,[1] Menon H,[2] Shet T[1]

Departments of [1]Pathology, and [2]Medical Oncology, Tata Memorial Centre, Mumbai, India

Introduction. Classical Hodgkin lymphoma (CHL) is a B-cell lymphoma characterized by the scarcity of tumor cells, lack of immunoglobulin expression, and the heavy somatic mutation load of the Ig gene rearrangements. The clonal B-cell nature is always considered difficult to detect by standard immunological and molecular techniques due to complex B-cell differentiation programme in CHL. Materials and Methods. We tested formalin fixed paraffin embedded (FFPE) tissues of 6 classical Hodgkin lymphomas (CHL) using BIOMED-2 primers sets for TCRG, IGH and IGK primer sets by multiplex polymerase chain reaction (PCR) with gel based heteroduplex detection as a pilot study to evaluate the feasibility for demonstrating B-cell clonality. Results. A total 7 histologically confirmed were subjected for study, 6 showed acceptable DNA quality (allowing PCR amplification upto 300bp) and were further evaluated. But none the cases demonstrated gene rearrangement for any IGH and IGK. Additional evaluation for IGL is being done and the results of the same will be presented. Conclusions. Though the study sample is small, but the study suggests the difficulty of demonstration of B-cell clonality in cases of FFPE tissues of CHL cases. Therefore one should be aware of inability to demonstrate the B-cell clonality in CHL but this observation needs to validate in a larger study.

PET and Prediction

T108
RESPONSE-ADAPTED THERAPY OF STAGE III-IV HODGKIN LYMPHOMA BASED ON INTERIM FDG-PET IMAGING: EARLY RESULTS. OF US INTERGROUP S0816

Press O, Li H, Schöder H, LeBlanc M, Rimsza L, Friedberg JW, Bartlett N, LaCasce A, Sweetenham J, Evens A, Straus D, Knopp M, Noy A, Hsi E, Cook J, Mittra E, Lechowicz MJ, Gascoyne RD, Miller TP, Kahl B, Cheson BD, Fisher RI

Fred Hutchinson Cancer Research Center/University of Washington; Memorial Sloan Kettering Cancer Center, University of Arizona; University of Rochester; Washington University, Dana Farber Cancer Institute/Harvard, University of Utah, University of Massachusetts, Ohio State University/CALGB Imaging Center, Cleveland Clinic, Stanford University,Emory University, British Columbia Cancer Center, University of Wisconsin, Georgetown University, and Fox Chase Cancer Center/Temple University, USA for SWOG, CALGB/Alliance, ECOG, and AIDS Malignancy Consortium.

Advanced stage Hodgkin Lymphoma (HL) is usually treated in North America with ABVD chemotherapy, with a cure rate of ~70%. BEACOPPescalated cures more patients (pts) with advanced HL, but is little utilized in the North America because it is perceived to be more toxic and renders most recipients infertile. Recent studies suggest that "interim" FDG-PET imaging performed after 2 cycles of ABVD identifies pts who will not be cured with ABVD, allowing early escalation to eBEACOPP in high risk pts. SWOG, CALGB/Alliance, ECOG and AMC conducted an intergroup trial to test such a "response-adapted" approach, enrolling 371 pts between 7/1/2009 and 12/2/2012 (356 eligible and evaluable). PET2- pts (Deauville score 1-3) received an additional 4 cycles of ABVD (6 total), while PET2+ pts (Deauville score 4-5) were switched to BEACOPPescalated for 6 cycles. The median age was 32 (18-60), with 51% stage III, 49% stage IV, 49% IPS 0-2, 51% IPS 3-7, and 4% HIV positive (13 pts). Turnaround time for centralized PET review was outstanding (77% <2 days, 95% <4 days). Of 362 pts with centralized review of the interim PET2 scan, 296 (82%) were PET2- and all continued with 4 more cycles of ABVD. PET2+ scans were seen in 65 pts (18%), with 54 switching to eBEACOPP and 12 refusing to switch. With a median followup of 16.1 months, the Kaplan-Meier estimate for 2-year overall survival in HIV-negative pts is 95% (95% CI: 91%, 98%) and 2-year progression-free survival (PFS) is 76% (95% CI: 69%, 81%). The landmark of 2-yr PFS for PET2+ pts planned to receive BEACOPP is 61% (95% CI: 44%, 74%), which appears promising compared with the expected 15-30% 2-yr PFS. PFS stratified by the interim PET2 score (see figure) suggests that the Deauville 4-5 cutoff selected for PET2+ dose escalation was optimal. Both non-hematologic and hematologic toxicities were significantly greater in the eBEACOPP arm than in the continued ABVD arm, as expected. Response-adapted therapy with centralized interim PET review is highly feasible in an intergroup setting. Early outcomes appear favorable for PET2+ pts, though longer follow-up is necessary.

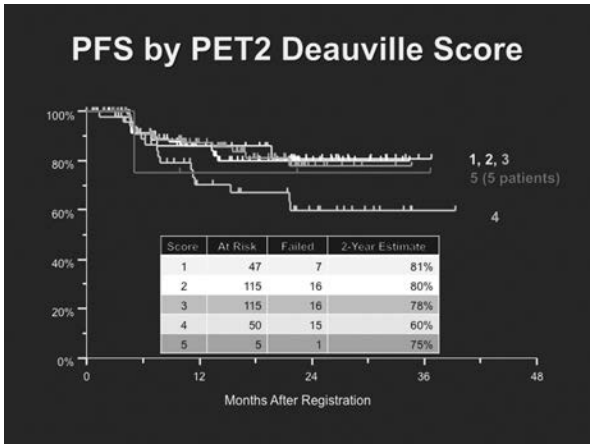

Figure 1.

T109
VERY EARLY RESPONSE AS MEASURED BY (18F)-FLUORODEOXYGLUCOSE-POSITRON EMISSION TOMOGRAPHY (FDG-PET) AFTER ONE CYCLE OF CHEMOTHERAPY IN NEWLY DIAGNOSED PEDIATRIC/ADOLESCENT LOW RISK HODGKIN LYMPHOMA (HL)

Keller FG,[1] Nachman J,[2] Castellino SM,[3] Constine LS,[4] Voss S,[5] Thomson J,[6] Dunphy C,[7] McCarten KM,[8] Chen L,[9] Schwartz CS[10]

[1]Aflac Cancer and Blood Disorders Center, Emory University, Atlanta, GA; [2]University of Chicago Comer Childrens Hospital, Chicago, IL; [3]Wake Forest University School of Medicine, Winston-Salem, NC; [4]University of Rochester Medical Center, Rochester, NY; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Primary Children's Hospital, Salt Lake City, UT; [7]University of North Carolina, Chapel Hill, NC; [8,10]Hasbro Children's Hospital/Brown University, Providence, RI; [9]Children's Oncology Group, Monrovia, CA, USA

Introduction. The Children's Oncology Group (COG) HL studies have focused on response based paradigms for titration of therapy in the context of potentially less toxic treatment regimens. Methods. AHOD0431 investigated the prognostic implications of very early response, measured by FDG-PET after one cycle of chemotherapy (PET-1). All subjects received AVPC chemotherapy. Patients who achieved a CR after 3 cycles of AVPC received no further therapy. Those with a PR received 21 Gy IFRT. CR was defined as at least 80% reduction in the size of each of the nodal masses, or return to normal size, and negative findings on FGD-PET or Gallium scanning. Results. 287 subjects were enrolled. The CR rate after 3 cycles of AVPC was 63.6%. Event free survival (EFS) at 4 years was 79.8%, and overall survival (OS) was 99.6%. Among 227 subjects with evaluable PET-1, 115 (51%) were PET-1 positive/equivocal and 112 (49%) were PET-1 negative. The 4 yr EFS for PET-1 positive/equivocal was 68.4% *vs* 88.1% for PET-1 negative (p=0.0008). Among 129 subjects who achieved a CR (no IFRT) the 4 year EFS for PET1 positive/equivocal *vs* negative was 59.5% *vs* 84.9% (p=0.001). Among 76 subjects who achieved a PR and received protocol directed IFRT the 4 year EFS for PET-1 positive/equivocal *vs* negative was 69.5% *vs* 95.8% (p=0.018). After 3 cycles of chemotherapy, 9.5% of evaluable patients remained FDG-PET positive/equivocal (PET-3). The 4 year EFS for PET-3 positive/equivocal (n=23) *vs* negative (n=218) was 71.7% *vs* 80.3% (p=0.38). In December, 2008 the Study Committee recommended IFRT for all CR patients who were PET-1 positive or PET-1 status unknown, and were within one year of completing chemotherapy. 13 subjects received IFRT based on this recommendation; 1 relapsed. Conclusions. PET-1 is a highly significant prognostic indicator in low-risk HL among children/adolescents treated with three cycles of AVPC. Post-amendment CR subjects that were PET-1 positive had excellent EFS with IFRT at the completion of chemotherapy. Future investigations should consider whether very early PET response is an indicator of chemotherapy sensitivity, identifying need for augmentation of therapy for slow responders receiving lower intensity or abbreviated chemotherapy regimens.

T110
TAILORED THERAPY IN HODGKIN LYMPHOMA, BASED ON PREDEFINED RISK FACTORS AND EARLY INTERIM PET/CT, ISRAELI H2 PROTOCOL: PRELIMINARY REPORT ON 317 PATIENTS

Dann EJ,[1] Bairey O,[2] Bar-Shalom R,[1] Izak M,[3] Korenberg A,[3] Akria L,[4] Attias D,[5] Filanovsky K,[6] Abadi U,[7] Ruchlemer R,[9] Abdah-Bortnyak R,[1] Goldschmidt N,[8] Epelbaum R,[1] Avivi I,[1] Lavie D,[8] Rowe JM,[1,9] Shpilberg O,[2] Paltiel O[8]

[1]Rambam Medical Center (MC); [2]Haifa; Rabin MC, Petach Tikva; [3]Assaf Harofeh MC, Zerifin; [4]Western Galillee MC, Nahariya; [5]Bnai Zion MC, Haifa; [6]Kaplan MC Rehovot; [7]Meir MC Kfar Saba; [8]Hadassah MC Jerusalem; [9]Shaare Zedek MC, Jerusalem, Israel

Introduction. The aim Hodgkin lymphoma (HL) therapy is to maximize response and minimize long term toxicity. Methods. This multicenter ongoing study, initiated in 2006, prospectively evaluates outcome of HL patients (pts) whose therapy is chosen according to baseline prognostic factors and is tailored based on PET/CT results performed after 2 cycles of chemotherapy. Pts with classic HL aged 18-60 years, stages I-IV are eligible. Those with early HL are categorized to early favorable (EFD) and unfavorable (EUD) disease. After 2 ABVD cycles, EFD pts and negative PET/CT undergo involved nodal radiation therapy (INRT) and EUD pts receive 2 more ABVD cycles (total 4) followed by INRT. If interim PET is negative RT could be waivered by 2XABVD.Pts with positive interim PET/CT are given 2 more ABVD cycles (total 4 or 6) followed by RT. Pts with advanced HL (B symptoms or stages III/IV) are assigned to therapy based on IPS. Standard risk pts (IPS 0-2) initially receive 2 ABVD cycles and those with IPS of ≥ 3 receive 2 cycles of escalated BEACOPP (EB). If interim PET/CT is negative or shows minimal residual uptake in a single site, further therapy with 4 ABVD cycles is given and RT to bulky mediastinal masses is omitted. If interim PET/CT is positive with no evidence of HL progression, therapy is escalated to EB with RT given to bulky mediastinal masses. Results. To date, 344 pts have been enrolled. Clinical data of patients with interim PET are presented in Table 1. Escalation of therapy performed in 16% of patients with early disease. De-escalation of therapy performed in 80% of pts with advanced high risk score. 2 pts succumbed: one during autologous BMT and other with acute myocardial ischemia. At a median follow up of 24 months (4-74), the current study has demonstrated PFS of 86% for the whole group, 94% for early disease, and 82% for advanced disease pts. Conclusions. Tailored therapy based on interim PET is feasible both in early and advanced disease. Further follow up and a larger cohort are needed to draw conclusions regarding the long term toxicity of this personalized approach.

Table 1.

	No. of patients. With interim PET	Pt with interim Positive PET	Pt with interim negative PET	Negative predictive value	Positive predictive value of a positive study	Patients with treatment escalation /reduction	Disease progression Pts (%)
Total	**317**	**45**	**272**	**91%**	**21%**	**31/ 55**	**33 (10)**
Early disease	**151**	**19**	**132**	93%	26%	**19/0**	**14 (9.5)**
favor	22	5	17	94%	20%	5/0	2 (9.5)
unfavorable	129	14	115	93%	29%	14/0	12 (9.4)
Advanced	**166**	**26**	**140**	**89%**	**16%**	**12/55**	**19 (12.7)**
Score 0-2	97	12	85	88%	17%	12/0	12 (12)
Score ≥3	69	14	55	91%	15%	0/55	7 (10)

[*]The research is funded by the Israel Cancer Association

P111
FDG PET-BASED PARAMETERS FOR TOTAL TUMOR BURDEN AT DIAGNOSIS ARE HIGHLY PREDICTIVE FOR OUTCOME IN PEDIATRIC HODGKIN LYMPHOMA (HL): A COG AHOD0031 RETROSPECTIVE STUDY

Chirindel A,[1] Kim J,[1] Chen L,[2] Buxton A,[2] Kessel S,[3] Leal J,[1] McCarten KM,[4] Wolden SL,[5] Schwartz CL,[6] Friedman DL,[7] Kelly KM,[8] Cho SY[1]

[1]Department of Radiology, Division of Nuclear Medicine, Johns Hopkins University, Baltimore, MD; [2]Statistics and Data Center, Children's Oncology Group, Monrovia, CA; [3]Quality Assurance Review Center, Lincoln, RI; [4]Diagnostic Imaging and Pediatrics, Rhode Island Hospital, Brown Medical School, Providence, RI; [5]Memorial Sloan Kettering Cancer Center, New York, NY; [6]Pediatrics, Hasbro Children's Hospital, Brown University, Providence, RI; [7]Vanderbilt-Ingram Cancer Center, Nashville, TN; [8]Division of Pediatric Oncology, Columbia University Medical Center, New York, NY, USA

Introduction. The purpose of this study was to assess the prognostic value of baseline tumor burden as determined by FDG PET-based parameters in pediatric HL. Methods. We retrospectively analyzed multi-site FDG PET/CT images from patients enrolled on COG AHOD0031, a Phase III study for newly diagnosed intermediate-risk pediatric HL. A cohort of 90 patients was identified based on availability of high quality archived PET/CT scans amenable to quantitative analysis and a predetermined selection process that ensured inclusion of patients representative of different chemotherapy response groups. Baseline PET images were analyzed by consensus of 2 readers blinded to clinical outcome data using MIMVista TM software. PET standardized-uptake value (SUV) threshold values based on various absolute, liver, blood pool and tumor were assessed to derive PET parameters for total body nodal tumor burden including: average tumor SUV (SUVavg), metabolic tumor volume (MTV) and total tumor glycolytic activity (TGA). Event free survival (EFS) was the clinical endpoint of interest and analyzed by log-rank test and Cox proportional hazard model. Selected parameters were further assessed using receiver-operating-characteristic (ROC) analysis where the outcome was 2-year EFS. Results. Baseline FDG PET SUV derived MTV and TGA parameters were found to be highly predictive for EFS

for a variety of thresholds (P<0.05). PET SUV threshold values found to be most predictive and reliable included: 1.5Lv + 2xliver standard deviation (1.5Lv+2SD), 2xmediastinal blood pool (2BP) and 20% maximal tumor SUV (TSUVmax). ROC area under the curve (AUC) for MTV using 1.5Lv+2SD, 2BP and TSUVmax threshold was 0.77, 0.84, and 0.79, respectively. Use of an "optimal cut-off" PET MTV value based on the ROC for 1.5Lv+2SD, 2BP and TSUVmax was able to separate EFS groups (P<0.005). Baseline tumor SUVavg was not found to be predictive for EFS. Conclusions. Baseline FDG PET SUV derived total body tumor burden as represented by tumor volume (MTV) and total tumor glycolytic activity (TGA) is highly predictive of EFS in pediatric HL. These parameters need further validation for incorporation into HL prognostic stratification schemes.

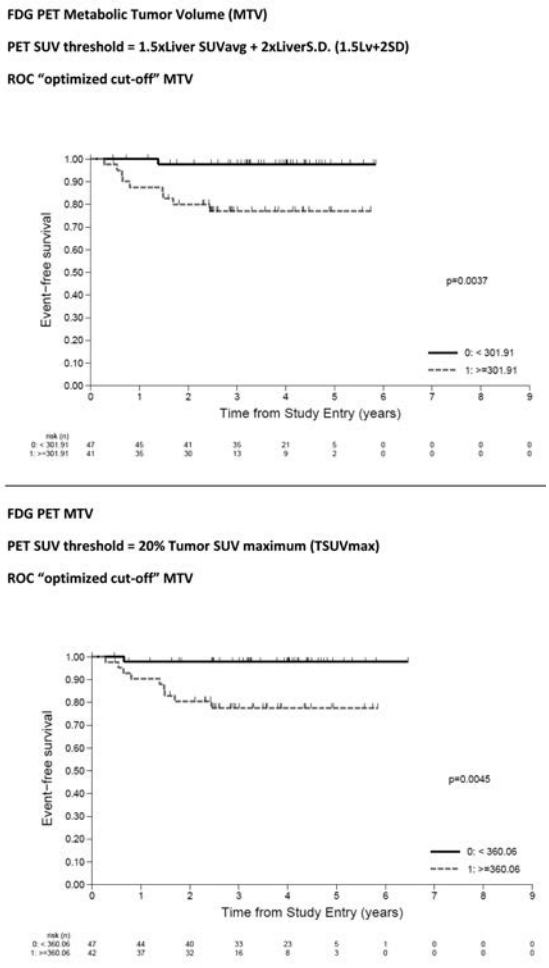

Figure 1.

P112
THE PROGNOSTIC ROLE OF INTERIM PET AFTER FIRST CHEMOTHERAPY CYCLE IN ABVD-TREATED HODGKIN LYMPHOMA (HL) PATIENTS- POLISH LYMPHOMA RESEARCH GROUP (PLRG) OBSERVATIONAL STUDY

Zaucha JM,[1] Chauvie S,[2] Malkowski B,[3] Warszewska A,[4] Biggi A,[2] Kobylecka M,[5] Danielewicz I,[1] Tajer J,[6] Subocz E,[7] Kulikowski W,[8] Dzietczenia J,[9] Wojtowicz M,[10] Romanowicz A,[11] Kroll-Balcerzak R,[12] Chamier-Cieminska A,[13] Dziuk M,[14] Mazurek A,[14] Piwkowski P,[15] Czepczynski R,[16] Damico A,[17] Bergesio F,[2] Fallanca F,[18] Lesniewski-Kmak K,[1]Wróbel T,[9] Walewski J,[6] Gallamini A[2]

[1]Gdynia Oncology Center and Medical University of Gda sk, Gdynia, PL; [2]Ospedaliera S. Croce e Carle Santa, Cuneo, I; [3]Nuclear Medicine Department, Oncology Center, Bydgoszcz, PL; [4]Nuclear Medicine, Maria Sklodowska-Curie Memorial Institute, Warszawa, PL; [5]Nuclear Medicine Department, Warsaw Medical University, Warszawa, PL; [6]Department of Lymphoproliferative Diseases, Maria Sklodowska-Curie Memorial Institute, Warszawa, PL [7]Department of Hematology, Military Institute of Medicine, Warszawa, PL; [8]Department of Hematology, Regional Oncology Center, Olsztyn,PL; [9]Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland, PL; [10]Hematology Unit, Regional Hospital, Opole, PL; [11]Department of Hematology, Central Clinical Hospital MSW, Warszawa, PL; [12]Department of Hematology, University Medical School, Pozna , PL; [13]Department of Clinical Oncology, Oncology Center, Bydgoszcz, PL; [14]Nuclear Medicine Department, Military Institute of Medicine, Warszawa; [15]EURO-MEDIC PET/CT Wroclaw, PL; [16]EURO-MEDIC PET/CT Pozna , PL; [17]Nuclear Medicine Center Maria Sklodowska-Curie Memorial Institute, Gliwice, PL; [18]San Raffaele Hospital, Milano, Italy

Introduction. Several studies confirmed the prognostic role of interim-PET after 2ABVD(iPET2) in advanced-stage-HL. The data on the role of iPET after first-cycle(iPET1) are scarce. For this reason, PLRG in 2010 launched the observational-study aimed at assessing the role of iPET1. We hypothesized that negative predictive value(NPV) of iPET1 will be higher than iPET2 identifying highly chemosensitive patients at the probable expense of reduction of the positive predictive value(PPV). Materials and Methods.Patients with classical-HL>=18 years treated with ABVD±radiotherapy were eligible. PET was performed after 1ABVD and interpreted locally according to the Deauville-5-point scale. Scores 1-to-3 were considered negative(-), score 4-to-5 a positive(+) scan. If iPET1 was scored 3-5, additional iPET2 after 2ABVD was performed. Subsequently PET scans were uploaded to WIDEN and Italian-Polish expert panel(EP) scored them afresh. Binary and overall concordance rates were calculated using Fleiss' k. Results. 279 patients from 9 centers were registered. 36 patients were excluded from the analysis for absence/poor-quality of images, or shorter interval than 7-days between ABVD and iPETs resulting in 70 assessable patients with early and 173 with advanced HL. At a median follow-up of 19.7 months 79% of pts achieved a complete response(CR), 21%(52) patients experienced a PFS event. Based on local assessment in "early" group iPET1 was(+) in 12(17%) pts. In 6 of them iPET2 remained (+) after 2ABVD. In advanced group PET1 was(+) in 56(32%) and remained(+) in 22 after 2ABVD. All "early" patients except from 2 with iPET1(-) remain in CR whereas 17(10%) advanced patients with iPET1(-) progressed. NPVs were 97% and 86% whereas PPV were 58% and 50% in patients with early and advanced stages, respectively. 32 patients (6 early) with PET1(+) became PET2(-). At a median follow-up 16.7 months only 4 such patients relapsed. PFS at 1 year for iPET1(-) and (+) were 97% and 28% in early stage and 87% and 42% for advanced. At the time of abstract submission 97 patients have been reviewed by the EP:the Fleiss' k among reviewers was 0.65. Conclusion. iPET1 with high NPV identifies highly chemosensitive patients as potential candidates for future studies with treatment de-escalation.

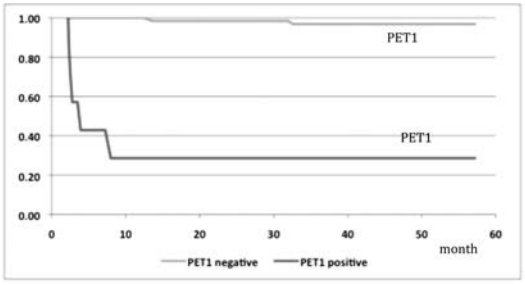

Figure 1. Progression free survival in patients with early stage HL stratified by the results of PET1

P113
UPSTAGING BY PET-ASCERTAINED BONE AND BONE MARROW INVOLVEMENT IN HODGKIN LYMPHOMA–DEFINITIONS MATTER

Borra A,[1] El-Galaly TC,[2] Zaucha JM,[3] Rigacci L,[4] Rapezzi D,[1] Rago A,[5] Bolis S,[6] Gavarotti P,[7] Rusconi C,[8] Trentin L,[9] Stelitano C,[10] Biggi A,[11] Gormsen LC,[12] d'Amore F,[13] Hutchings M,[14] Gallamini A[1]

[1]Hematology Department Cuneo Hospital, Italy; [2]Hematology Department, Aarhus and Aalborg University Hospital, Denmark; [3]Onco-Hematology Department, Gdynya University Hospital, Poland; [4]Hematology Chair , Policlinico Careggi, University of Florence, Florence, Italy; [5]University Chair, Hematology Department, Latina Hospital; [6]Hematology Department, S. Gerardo Hospital, Monza, Italy; [7]Hematology Chair, S. Giovanni Battista Hospital, Turin University, Turin, Italy; [8]Hematology Department, Ca' Granda Niguarda Hospital, Milan, Italy; [9]Hematology Department, University of Padua, Italy; [10]Hematology Department, Melacrino and Morelli Hospital, Reggio Calabria, Italy; [11]Nuclear Medicine Department, Cuneo Hospital, Italy; [12]Nuclear Medicine Department, Aarhus University Hospital, Denmark; [13]Hematology Department, Aarhus University Hospital, Denmark; [14]Department of Hematology, Rigshospitalet, Copenhagen University Hospital, Denmark

Background. PET/CT is sensitive for extranodal involvement in Hodgkin lymphoma (HL). Different patterns of FDG-uptake in the bone/bone marrow (B/BM) are reported indicating HL infiltration. Methods. Patients with intermediate-advanced stage HL from 11 Italian, Danish and Polish centres were included in this retrospective study. All patients had been treated with ABVD chemotherapy +/- consolidating radiotherapy. Baseline CT and PET/CT scans were reviewed according to a predefined scheme. FDG-uptake in the B/BM was categorized as: 1) focal uptake > liver-uptake, 2) diffuse uptake > liver-uptake, 3) no uptake. The CT and PET/CT stages were compared when applying different definitions for B/BM involvement. In setting A) criteria only 1) was accepted as B/BM disease. In setting B) criteria 1) and 2) were equally accepted as B/BM disease. Results. 143 patients mainly with classical HL (99%) were included. In setting A) PET/CT upstaged 19% (n=27) and downstaged 7% (n=10) of the patients. In setting B) PET/CT upstaged 30% (n=43) and downstaged 6% (n=8), p=0.04 for setting A *vs* B. In setting A) upstaging to stage IV by PET/CT was due to B/BM alone in 10% (n=14) and other extranodal involvement +/- B/BM in 4% (n=6).In setting B) upstaging to stage IV by PET/CT was due to B/BM alone in 21% (n=33) and other extranodal involvement +/- B/BM in 4% (n=6). In 8 out of 9 patients with positive BM biopsy focal B/BM FDG-uptake was present, while none had diffuse BM FDG-uptake. Patients with diffuse BM FDG-uptake had higher median leukocyte count (11400 *vs* 9445/mm^3, p=0.0006) and lower median haemoglobin level (117 *vs* 131 g/L, p=0.01) as compared to patients without diffuse uptake. In patients with FDG-uptake in B/BM, a diffuse FDG-uptake was associated with trend toward better outcome (p=0.3) as compared to focal FDG-uptake. Conclusions. Detection of B/BM involvement by PET/CT is the most frequent cause of stage IV upstaging by PET/CT and magnitude of upstaging depends on the criteria used for B/BM disease. Diffuse uptake even when exceeding liver uptake is unlikely related to B/BM invasion. Strict and uniform interpretation criteria for FDG-uptake in the BM are needed.

P114
COMPARATIVE ASSESSMENT OF BONE MARROW INVOLVEMENT (BMI) BY BM BIOPSY (BMB) OR POSITRON EMISSION TOMOGRAPHY / COMPUTED TOMOGRAPHY (PET/CT) IN HODGKIN LYMPHOMA (HL)

Vassilakopoulos TP,[1] Angelopoulou MK,[1] Prassopoulos V,[2] Chatziioannou S,[3] Moschogiannis M,[4] Tsirkinidis P,[4] Poziopoulos C,[5] Symeonidis A,[6] Repoussis P,[7] Matsouka Ch,[8] Kontopidou FN,[9] Sotiropoulos V,[10] Variami E,[11] Viniou NA,[11] Zikos P,[12] Petevi K,[1] Boutsikas G,[1] Kanellopoulos A,[1] Papageorgiou L,[1] Panayiotidis P,[13] Pangalis GA,[13] Datseris I,[14] Meletis J,[1] Rondogianni Ph[14]

[1]Department of Haematology, National and Kapodistrian University of Athens, [2]Department of Nuclear Medicine/PET, HYGEIA Hospital, [3]Department of Nuclear Medicine/PET, Biomedical Research Foundation, Academy of Athens, [4]Department of Haematology, Athens Medical Center, [5]Department of Haematology, Metropolitan General Hospital, [6]Department of Haematology, University of Patras, [7]Department of Haematology, Metaxas Anticancer Hospital, [8]Department of Therapeutics, National and Kapodistrian University of Athens, [9]2nd Department of Internal Medicine, National and Kapodistrian University of Athens, [10]Department of Nuclear Medicine, Athens Medical Center, [11]1st Department of Internal Medicine, National and Kapodistrian University of Athens, [12]Department of Haematology, Ag. Andreas General Hospital, [13]1st Propedeutic Department of Internal Medicine, National and Kapodistrian University of Athens, [14]Department of Nuclear Medicine/PET, Evangelismos General Hospital, Greece

Introduction. PET/CT is a sensitive tool for HL staging. Data suggest that few pts may have positive BMB in the absence of PET/CT evidence. Aims. 1)To correlate BMB and disease characteristics with BM-PET/CT findings; 2)to assess the impact of our published clinical prediction rule (Vassilakopoulos et al, Blood. 2005) on the frequency of BMI; 3)to assess the ability to omit BMB in selected or even all pts. Methods. Data regarding BMB, clinical and laboratory characteristics were retrieved. PET/CT data were reviewed according to osseous/BM findings and were visually graded as follows: (1)no increased; (2)increased ≤liver; (3)increased BM FDG uptake >liver; (4)solitary osseous/BM focus without CT correlate; (5)multiple osseous/BM foci. Pts were classified according to our prediction rule for BMI in low-, standard- and high-risk groups. Results. PET/CT and BMB data were available for 172 pts; PET/CT was negative for BMI in 142 (82%) and positive in 30 pts: 3 had a single focus and 27 had multiple foci. 13 had BMI by BMB (7.6%). None of the pts of PET/CT categories 1,2,3 or 4 had positive BMB; 13/27 pts graded as "5" had positive BMB (48%). Our prediction rule was well validated. The frequency of BMI was 0%, 1.7% and 20.8% by BMB and 0%, 6.9% and 37.7% by PET/CT in low-, standard- and high-risk groups respectively. The outcome of pts with BMI by PET/CT was significantly inferior (3-yr FFS 49% *vs* 86%, p=0.0002). Pts with BMI by PET/CT and negative or positive BMB had similar outcomes (p=0.54). Among pts with negative BM by PET/CT, those with diffuse FDG uptake >liver had increased "inflammatory" activity (higher leukocyte and platelet counts, ESR, CRP). Conclusions. PET/CT is more efficient than BMB in detecting BMI. Increased diffuse BM FDG uptake reflects "inflammatory" activity. Our clinical prediction rule was validated regarding the prediction of BMI by either BMB or PET/CT. There was no case of positive BMB in the absence of BMI by PET/CT. There was no high risk group, which could obtain benefit from BMB. Thus, BMB can be safely omitted in all HL pts staged by PET/CT.

P115
PRETREATMENT AND INTERIM TUMOR BURDEN BY CT PREDICTS EVENT-FREE SURVIVAL IN CHILDREN AND ADOLESCENTS WITH HODGKIN LYMPHOMA (HL): A COG AHOD0031 RETROSPECTIVE STUDY

Kelly KM,[1] Xie C,[2] Chen L,[3] Buxton A,[3] Tan Y,[4] Friedman DL,[5] Schwartz CL,[6] Zhao B,[4] Schwartz L[4]

[1]Division of Pediatric Oncology, Columbia University Medical Center (CUMC), New York, NY; [2]Department of Medical Imaging and Interventional Radiology, Cancer Center of Sun Yat-sen University, State Key laboratory of Oncology in Southern China. Guangzhou, China; [3]Statistics and Data Center, Children's Oncology Group, Monrovia, CA; [4]Department of Radiology, Columbia University Medical Center (CUMC), New York, NY; [5]Vanderbilt-Ingram Cancer Center, Nashville, TN; [6]Pediatrics, MD Anderson Cancer Center, Houston, TX, USA

Introduction. Pretreatment disease burden and early response to treatment of HL are strong prognostic indicators for risk-stratification in pediatric and adult HL, however the optimal imaging study and criteria used to assess tumor burden is not adequately defined, especially as measured by anatomic scans including CT. The purpose of this study was to assess the prognostic value of baseline and interim tumor burden as determined by CT in pediatric HL. Methods. We retrospectively analyzed multi-site CT images from COG AHOD0031, a phase III study for newly diagnosed pediatric intermediate-risk HL. We randomly selected patients who were randomized or assigned to the same standard therapy and had PET post-cycle 2, with 50 patients from each of the three response groups in the study defined by post-cycle 2 and end-of-therapy CT. From this cohort, a subset of patients (N=84) with qualified CT scans were selected for review. Using software developed by the Computational Image Analysis (CIA) Lab at CUMC that incorporates an advanced segmentation algorithm for assessment of tumor volume, uni-dimensional, bi-dimensional and 3-dimensional measures of total tumor burden were assessed at baseline and after 2 cycles of chemotherapy. Event free survival (EFS) was chosen as a clinical endpoint of interest. Receiver-operating-characteristics (ROC) analysis was used to select an "optimal" cut-

off of tumor burden for predicting 2-year EFS. Association between tumor burden (above/below median or "optimal" cutoff) and EFS was examined by log rank test. Results. Baseline tumor burden as assessed by uni, bi and 3-D measures was highly predictive of EFS ($p<0.05$ for analyses with median; <0.003 with "optimal" cutoffs). Similarly, tumor burden following 2 cycles of chemotherapy was prognostic for EFS ($p<=0.05$ for analyses with median; <0.02 with "optimal" cutoffs). Further analyses evaluating percentage change with/without threshold tumor measure were not significantly prognostic of EFS. Conclusions. Baseline and interim total tumor burden but not change in tumor burden as measured by CT is highly predictive of EFS in pediatric HL. Incorporation of tumor burden assessment by CT may be useful for baseline risk stratification and for further refinement of therapy in conjunction with PET as part of a response-based strategy

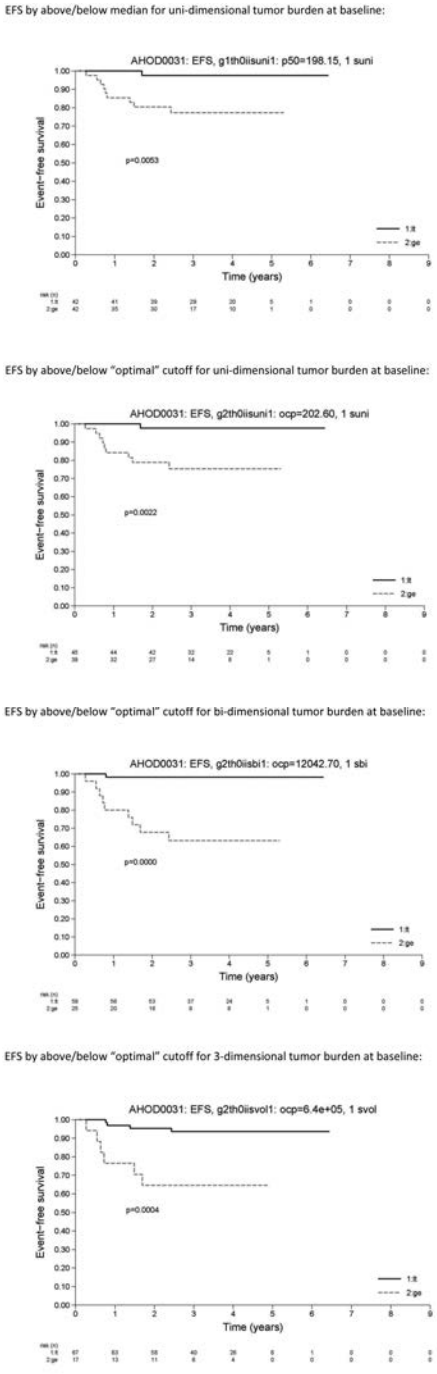

Figure 1.

P116
STAGE MIGRATION IN HODGKIN LYMPHOMA AFTER THE INTRODUCTION. OF FDG-PET/CT

Enblad G,[1] Jerkeman M,[2] Raud C,[1] Björkholm M,[3] Goldkuhl C,[6] Linderoth J,[2] Lagerlöf I,[4] Johansson AS,[5] Molin D[1]

[1]Department of Radiology, Oncology and Radiation science, section of Oncology, Uppsala University, Sweden; [2]Department of Oncology, University Hospital, Lund, Sweden; [3]Division of Hematology, Department of Medicine, Karolinska University Hospital, Stockholm, Sweden; [4]Department of Hematology, Linköping, Sweden; [5]Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden; [6]Department of Oncology, Sahlgrenska University Hospital, Göteborg, Sweden

During the last decade CT-scan has been replaced by FDG-PET/CT as staging for Hodgkin lymphoma (HL). FDG-PET/CT more precisely determines disease extent but it is not entirely known whether the higher sensitivity of FDG-PET/CT influences stage distribution by defining more involved sites. In Sweden, FDG-PET was gradually introduced as staging for HL patients from the beginning of this century and since 2010 almost all young patients are staged with FDG-PET/CT. In Sweden all patients with lymphomas are since 2000 registered in a National registry, containing information on stage, survival and, from 2007, also treatment. Furthermore, between 1999 and 2005, patients with early and intermediate stage HL in Sweden and Norway were included in a Nordic phase II study. In the study patients with stage IA and IIA were treated with 2 or 4 ABVD followed by 30Gy IFRT according to absence or presence of risk factors (bulky disease, ESR≥50 mm or ≥3 involved sites). The principles are similar to those used today, except that patients without risk factors now receive 20Gy INRT. Almost no patients were staged with FDG-PET/CT. We conducted a comparison on stage distribution between the Nordic trial and the Swedish lymphoma registry in order to study if the Introduction. of FDG-PET/CT as staging has resulted in a stage migration. Between 2000 and 2012 the proportion of patients in stage IV, in the national lymphoma registry, increased from 15% 2000-2006 to 23% 2007-2012 ($p<0.05$). Furthermore, the proportion of early stage patients treated with 2 ABVD decreased from 44% in the Nordic trial to 33% 2010 (data still lacking from 2011-2012), reflecting less patients without risk-factors *i.e.* probably less sites involved There was a stage migration between the years 1999 and 2012 with no other obvious explanation than the Introduction. of FDG-PET/CT. The stage migration is not only between stages but also between early stages without and with risk factors. This leads to less patients receiving 2 ABVD and 20Gy than before. Current treatment recommendations probably need to be adjusted for stage migration, but this requires prospective studies.

P117
EVALUATION OF TARC AND SCD163 AS BIOMARKERS IN CLASSICAL HODGKIN LYMPHOMA

Montgomery D,[1] Tiplady E,[1] Lake A,[1] Crae S,[1] Farrell K,[2] McKay P,[2] Jarrett RF[1]

[1]MRC-University of Glasgow Centre for Virus Research, Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK; [2]The Beatson West of Scotland Cancer Centre, , Glasgow, UK

There is a well-recognized need to develop biomarkers to predict and monitor response to treatment in classical Hodgkin lymphoma (cHL). The chemokine TARC (CCL17) is expressed by Hodgkin and Reed-Sternberg (HRS) cells and is present at high levels in the plasma and serum of untreated cHL patients. Recent studies suggest that TARC can be used to predict response to treatment, and to assess treatment response (Sauer *et al*, 2012; Plattel *et al*, 2012). In an investigation of serum TARC and the macrophage marker CD163, Jones *et al* (2012) suggested that combined analysis of both markers was beneficial for monitoring tumour burden. We analysed plasma TARC in 239 pre-treatment cHL patients and 130 healthy individuals. Follow-up samples (n=310) were available from 82 cHL patients with an initial high TARC level. Serum sCD163 levels were measured in samples from 62 healthy controls and in sequential samples (n=306) from 64 cHL patients. ROC analysis of TARC in pre-treatment cHL patients and healthy controls revealed 100% specificity and 89% sensitivity at a plasma level of 242

pg/ml. In subsequent analyses, TARC ≥285 pg/ml was defined as raised and ≥666 pg/ml as high. Nodular sclerosis subtype and EBV-negative disease were independently associated with a high pre-treatment TARC. All patients with a high TARC level during treatment or the immediate follow-up period (n=6) relapsed and four died from their disease. A further three patients relapsed: two patients had raised TARC levels prior to relapse and one had normal levels. All samples collected at relapse had high TARC levels. Pre-treatment sCD163 levels were less good at discriminating cHL patients from healthy controls; in ROC analysis 100% specificity was associated with 29.7% specificity at a level of 1061 ng/ml. High sCD163 was independently associated with advanced stage and EBV-positive disease, and with a poorer overall and disease-specific survival (p=0.003 and p=0.007, respectively). No clear patterns between sCD163 levels during and after treatment and clinical outcome were observed. This study provides further evidence to support the use of TARC as a disease response marker in cHL. Further analysis of sCD163, particularly in relation to outcome prediction, is warranted.

P118
ROUTINE BONE MARROW EVALUATION IN NEWLY DIAGNOSED HODGKIN LYMPHOMAS STAGED WITH PET/CT: IS IT REALLY NECESSARY? EXPERIENCE OF TWO ITALIAN HEMATOLOGICAL CENTERS

Puccini B,[1] Volpetti S,[2] Rigacci L,[1] Zaja F,[2] Kovalchuk S,[1] Fabbri E,[1] Chiozzotto M,[2] Benelli G,[1] Puglisi S,[2] Mazzucco M,[2] Perali G,[2] Bosi A,[1] Fanin R[2]

[1]Hematology Department,AOU Careggi, University of Florence, Florence, Italy; [2]Department of Hematology, University of Udine, Italy

In a recent retrospective study published by El-Galaly *et al* (JCO, 2012), 454 patients (pts) with a new diagnosis of classical Hodgkin Lymphoma (cHL) were staged with PET/CT. In this cohort, no positive bone marrow biopsies (BMB) were observed in pts in stage I to II according to PET/CT; moreover, neither in limited nor in advanced stages, a positive BMB caused a modification of treatment planned. In order to confirm these observations, we retrospectively analyzed data from pts with newly diagnosed cHL referring to Hematology Divisions of Florence and Udine since 2006 to 2012. All pts underwent to both unilateral BMB and PET/CT; stage and risk assessment were defined according to the Ann Arbor classification and the German Hodgkin Study Group (GHSG) criteria, respectively. Stage and risk group obtained with PET/CT alone were compared to those resulting from PET/CT combined to BMB. In this survey we included 212 pts, median age 33 (range, 14-71 years); 116/212 pts were male (55%); 36/212 pts (17%) presented one ore more focal skeletal lesions at PET/TC and 7/212 pts (3%) had a positive BMB; other patients characteristics are summarized in table 1. BMB did not upstaged any patient who resulted in stage I-II according to PET/CT, and in none of the 212 pts BMB modified the therapeutic approach initially planned on the basis of PET/CT. In 2/212 pts with a PET/CT negative for skeletal lesions BMB was positive, causing an upstaging from stage III to stage IV. Focal skeletal lesions at PET/CT had a sensitivity and specificity of 85% each to detect a positive or a negative BMB. The positive (PPV) and negative predictive value (NPV) of focal skeletal PET/CT lesions to detect a positive BMB were 17% and 99%, respectively. Concluding, consistently to data previous reported, we did not observed any positive BMB in stages I-II according to PET/CT, in which the clinical relevance seems questionable. Moreover we did not observed any influence of BMB on the planning of treatment in all stages. Lastly, we remarked the very high NPV (99%) of PET/CT for the bone marrow lesions. Further studies are required to define if BMB maintains a role in HL staging.

P119
PET/CT IN THE SETTING OF AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA PET/CT IN THE SETTING OF AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA (HL): PERFORMANCE OF VARIOUS INTERPRETATION SYSTEMS

Angelopoulou MK,[1] Moschogiannis M,[2] Rondogianni P,[3] Tsirkinidis P,[4] Nikaki A,[5] Chatziioannou S,[6] Galani Z,[1] Tsaftaridis P,[1] Sachanas S,[2] Telonis V,[1] Flevari P,[1] Petevi K,[1] Zannou A,[1] Datseris K,[3] Prassopoulos V,[5] Kyrtsonis M,[7] Panayiotidis P,[7] Meletis J,[1] Pangalis G,[2] Vassilakopoulos TP[1]

[1]Hematology and Bone Marrow Transplantation, National and Kapodistrian Uninersity of Athens, Athens, Greece; [2]Athens Medical Center, Athens, Greece; [3]Nuclear Medicine, Evangelismos Hospital, Athens, Greece; [4]Hematology, 401 General Army Hospital, Athens, Greece; [5]Nuclear Medicine, Hygeia Hospital, Athens, Greece; [6]Nuclear Medicine-Pet/Ct, Iibea, National and Kapodistrian University Of Athens, Athens, Greece; [7]First Propedeutic Department of Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece

Introduction. The predictive significance of PET/CT and criteria for PET positivity in the ASCT setting have not been firmly established yet. Aim: To evaluate the significance of PET findings before and after ASCT according to 3 different methods in a series of 71 patients with relapsed/refractory HL from a single Transplant Unit. Methods. PET/CT was performed just prior to ASCT and at 3 months post transplant. Three Methods were used for the interpretation of PET/CT: 1. Deauville criteria (levels1-5), 2. Cheson criteria (levels 1-3) and 3. SUV (SUV decrease ≥ or < 66%). Results. Among 71 patients, 48% were treated for primary refractory disease, 41% at first relapse, 11% beyond first relapse and 75% were chemosensitive prior to ASCT. At the pre-ASCT evaluation the same pattern of PET/CT positivity was observed with both Deauville and Cheson criteria: 38% of patients were negative (level 1) and 60% were Deauville levels 4-5 or Cheson level 3 positive. Intermediate levels of positivity (Deauville 2-3 and Cheson 2) were almost absent (2%). Chemosensitivity was highly correlated with PET findings (p<0.0001). Pre-ASCT PET/CT by Deauville criteria had a stronger prognostic significance for failure free survival (FFS), compared to Cheson (p< 0.0001 *vs* 0.013): Deauville level 1 patients had a 2-year FFS of 80%, compared to 57% and 18% for levels 4 and 5 respectively. The corresponding FFS values were 80% and 44% for Cheson level 1 and 3 respectively. Post-ASCT PET scan had the strongest predictive value for outcome, by both methods (p< 0.0001). However Deauville scale could stratify patients better: 2-year FFS was 89% for level 1, 36% for level 4 and 6% for level 5. No relapses were observed in 12/31 patients who converted from a Deauville level 4-5 before ASCT to a level ≤ 3 after ASCT. Conclusions. PET/CT interpreted according to Deauville criteria has a highly significant prognostic value, both pre- and post-ASCT, for patients with relapsed/refractory HL undergoing ASCT. Patients who are level 5 positive post-ASCT have a dismal outcome. On the contrary, patients who convert from level 4-5 to level ≤ 3 have an excellent prognosis.

P120
GENE EXPRESSION PROFILES AND PROGNOSTIC ASSOCIATIONS IN CHILDREN AND ADOLESCENTS WITH CLASSICAL HODGKIN LYMPHOMA

Vera-Lozada G,[1] Segges P,[1] Scholl V,[1] Stefanoff CG,[2] Barros MHM,[3] Hassan R[1]

[1]Bone Marrow Transplantation Center, Instituto Nacional de Câncer (INCA), Rio de Janeiro, Brazil; [2]Clinical Research Coordination, INCA, Rio de Janeiro, Brazil;[3]Institute for Pathology, Unfallkrankenhaus Berlin, Berlin, Germany

Complexity of classical Hodgkin lymphoma (cHL) in respect of the tumor, H-RS cells and the heterogeneity of the inflammatory cellular infiltrate known as tumor microenvironment (TM), impact on the reproducibility of prognostic biomarkers. Recently, genes attributed to cell cycle, apoptosis and the microenvironment were able to determine functional signatures associated with treatment response in adults with advanced cHL (Blood 2010;116(8):e12-7). This study analyzed the expression profiles in a set of genes with prognostic value for adults, in 93 cases of pediatric cHL in order to validate the utility of this molecular score in children. A set of 11 genes including CENPF, CDK1, CCNA2, CCNE2 and HMMR (cell cycle), BCL2, BCL2L1 and CASP3 (apoptosis), STAT1 and LYZ (monocytes/macrophages) and IRF4 were analyzed by quantitative RT-qPCR from FFPE-lymph nodes extracted RNA. Gene expression was correlated with EBV status and TM composition evaluated by immunohistochemistry. EBV was present in 40.0% of cases. Nodular sclerosis (NS) was the main subtype (71%) followed by mixed cellularity (22.6%). By Principal Component Analysis (PCA), three PCAs were identified which explained 65.7% of total variation: PC1, representing cell cycle genes (39.1%); PC2, TM and apoptosis genes (STAT1, LYZ, BCL2 and CASP3) (15.6%); PC3, the BCL2L1 gene (11%). Using non-supervised analyses, two clusters were defined by cell cycle and CASP3 gene expression levels, with 29.7% of cases showing low expression,

most EBV- and grade 2 NS subtype. Positive correlations were observed between number of cytotoxic cells (CD8+, GRZB+, TIA1+) and CASP3, CDK1 and BCL2 (P<0.05), number of TIA1+ or GRZB+ with STAT1 and/or LYZ and number of macrophages (CD68+ and CD163+) with STAT1, LYZ and IRF4 (P<0.01). EBV+ cases exhibited high expression of LYZ and STAT1 (P<0.05). Progression-free survival (PFS) was significantly lower in cases with high expression of CASP3 (87.2% *vs* 68.4%, P=0.04), mainly in the EBV- cases (P= 0.012). Our results show that there are distinguishable gene expression patterns with biological meaning in pediatric cHL, associated with cell pathways and TM. However, the 11-gene expression based score proposed for molecular prediction in adult cHL is not directly reproducible in children.

P121
INTERIM AND SUBSEQUENT 18FDG-PET-CT DETERMINE THE OUTCOME OF PEDIATRIC HODGKIN'S LYMPHOMA

Zaghloul MS, Elhaddad A, Attia E, Omar W, Mohamed O, Elmenawy S

Children's Cancer Hospital, Egypt ana National Cancer Institute, Cairo University, Cairo, Egypt

Purpose. To investigate the value of interim and subsequent 18 FDGP-PET-CT as a predictor and prognostic factor in pediatric Hodgkin's lymphoma treated according to patients' risk status. Patients and Methods. Four hundreds twelve children below the age of 18 years were treated at Children's Cancer Hospital, Egypt (CCHE) during the period from July 2007 and June 2012. Mixed cellularity was the major pathological subtype (199= 48%) followed by nodular sclerosis (172=42%). Stage I was encountered in 11%, stage II in 49%, stage III in 25% and stage IV in 15%. They were treated via risk-adapted protocol, entailing 4 or 6 courses of ABVD chemotherapy and involved field (IF) radiotherapy for low and intermediate risk patients respectively. High-risk patients received 6-8 ABVD courses ± IF radiotherapy. Two hundreds and six (45%) had low risk status, 107 (26%) and 119 (29%) had intermediate and high risk, respectively. Results. The 5-year overall survival (OS) and event-free survival (EFS) of the whole group was 96.5 ± 1.4% and 88.0±2.4%, respectively. Early responders showing negative PET-CT after 2 courses had significantly higher OS and EFS (99.2±2.7% and 95.5±2.4%) than late responders (with positive PET-CT after 2 courses) who had 93.2±3.2% and 80.6±7.0% OS and EFS respectively. These differences are statistically significant (p 0.001for both). Late PET-CT (after 4 courses) can still determine the EFS in these late responders. Negative PET had EFS of 92.2±5.3% compared to 58.4± 13.8% for those having positive PET (p=0.029). The OS though higher with negative PET yet, it did not rank to the level of significance. Other OS and EFS prognostic factors were: stage (p=0.011& 0.005), risk status (0.038 & 0.000), pathology subtype (p=0.003 & 0.000). The Cox multivariate analysis revealed that Interim PET-CT is an independent working predictor factor. Conclusion. Early response for pediatric Hodgkin's Lymphoma to 2 courses of chemotherapy, predict both the OS and EFS in risk adapted treatment protocol. The subsequent PET predicts the EFS in late responders.

P122
COMPARISON OF PLASMA TARC WITH GALECTIN-1 AS BIOMARKERS FOR RESPONSE IN CLASSICAL HODGKIN LYMPHOMA

Plattel WJ,[1,2] Van den Berg A,[2] Van Imhoff GW,[1] Diepstra A,[2] Visser L[2]

[1]Department of Hematology, University Medical Center Groningen, University of Groningen, The Netherlands; [2]Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, The Netherlands

We previously reported plasma Thymus and Activation Regulated Chemokine (TARC) to be a very sensitive biomarker for classical Hodgkin Lymphoma (cHL) tumor burden and a highly promising marker for early response evaluation. Recently, Galectin-1 gained interest as a potential biomarker since elevated levels of Galectin-1 were found in serum of cHL patients and associated with parameters of cHL tumor burden. Galectin-1 may be involved in the pathogenesis of classical Hodgkin Lymphoma (cHL) by suppressing Th1 and Th17 cells and stimulating regulatory T cells. We therefore investigated circulating Galectin-1 levels before and after treatment in plasma of 66 newly diagnosed cHL patients and compared it to plasma TARC levels. Pre-treatment plasma Galectin-1 levels among cHL patients were significantly elevated compared to healthy controls (mean Galectin-1 level 22.8 ng/ml *vs* 2.4 ng/ml, p<.001). Plasma TARC could more accurately discriminate patients from controls with pre-treatment samples being elevated in 92% of patients compared to 45% for Galectin-1. In contrast to plasma TARC, plasma Galectin-1 did not correlate with stage of disease, presence of bulky disease or tumor volume as measured by quantification of pre-treatment FDG-PET scans. In the entire group, plasma Galectin-1 levels significantly decreased after treatment compared to pre-treatment (mean 4.6 ng/ml, p<.001). In three responsive patients Galectin-1 levels rose from normal levels before treatment to elevated levels after treatment and remained high before and after treatment in two other responsive patients. In one out of three non-responsive patients Galectin-1 levels were elevated before and after treatment, while levels were not elevated before and after treatment in the two other non-responsive patients. In contrast, TARC levels decreased to normal in all responsive patients and remained high in the three non-responsive patients. There was no correlation between plasma TARC and plasma Galectin-1 levels. In conclusion, in our cohort pre-treatment plasma Galectin-1 levels are significantly elevated in cHL patients but in contrast to plasma TARC, Galectin-1 levels do not correlate with tumor burden and levels after treatment do not correlate with treatment response.

P123
INTERIM PET/CT IN HODGKIN-LYMPHOMA- FINAL RESULTS. OF THE HUNGARIAN CHEAP STUDY (2007-2011)

Miltényi Z,[1] Simon Z,[1] Jóna A,[1] Magyari F,[1] Barna S,[2] Garai I,[2] Illés A,[1] and the CHEAP study group

[1]University of Debrecen, Hematology Department, [2]Scanomed Ltd, Hungary

Background. Interim 18FDG-PET/CT is predicting prognosis better than any of the available prognostic factors. Patients and Methods. Between 2007 and 2011 a total of 113 Hodgkin-lymphoma (HL) patients underwent satging, interim and restaging 18FDG-PET/CT. We investigated the value of 18FDG-PET/CT for prediction of progression-free survival (PFS) and overall survival (OS). Results. We examined 113 patients (57 men, 56 women). The median age of the patients was 38 years. 62 patients had early and 51 advanced stage disease at the time of diagnosis. 59 patients had B signs. All of the patients got ABVD therapy, and there was no treatment change based ont he result of the interim PET/CT. 83 patients had negative interim FDG-PET (intPET) scans, 30 patients had intPET positive scans by the Deauville criteria. The negative predictive value was 0.927, and the positive predictive value was 0.566. Three patients died of the negativ intPET group, all of them with second malignancy, and eight patients died in the int positive group, all of them due to Hodgkin's lymphoma. There were 6 relapse in the intPET negativ group, they had advanced stage disease at the time of diagnosis, they underwent autolog stem cell transplantation. There was significant different between the groups in progression free survival (PFS) (p<0,001) based on the results of interim PET/CT. PFS was 92,7% in the intPET negative group, and 40.8% in the intPET positive group at 60 months. The 5 year overall survival was 93.4% in the interim PET negative and 58% in the positive group (p<0.001). Patients with early stage disease had 100% PFS at 60 months in intPET negative group, and 35.9% in the intPET positive group (p<0.0001). Conclusion. Interim FDG-PET/CT is an useful and independent predictor of PFS in HL. It could be possible to avoid under- and over treatment of patients with used of interim PET/CT.

P124

UTILITY OF PET SCAN FOR EARLY DIAGNOSIS OF BLEOMYCIN INDUCED PNEUMONITIS IN HODGKIN'S LYMPHOMA

Mittal S, Sengar M, Rangarajan V, Purandare N, Tandon S, Dangi U, Menon H

Tata Memorial Hospital, Mumbai, India

Introduction. Bleomycin induced pneumonitis (BIP) is an inflammatory process occurring with use of Bleomycin. This is an idiosyncratic response which is debilitating, potentially irreversible and at times ending in fatality (up to 27%). Currently, signs & symptoms, pulmonary function tests (PFT), carbon monoxide diffusion capacity (DLCO) and high resolution computed tomography (HRCT) are used to diagnose BIP. Unfortunately these reveal only manifest BIP. Positron emission tomography (PET), has shown promise to detect early inflammatory changes, a key feature of early BIP. We prospectively explored the abilty of PET scan to detect early BIP and compared it with standard existing modalities such as DLCO and HRCT in our patients with Hodgkin's Lymphoma (HL). Methods. This was a prospective observational single centre study wherein, newly diagnosed HL treated with the ABVD regimen from November 2011 to July 2012 was included. After baseline staging evaluation, ABVD was instituted. All were monitored every two cycles for any form of BIP, assessed clinically, by PFT, DLCO and PET scan with HRCT chest. If none occurred they were followed up until completion of treatment. Data was analyzed using SPSS v 16.0. Results. 75 patients were enrolled in the study and 59 were evaluable for final analysis. 49% had advanced stage, 12% were smokers and 8% had history of tuberculosis. 25 (40%) had features suggestive of BIP based on any one or combination of tests. 11/25 showed PET positivity but 14/25 were negative on PET while showing clinical or PFT findings indicative of BIP. 7/25 and 9/25 were positive only on PET and DLCO respectively but were asymptomatic for BIP. 5/25 were clinically symptomatic for BIP and correlated with DLCO but were negative on PET. Only 2/25 was both positive by PET and PFT combined but remained asymptomatic. 2/25 patients had all three parameters indicative of BIP. 34 patients remained negative. Conclusions. Our study showed PET scan to be sensitive in detecting early BIP but did not directly correlate with standard testing and clinical suspicion. It however provides a platform for exploring its utility for detecting early BIP.

Table 1.

BLEOMYCIN TOXICITY	NUMBERS(25)	PERCENTAGE
CLINICAL +PFT	5	8.5
PFT	9	15.3
PET	7	11.9
PET+PFT	2	3.4
CLINICAL+PFT+PET	2	3.4

P125

EARLY EVALUATION OF RESPONSE BY PET/TAC IN PATIENTS DIAGNOSED OF HODGKIN LYMPHOMA IN EARLY AND ADVANCED DISEASE

García Feria A, Escrivà A, Andreu R, Varzaru A, Ribas P, Fernández Llavador MJ, Sayas MJ, Fernández Zarzoso M, Juan ML, Cejalvo MJ, Pedreño M, Ros J, Tolosa A, Panero M, Ferrer S

Department of Haematology. University Doctor Peset Hospital. Valencia, Spain

Introduction. The prognosis in Hodgkin lymphoma (HL) has improved due to the polychemotherapy schemes (QT), but the long-term toxicity forces us to optimize the administered treatment. The response evaluation by PET/TC allows to individualize the management of patients. Methods. Descriptive study of patients diagnosed with HL and the help of PET/TC in early evaluation. There were studied, retrospectively, clinical-biological characteristics, treatment and follow-up of 70 patients diagnosed of HL between 2000 and 2011. There were considered unfavorable prognosis factors those established by the EORTC for early stages and Hassenclever's IPS for advanced. Results, The median of age was 34 years (16-77). QT scheme was in all cases ABVD (median of 4 cycles in early stage, 6 in IIB and 7 in advanced), except in a case (COPP). Patients with early stage disease (38) were treated by combined therapy (QT + RT), except 4 (only QT). The rate of complete response (CR) was 92% and of relapses 6%. With early evaluation of the response by PET/TC in 23 patients, the progression free survival(PFS) in patients with negative PET/TC (78%) was 100% and in cases with positive PET/TC (22%) of 60%. With a median of follow-up of 68 months, the overall survival rate(OSR) is 94%. Patients with advanced disease (32, including 8 IIB, all of them with poor prognosis factors), 21 received only QT and 11 QT + RT. The prognosis evaluation of response with PET/TC was negative in 13 patients, with a PFS of 85% (2 early relapses) and positive in one case, which reached CR and has not relapsed. The other patients, without early evaluation, reached CR and have not relapsed. Though 71% of the patients was presenting unfavorable risk factors (IPS=3), with a median of follow-up of 77 months, CR rate is 88% and the rate of relapses of 14%, with a OSR of 91% (82% in patients with high IPS). Conclusions. HL has a high OSR, even in advanced stages and unfavorable prognosis factors. The early evaluation by PET/TC has a high negative predictive value (NPV) in patients with HL, helping to reduce secondary toxicity.

Relapsed and Refractory Hodgkin lymphoma

T126
PHASE 2 STUDY EVEROLIMUS FOR RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA (CHL)

Johnston PB,[1] Pinter-Brown L,[2] Rogerio J,[3] Warsi G,[3] White K,[3] Ramchandren R[4]

[1]Mayo Clinic, Rochester, MN, USA; [2]Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [4]Karmanos Cancer Institute, Detroit, MI, USA

Background. Novel treatment options are needed to improve outcomes in patients with cHL that is refractory to or relapses after initial chemotherapy or subsequent high-dose chemotherapy with autologous hematopoietic stem cell transplant (AHSCT). The oral mammalian target of rapamycin inhibitor everolimus showed promising efficacy and acceptable toxicity in 19 patients with heavily pretreated cHL enrolled in a phase 2 study of everolimus for relapsed, rare lymphomas. To confirm everolimus efficacy and safety in patients with relapsed/refractory cHL, we conducted a multicenter, open-label, 2-step, phase 2 study. Methods. Adults with cHL that progressed after high-dose chemotherapy with AHSCT or a gemcitabine-, vinorelbine-, or vinblastine-containing regimen received everolimus 10 mg/day until disease progression or unacceptable toxicity. Response was assessed every 12 weeks via computed tomography with contrast or integrated positron emission tomography/computed tomography with contrast. The primary study endpoint was the overall response rate (ORR) per the modified response criteria for malignant lymphoma (Cheson 2007). Secondary endpoints included the disease control rate (DCR; percentage of patients with complete or partial response), duration of response, duration of disease control, progression-free survival (PFS), and safety. Results. Fifty-seven patients were enrolled (57.9% women; median age, 32.0 years; 57.9% pretreated with AHSCT; 66.7% experienced disease progression during previous therapy). ORR and DCR were 42.1% and 77.2%, respectively. Median time to response, duration of response, and PFS were 57 days, 85.5 days, and 9.0 months, respectively. Seven patients remain on treatment (average duration, 2.08 years), including 1 patient who experienced a partial response and has been on therapy for 2.88 years (Table). The most common grade 3/4 adverse events were thrombocytopenia (21.1%) and anemia (12.3%). Stomatitis was experienced by 24.6% of patients and was of grade 3 severity in 3.5%. Pneumonitis was observed in 10.5% of patients and was of grade 1 severity in 3.5% and grade 2 severity in 7.0%; only 1 patient discontinued therapy due to pneumonitis. Conclusions. The favorable efficacy, short time to response, and manageable safety profile observed in this heavily pretreated, relapsed/refractory cHL population confirm previous results and support further evaluation of everolimus in cHL.

Table 1.

Patient	Best Overall Response	Current Response	Duration of Therapy, years
1	Partial response	Partial response	2.88
2	Partial response	Partial response	1.95
3	Unknown	Unknown	1.54
4	Partial response	Partial response	2.45
5	Partial response	Partial response	1.94
6	Complete response	Complete response	1.54
7	Stable disease	Stable disease	2.26

T127
OUTCOME OF PATIENTS TREATED WITH AUTOLOGOUS STEM-CELL TRANSPLANTATION FOR FIRST RELAPSED OR REFRACTORY HODGKIN LYMPHOMA: A LONG-TERM ANALYSIS OF THE PROSPECTIVE LYSA/SFGM-TC H96 TRIAL

Sibon D,[1] Resche-Rigon M,[2] Morschhauser F,[3] Fermé C,[4] Dupuis J,[5] Marçais A,[6] Bouabdallah R,[7] Sebban C,[8] Salles G,[9] Brice P[10]

[1]Necker University Hospital, Paris, France; [2]Saint-Louis University Hospital, Paris, France; [3]Claude Huriez University Hospital, Lille, France; [4]Gustave Roussy Institute, Villejuif, France; [5]Henri Mondor University Hospital, Créteil, France; [6]Necker University Hospital, Paris, France; [7]Paoli-Calmettes Institute, Marseille, France; [8]Léon Bérard Cancer Center, Lyon, France; [9]Lyon-Sud University Hospital, Pierre Bénite, France; [10]Saint-Louis University Hospital, Paris, France

Aims. To assess prospectively the long-term efficacy and toxicity of autologous stem-cell transplantation (ASCT) for first relapsed or refractory Hodgkin lymphoma (HL) patients (pts) included in the H96 trial (Morschhauser F, J Clin Oncol 2008, median follow-up 4.25 years). Here we present an updated analysis after a median follow-up of 10.4 years. Patients and Methods. H96 trial evaluated a risk-adapted salvage treatment with single or tandem ASCT for 245 HL pts. Poor-risk pts (n=150) had primary refractory HL (n=77) or unfavorable relapse (≥2 of the following risk factors at first relapse: time to relapse <12 months, stage III or IV at relapse, and relapse within previously irradiated sites, n=73) and were eligible for tandem ASCT. Intermediate-risk pts (n=95) had one risk factor at first relapse and were eligible for single ASCT. Freedom from second failure (FF2F) was the primary end-point. Results. By intent-to-treat analysis, the 10-y FF2F and overall survival (OS) rates were 64% and 70%, respectively, for the intermediate-risk group, and 40% and 47%, respectively, for the poor-risk group. Disease status at time of ASCT (1999 international response criteria) was a major prognostic factor driving outcome. In the poor-risk group, the 10-y OS was 68%, 58%, 16% and 22% for pts in complete remission (CR)/unconfirmed CR (CRu), partial remission (PR), stable disease (SD) and progressive disease (PD), respectively (p<0.0001), without significant difference between CR/CRu and PR pts (p=0.12). In the intermediate-risk group, 92/95 pts were in CR/CRu or PR at time of ASCT. The 10-y OS was 72% and 66% for pts in CR/CRu and PR, respectively, without significant difference (p=0.96).In the poor-risk group and the intermediate-risk group, the 10-y cumulative incidence of relapse was 51% and 27%, respectively. In all, 110 pts died (intermediate-risk group, n=30; poor-risk group, n=80). The main cause of death was HL (50% and 85% of causes of death, in the intermediate-risk group and the poor-risk group, respectively). Conclusion. With long-term follow-up, single ASCT remains appropriate for intermediate-risk pts. For poor-risk-pts, tandem ASCT remains a valuable option for pts in CR/CRu or PR at time of ASCT.

T128
PET ADAPTED SEQUENTIAL SALVAGE THERAPY WITH BRENTUXIMAB VEDOTIN AND AUGMENTED ICE FOR TRANSPLANT ELIGIBLE PATIENTS WITH RELAPSED AND REFRACTORY HODGKIN LYMPHOMA

Moskowitz AJ, Schöder H, Gerecitano J, Hamlin P, Horwitz S, Matasar M, Keskinyan VS, McCall S, Noy A, Palomba ML, Portlock C, Straus D, Yahalom J, Younes A, Zelenetz A, Moskowitz CH

Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Background. Pre-transplant FDG-PET (PET) normalization is one of the strongest predictors of outcome following autologous stem cell transplant (ASCT) for patients with relapsed or refractory (rel/ref) Hodgkin lymphoma (HL). We have previously shown that the outcome for patients with normal pre-transplant PET is excellent, regardless of whether PET normalization is achieved following ICE therapy alone or ICE followed by additional non-cross resistant chemotherapy. Due to its high efficacy and excellent tolerability in ASCT failures, we aimed to determine whether brentuximab vedotin (BV) can replace ICE salvage therapy or increase the rate of PET normalization through PET-adapted sequential administration with augmented ICE (aug-ICE). Methods. Patients with rel/ref HL who have failed 1 prior regimen are enrolling on this phase II clinical trial. Patients receive weekly BV administered at 1.2 mg/Kg IV weekly for 3 weeks on and 1 week off for 2 cycles, followed by PET. Patients who achieve normalization of PET (Deauville 2 or less) proceed to ASCT. Patients with PET scores of Deauville 3 or

higher receive 2 cycles of aug-ICE. Results. 40 of planned 46 patients have enrolled and 33 are evaluable for response, including 70% males and 45% with primary refractory disease. The most common adverse reactions of any grade with BV are rash (70%) and neuropathy (45%). Of the 33 evaluable pts, 10 (30%) achieved PET normalization following BV alone; 26 (79%) achieved normalization of PET following the entire treatment program and proceeded to ASCT. Among the remaining 7 pts, 1 proceeded to ASCT in good PR, 5 received radiation therapy with continued response and proceeded to ASCT, and 1 remains with active disease. Overall, 32 of 33 pts have undergone ASCT and with a median follow-up of 6 months following ASCT, there have been 2 relapses and 1 death due to progressive multifocal leukoencepalopathy. Conclusion. PET-adapted sequential salvage therapy with BV followed by augICE has allowed 30% of patients to avoid ICE-based therapy, produces high CR rates, and facilitates referral to ASCT for virtually all pts. Updated results. Will be presented at the meeting.

P129
THE PROGNOSTIC ROLE OF DIFFERENT HISTOPATHOLOGIC GROWTH PATTERNS IN NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA: A REPORT FROM THE GERMAN HODGKIN STUDY GROUP (GHSG)

Hartmann S,[1] Eichenauer DA,[2,3] Plütschow A,[2,3] Mottok A,[4] Roshanak B,[5] Koch K,[6] Bernd HW,[7] Cogliatti S,[8] Hummel M,[9] Feller AC,[7] Ott G,[10] Möller P,[11] Rosenwald A,[4] Stein H,[5] Hansmann ML,[1] Engert A,[2,3] Klapper W[6]

[1]Dr. Senckenberg Institute of Pathology, Goethe University, Frankfurt am Main, Germany; [2]First Department of Internal Medicine; [3]German Hodgkin Study Group, University Hospital of Cologne, Germany; [4]Institute of Pathology, UniversityWürzburg, Germany; [5]Practice of Pathology, Berlin, Germany; [6]Institute of Pathology, Haematopathology Section and Lymph Node Registry, UniversitätsklinikumSchleswig-Holstein, Campus Kiel, Germany; [7]Institute of Pathology, UniversitätsklinikumSchleswig-Holstein, Campus Lübeck, Germany; [8]Institute of Pathology, Kantonsspital St. Gallen, Switzerland; [9]Institute of Pathology, Charité University Hospital, Berlin, Germany; [10]Department of Clinical Pathology, Robert-Bosch-Krankenhaus, and Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany; [11]Institute of Pathology, University Hospital Ulm, Germany

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) accounts for an estimated 5% of all Hodgkin lymphoma cases. NLPHL represents a diagnostic challenge since histopathologic variants can mimic aggressive B-cell non-Hodgkin lymphoma. The aim of the present study was to evaluate the possible role of histopathologic variants on the clinical outcome. Biopsies of 423 NLPHL patients treated within the prospective German Hodgkin Study Group trials HD10-HD15, LPHD, LP and RIPL were reviewed and classified as tumor-cell rich (TCR, n=10), typical NLPHL (n=308) or histopathologic variants characterized by lymphoma cells outside of B-cell nodules or B-cell depletion of the microenvironment (n=105). Differences in terms of baseline characteristics and clinical outcome between patients presenting with typical NLPHL histology and histopathologic NLPHL variants were evaluated. A variant histopathologic growth pattern was associated with advanced disease (29.5% versus 14.6%) and an increased 5-year progression/relapse rate (18.1% versus 6.5%) as compared with a typical NLPHL histology. Variant NLPHL histology represented an independent prognostic factor (odds ratio=2.955) in a multivariate model for progression/relapse. A prognostic score including the risk factors variant histopathologic growth pattern, low serum albumin and male gender was derived from the model and allowed the definition of three distinct risk groups. Patients presenting with histopathologic NLPHL variants have a poorer outcome as compared with typical NLPHL. According to a newly developed prognostic score combining histology and clinical features, NLPHL patients can be allocated to defined risk groups for progression/relapse. High-risk patients may benefit from novel treatment strategies.

P130
A PHASE I STUDY OF BISPECIFIC ANTI-CD30 X ANTI-CD16A ANTIBODY CONSTRUCT AFM13 IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

Rothe A,[1] von Tresckow B,[1] Topp MS,[2] Younes A,[3] Eichenauer DA,[1] Hummel H,[2] Reiners KS,[4] Dietlein M,[5] Kessler J,[4] Ravic M,[6] Hucke C,[6] Pogge von Strandmann E,[4] Engert A[1]

[1]Department I for Internal Medicine, University Hospital of Cologne, Cologne, Germany; [2]Department of Internal Medicine II, Division of Hematology and Medical Oncology, Wuerzburg University Medical Center, Wuerzburg, Germany; [3]Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Laboratory for Immunotherapy. Department I for Internal Medicine, University Hospital of Cologne, Cologne, Germany; [5]Department of Nuclear Medicine, University Hospital of Cologne, Cologne, Germany; [6]Affimed Therapeutics AG, Heidelberg, Germany

Background. AFM13 is a bispecific, tetravalent human antibody construct (TandAb®) designed for the treatment of CD30-expressing malignancies. AFM13 specifically targets CD30 on Hodgkin tumor cells and CD16A on NK cells. Preclinical data demonstrate a specific and efficient anti-tumor activity. Methods. This was an open, single arm phase I dose escalation trial for patients with relapsed and/or refractory Hodgkin Lymphoma. The overall objective of this study was to evaluate safety, tolerability, pharmacokinetics, immunogenicity, antitumor activity, the maximum tolerated dose (MTD) and the optimal biological dose (OBD) of AFM13. Each patient received a single cycle, consisting of four weekly doses of AFM13. The doses were escalated in cohorts of three patients at dose levels of 0.01, 0.04, 0.15, 0.5, 1.5, 4.5 and 7.0 mg/kg. An additional group of patients received 4.5 mg/kg twice weekly. Antitumor activity was assessed using Cheson criteria. Results. 24 patients with Hodgkin Lymphoma completed the escalation phase. The median age was 38. 22/28 patients had received prior high-dose chemotherapy and autologous stem cell transplantation. Patients had received a median of 6 prior lines of treatment; 14/28 patients were refractory to their most recent therapy. All weekly doses from 0.01 mg/kg to 7mg/kg, as well as the twice weekly dosing regimen, proved to be well tolerated and safe, and the MTD was not reached. Adverse events were generally mild, with the most frequent drug-related event being grade 1/2 infusion reaction in 15/28 patients. One patient developed a possibly drug-related dose-limiting grade 4 hemolytic anemia. Of 26 evaluable patients 2 patients achieved PR and 14 SD. Around 50% of patients achieved reduction in their tumor volumes. There was a statistically significant dose dependent increase in activation of NK cells, and reduction in sCD30. Geometric mean apparent terminal half-life of AFM13 was 22.4 h. Conclusions. AFM13 has demonstrated encouraging biologic activity and seems to be a new feasible targeted therapy for heavily pre-treated patients with Hodgkin Lymphoma. Full analysis and clinical data from all patients will be presented.

P131
BRENTUXIMAB VEDOTIN AS FIRST LINE SALVAGE THERAPY IN RELAPSED/REFRACTORY HL

Chen R, Palmer J, Thomas S, Kim Y, Chen BT, Krishnan A, Nathwani N, Sahebi F, Martin P, Mott M, Matsuoka D, Forman S

City of Hope National Medical Center, Weill Cornell Medical College, New York, NY, USA

Brentuximab vedotin (BV), an antibody-drug conjugate, selectively delivers monomethyl auristatin E to CD 30+ lymphoma cells. In a pivotal phase II trial for relapsed/refractory Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT), BV demonstrated an overall response rate (ORR) of 75% and complete response (CR) rate of 34%. To examine outcomes of BV given prior to ASCT, we retrospectively analyzed data from a consecutive case-series of HL patients who received BV as first -line salvage therapy at City of Hope. Three patients received BV as salvage therapy on an expanded access protocol and 18 were on a prospective phase II trial. All patients had relapsed/refractory HL post-induction therapy +/- consolidative radiotherapy. Patients were treated with 1.8 mg/kg of BV intravenously every 3 weeks as outpatients for up to 4 cycles. Response rate was determined with either CT or PET at cycle 2 and CT/PET at cycle 4 as per 2007 Cheson criteria. 21 patients were treated between 8/2011 to 5/2013. See table 1 for characteristics. All patients received ABVD or ABVD/BEACOPP combination except one pediatric patient who received ABVE-PC + vinorelbine/ifos-

famide. The ORR was 80.9%; CR was 38%; PR was 42.8%; and SD 19%. Grade 1-2 adverse events (AEs) >20% include peripheral neuropathy (52%), rash (52%), hypoglycemia (28.5%), fatigue (23.8%), and AST elevation (23.8%). No G2 neuropathy was reported. Grade 3-4 AE include 1 rash (g3) , 1 fever (g3) , 1 pneumonitis (g3), 1 non-cardiac chest pain (g3), and 1 lymphopenia (g4). All grade 3-4 AEs resolved. The use of growth factors or red blood cell or platelet transfusions was not required. 15/21 patients have undergone stem cell mobilization with cyclophosphamide/G-CSF or G-CSF alone. The median cell dose collected was 5.05 x 10^6 CD34+ cells (2.78-22.41,). All fifteen patients have undergone ASCT using either BEAM or CBV conditioning. The median time for ANC>500 was 10 days (7-11) and platelet >20K was 9 days (7-11). Brentuximab vedotin as first-line salvage therapy can produce adequate response rates, has acceptable toxicity and does not adversely impact stem cell collection or post-ASCT engraftment.

Table 1.

Characteristics	N (%) or Median (range)
Age	36.5 (11-64)
Gender	Female 13
Stage	Stage II (11)
	Stage III (5)
	Stage IV (4)
Bulky disease (>5 cm)	13 (61.9%)
B symptoms	14 (66.7%)
Consolidative XRT	6 (28.6%)
Response to induction	Primary refractory (11)
	Relapsed (10), median 7 month (3-45)
Induction therapy	ABVD (17)
	ABVD/BEACOPP (2)
	ABVE-PC/Vinorelbine+Ifosphamide (1)

P132
PHASE 1/2 STUDY OF BRENTUXIMAB VEDOTIN IN PEDIATRIC PATIENTS WITH RELAPSED OR REFRACTORY (RR) HODGKIN LYMPHOMA (HL) OR SYSTEMIC ANAPLASTIC LARGE-CELL LYMPHOMA (SALCL): INTERIM PHASE 1 SAFETY AND PHARMACOKINETIC (PK) DATA

Locatelli F,[1] Gore L,[2] Mauz-Körholz C,[3] Rosolen A,[4] Landman-Parker J,[5] Sanchez de Toledo J,[6] Beishuizen A,[7] Franklin A,[8] Fasanmade A,[9] Wang J,[9] Fingert H,[9] Labotka R,[9] Neville K[10]

[1]Ospedale Pediatrico Bambino Gesù, Rome, and University of Pavia, Pavia, Italy; [2]Children's Hospital Colorado, Aurora, USA; [3]Universitaetsklinikum Halle, Halle, Germany; [4]Università di Padova, Padova, Italy; [5]Hopital D'Enfants Armand-Trousseau, Paris, France; [6]Hospital Infantil Vall d'Hebron, Barcelona, Spain; [7]Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; [8]Children's Cancer Hospital, MD Anderson Cancer Center, Houston, USA; [9]Millennium: The Takeda Oncology Company, Cambridge, USA; [10]Children's Mercy Hospital, Kansas City, USA

Brentuximab vedotin (ADCETRIS®) is a CD30-targeted antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E. Data on brentuximab vedotin in children with malignant lymphomas are limited but encouraging. The phase 1 portion of this open-label, multicenter study prospectively evaluated safety, PK and recommended phase 2 dose (RP2D) of brentuximab vedotin in children with RR, CD30-expressing HL or sALCL. Patients, aged 2 to <18 years (sALCL) or 5 to <18 years (HL), received brentuximab vedotin by IV infusion Q3wk; starting dose of 1.4 mg/kg with escalation to 1.8 mg/kg (3+3 design). Blood samples for PK analysis: before, and 5 mins after infusion on day 1 (all Cycles); Days 2, 3, 5, 14 (Cycles 1, 8); Days 2, 3, 5 (Cycle 2). 12 patients (median 14.5 years [range, 9–17]; 10 HL, 2 sALCL) received brentuximab vedotin (mg/kg/dose: 1.4, n=3; 1.8, n=9). The 1.8 mg/kg cohort was expanded from 6 to 9 patients to increase the total phase 1 pediatric experience to 12 patients before the phase 2 portion. At data cut-off, patients had received median 7 cycles (range, 1–14); 11 (92%) had ≥1 drug-related adverse-event (DRAE): 2 at 1.4 mg/kg, 9 at 1.8 mg/kg. 5 patients (42%) had Gr ≥3 DRAEs at 1.8 mg/kg. Most frequent treatment-emergent AEs: nausea (67%), pyrexia (50%), upper abdominal pain, paresthesia (33% each), abdominal pain, diarrhea, musculoskeletal pain, rhinitis (25% each). 7 serious AEs occurred in 6 patients at 1.8 mg/kg: Gr 1 pyrexia (n=1) unrelated to treatment; Gr 1 pain in extremity (n=1); Gr 2 supraventricular tachycardia (n=1) unrelated; Gr 3 febrile neutropenia and prolonged Gr 3 hepatotoxicity (n=1); Gr 3 anaphylaxis (n=1); 1 death (cardiac arrest) considered unrelated to treatment. Repeat cycles were generally well tolerated with starting doses up to 1.8 mg/kg Q3wk with 1st-cycle dose-limiting toxicities in 1 of 9 patients; Gr 3 hepatotoxicity (Day 13), Gr 3 febrile neutropenia (Day 14). PK analyses showed dose-dependent exposure. Preliminary efficacy data will also be presented. The phase 2 portion is ongoing with starting dose 1.8 mg/kg Q3wk, the RP2D in this pediatric population.

P133
ANTITUMOR ACTIVITY OF BRENTUXIMAB VEDOTIN IN PATIENTS WITH RELAPSED OR REFRACTORY (RR) HODGKIN LYMPHOMA (HL) FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANT (ASCT): META-ANALYSIS COMPARISON

Bonthapally V,[1] Wu E,[2] Macalalad A,[2] Yang H,[2] Shonukan O,[1] Liu Y,[1] Chi A,[1] Huebner D[1]

[1]Millennium: The Takeda Oncology Company, Cambridge, MA, USA; [2]Analysis Group Inc., Boston, MA, USA

Background. Brentuximab vedotin (ADCETRIS®), a CD30-targeted antibody-drug conjugate, has conditional approval in Europe for the treatment of adult patients with RR CD30-positive HL following ASCT or following ≥2 prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. This meta-analysis compared the antitumor activity of brentuximab vedotin in patients with RR HL post-ASCT patients to that of other agents as published in the literature. Methods A systematic literature review was conducted to identify studies, published 1993–February 2013, which reported complete remission (CR) rates of different treatments in patients with RR HL post-ASCT. Five databases were searched, including EMBASE and MEDLINE, and the WHO International Clinical Trials Registry Platform. References in relevant reviews published since 2011 were searched manually for additional studies. English-language publications reporting a CR rate for the RR HL population were included if ≥20 RR HL patients were in the study, of whom ≥80% were aged ≥12 years and ≥50% had failed prior ASCT. Principle treatments of allogeneic stem cell transplant, ASCT, or radiotherapy were excluded. CR rates of agents from the studies identified were compared in a meta-analysis to that of brentuximab vedotin observed in a single-arm phase 2 trial of adult patients with RR HL post-ASCT (SG035-0003; NCT00848926). Results. Of the 4092 publications screened, 17 studies were eligible for inclusion. Thirteen studies were prospective (mostly phase 1 or 2); four were retrospective. Fourteen studies reported various drug regimens, including 4 with gemcitabine. Studies were generally small, comprising 22–129 HL patients, with widely varying baseline patient characteristics. Median number of prior regimens was >2–5, with 62–100% having prior ASCT. In SG035-0003, all RR HL patients (N=102) had prior ASCT, with a median of 3.5 prior regimens. In the 17 studies identified (N=812), the estimated overall CR rate was 10.96% (95% confidence interval [CI]: 4.5, 17.4; range, 0-38.5%) compared with 33.3% (95% CI: 24.3, 43.4) for brentuximab vedotin (p=0.00009). Conclusions. This meta-analysis showed the antitumor activity of brentuximab vedotin appears to exceed that of other therapies in RR HL post-ASCT.

P134

PROGRESSION-FREE SURVIVAL (PFS) ANALYSES OF TWO PIVOTAL PHASE 2 STUDIES OF BRENTUXIMAB VEDOTIN IN PATIENTS WITH RELAPSED OR REFRACTORY (RR) HODGKIN LYMPHOMA (HL) OR SYSTEMIC ANAPLASTIC LARGE-CELL LYMPHOMA (SALCL)

Radford J,[1] Younes A,[2] Pro B,[3] Chi A,[4] Westin E,[4] Huebner D,[4] Engert A[5]

[1]The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [3]Thomas Jefferson University and Hospitals-Kimmel Cancer Center, Philadelphia, PA, USA; [4]Millennium: The Takeda Oncology Company, Cambridge, MA, USA; [5]University Hospital of Cologne, Cologne, Germany

Introduction. Brentuximab vedotin (ADCETRIS®), a CD30-targeted antibody-drug conjugate, has demonstrated notable antitumor activity, in terms of overall response and complete remission rates, and a manageable safety profile in two pivotal phase 2 trials (SG035-0003: RR HL following autologous stem cell transplant [ASCT]; SG035-0004: RR sALCL. Both studies funded by Seattle Genetics, Inc. and Millennium: The Takeda Oncology Company). A post-hoc analysis was conducted to compare PFS achieved with brentuximab vedotin versus last prior systemic therapy in these patient populations. Methods PFS (as assessed by the investigator) was determined with brentuximab vedotin (02 April 2012 data cutoff) and last prior systemic therapy in the intent-to-treat populations. Results. Median age of RR HL post-ASCT patients in SG035-0003 (N=102) was 31 years (range, 15–77); median 3.5 prior therapies (range, 1–13); 91% received prior ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). After a median of 27 months' follow-up, 62% patients had achieved a longer PFS with brentuximab vedotin than with their last prior systemic therapy. 72 patients relapsed <12 months post-ASCT; median PFS was 8.4 months (range, 1.2+–36.4) with brentuximab vedotin and 5.1 months (range, 1.0–35.5) with last prior systemic therapy. 46 patients relapsed <6 months post-ASCT; median PFS was 9.3 months (range, 1.2+–35.3+) with brentuximab vedotin versus 5.9 months (range, 1.1–12.0) with last prior systemic therapy. Median age of RR sALCL patients in SG035-0004 (N=58) was 52 years (range, 14–76); median 2 prior therapies (range, 1–6); 26% underwent prior ASCT, 72% received prior CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). After a median of 22 months' follow-up, 67% patients experienced longer PFS with brentuximab vedotin than with their last prior systemic therapy. Conclusion. In this post-hoc analysis, more than 60% of heavily pretreated patients with RR HL post-ASCT and RR sALCL achieved a longer PFS with brentuximab vedotin than with the last prior systemic therapy. In contrast to prior treatment paradigms, PFS with last prior systemic therapy did not predict PFS with brentuximab vedotin, suggesting lack of cross-resistance to brentuximab vedotin.

P135

A MULTICENTER, PHASE 1/2 STUDY OF JNJ-40346527, A COLONY STIMULATING FACTOR-1 RECEPTOR (CSF-1R) INHIBITOR, IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

von Tresckow B,[1] Morschhauser F,[2] Ribrag V,[3] Topp M,[4] Chien C,[5] Seetharam S,[6] Aquino R,[6] Kotoulek S,[6] Khan I,[5] de Boer C,[7] Engert A[1]

[1]University Hospital of Cologne, Department I of Internal Medicine, Cologne, Germany; [2]Centre Hospitalier Régional Universitaire (CHRU) de Lille, Lille, France; [3]Institut Gustave Roussy, Villejuif, France; [4]University Hospital of Wurzburg, Medical Clinic and Polyclinic II, Wurzburg, Germany; [5]Janssen Research & Development, L.L.C., NJ, USA; [6]Janssen Research & Development, L.L.C., PA, USA; [7]Janssen Biologics B.V, Leiden, Netherlands

Introduction. JNJ 40346527 is a selective inhibitor of the colony stimulating factor-1 receptor (CSF-1R) tyrosine kinase. It impairs macrophage recruitment in animal models and reduces viability of Hodgkin lymphoma (HL) cell lines in vitro. This study investigates JNJ-40346527 as treatment for relapsed or refractory classical HL. Methods Patients (pts) were assigned to sequential cohorts of oral daily dose of JNJ-40346527 (150, 300, 450, 600 mg QD, and 150 mg BID). For dose escalation phase, primary endpoint was to establish the recommended phase 2 dose. Secondary endpoints included safety, overall response rate (ORR), pharmacokinetics (PK), and pharmacodynamics (PD). Results. The study is ongoing in escalation phase. 18 pts ([150 mg: 3; 300 mg: 5; 450 mg: 3, 600 mg: 3] QD, and 150 mg: 4 BID) were enrolled, median age 37 (range, 19–75) years, and median number of prior systemic therapies were 6 (range, 3–12); 10/18 pts: >5 prior systemic therapies and 15/18 pts: autologous stem cell transplant. In addition, 15/18 pts underwent radiotherapy and 3/18 pts had HL related surgery. No dose limiting toxicities were observed. Maximum tolerated dose has not been established yet. As per 21 Feb 13, 10 pts are ongoing in the study with 1 pt showing a complete response and 5 pts showing stable disease. 7 pts discontinued treatment due to progression of disease, and 1 pt due to treatment-emergent adverse events (TEAEs). Median number of cycles received was 2 (range, 1–11). Most common (≥20% of pts) possibly drug-related TEAEs (per investigator assessment) were headache, nausea, and fever. Preliminary PK analysis showed that JNJ-40346527 exposure increased in a near dose-proportional manner over the dose range of 150–450 mg QD but plateaued at 600 mg QD. Serum trough levels were within projected pharmacologically active concentration range at a dose as low as 150 mg QD. Preliminary PD analysis confirmed target engagement and showed >80% inhibition of CSF-1R phosphorylation at 4 hours post dosing in peripheral blood mononuclear cells stimulated with CSF-1. Conclusion Preliminary results indicate that JNJ-40346527 may be effective for the treatment of Hodgkin lymphoma and has a favorable safety profile.

P136

PHASE II STUDY OF OFATUMUMAB PLUS ESHAP (O-ESHAP) AS SALVAGE TREATMENT FOR PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN'S LYMPHOMA AFTER FIRST-LINE CHEMOTHERAPY

Martínez C, Rodriguez-Calvillo M, García-Sanz R, Terol MJ, Pérez-Ceballos E, Xicoy B, Cantalapiedra A, Domingo E, Rodriguez-Salazar MJ, Sampol A, Espeso M, López J, Briones J, Sureda A

Hodgkin's Lymphoma Subcommittee of Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO)

The management of recurrent/refractory Hodgkin's lymphoma (HL) remains challenging. Previous published data have suggested that infiltrating normal B lymphocytes in classic HL lesions may contribute to the survival of Hodgkin and Reed-Sternberg cells in vivo. The objective of this prospective, multicenter, phase II trial was to investigate the activity of an anti-CD20 monoclonal antibody, ofatumumab, in combination to a standard platinum-based salvage regimen, ESHAP (O-ESHAP), for patients with classical HL failing to first line chemotherapy. Fifty-nine patients (34 M / 25 F, median age 32 years, range 18-71) were enrolled in the study. Treatment consisted on three cycles of ESHAP plus ofatumumab 1,000 mg days 1 and 8 on first cycle and day 1 on second and third cycles. At the time of study entry, 65% of patients had III-IV nn Arbor satge, 20% bulky disease, 24% B symptoms, 41% extranodal HL and 55% > 3 involved nodal areas. Eighty-seven percent patients received 3 cycles of O-ESHAP as scheduled; three patients 2, and four 1 cycle (2 patients due to toxicity, 2 patient's consent withdraw, 2 HL progression, and 1 physician's decision). Grade 3-4 WHO hematological and non-hematological toxicities were observed in 16%/30%, 17%/16%, and 13%/15% after cycles 1, 2, and 3, respectively. Overall response rate (ORR) was 73% (45% CR and 28% PR). In multivariate analysis, B symptoms (p=.001) and response to 1st line chemotherapy (p=.08) were the most important prognostic factors for response. Adequate PBSCs collection was achieved in 97% mobilized patients. In conclusion, the high response rate, in particular the CR rate, the low toxicity profile, and the very high mobilizing potential of the O-ESHAP regimen strongly suggest that patients with relapsed/refractory HL may benefit from the use of this salvage induction regimen. Authors thank GlaxoSmithKline for its support in this trial.

P137

A PHASE III RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED MULTI-CENTER STUDY OF PANOBINOSTAT FOR MAINTENANCE OF RESPONSE IN PATIENTS WITH HODGKIN LYMPHOMA WHO ARE AT RISK FOR RELAPSE AFTER HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT: FINAL RESULTS AFTER EARLY TRIAL DISCONTINUATION

von Tresckow B,[1] Skotnicki A,[2] Lisukov I,[3] Srivastava S,[4] Morgan D,[5] Morschhauser F,[6] Stelitano C,[7] Szer J,[8] Eichenauer DA,[1] Abramson J,[9] Sureda A,[10] Ferme C,[11] Engert A[1]

[1]German Hodgkin Study Group (GHSG), Department of Internal Medicine I, University Hospital of Cologne, Germany; [2]Malopolskie Centrum Medyczne s.c., Krakow, Poland; [3]Pavlov St Petersburg State Medical University, St. Petersburg Russian Federation; [4]Indiana University Melvin and Bren Simon Cancer

Center, Hematology/Oncology Department, Indianapolis, USA; [5]Vanderbilt University Medical Center, Nashville, USA; [6]CHRU Lille Hopital Claude Huriez, Lille, France; [7]Azienda Ospedaliera Bianchi E Melacrino Morelli, Reggio Calabria, Italy; [8]Royal Melbourne Hospital, Parkville, Australia; [9]Massachusetts General Hospital, Boston, MA, USA; [10]Hospital de la Santa Creu I Sant Pau, Barcelona, Spain; [11]Hematology, Medecine Departement, Institut de Cancerologie Gustave Roussy, Villejuif, France

Introduction. High dose chemotherapy with autologous stem cell transplant (ASCT) is the treatment of choice for Hodgkin Lymphoma (HL) patients suffering from relapse or progression after first line therapy. However, patients with recurrence after ASCT have a very poor prognosis. Thus, the oral deacetylase inhibitor panobinostat was evaluated as maintenance therapy for patients at risk for relapse after ASCT to prevent recurrences. Methods. HL patients after ASCT with at least one of the risk factors primary refractory disease, early relapse (<12 months), multiple relapses, stage III/IV disease or hemoglobin <10,5 g/dl at relapse prior to transplant were randomized to receive oral panobinostat (45mg three times a week, every other week) or placebo (2:1 randomization) in this phase III randomized, double blind, placebo controlled multi-center trial. As per the original protocol, disease-free survival (DFS) was the primary endpoint. However, the trial was terminated prematurely due to slow recruitment and the primary objective was changed to the provision of drug to ongoing patients randomized to panobinostat and to the evaluation of safety in this patient population. Results. The study was closed to enrollment with only a total of 41 patients out of the planned 367 patients enrolled; 27 patients in the panobinostat arm and 14 patients in the placebo arm. Grade 3/4 AEs occurred in 65.4% patients in the panobinostat arm (randomized phase) and 41.7% patients in the placebo arm, most commonly gastrointestinal disorders. Although efficacy could not be formally evaluated due to the small number of patients in this trial, it is interesting to note that more patients from the placebo arm discontinued from the study due to disease progression (28.6% *vs* 14.8% panobinostat patients). Conclusion. Maintenance therapy with oral panobinostat is safe and feasible in HL patients after ASCT. Although the trial could not meet ist original objective due to early termination, descriptive comparison of the disease progression rates suggest a possible role for maintenance therapy after ASCT in HL patients.

P138
PROGNOSTIC FACTORS IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) HODGKIN'S LYMPHOMA (HL) TREATED WITH IGEV AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT): A NATIONWIDE RETROSPECTIVE SURVEY FROM FONDAZIONE ITALIANA LINFOMI (FIL)

Balzarotti M, Anastasia A, Zilioli VR, Spina M, Pulsoni A, Gotti M, Cascavilla N, Angrilli F, Ortu La Barbera E, Botto B, Carella AM, Puccini B, Levis A, Conticello C, Gandolfi S, Tedeschi L, Re A, Massidda S, Giordano L, Brusamolino E, Bellei M, Santoro A

Hematology Unit from: Milano Humanitas Cancer Center , Milano Niguarda, Roma La Sapienza, Pavia San Matteo, S. Giovanni Rotondo, Pescara, Latina, Torino 2, Genova, Firenze, Alessandria, Brescia, Cagliari-Medical Oncology Unit from: Aviano, Catania Mediterraneo, Milano S Carlo, Modena, Italy

Introduction. Pts with R/R HL are treated with induction chemotherapy followed by ASCT. IGEV (ifosfamide , vinorelbine, gemcitabine) attains both high complete remission (CR) rate and mobilizing potential and it is the most widely used induction regimen in this setting in Italy. Thus, we carried out a retrospective analysis in order to reassess the most common prognostic factors in a homogeneously treated pts population. Methods. We collected data of pts treated with IGEV and ASCT in Italy from 1997 to 2007. Pts were at least 18 year-old and were scheduled to receive 2 to 4 pre-transplant IGEV courses . For each prognostic factor, the survival distribution was estimated through Kaplan–Meier method. Log-rank test was used to test differences between survival distributions in univariate analysis. Results. 330 patents are evaluable. Main clinical characteristics: median age 32; M/F 57%/43%; previous regimens 1 64%, >2 36%; refractory/relapsed: 51%/49%; B symptoms 15%, bulky disease 21%, extranodal disease 13%. Post-IGEV CR was obtained in 39% of cases evaluated with CT scan, and in 52% of 204 cases evaluated with PET. Overall, 269 pts proceeded to transplant after IGEV or further chemo. With a median follow-up of 57.7 months for the whole population, median PFS was 50,6 months and median OS was not reached. The table reports factors influencing 4-yr outcome in univariate analsysis : In multivariate analysis, relapsed versus refractory disease influenced both PFS and OS, whereas age , bulky disease and B symptoms influenced only OS. Conclusions. Factors influencing PFS and OS were identified, and will be used to build a prognostic score in IGEV homogenously treated patients with R/R HL.

Table 1.

Characteristic	PFS 4 ys	P value	OS 4 ys	P value
All	52.3		73.3	
Age		0.793		0.015
<40	53.3		78.0	
≥40	50.9		63.3	
Systemic symptoms		<0.001		<0.001
A	57.3		79.0	
B	33.6		52.9	
Bulky		0.191		0.008
No	53.8		75.9	
Yes	44.1		57.7	
Stage		0.028		0.227
I-II	59.5		77.2	
III- IV	44.4		68.8	
Disease Status		<.001		0.007
Relapse > 12	62.7		82.6	
Relapse <12	62.1		84.1	
Refractory	42.6		63.0	

P139
BRENTUXIMAB VEDOTIN IN RELAPSED/REFRACTORY (RR) HODGKIN LYMPHOMA (HL) AND RR SYSTEMIC ANAPLASTIC LARGE-CELL LYMPHOMA (SALCL): A REVIEW OF INTERNATIONAL EXPERIENCE IN THE NAMED PATIENT PROGRAM (NPP)

Zinzani PL,[1] Sasse S,[2] Radford J,[3] Shonukan O,[4] Bonthapally V[4]

[1]Institute of Hematology "Seragnoli", University of Bologna, Bologna, Italy; [2] University Hospital of Cologne, Cologne, Germany; [3]The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [4]Millennium: The Takeda Oncology Company, Cambridge, MA, USA

Introduction. Brentuximab vedotin (ADCETRIS®), a CD30-targeted antibody-drug conjugate, received accelerated approval in the United States for relapsed HL and RR sALCL and conditional approval in Europe for RR CD30+ HL and RR sALCL. The NPP was available to eligible non-US/Canadian patients with RR HL or sALCL until drug approval in their respective countries. We reviewed the published data for brentuximab vedotin given to heavily pretreated patients (Table 1) in the NPP. Methods To identify NPP publications, a systematic literature review (data cut off: May 3, 2013) was conducted (search terms: brentuximab vedotin, SGN-35, ADCETRIS) using PubMed and pre-specified abstract books from 2012 and 2013. References were reviewed manually and selected if patients were treated in the brentuximab vedotin NPP. Patient demographics, prior treatment histories, response, survival, and safety data were reviewed. Results. The literature search found 105 manuscripts and 60 abstracts. 20 NPP publications were identified, describing 14 unique patient cohorts, including 213 patients; 193 received brentuximab vedotin in the NPP, including 4 individual patient case studies. Of the 213 patients, 188 had HL, 24 sALCL, and 1 CD30+ T-cell lymphoma. Table 1 presents the baseline patient characteristics for the 14 cohorts. Among patient cohorts reporting stem cell transplant (SCT) history (12 cohorts, n=161), 65% had received prior autologous SCT; in 5 cohorts (n=106), 10% had prior allogeneic SCT. Table 1 reports the brentuximab vedotin dose and median number of cycles received per cohort. The overall response rate (ORR) for 13 reporting cohorts (n=204; not stated for 1 cohort) was 67%, including a complete remission rate of

28%. Where reported, responses typically occurred in the first 3–4 cycles of brentuximab vedotin. Of 125 available patients, grade 3/4 neuropathy was documented in 13 (12%) patients, grade 3/4 neutropenia in 14 (11%) patients, and grade 3/4 thrombocytopenia in 7 (6%) patients. Across 6 cohorts (n=137), 6 (4%) patients discontinued brentuximab vedotin, all due to peripheral neuropathy. Conclusion In the 'real-world' setting, response rates to brentuximab vedotin are similar to those reported in phase 2 trials. Brentuximab vedotin is generally well tolerated, with reported grade 3/4 toxicity experienced by ≤12% patients.

Table 1. Baseline patient characteristics and median number on brentuximab vedotin cycles received by atoents treated with brentuximab vedotin under the NPP (N=213).

Unique cohort, N (NPP)	Disease	Median age, years (range)	Median number of prior therapies (range)	Brentuximab vedotin dose, mg/kg (frequency)	Median number of brentuximab vedotin cycles received (range)
65 (65)	HL	27.5 (12–66)	4 (2–13)	1.8 (Q3wk)	8 (3–16)
45 (34)	HL	35 (NS)	4 (2–12)	1.8 (Q3wk)	7 (1–12)
30 (21)	20 HL, 10 ALCL	31 (19–69)	4 (1–8)	NS	7 (1–16)
24 (24)	18 HL, 5 ALCL, 1 CD30+ TCL	41.5 (21–78)	3 (2–8)	1.8 (Q3wk)	5.5 (1–13)
16 (16)	14 HL, 2 ALCL	48.5 (NS)[a]	3 (NS)[b]	1.8 (Q3wk)	NS[c]
9 (9)	6 HL, 3 sALCL	36 (21–59)	3 (2–5)	1.8 (Q3wk)	7 (4–9)
8 (NS)	6 HL, 2 ALCL	32 (24–43)	3 (1–7)	NS (Q3wk)	6.5 (2–10)
5 (NS)	HL	25 (18–28	4 (3–5)[d]	1.8 (Q3wk)	NS
4 (4)	HL	19.5 (18–39)	7 (5–9)	1.8 (Q3wk)[f]	10.5 (3–11)
3 (NS)	HL	26 (25–32)	4 (3–7)	NS	10 (4–10)
Case report, N (NPP)	**Disease**	**Age, years**	**Number of prior therapies**	**Brentuximab vedotin dose, mg/kg (frequency)**	**Number of brentuximab vedotin cycles received (range)**
1 (1)	HL	21	2	1.8 (Q3wk)	NS
1 (1)	HL	17	4	1.8 (Q3wk)[g]	NS
1 (1)	ALCL	29	4	NS	NS
1 (1)	sALCL	3	4	1.2 QW, 1.0 Q3wk[e]	16[e]

[a]For n=14, median age was 45 years (range, 24–74); [b]for n=14, median number of prior therapies was 3 (range, 2–6); [c]for n=14, median number of brentuximab vedotin cycles received was 4.5 (range, 2–12); [d]excluding autologous SCT; [e]patient received brentuximab vedotin 1.2 mg/kg QW for 2 cycles, then 1.0 mg/kg Q3wk for 14 cycles; [f]administered with maximum 5 doses of DLI in alternating regimen; [g]administered concomitantly with G-CSF, TPO, IL-11

ALCL, anaplastic large cell lymphoma; DLI, donor-lymphocyte infusion; G-CSF, granulocyte-colony stimulating factor; HL, Hodgkin lymphoma; IL, interleukin; Q3wk, every 3 weeks; QW, every week; NPP, named patient program; NS, not specified; sALCL, systemic ALCL; TCL, T-cell lymphoma; TPO, thrombopoietin

P140
DOUBLE TRANSPLANTATION AUTO/AUTO OR AUTO/ALLO IN REFRACTORY AND VERY UNFAVORABLE RELAPSE OF HODGKIN LYMPHOMA (HL) PATIENTS: FIRST ANALYSIS OF EARLY DEATHS OF THE PROSPECTIVE MULTICENTRIC OBSERVATIONAL STUDY

Deau B,[1] Amorin S,[2] Robin M,[2] Bologna S,[3] Delmer A,[4] Lissandre S,[5] Thepot S,[6] Quittet P,[7] Chaoui D,[8] Gabarre J,[9] Bouabdallah K,[10] Jaubert J,[2] Brice P[2]

[1]Hematology department, Hôpital Cochin, Paris, France; [2]Hematology department, Hôpital Saint Louis, Paris, France; [3]Hematology department, CHU, Nancy France; [4]Hematology department, CHU, Reims, France; [5]Hematology department, CHU, Tours, France; [6]Hematology department, CHU, Bobigny, France; [7]Hematology department, CHU, Montpellier, France; [8]Hematology department, CH Argenteuil, France; [9]Hematology department,CH Pessac, France; [10]Hematology department, CH St Priest, France

Patients with refractory HL or early and disseminated relapse have a very poor outcome with a 5-year EFS of 46% and survival at 58% with tandem autotransplantation. Non myeloablative allogeneic (NMA) transplantation was associated with a 4-year PFS at 24%. We decided to propose to this high-risk group tandem transplantation with a second allotransplantation if a match donor was available. Patients received chemotherapy (CT) than a BEAM regimen followed in 2 or 3 months by NMA transplantation (after fludarabine and busulfan regimen) or a second autotransplant (BAM regimen) for patients without a match donor. From January 2010 to May 2013, 75 patients have been included and we focused on the analysis of early deaths in the 62 patients with available data. Patients characteristics are : median age at 28 yrs [18-52], sex ratio at 1, 30% of patients had primary refractory disease (biopsy proven in 50%) and 70% unfavorable relapse (median time to relapse : 6 months). First line CT was ABVD (n=46), BEACOPP (n=16), with radiotherapy (n=16). 44% of patients received only one second line CT (mostly MINE, DHAP or ICE) before the BEAM regimen, the remaining received 2 to 4 lines (with Brentuximab in 6 patients). Results. 94% of patients received the first autotransplantation and 10 patients progressed before the second transplant. 55% (n=34) of patients received the second transplant including 70% of NMA (in tandem in 28 cases and after CT for early relapse in 6 cases). 12 patients did not receive the second transplant (toxicities n=5, early progression n = 4 or physician decision n = 4). The remaining patients are on ongoing therapy. Eight patients died : six patients from HL and 2 deaths were related to the allogeneic procedure : one bacterial sepsis 5 months after the transplantation; one pneumonitis 50 days after the transplantation. As previously published, double autotransplantation is safe. This protocol is still ongoing up to 100 patients. We are aware of the toxicity of allogeneic transplantation in this setting but the major problem is chemoresistance and death from HL.

P141
SITE OF RELAPSE AFTER RADIOTHERAPY IN STAGE I/II HODGKIN LYMPHOMAS (HL): A MONOCENTRIC RETROSPECTIVE STUDY OF 60 PATIENTS.

Krebs L, Quero L, Franchi P, Amorin S, Menard J, Hennequin C, Brice P

Radiotherapy & Haematology Department, Hopital Saint Louis, Paris, France

The use of radiotherapy (RT) in localized Hodgkin Lymphoma (HL) has changed among time with reduced fields and doses since 1990. RT remains the standard of care after ABVD chemotherapy (CT) in most patients with stage I/II HL disease. To better define optimal RT in first-line treatment we retrospectively reviewed clinical charts of 60 relapsing patients to correlate the site of relapse and the radiation fields. Patients and Methods. Among 760 patients treated from 1987 to 2011 for stage I/II HL with RT (and CT in 94%), we observed 80 relapses, among these we analyzed those 60 cases with full clinical data. Median age at diagnosis was 35 yrs [14-72] with a sex ratio M/F of 1.2. Histology was nodular sclerosis in 73%, mixed cellularity in 12% and nodular lymphocyte predominant HL in 5%. Initial staging was performed by CT scans and 75% were stage II disease; 2 patients had a subdiaphragmatic presentation. According to the EORTC prognostic score, 38% of patients had favorable disease, bulky disease was present in 18% and B symptoms in 27%. Initial treatment was combined modality (ABVD n = 28, EBVP n =8, MOPP/ABVD n = 15 CVPP n = 1) (3 to 6 cycles) in 87% of patients, with involved field radiotherapy in 57% of patients (doses ranging from 20-40 Gy). Results. The mean time from diagnosis to relapse was 3.4 yrs [0.3-24] with 53% of relapses outfield RT, relapses occurred significantly later for favorable disease (4.5 yrs *vs* 3 yrs, p 0.06). Bulky disease and unfavorable disease appeared to be prognostic factors for infield relapse (p=0,005 and p=0,02) as well as radiation therapy dose equel or under 30 grays (p= 0,013). Discussion and Conclusions. This analysis confirms the low risk of relapse with a long follow-up in stage I/II HL treated mostly with combined modality. Relapses were more often outfield for patients with favorable disease while more infield relapses occured in bulky mediastinal disease. In this last subgroup, intensification of chemotherapy seems warranted and if RT is performed, radiation dose de-escalation is not recommended and a 30 Gy minimal dose must be administered.

P142

SIGNIFICANT ACTIVITY OF THE MTOR INHIBITOR SIROLIMUS AND HDAC INHIBITOR VORINOSTAT IN HEAVILY PRETREATED REFRACTORY HODGKIN LYMPHOMA PATIENTS

Janku F, Garrido-Laguna I, Velez-Bravo VM, Subbiah V, Hong DS, Falchook GS, Oki Y, Fayad LE, Kwak LW, Shpall EJ, Davis RE, Liang W, Salhia B, Carpten JD, Kurzrock R, Fanale MA

Investigational Cancer Therapeutics (Phase I Clinical Trials Program), Department of Lymphoma/Myeloma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Internal Medicine, Oncology Division, University of Utah School of Medicine, Huntsman Cancer Institute, Salt Lake City, UT, USA; Translational Genomic Research Institute, Phoenix, AZ, USA; Moores Cancer Center, University of California San Diego, La Jolla, CA, USA

Background. Preclinical models have suggested that HDAC and mTOR inhibitors have synergistic antineoplastic activity in Hodgkin lymphoma and other cancers by reducing the activity of AKT, mTOR and HDAC. Methods. We designed a phase I study to determine the safety of the mTOR inhibitor sirolimus (1mg-5mg PO daily q 28 days) and HDAC inhibitor vorinostat (100mg-400mg PO daily q 28 days) in advanced cancers with an expansion cohort at the recommended phase 2 dose (RP2D) of sirolimus 4mg and vorinostat 300mg for patients with refractory classical Hodgkin lymphoma. The expansion cohort included optional pre- and post-treatment tumor biopsies, peripheral blood mononuclear cells (PBMCs), plasma/serum collections for pharmacodynamic (PD) and pharmacokinetic (PK) endpoints. Results. A total of 10 patients (men, n=5; women, n=5), median age 36 years, median of 6.5 prior therapies (including autologous SCT [n=9], autologous and allogeneic SCT [n=2]) were enrolled in dose escalation (n=1) or RP2D (n=9) cohorts. At the median follow-up of 2.5 months 8 (88%) of 9 patients with at least one restaging PET/CT scan demonstrated decreased FDG uptake with a disease control rate (CR+PR+SD) of 88% and one patient attained a PR. The median reduction of tumor per CHESON criteria was -26% (-58% to +20%). The median time-to-treatment failure was 3 months (95% CI, 1.8-4.2) and 50% of the patients continued on therapy with further improvement in their level of disease response. Major grade 3-4 treatment-related toxicities included grade 3 thrombocytopenia (2 patients, 20%), grade 4 thrombocytopenia (4, 40%), grade 3 anemia (1, 10%), febrile neutropenia (1, 10%) and led treatment interruptions and/or dose modifications in 6 (60%) patients. Five (50%) patients had archival tissue available for targeted next-generation sequencing and one patient had loss of TSC2, an abnormality that putatively activates mTOR. This patient has had continuing response to therapy (-44%) for 6.2+ months. PD studies in pre- and post-treatment tumor biopsies, PBMCs and plasma as well as PK analysis continue. Conclusion. The combination of sirolimus and vorinostat is well tolerated with encouraging activity in very heavily pretreated patients with Hodgkin lymphoma refractory to standard therapies. Enrollment continues.

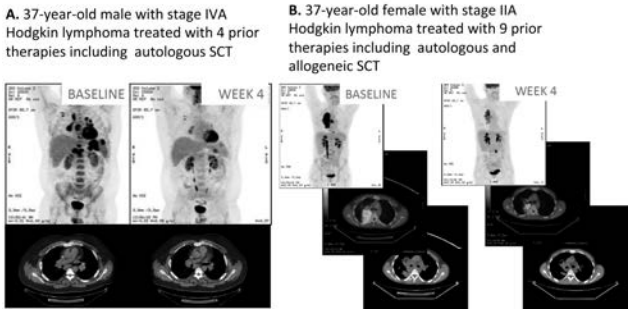

Figure 1. PET/CT response to therapy

P143

DEFINING A HODGKIN LYMPHOMA POPULATION FOR NOVEL THERAPEUTICS AFTER RELAPSE FROM AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

Arai S,[1] Fanale M,[2] deVos S,[3] Engert A,[4] Illidge T,[5] Borchmann P,[4] Younes A,[2] Morschhauser F,[6] McMillan A,[1] Horning SJ[1]

[1]Stanford University; [2]MD Anderson Cancer Center; [3]University of California-Los Angeles; [4]German Hodgkin Lymphoma Study Group-Cologne, Germany; [5]Manchester, UK; [6]Société Française de Greffe de Moelle (SFGM)

Background. Autologous hematopoietic cell transplantation (AHCT) is well established as effective therapy for Hodgkin lymphoma (HL) patients who relapse after primary treatment with chemotherapy. The outcome of those patients who relapse after AHCT, however, has been less well studied. Further definition of this population can provide an important niche for novel therapy development. Patients and Methods. Representatives from five collaborative groups or transplant centers (German Hodgkin Study Group-Cologne, Germany, Houston, Los Angeles, Manchester, Stanford) and the Société Française de Greffe de Moelle (SFGM) registry agreed to share data on patients with documented relapse after AHCT for recurrent HL. Each center provided data on age, gender, date of AHCT, date of relapse after AHCT, date of last follow-up, and vital status at last follow-up. The analysis was limited to patients with a minimum >1 year follow-up from transplant. Results. Survival data for 756 HL patients failing AHCT were analyzed by era of transplant (<1990, 1990-2000, >2000) and by time to relapse (TTR) after transplant. Survival was generally unchanged from 1990 forward. With all sites combined, median post-progression survival (PPS) were 0.99, 1.34 and 1.39 years for the <1990, 1990-2000 and >2000 eras, respectively (nonsignificant). TTR after AHCT correlated with survival. Patients relapsing within 12 months, who comprised 71% of the total, had a median post-progression survival of 0.98 years compared to 2.26 years for those relapsing after 12 months (p<0.001). In addition, there was a notable differentiation according to TTR within one year (Figure). Median PPS were 0.55, 1.6, 1.68, and 2.26 years for TTR after AHCT of 0-3, >3-6, >6-12, and >12 months respectively (p<0.0001). Conclusions. Early TTR after AHCT is an important prognostic factor for post-transplant survival and defines the HL population with the greatest need for novel therapeutics.

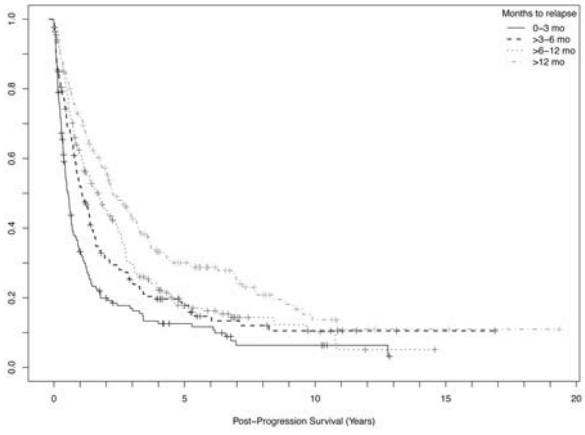

Figure 1. PPS differs according to TTR within one year after AHCT

P144

RELAPSED/REFRACTORY (RR) HODGKIN LYMPHOMA (HL) FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANT (ASCT): BURDEN OF ILLNESS AND ADVANCEMENT IN TREATMENT

Singh M,[1] Eaton J,[1] Hatton C,[2] Baculea S,[1] Bonthapally V[3]

[1]Oxford Outcomes, an ICON plc company, Oxford, UK; [2]Churchill Hospital, Oxford, UK; [3]Millennium: The Takeda Oncology Company, Cambridge, MA, USA

Background. HL is a rare disease that accounts for ~10% of lymphomas. There are few publications on RR HL post-ASCT, limiting the

possibility of assessing the associated burden of illness. Methods. A systematic search was conducted in Medline, Embase, and the Centre for Reviews and Dissemination to identify studies on epidemiology, efficacy, economic and health-related quality-of-life burden (from database inception to May 2013). Guideline searches on major websites were also performed. Results. Globally, the annual incidence of HL is 1.6-2.97/100,000. In the European Economic Area incidence is 2.1-3.5/100,000. Prevalence data are less well reported, however, HL meets the orphan disease criteria for the EU (prevalence <5/10,000). Approximately 500 patients in the EU-5 and ~40 patients in Australia and New Zealand experience RR HL post-ASCT annually. Historically, the prognosis for RR HL post-ASCT is poor, with estimated median overall survival (OS) of 2.4 years (all patients). However, brentuximab vedotin has been shown to improve survival; in a phase 2 study 59% patients were alive after a median observation time of 2.5 years. Median OS has not yet been reached; the estimated 2-year survival rate was 65% (Chen ASH 2012, abstract 3689). Until recently, patients with RR HL post-ASCT received either chemotherapy or transplant. The US National Comprehensive Cancer Network guidelines now include brentuximab vedotin as an option for these patients. HL leads to significant productivity loss as it affects individuals of working age (median age at diagnosis: 38 years). Consequently, HL is the second most costly cancer/death. Indirect cost due to lost productivity is reported as $544,118/death in the US and €69m in total in Germany. HL also poses a significant humanistic burden, including debilitating B-symptoms in 34-41% of patients. Chronic fatigue, and decreased social, emotional, physical, and sexual functioning are also reported. Notably, 77% of patients receiving brentuximab vedotin experienced resolution of B-symptoms (median time: 0.7 months from treatment). Conclusions. RR HL post-ASCT is a rare disease with poor prognosis, and poses a considerable economic and humanistic burden for healthcare providers and patients. Recent treatment advances suggest the potential for improved survival and resolution of patients' B-symptoms.

P145
NODULAR LYMPHOCYTE PREDOMINANT HODGKIN'S LYMPHOMA–EVALUATION OF A SCORING SYSTEM TO PREDICT RECURRENCES

Panjwani P,[2] Epari S,[2] Sengar M,[2] Laskar S,[1] Menon H,[2] Shet T[2]

[1]Department of Pathology, Radiation Oncology, Tata Memorial Hospital, Mumbai,India; [2]Department of Pathology, Medical Oncology, Tata Memorial Hospital, Mumbai, India

Introduction. Nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) is a rare but unique disease. Within the described morphology there are some deviations like presence of focal T cell areas, focal loss of nodularity and there is not much data evaluation the significance of these findings.

Table 1. Scoring system for patients of NLPHL

Histolopathological feature	Classifying feature	Score
1.Nodularity	Nodular throughout - 0	0
	Nodular + diffuse areas < 25%	1
	Diffuse areas > 25%	2
2.Type of nodules	Well defined throughout	0
	Multinodular interconnected	1
	Irregular	2
3.Splattering of nodules	None seen	0
	Present but <30% nodules	1
	>30% nodules are splattered	2
4.T cell areas	Nil	0
	<25% of total node volume	1
	>25% of node volume	2
5.CD23 staining pattern	Present throughout nodules	0
	Nodules with delicate dendritic network	1
	Loss of dendritic network but with some discernible fragments	2

This study is an attempt to evaluate a scoring system for NLPHL with view to guide therapy in future patients. Material and Methods. The 82 patients included in the study protocol were accessioned at our institute from a period of 2001 to 2010. The histopathology required at least one typical nodule of NLPHL for a case to be included. Histopathological review was done using features listed in Table 1 to develop a score which ranged from 0 to 10 points. Results. These included 69 males and 13 females. Except for 10 patients, patients were <50 years of age. Ann Arbor staging was computable in 76 patients and 32 had stage I, 23 patients had stage II, 11 patients had stage III and 10 patients had stage IV disease. Of these patients, follow up was present in 76 patients and 47 patients had no relapse while 29 patients did relapse. Six patients died due to progression to large cell lymphoma. Scoring was evaluable in 50 cases. Cases were scored without knowledge of the clinical details initially and then disease free survival was calculated using the Kaplan Meier analysis and PASW 18. Of the 25 patients with score of 5/<5, only 2 had relapses while 13/25 patients with score of 6 or above had relapse. Conclusion.- The histological score thus predicted the relapses accurately and could help us upfront treat patients differently.

P146
BRENTUXIMAB VEDOTIN AND NEUROPATHY, A SINGLE CENTER STUDY ON 46 PATIENTS

Madaoui C, Madelaine I, Deville L, Faure P, Thieblemont C, Brice P

Pharmacy, Saint-Louis Hospital, APHP,Paris, France; Department of Hematology, Saint-Louis Hospital, APHP, Paris, France

Background. This retrospective study was designed to evaluate the rate and severity of neuropathy induced by Brentuximab vedotin (BV) in unselected relapsed or refractory Hodgkin Lymphoma (HL) and anaplasic large-cell lymphoma (ALCL). Our main objectives were to analyze the proportion of patients affected by neuropathy before, during and after treatment and assess their grades according to the National Cancer Institute (Version (4.0)). Methods. Forty-six patients (32 HL, 14 ALCL) received at least 1 dose of BV. The median number of previous chemotherapy lines was 5 [3;9]. Before BV, 93.5% of patients received vinca-alkaloid, among them 10% had neuropathy, however 30% received oxaliplatin and 6.9% had neuropathy. Results. The median age was 38.5 years. The average number of cycles was 7 [1;16]. During treatment, 14 patients (30.4%) had neuropathy. Among them 7 patients (50%) (3 grade I, 3 grade II and 1 grade III) had no neuropathy history, 5 patients (36%), 2 grade I and 3 grade 2 had neuropathy history (3 oxaliplatin-induced neuropathy, 2 with vinca-alcaloid). Only 2 of the 5 were worsened. For 2 patients neuropathy history was unknown. 32 patients (69.4%) didn't develop neuropathy during treatment by BV: including 30 patients (94%) without any neuropathy history and 2 patients (6.25%) with vinca-alcaloid-induced neuropathy At the end of the treatment with BV, neuropathies of 5 patients (35.7%) were not resolved despite drug therapy for 71.4% of them (the dose was reduced in patients with neuropathies higher than grade I) Finally, the percentage of patients who developed neuropathy is higher when they had neuropathy history (71% (5/7) *vs* 19% (7/37)) Conclusion. Most patients had no neuropathy and benefited from brentuximab therapy. Although the low number of patients studied, this work shows a risk to developed early neuropathy with BV (30% instead of 11% in the product information) and higher 71% in case of previous neuropathy. Most of them remained reversible and manageable. These results should be taken in account when brentuximab will be associated with other chemotherapies to avoid those with neurotoxicities.

P147
CHARACTERISTICS AND OUTCOME OF NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA (NLPHL). A MULTICENTRE AUDIT STUDY FROM THE POLISH LYMPHOMA RESEARCH GROUP

Paszkiewicz-Kozik E,[1] Brzeska B,[1] Tajer J,[1] Kotarska M,[1] Maciej Zaucha J,[2] Zaucha R,[3] Kurczab P,[4] Kyrcz-Krzemien S,[5] Wrobel T,[6] Kuniega B,[7] Drozd-Sokolowska J,[8] Subocz E,[9] Romejko-Jarosinska J,[1] Kraszewska E,[10] Walewski J[1]

[1]Maria Sklodowska-Curie Institute–Oncology Centre, Warsaw, Poland; [2]Oncology Centre, Gdynia, Poland; [3]Medical University of Gdansk, Poland; [4]Medical Center Mrukmed, Rzeszow, Poland; [5]Silesian Medical University, Katowice, Poland; [6]Medical University, Wroclaw, Poland; [7]Markiewicz Memorial Oncol-

ogy Center, Brzozow, Poland; [8]Medical University of Warsaw, Poland; [9]Military Institute of Medicine, Warsaw, Poland; [10]CMKP, Warsaw, Poland

Background. NLPHL is treated the same way as classical HL in all stages except stage IA without risk factors. However, it is not clear if the outcome is acceptable. We evaluated clinical characteristics, treatment approach and outcome of consecutive NLPHL patients treated at 8 hemato-oncolgy centers in Poland between 2004 and 2013. Patients and Methods. 43 patients with histopathologic diagnosis of NLPHL were identified. The median age (range) at diagnosis was 39 (18-78), 38 (88%) were male, 8 pts (19%) had stage IA disease. Mediastinum was involved in 6 (14%) and bulky disease was present in 2 (5%) pts. Extranodal sites were involved in 14 (33%) cases including bone marrow in 2 (5%). B symtoms were present in 6 (14%) pts. A variety of treatment methods were used. Of 8 pts in CS IA, IFRT alone received 4, ABVD-3, and R-CC (rituximab, cladribine, cyclophosphamide)–1 pt. CS>IA pts received ABVD (25), R-CHOP (4), R-CVP (1), R-FC (1), and 1 pt was followed without treatment. 2 CSIIA pts received IFRT alone. Results. Overall response to first-line therapy was 93% (40/43) including CR in 88% (38/43) of pts. Histological transformation to aggressive lymphoma was diagnosed in 2 cases. 13 (30%) pts relapsed or progressed including 1 of 4 CSIA pts treated with IFRT, and 1 pt died. 5 (38%) pts received ASCT after second-line treatment. Median (range) follow up of living pts was 31 (0.5-128) months. 2 and 5 year PFS was 81% (95%CI: 65%, 91%) and 62% (95%CI: 37%, 80%), respectively. 5 and 10 year OS was 100% and 90% (95%CI: 47%, 99%), respectively. No clinical feature including age, stage, disease site or method of therapy had significant effect on PFS in univariate analysis. Conclusion. Despite good prognosis for overall survival in NLPHL, a continued relapse pattern is apparent without signs of plateau on PFS curve. New treatment methods for long-term disease control are needed.

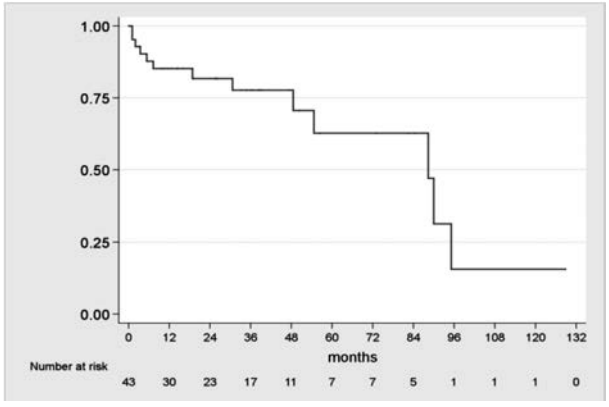

Figure 1. PFS of 43 NLPHL patients

P148
IGEV AS SALVAGE REGIMEN THERAPY FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA

Kacem K,[1] Zriba S,[2] Ghédira H,[2] Mansouri R,[1] Manaï Z,[1] Ben Neji H,[1] Zarrouk M,[1] Ben Abdennebi Y,[1] Jeddi R,[1] Aïssaoui L,[1] Belhadj Ali Z,[1] Ben Abid H,[1] M'Sadek F,[2] Ben Lakhal R,[1] Meddeb B[1]

[1]Clinical hematology department of Aziza Othmana Hospital of Tunis; [2]Clinical hematology department of Military hospital of Tunis

Background. Although Hodgkin Lymphoma (HL) usually presents a good response to initial treatment, a proportion of patients does not response or relapse. Purpose : To evaluate the clinical characteristics and treatment results of IGEV (Ifosfamide, Gemcitabine, Vinorelbine) in relapsed/refractory HL in two departments of clinical hematology. Patients and Methods. : A retrospective study was carried out from 2008 to 2012. We have analysed 29 patients with refractory/relapsed HL treated with IGEV as a second line treatment. Results. The median age was 26 years (15-56), sex ratio of 1.63. Nodular sclerosis type in 90%. CD15+ in 68%, CD20+ in 12.5% and LMP1+ in 7/9 cases. 66% of patients were initially advanced stages and 34% were stage II with mediastinal enlargement . 83% were Bb. 19 patients were refractory, 4 showed progressive disease and 6 were relapsed with a median delay of 12 months (4-114). IGEV was complicated respectively in the first and the second cycles by: fever in 31% and 21%, mucositis in 20% and 14%, neutropenia grade 4 in 62% and 38%. 2 cases of hemorrhagic cystitis were noted. Stem cell collection was done in 14 and 15 patients respectively after the first and the second cycle. The median number of apheresis was 1(1-4). 54% of patients had only one apheresis. A median of 6x106/kg CD34+ cells were collected. 32% of patients were refractory, 52% had partial response and 16% a very good partial response. 2 cycles of IGEV induced a median improvement of response of 9% (0-41) for refractory HL and of 70% (47-79) for relapsed patients. 44.8% of patients showed an improvement of their response after 2 cycles of IGEV. 10 patients received a third line therapy (6 Gemcitabine-Cisplatine, 1 DHAP, 2 ESHAP and 1 ICE). Autologous stem cell transplantation was done for 24 patients. A median follow-up of 24 months (8-50), OS at 2 years was of 82.7% and PFS was of 79.3%. Conclusion. IGEV was safe and showed a better improvement of response in relapsed patients than in refractory disease. PET-CT may be proposed to deviate fibrotic residual masses from these refractory shaps.

P149
POST-AUTHORISATION SAFETY STUDY (PASS) MA25101: AN OBSERVATIONAL COHORT STUDY OF THE SAFETY OF BRENTUXIMAB VEDOTIN IN THE TREATMENT OF RELAPSED OR REFRACTORY (RR) CD30+ HODGKIN LYMPHOMA (HL) AND RR SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA (SALCL). THE ARROVEN STUDY

McAuliffe M, Huebner D, Shonukan O, Porter J, Ponsillo M, Exter B, Bowers S, Conlon J, Partyka J, Wang B, Sachs J

Millennium: The Takeda Oncology Company, Cambridge, MA, USA

Introduction. Brentuximab vedotin (ADCETRIS®), a CD30-targeted antibody-drug conjugate, has conditional approval in Europe for treatment of RR CD30+ HL and RR sALCL. Brentuximab vedotin was evaluated in more than 300 patients during clinical development and analyses indicate a manageable and tolerable safety profile in approved indications. As is common with new therapies for rare conditions, the European Commission (EC) has requested a PASS to further evaluate the safety profile of brentuximab vedotin. The conduct and findings of the PASS are important to ensure continued access to brentuximab vedotin for patients with RR CD30+ HL and RR sALCL in Europe. Methods The objectives of ARROVEN are to evaluate the serious adverse events (SAEs) and specified adverse events of special interest (AESI), both serious and non-serious, in patients actively treated for RR CD30+ HL or RR sALCL with brentuximab vedotin in routine practice; and to identify and describe potential risk factors for peripheral neuropathy. Enrolment will occur over 3 years at 75–100 sites in Europe with a planned accrual of approximately 500 patients (~50 sALCL) receiving brentuximab vedotin. Study duration will be 5 years from first patient enrolled. Patients will remain in follow-up until death, withdrawal of consent, loss of follow-up or study closure, whichever comes first. PASS data will be collected from information routinely recorded in the medical record. No study visits, examinations, laboratory tests or procedures are mandated by the study. Baseline patient and disease characteristics, relevant medical history, and all initial and subsequent treatment for RR CD30+ HL or RR sALCL will be recorded. Follow-up information and safety data will be collected during the patient's routine visits with their oncologist, typically every 3 months. Results. The ARROVEN study is open and enrolling as of March 2013. Initial sites include Austria, Denmark, and Germany with enrolment planned in additional European countries over the next 3 years as brentuximab vedotin becomes commercially available. Conclusions. ARROVEN is an observational cohort study to further evaluate the safety profile of brentuximab vedotin in support of the conditional approval granted by the EC.

P150

BRENTUXIMAB VEDOTIN (SGN-35) IN HODGKIN LYMPHOMA PATIENTS WITH RELAPSED AFTER AUTOLOGOUS PERIPHERAL BLOOD STEM-CELL TRANSPLANTATION

Erdem G,[1] Karadurmus N,[1] Ozaydin S,[1] Karacalioglu AO,[2] Yeginer C,[3] Ozturk M,[1] Ataergin S,[1] Nevruz O,[4] Cetin T,[4] Arpaci F[1]

[1]Medical Oncology, Gulhane School of Medicine, Ankara, Turkey; [2]Nuclear Medicine, Gulhane School of Medicine, Ankara, Turkey; [3]Public Health, Gulhane School of Medicine, Ankara, Turkey; [4]Hematology, Gulhane School of Medicine, Ankara, Turkey

Background. Approximately 15 to 30% of patients with Hodgkin's lymphoma (HL) do not have a long-term remission with conventional therapy. Autologous peripheral blood stem-cell transplantation (APBSCT) represents a potentially curative treatment for some patients with recurrent or progressive HL after failure of initial combination chemotherapy. Unfortunately, APBSCT is only effective in approximately 50% of such patients. Brentuximab vedotin comprises an anti-CD30 antibody conjugated by a plasma-stable linker to the potentantial microtubule agent, monomethyl auristatin. Brentuximab vedotin selectively induces apoptotic death of CD30+ cells. Methods. We evaluated the efficacy and safety of brentuximab vedotin in patients (pts) with relapsed HL after APBSCT. Pts received brentuximab vedotin1.8 mg/kg q3 weeks (wks) as a 30 minute out patient IV infusion for upto 16 cycles. The primary endpoint was the objective response rate (ORR) and toxicity. Results. Ten pts were enrolled; eight pts were male and median age was 26 yrs (range, 22-30 yrs). Pts had received a median of 4 (range 3-5) prior cancer-related systemic therapies excluding APBSCT. Fifty percent of pts had primary refractory disease and 80% had not responded to their most recent prior therapy. We evaluated all pts every three cycles. After 6 cycles of therapy, tumor regression occurred in 80% of patients and the overall objective response rate was 80% (n=8), with partial remissions (PRs) in 7 pts. and complete remissions (CRs) in 1 pt. The most common treatment-related adverse events (AEs) of any grade were alopecia, abdominal pain, fatigue, insomnia and diarrhea. AEs ≥ grade 3 occurred in ≥60% of pts were fatigue, insomnia artralgia and diarrhea. Conclusions. With manageable AEs, single-agent brentuximab vedotin induced objective responses in 80% of pts with relapsed HL after APBSCT. Brentuximab vedotin is effective in the early period of treatment. This agent can be considered as a method of bridge treatment prior allogeneic stem cell transplantation.

P151

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN HODGKIN'S LYMPHOMA–A SINGLE CENTER EXPERIENCE

Sucak G,[1] Kurt B,[2] Yeğin ZA,[1] Akı SZ,[1] Nur Özkurt Z, Acar K

[1]Gazi University School of Medicine Department of Hematology; [2]Gazi University School of Internal Medicine, Turkey

Outcome of the patients with Hodgkins Lymphoma (HL) refractory to first line treatment and/or relapsing after autologous stem cell transplantation(ASCT) remains to be poor.. Non-myeloablative conditioning regimens have replaced myeloablative regimens due to high nonrelapse mortality. We present the retrospective analysis of 15 heavily pretreated patients who received allografts after non myeloablative conditioning. A total of 15 patients median age: 24(18-61) years; M/F : 11/4 with Hodgkin's lymphoma underwent non myeloablative allogeneic (allo) hematopoietic stem cell transplantation (HSCT) at Gazi University Stem Cell Transplantation Unit. Histological subtypes were nodular sclerosing in 12, mixed cellular in 1 and lymphocyte rich in 2 patients. Based on Ann-Arbor staging system 9 patients were classified as stage 4, 3 patients stage 3 and 3 patients stage 2. Fourteen of the patients had advanced stage disease according to GHSG and EORTC risk assessment systems. Median international prognostic score (IPS) was 2(1-4). Two patients had bulky disease and 9 patients presented with extranodal involvement. Median time from diagnosis to HSCT was 880(150-2468) days. Nine patients had a previous ASCT, with a median interval of 300(45-718) days between auto and allo HSCTs. Four patients were in complete remission, 6 in partial remission and 5 patients had progressive disease at the time of HSCT. Conditioning regimens were Bu/Cy/Flu in 7 patients, TBI/Flu in 1 patient and Flu/Mel in 7 patients. Median number of CD34+ cells was 3,3(2,04-5,53)x10^6/kg. Median neutrophil and platelet engraftment days were 20(11-32) and 17(0-54) respectively. A total of 10 patients experienced GVHD (5 acute and 5 chronic) status post allogeneic HSCT. Disease relapse was demonstrated in 10 patients and median progression free survival was found to be 180(59-3027) days. A total of 12 patients died after a median follow-up of 761(59-3027) days. Eight of them were disease related, whereas 4 were non relaps mortality. Although long term survival is feasible with allogeneic HSCT in heavily pretreated patients, transplant related mortality and relapse remains to be a problem. Incorporation of novel agents such as Brentuximab to conditioning regimens, or post transplant consolidation protocols and donor lymphocyte infusions (DLI) can be considered to improve the outcome.

P152

SEQUENCE OCCURRENCE OF HODGKIN LYMPHOMA AND DIFFUSE LARGE B-CELL LYMPHOMA

Jóna A,[1] Irsai G,[2] Barna S,[3] Garai I,[3] Bedekovics J,[2] Magyari F,[1] Gergely L,[1] Illés A[1]

[1]University of Debrecen, Medical and Health Science Center, Department of Hematology; [2]University of Debrecen, Medical and Health Science Center, Department of Pathology; [3]Scanomed Ltd, Hungary

Introduction. Hodgkin and non-Hodgkin lymphoma are different entities, they rarely occur in the same patient, but when they do so, that can either occur in the same anatomic location (composite lymphoma), different anatomic location (synchronous lymphoma), they can originate from a common clone (transformation), or occur sequentially. Case history: A female patient born in 1965, underwent axillary block dissection and combined chemo-radiotherapy due to breast cancer in 2004. Later in 2011, during her routine follow up, pathological retroperitoneal, axillary, inguinal and mesenteric lymph nodes have been identified. Biopsy taken from explorative laparotomy confirmed lymphocyte rich classical Hodgkin lymphoma (LR cHL). During the patient' s routine staging work up clinical stage III/A with favourable prognosis has been revealed, hence 6 cycles of ABVD chemotherapy was planned, which she received between August 2011 and January 2012. Interim and restaging PET/CT scan confirmed complete metabolic remission. In June 2012 the patient presented again with sweating and gastric pain. Gastroscopy and C13 breath tests were both negative. A control PET/CT scan in September 2012 confirmed pathological FDG uptake in the neck, left axilla, right inguinal lymph nodes with a SUVmax: 13.6. A biopsy of the lymph node in the neck revealed diffuse large B-cell lymphoma (DLBCL). Routine work up confirmed clinical stage III/A, IPS 0. 2 cycles of DHAP was administered. Interim PET/CT confirmed complete metabolic remission, hence her disease could have been considered as chemosensitive disease, hence peripheral stem cell collection was done during third cycle of DHAP and she underwent AHSCT in February 2013. Since that time patient is checked regularly and is well. Discussion: Immune dysregulation, peripheral immune tolerance and administration of chemo-radiotherapy due the patient' s previous breast cancer could have been contributed to the patient's 3 malignancies in order. Polyclonal immunoglobulin heavy chain pattern have been seen in both biopsy samples, hence no clonal origin could have been confirmed. Adequate diagnostic tools and therapy was also of importance.

Survivorship

T153
CHANGES IN BREAST CANCER RISK AS LONG-TERM HODGKIN LYMPHOMA SURVIVORS REACH MENOPAUSAL AGE

Wong JS,[1] Catalano PJ,[2] Chen Y,[2] Marcus KJ,[1] Michaelson EM,[1] Mauch PM,[1] Ng AK[1]

[1]Department of Radiation Oncology; [2]Department of Biostatistics and Computational Biology; Dana-Farber Cancer Institute/Brigham and Women's Hospital, Baltimore, USA

Women who received chest irradiation (RT) for Hodgkin lymphoma (HL) at a young age are at increased risk for breast cancer (BC). Treatment-related early menopause is protective against BC, although limited data are available on changes in risk as survivors enter menopause. This study aims to assess the excess BC risk of HL survivors compared with a normal, age-matched population as survivors pass menopause, and to compare the excess risks of premenopausal versus postmenopausal survivors. HL treatment history, subsequent BC development, menopausal status, and hormone-replacement therapy (HRT) history were abstracted from a HL database and medical records with IRB approval. The study included 555 women who had chest RT at age <35 between 1968 and 2005. Age >50, pelvic RT or MOPP chemotherapy exposure was used as a surrogate for menopause in cases of missing menopausal status data. Postmenopausal women on HRT were considered premenopausal. Median follow-up was 20 years (range 0.7-42). Median age at RT was 23 (range 6-35). Median current attained age was 39 (range 12-69) and median time from RT to BC diagnosis was 18 years (range 6-39). 107 women had at least one breast cancer. SEER data were used to calculate relative (RR) and absolute excess risk (AR, per 10,000 person-years). The overall RR for developing BC was 14.4 (95% CI 11.8-17.4) with an AR of 107.8. For survivors with attained age <50, 50-55 and 56-60, the RR was 32 (25.7-39.5), 6.51 (3.56-10.93) and 3.69 (1.2-8.6), respectively (p-trend <0.001). The corresponding ARs were 134, 73.6 and 47.2. The RRs of premenopausal and postmenopausal survivors were 27.74 (22.03-34.48) and 5.78 (3.77-8.47), respectively (p <0.001). The corresponding ARs were 136.81 and 60.87. These results show a significant drop in BC risk as HL survivors reach menopausal age, although the risk remains elevated compared with normal women. The decline in BC risk in postmenopausal survivors suggests that they may be considered for less aggressive BC screening (e.g., mammogram alone), and may have implications for broadening breast-conserving therapy options and for preserving the contralateral breast in postmenopausal survivors who developed BC.

T154
SECOND CANCER RISK FORTY YEARS AFTER CURE FOR HODGKIN LYMPHOMA

Schaapveld M,[1,2] Aleman BMP,[3] van Eggermond AM,[1] Janus CPM,[4] Krol ADG,[5] van der Maazen RWM,[6] Raemaekers JMM,[7] de Boer JP,[8] Zijlstra JM,[9] van Imhoff GM,[10] Beijert M,[11] Lybeert ML,[12] Poortmans PhMP,[13] Visser O,[2] Louwman M,[14] Lugtenburg PJ,[15] van Leeuwen FE[1]

[1]Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam; [2]Comprehensive Cancer Centre the Netherlands, Utrecht; [3]Department of Radiotherapy, Netherlands Cancer Institute, Amsterdam; [4]Department of Radiotherapy, Daniel den Hoed Cancer Center/ Erasmus MC, Rotterdam; [5]Department of Radiotherapy, Leiden University Medical Center, Leiden; [6]Department of Radiotherapy, Radboud University Nijmegen Medical Center, Nijmegen; [7]Department of Haematology, Radboud University Nijmegen Medical Center, Nijmegen; [8]Department of Haematology, Netherlands Cancer Institute, Amsterdam; [9]Department of Haematology, VU University Medical Center Amsterdam, Amsterdam; [10]Department of Haematology, University Medical Center Groningen, Groningen; [11]Department of Radiotherapy, University Medical Center Groningen, Groningen; [12]Department of Radiotherapy, Catharina hospital, Eindhoven; [13]Department of Radiation Oncology, Dr. Bernard Verbeeten Institute, Tilburg; [14]Comprehensive Cancer Centre South Netherlands, Eindhoven; [15]Department of Haematology, Daniel den Hoed Cancer Center/ Erasmus MC, Rotterdam; the Netherlands

Background. Over the last decades Hodgkin Lymphoma (HL) treatment changed towards less toxic chemotherapy schemes and more limited radiotherapy target volumes and doses. The impact of these changes on second cancer (SC) risk is still unknown. Method. We calculated standardized incidence ratios (SIR), comparing SC risk after HL treatment with expected risk, based on cancer incidence in the general population, and compared SC risk between treatment modalities, accounting for competing events, in a Dutch cohort comprising 3,390 5-years HL survivors, diagnosed between 1965-2000 and aged 15-51 years at HL treatment. Results. The median follow-up was 18.2 years; follow up was ≥25 years in 23%. During follow-up 734 SCs and 92 third cancers (TC) occurred. The SIR for any SC was 4.5 (95% confidence interval (95%CI) 4.1-4.9). SC risk was still elevated after 35 years of follow-up (SIR 3.9; 95%CI 2.5-5.8) and cumulative incidence (CI) reached 47.1% (95%CI 43.6-50.5) at 40 years follow-up. For TCs the SIR was 5.5 (95%CI 4.4-6.9); the 20-year CI was 22.3% (95%CI 17.8-27.2). Risks of NHL and leukemia strongly decreased in more recent treatment periods (P-trend <0.001). The CI of solid tumors (ST) 5-19 years after HL treatment did not differ for patients treated between 1965-1979, 1980-1989 or 1990-2000 (P=0.21; 19-year CI 9.1%, 11.6% and 11.4%, respectively). Supradiaphragmatic radiotherapy (RT) increased risk of supradiaphragmatic STs (hazard ratio (HR) 2.4, P<0.001), while subdiaphragmatic RT was associated with a 1.7-fold increased HR of a subdiaphragmatic ST (P=0.001). An incomplete mantle field was associated with significantly lower breast cancer (BC) risk compared to a full mantle field (hazard ratio (HR) 0.4, 95%CI 0.2-0.8). A cumulative procarbazine dose >4.2 g/m2 yielded a 1.3-fold increased HR (95%CI 1.0-1.7) for non-breast STs and a 2-fold (95%CI 1.2-3.1) increased HR for gastrointestinal STs, but was associated with a strongly decreased BC risk (HR 0.3, 95%CI 0.2-0.6). Conclusions. SC risk after HL has decreased over the last decades, due to strongly decreasing risk of leukemia and NHL. Smaller radiation fields and procarbazine doses >4.2 g/m^2 are associated with lower BC risk, while high procarbazine doses are associated with increased risk of gastrointestinal STs.

T155
A DUTCH NATIONWIDE SURVIVORSHIP CARE PROGRAMME FOR HODGKIN LYMPHOMA SURVIVORS

van Leeuwen FE,[1] Dekker N,[1] van 't Veer MB,[1] Lugtenburg P,[2] Krol ADG,[3] van der Maazen RWM,[4] van Imhoff GM,[5] Zijlstra JM,[6] Janus CPM,[2] Ong F,[7] Borger J,[8] Petersen EJ,[9] Poortmans PMP,[10] Kersten MJ,[11] Vos-Westerman J,[12] Schouten HC,[13] Roesink JM,[9] Beijert M,[5] Meijer OWM,[6] Noordijk EM,[3] de Boer JP,[1] Lybeert M,[14] Schaapveld M,[1] Kremer LC,[11] Aleman BMP,[1] Raemaekers JMM[4,15]

[1]The Netherlands Cancer Institute, Amsterdam, the Netherlands; [2]Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands; [3]Leiden University Medical Center, Leiden, the Netherlands; [4]Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; [5]University Medical Center Groningen, Groningen, the Netherlands; [6]VU University Medical Center, Amsterdam, the Netherlands; [7]Medisch Spectrum Twente, Enschede, the Netherlands; [8]MAASTRO clinic, Maastricht, the Netherlands; [9]University Medical Center Utrecht, Utrecht, the Netherlands; [10]Dr. Bernard Verbeeten Instituut, Tilburg, the Netherlands; [11]Academic Medical Center, Amsterdam, the Netherlands; [12]Isala Klinieken, Zwolle, the Netherlands; [13]Academic Hospital Maastricht, Maastricht, the Netherlands; [14]Catharina Hospital, Eindhoven, the Netherlands; [15]Rijnstate, Arnhem, the Netherlands

Background. Survivors of Hodgkin lymphoma (HL) are at increased risk of various late adverse effects of treatment, leading to substantial excess morbidity and mortality. The need for long-term follow-up is increasingly recognized. Long-term follow-up care programmes have been established for childhood cancer survivors, but not yet for HL survivors. Therefore, the Dutch BETER consortium (Better care after Hodgkin lymphoma: Evaluation of long-term Treatment Effects and screening Recommendations) is developing a nationwide infrastructure for Survivorship Care Clinics for survivors of HL (and subgroups of NHL). The consortium aims to: 1) establish evidence-based follow-up guidelines for survivors; 2) identify and trace survivors eligible for follow-up care; 3) educate survivors about possible late adverse effects of treatment; and 4) provide risk-based care and advice regarding prevention. Methods and Results. Follow-up guidelines were developed according to international standards. The guideline development group consisted of clinicians, methodological experts and patient representatives. We developed guidelines for second malignancies, cardiovascular

disease, thyroid disease and osteoporosis after premature menopause. Recommendations are given for fertility care and family planning, therapy for neck muscle weakness, and functional asplenia infection prophylaxis. We are currently identifying and tracing a cohort of approximately 8,500 HL survivors in 20 centers throughout the Netherlands. Eligible patients for follow-up care survived for ≥5 years and were treated at ages 15-70 years from 1970 onwards. Survivors are identified through the Netherlands Cancer Registry, the nationwide Pathology database and hospital-based registries. Tracing of current addresses of survivors is done through the nationwide database of Municipal Offices. For all survivors, HL treatment data are collected from medical records to provide risk-based screening recommendations. The website http://www.beternahodgkin.nl was developed to inform and educate survivors about late effects. A survivorship care plan is being developed. A nationwide database, including screening and adverse events, will be developed to evaluate the follow-up guidelines for diagnostic value and efficacy. Conclusions. We expect that the BETTER project will improve healthy life expectancy and quality of life for HL survivors. Evaluation of follow-up care will lead to improved knowledge regarding the diagnostic value and efficacy of the proposed screening methods, contributing to more evidence-based follow-up programmes

P156
SYSTEMATIC REVIEW AND INDIVIDUAL PATIENT DATA META-ANALYSIS OF TREATMENT-RELATED RISK OF SECONDARY MALIGNANT NEOPLASMS AFTER HODGKIN LYMPHOMA: FIRST RESULTS

Eichenauer D,[1] Franklin J,[2] Kaul I,[2] Engert A[1]

[1]Dept. of Internal Medicine, University Hospital, Cologne, Germany; [2]Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Germany

Introduction. Secondary malignant neoplasms (SMN) are a major late effect of treatment for Hodgkin lymphoma (HL). Single trials have inadequate power to detect differences in SMN rates, while the many large-scale cohort-based studies of SMN after HL suffer from non-randomised, potentially biased comparisons of treatment strategies. The consequences of choice of first-line treatment for SMN risk remain unclear. We performed a Cochrane systematic review addressing this question based on our previous such review in 2000-2004. Material and Methods. Individual patient data (IPD) were collected from randomised controlled trials testing 5 currently relevant experimental strategies: avoidance of additional radiotherapy (RT) after chemotherapy (CT); reduction of RT field; reduction of RT dose; use of fewer CT cycles; intensification of CT regimen. All trials employed modern ABVD-like regimens and limited radiation fields, and recruited at least 50 patients per treatment group. Incidence of SMN, overall survival (OS) and progression-free survival (PFS) were analysed. Due to small numbers of events, SMN was analysed using Peto's method. Results. Data from 16 of the 21 eligible trials were obtained, including 9498 patients. These trials recruited between 1984 and 2007 and randomised between 100 and 1351 patients each. Standard chemotherapy was predominantly ABVD, followed by COPP/ABVD and MOPP/ABV. Most frequent intensified chemotherapy was BEACOPP escalated, then Stanford V. For each study question, the number of trials, total number of patients (N), median length of follow-up and total number of SMN events were: Avoidance of RT: 3 trials, N=1011, 7.8 years, 40 SMN; Smaller RT field: 4 trials, N=2397, 10.8 years, 188 SMN; Lower RT dose: 3 trials, N=2962, 7.4 years, 110 SMN; Fewer CT cycles: 3 trials, N=2403, 7.8 years, 101 SMN; Intensified CT regimen: 7 trials, N=2996, 6.7 years, 91 SMN. Avoidance of additional RT significantly reduced the SMN risk (Peto odds ratio 0.433, 95% confidence interval (0.28; 0.82), p=0.010). Intensified chemotherapy regimens were associated with a consistent slightly higher risk but the effect was not significant. Other study questions showed no marked effects on SMN risk. Discussion. Further results. will be presented and evaluated.

P157
LONG-TERM RISK OF ISCHEMIC HEART DISEASE FOLLOWING HODGKIN LYMPHOMA TREATMENT

van Nimwegen FA,[1] Schaapveld M,[1,2] Krol ADG,[3] Janus CPM,[4] Cutter D,[5,6] Darby S,[6] Aleman BMP,[7] van Leeuwen FE[1]

[1]Department of Epidemiology, The Netherlands Cancer Institute, Amsterdam, the Netherlands; [2]Comprehensive Cancer Centre, the Netherlands, the Netherlands; [3]Division of Radiotherapy, Leiden University Medical Center, Leiden, the Netherlands; [4]Division of Radiotherapy, Erasmus Medical Center-Daniel den Hoed, Rotterdam, the Netherlands; [5]Oxford Cancer Center, Oxford University Hospitals NHS Trust, Oxford, United Kingdom; [6]Clinical Trial Service Unit, University of Oxford, Oxford, United Kingdom; [7]Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, the Netherlands.

Background. Hodgkin lymphoma (HL) is the prototype of a curable malignancy. However, treatment causes excess cardiovascular morbidity and mortality in long-term survivors. The objective of this study is to identify risk factors for ischemic heart disease (IHD), defined as myocardial infarction (MI) and angina pectoris (AP) (≥ grade 2 CTCAE4.0). We quantified separate and joint effects of radiation dose to the heart, anthracycline dose, other chemotherapeutic agents, lifestyle factors and established cardiovascular risk factors. Methods. A nested case-control study was conducted in a cohort of 2201 5-year HL survivors, diagnosed before age 51 and treated in the Netherlands between 1965 and 1995. Cases with IHD were matched to controls with HL who did not develop IHD (ratio 1:2 at least) on sex, age at HL diagnosis, date of HL diagnosis and duration of follow-up. Detailed treatment information was collected from medical records. Radiation dose to the heart was based on the prescribed mediastinal dose reported in the radiotherapy charts. Conditional logistic regression was used for analyses. Results. 180 cases with IHD as a first cardiac event were identified from the cohort and matched with 499 controls, with a mean time to event of 16.7 years (range 0.2–40.8 years). 148 cases were diagnosed with MI, 32 with AP. Mediastinal radiotherapy (usually performed using parallel opposed fields) was associated with an increased risk of IHD (OR: 3.0, 95%CI: 1.7-5.4). A dose-response relationship was identified (OR per 10 Gy: 1.2, p=0.004). As compared to patients who did not receive mediastinal irradiation, we observed increased risks of IHD for patients who received 20-34 Gy (OR: 2.1, 95%CI: 0.97-4.63), 35-39 Gy (OR: 2.0, 95%CI: 1.10-3.51) or ≥40 Gy to the mediastinum (OR: 3.6, 95%CI: 1.94-6.77) (p<0.001), after adjusting for smoking at HL diagnosis and the presence of cardiovascular risk factors at cut-off (Diabetes Mellitus type II, hypertension, hypercholesterolemia) or obesity at diagnosis or at time of cut-off. No associations were found with (anthracycline-containing) chemotherapy. Conclusions. Mediastinal irradiation is associated with a dose-dependent increased risk of IHD in patients treated for Hodgkin lymphoma.

P158
TEMPORAL TRENDS IN MORTALITY FROM DISEASES OF THE CIRCULATORY SYSTEM AFTER TREATMENT FOR HODGKIN LYMPHOMA-A POPULATION-BASED COHORT STUDY IN SWEDEN (1973-2006)

Eloranta S,[1] Lambert PC,[1,2] Sjöberg J,[3] Andersson TML,[1] Björkholm M,[3] Dickman PW[1]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [2]Department of Health Sciences, University of Leicester, Leicester, United Kingdom; [3]Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden

Background. Hodgkin lymphoma survival in Sweden has improved dramatically over the past 40 years (Sjöberg *et al* Blood. 2012;119:990), but little is known about the extent to which efforts aimed at reducing long-term treatment-related mortality have contributed to the improved prognosis. Aims. To estimate the contribution of treatment-related mortality due to diseases of the circulatory system (DCS) to temporal trends in excess Hodgkin lymphoma mortality among Swedish patients. Methods. We used population-based data from the national Swedish cancer register. Flexible parametric survival models were used to estimate excess mortality among 5,462 patients diagnosed at ages 19 to 80 between 1973 and 2006. The total excess mortality experienced by the patients was partitioned into component parts in order to isolate the excess DCS mor-

tality (assumed to be caused by the treatment) from the remaining excess mortality (such as that from the underlying disease, second malignancies and infections). In addition we utilized recent advances in statistical methodology to estimate excess mortality in the presence of competing causes of death. These models were used to predict the long-term risk for patients diagnosed in the modern era to die from treatment-related DCS. Results. Excess DCS mortality within 20-years after diagnosis has decreased continually since the mid 1980 s and is expected to further decrease among patients diagnosed in the modern era. Age at diagnosis and sex were important predictors for excess DCS mortality, with advanced age and male sex being associated with higher excess DCS mortality. However, when accounting for competing causes of death, we found that excess DCS mortality constitutes a relatively small proportion of the overall mortality among Hodgkin lymphoma patients in Sweden. Summary/Conclusions. Excess DCS mortality is no longer a common source of mortality among Swedish HL patients. The main causes of death among long-term survivors today are deaths from other causes than Hodgkin lymphoma, although other (non-DCS) excess mortality also persists as long as 20 years after diagnosis, particularly among older patients. Results from this study were recently published (Eloranta *et al*, J Clin Oncol. 2013; 31:1435).

P159
RISK OF VALVULAR HEART DISEASE AFTER RADIOTHERAPY FOR HODGKIN'S LYMPHOMA

Cutter DJ,[1,2] Schaapveld M,[3,4] van Leeuwen FE,[3] Hauptmann M,[3] Janus C,[5] Krol ADG,[6] van Nimwegen FA,[1] Darby SC,[6] Aleman BMP[7]

[1]Oxford Cancer Center, Oxford University Hospitals NHS Trust, Oxford, United Kingdom; [2]Clinical Trial Service Unit, University of Oxford, Oxford, United Kingdom; [3]Department of Epidemiology and Biostatistics, Netherlands Cancer Institute, Amsterdam, the Netherlands; [4]Comprehensive Cancer Centre, the Netherlands, the Netherlands; [5]Division of Radiotherapy, Erasmus Medical Center-Daniel den Hoed, Rotterdam, the Netherlands; [6]Division of Radiotherapy, Leiden University Medical Center, Leiden, the Netherlands; [7]Department of Radiotherapy, Netherlands Cancer Institute, Amsterdam, the Netherlands

Introduction. Mediastinal radiotherapy (MRT) for Hodgkin Lymphoma (HL) is known to increase cardiovascular disease (CVD) risk in HL survivors, including valvular heart disease (VHD). Little is known, however, about the dose-response for radiation-induced VHD or other risk factors for VHD. Methods. We performed a nested case-control study of VHD in a cohort comprising 1,861 5-year HL survivors, diagnosed between age 14 and 41 years, treated between 1965 and 1995, and identified through hospital-based cancer registries in the Netherlands. Cases were diagnosed with VHD (CTCAE v.4 grade ≥2) as a first CVD following HL treatment. For each case we selected at least two controls, who were free from CVD at the cut-off date, matched for gender, era of diagnosis, age at diagnosis and follow-up interval. Detailed data were collected from patient records including HL staging, chemotherapy and radiotherapy (RT) (primary and salvage), other medical conditions and CVD risk factors. RT data included original RT prescriptions and X-ray imaging. RT doses to the heart and cardiac substructures were retrospectively estimated by reconstructing the RT treatment on surrogate CT data sets using a CT-based treatment planning system. Results. We identified 89 cases and selected 200 controls. Of these cases, 45 presented with an aortic valve defect, 22 with a mitral valve defect, 12 with combined aortic and mitral valve defects and the remaining 10 with other combined valve defects. The mean dose to the affected valve in equivalent dose of 2 Gray fractions was higher for cases than controls (37.0 *vs* 30.2, p=0.001). A linear model gave an Excess Odds Ratio of 0.116 (95% Confidence Interval 0.018- 0.761) per Gray. However, a linear model did not fit the data well as there was evidence for an upward curvature in the data (p=0.011). In multivariate analysis, besides valve dose splenectomy was associated with increased VHD risk (Odds Ratio (OR)=2.07, p=0.037). VHD risk was not significantly increased after anthracycline treatment (OR=2.48, p=0.14). Conclusions. Radiation dose to the (affected) valve was associated with a non-linear increasing risk of VHD in HL survivors. Our analysis may benefit future MRT planning and improve counselling of patients regarding risks.

P160
ACCELERATED TELOMERE SHORTENING IN PERIPHERAL BLOOD LYMPHOCYTES OF HODGKIN LYMPHOMA WITH CORONARY ARTERY DISEASE

M'kacher R,[1,2] Girinsky T,[3] Colicchio B,[4], Ricoul M,[1] Dieterlen A,[4] Jeandidier E,[5] Heidingsfelder L,[6] Cuceu C,[1] Lenain A,[1] Bourhis J,[2,5] Hempel WM,[1] Carde P,[7] Sabatier L[1]

[1]Radiobiology and Oncology laboratory, CEA, DSV/iRCM, Fontenay-aux-Roses; [2]Laboratory of Radiation Sensitivity and Radio-carcinogenesis INSERM , IGR Villejuif; [3]Department of Radiation Oncology, IGR; [4]Laboratoire MIPS-Groupe TIM3D Université de Haute-Alsace, Mulhouse Cedex; [5]Department of hematology, Mulhouse; [6]MetaSystems GmbH , Altlussheim, Germany; [7]Department of Medicine, Institut Gustave Roussy,Villejuif, France

Background. Telomere length (TL) has been proposed as a marker of mitotic cell age and as a general index of human organism aging. Short absolute leukocyte telomere length has been linked to cardiovascular-related morbidity and mortality. Survivors of Hodgkin lymphoma (HL) are at significant risk for radiation therapy (RT)–induced cardiovascular disease. In our previous study, multivariate analysis demonstrated that hypertension and TL were the only independent risk factors of acute coronary artery disease (CAD). The goal of the present study was to investigate this telomere shortening in the same cohort of HL patients who developed CAD. Experimental design: we compared TL in peripheral blood lymphocytes and the morphology of the cells from 176 HL patients mostly treated with a combination of chemotherapy and radiotherapy and with a median follow-up of 9 years (range : 3-40 years). Sequential analysis of TL was established in 40 patients before treatment and during the follow-up. One hundred age matched controls were included. The Teloquant technique, based on the Q-FISH technique, measures not only telomere length, for which the values correlate well with telomere length measured by Southern blot and PCR, but also the morphological heterogeneity of the cells. CAD complications were detected by coronary CT angiography. Results. Compared with controls, HL patients showed drastic telomeres shortening ($p<10^{-6}$), higher irregularity of the nucleus ($p<10^{-16}$) and specific concavity of cells ($p<10^{-4}$). A significant correlation was observed between the occurrence of CAD and TL in the peripheral blood lymphocytes ($p<10^{-4}$) specially in young patients at treatment (<21 years of age) ($p<10^{-6}$). Moreover, 9 out 40 HL patients sampled sequentially before treatment and during the follow-up, had developed CAD. These patients presented a drastic telomere shortening before treatment. Conclusion. This is the first study in a large cohort of patients that demonstrates significant telomere shortening in HL patients who developed CAD. In addition, the follow-up of patients revealed that drastic telomere shortening in CAD patients occurs prior to treatment. TL appears to be an independent prognostic factor that could help determine patients at high risk of developing CAD after treatment in order to implement early detection and prevention.

P161
PROSPECTIVE CORONARY HEART DISEASE SCREENING IN ASYMPTOMATIC HODGKIN LYMPHOMA PATIENTS USING CORONARY CT ANGIOGRAPHY (CCTA): RESULTS AND RISK FACTOR ANALYSIS

Girinsky T,[1] M'Kacher R,[2] Lessard N,[1,7] Koscielny S,[3] Elfassy E,[4] Raoux F,[4] Carde P,[5] Dos Santos M,[1] Margainaud JP,[6] Sabatier L,[2] Ghalibafian M,[1,8] Paul JF[4]

[1]Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France; [2]Laboratory of radiobiology and oncology, IRCM/DSV CEA, Fontenay aux Roses, France; [3]Biostatistics and Epidemiology Unit, Institut Gustave Roussy, Villejuif, France; [4]Department of Radiology, Marie Lannelongue, Chatenay- Malabry, France; [5]Department of hematology, Institut Gustave Roussy, Villejuif, France; [6]Department of head and neck surgery, Institut Gustave Roussy, Villejuif, France; [7]Department of Radiation Oncology,Hotel-Dieu, Québec, Canada; [8]Department of Radiation Oncology, Mahak Charity Hospital, Tehran, Iran

Purpose. To prospectively investigate the coronary artery status using coronary CT angiography (CCTA) in patients with Hodgkin lymphoma treated with combined modalities and mediastinal irradiation Patients and Methods. All consecutive asymptomatic patients with Hodgkin lymphoma entered the study during follow-up, from August 2007 to May 2012. CCTA was performed and risk factors were recorded along with leucocyte telomere length (LTL) measurements. Results. One hundred and seventy-nine patients entered the 5-year study. The median fol-

low-up was 11.6 years (range: 2.1-40.2), the median interval between treatment and the CCTA was 9.5 years (range: 0.5- 40). Coronary artery abnormalities were demonstrated in 46 patients (26%). CCTA abnormalities were fdetected in nearly 15% of the patients within the first 5 years after treatment. A significant increase (34%) occurred 10 years after treatment (p=0.05). Stenoses were mostly non ostial. Severe stenoses were observed in 6.7% (12) of the patients entailing surgery with either angioplasty with stent placement or bypass grafting in 10 of them (5.5%). A multivariate analysis demonstrated that age at treatment, hypertension, hypercholesterolemia as well as the radiation dose to the coronary artery origins (CAO) were prognostic factors. In the group of patients with leucocyte telomere length (LTL) measurements, hypertension, and LTL were the only independent risk factors. Conclusions. The findings suggest that coronary CT angiography can identify asymptomatic individuals at risk of acute coronary artery disease who might require either preventive or curative measures. Conventional risk factors, the radiation dose and LTL were independent prognostic factors.

P162
ROLES OF RADIOTHERAPY, CHEMOTHERAPY, AND HORMONAL FACTORS IN THE RISK OF BREAST CANCER FOLLOWING TREATMENT FOR HODGKIN'S LYMPHOMA

van Eggermond AM,[1] Schaapveld M,[1] De Bruin ML,[2] Janus CPM,[3] Krol ADG,[4] Aleman BMP,[5] Russell NS,[5] van Leeuwen FE[1]

[1]Department of Epidemiology, The Netherlands Cancer Institute–Amsterdam [2]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University-Utrecht; 3Division of Radiotherapy, Daniel den Hoed Cancer Center/ Erasmus Medical Center–Rotterdam; [4]Division of Radiotherapy, Leiden University Medical Center–Leiden; [5]Department of Radiotherapy, The Netherlands Cancer Institute–Amsterdam, The Netherlands

Background. Female patients treated with radiotherapy (RT) for Hodgkin's lymphoma (HL) at a young age have a strongly increased risk of breast cancer (BC). There are still many questions about the influence of reproductive and hormonal factors on BC risk in these patients. This study assesses the influence of radiation dose, and modification of this effect by chemotherapy (CT), menopausal age and hormonal factors for the risk of BC after HL treatment. Methods. We conducted a matched case-control study within a cohort of 1,011 female 5-year HL survivors diagnosed before age 41 between 1965 and 1995. We compared HL treatments and hormonal factors between 143 patients with and 368 controls without breast cancer after HL. Analyses were restricted to cases and controls who received chest irradiation. Results. Patients treated with RT and CT had a lower risk of developing BC compared with patients treated with RT alone (Odds ratio (OR) 0.57, (95% confidence interval (CI) 0.37-0.88)). Compared with women treated with RT only, the OR for BC was 0.43 (95%CI 0.22-0.85) for women treated with 4.2-8.4 g/m2 procarbazine and 0.30 (95%CI 0.10-0.89) for those treated with more than 8.4 g/m^2 procarbazine. This association appeared to be due to the effect of CT on ovarian function: 14% of women treated with RT only became menopausal before age 41 compared to 93% of women treated with 4.2 g/m^2 procarbazine or more. Reaching menopause before age 31 was associated with a lower risk of BC compared to women who reached menopause after age 50 (OR 0.35, 95%CI 0.13-1.46). Analyses concerning the influence of other hormonal factors and dosimetry are currently being performed. Conclusion. A procarbazine dose of 4.2 g/m^2 or more reduces the risk of RT-induced BC due to CT-induced premature menopause. results Regarding other hormonal factors and radiation dosimetry will be presented.

P163
RISK OF DIABETES MELLITUS IN LONG-TERM SURVIVORS OF HODGKIN LYMPHOMA

van Nimwegen FA,[1] Schaapveld M,[1,2] Janus CPM,[3] Krol ADG,[4] van der Maazen RWM,[5] Kremer LCM,[6] Aleman BMP,[7] van Leeuwen FE[1]

[1]Department of Epidemiology, The Netherlands Cancer Institute, Amsterdam; [2]Comprehensive Cancer Centre; [3]Division of Radiotherapy, Erasmus MC-Daniel den Hoed, Rotterdam; [4]Division of Radiotherapy, Leiden University Medical Center, Leiden; [5]Department of Radiotherapy, Radboud University Nijmegen Medical Centre, Nijmegen; [6]Department of Pediatric Oncology, Emma Children's Hospital/Academic Medical Center, Amsterdam,; [7]Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, the Netherlands

Background. In childhood cancer survivors, an association has been observed between radiotherapy to the pancreas and an increased risk of diabetes mellitus (DM). Hodgkin lymphoma (HL) survivors may also experience an increased risk of DM, as they often received infradiaphragmatic radiation in the past. We evaluated the association between treatment and DM risk in 5-year HL survivors. Methods. Our Dutch study cohort comprised 2264 5-year HL survivors, diagnosed before age 51 and treated between 1965 and 1995. Treatment and follow-up information was collected from medical records and general practitioners. DM cases were confirmed by general practitioners. Para-aortic radiation and splenic/splenic hilum radiation were used as proxy for radiation to the pancreatic head and body, and pancreatic tail, respectively. Cumulative incidence of DM was estimated and risk factors for DM were evaluated using Cox regression. Results. 151 cases of DM after HL were identified after a median follow-up of 22 years (range 5.1–44.6 years). Median age at treatment was 27 years, median age at diagnosis of DM was 54 years. Overall cumulative incidence of DM 30 years after initial treatment, with death as a competing risk, was 7.9% (95%Confidence Interval (CI): 6.5-9.3). After irradiation of the spleen/splenic hilum, 30-year cumulative incidence of DM was 11.1% (95%CI: 8.2-14.4). Radiation to the spleen/splenic hilum was associated with an increased risk of DM (Hazard Ratio (HR): 1.6, 95%CI: 1.1-2.3), compared to patients who did not receive infradiaphragmatic radiotherapy (reference group). Infradiaphragmatic radiation to the para-aortic lymph nodes without radiation of the spleen/splenic hilum was not associated with an increased risk of DM (HR:1.3, 95%CI:0.9-2.1). Analyses were adjusted for year of diagnosis and treatment with procarbazine-containing chemotherapy, which decreased the risk of DM. Patients who received a high radiation dose to the spleen (40 Gy or more) experienced the highest risk of DM (HR: 2.5, 95%CI: 1.26–5.10). Conclusion. Radiation to the spleen/splenic hilum, leading to radiation exposure of the pancreatic tail, increased the risk of developing DM in 5-year HL survivors. Para-aortic radiation alone did not increase DM risk.

P164
HODGKIN LYMPHOMA IN ADULTS: AN INTERDISCIPLINARY EVIDENCE-BASED GUIDELINE

Skoetz N, Rancea M, Borchmann P, von Tresckow B, Halbsguth T, Behringer K, Wongso D, Böll B, Klimm B, Thielen I, Eichenauer D, Engert A

Department I of Internal Medicine, University Hospital of Cologne, Germany

Hodgkin lymphoma (HL) is rare, but nonetheless one of the most common cancers in young adults. It is regarded as curable disease, even in advanced stages. Current research focuses on the avoidance of short- and long-term toxicity and secondary malignancies. To improve and standardise diagnosis, therapy and follow-up for these patients, a clinical practice guideline was developed and consented by all major medical societies. The guideline was funded by the German Program for Guidelines in Oncology (No: 109230). Methods. We searched MEDLINE, CENTRAL, and the Guideline International Network for guidelines, systematic reviews, randomised controlled trials and cohort studies. Two experts independently screened references, assessed study quality and extracted data from potentially relevant publications into evidence tables. Results. On the basis of evidence 32 key questions were answered with 160 recommendations. There is a strong consensus that all patients should be offered the opportunity to be treated within a clinical trial unless they fail to meet the inclusion criteria. Two cycles of ABVD followed by involved-field radiotherapy (IF-RT) at 20Gy are strongly recommended in early favorable stages. Patients in early unfavorable (intermediate) stages should be treated with 2 cycles of BEACOPP escalated followed by 2 cycles of ABVD and IF-RT of 30Gy. Patients up to the age of 60 in advanced stages should be treated with 6 cycles of BEACOPP escalated. Consolidation radiotherapy (30 Gy) of PET-positive residual mass ≥2.5 cm is strongly recommended. There is unclear evidence for the additional value of PET, and the recommendations differ between staging, interim and follow-up evaluations. For patients up to the age of 60 with relapsed HL high-dose chemotherapy with autologous stem-cell transplantation is strongly recommended. Structured follow-up care should be provided to detect relapses, long-term organ toxicities and secondary malignancies. The guideline is available at www.awmf.org and http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html. The patient guideline will be published soon. Con-

clusion. This is the first published S3 guideline giving evidence- and consensus-based recommendations for the diagnosis, treatment, and follow-up of HL. With these freely available treatment recommendations all HL patients can receive optimized, individually adapted care.

P165
INFRADIAPHRAGMATIC RADIOTHERAPY IN PATIENTS WITH HODGKIN S LYMPHOMA (HL)-INFERTILITY AS A POSSIBLE CONSEQUENCE

Baues CM,[1] Müller H,[2] Nast-Kolb B,[1] Celic E,[1] Kriz J,[3] Görgen H,[2] Semrau R,[1] Engert A,[2] Borchmann P,[2] Behringer K[2]

[1]Radiooncology University Hospital of Cologne, Cologne, Germany; [2]German Hodgkin Study Group, First Department of Internal Medicine, University Hospital of Cologne, Cologne, Germany; [3]Radiooncology University Hospital of Münster, Münster, Germany

Purpose. Toxicity of chemotherapy in the treatment of HL is often described but there is still few data about the impact of radiotherapy. Here we analyze effects of infradiaphragmatic involved field radiotherapy (IF-RX-infra) on gonadal hormone function. Patients and Methods. In the HD14 trial 1,528 patients with early unfavorable HL were treated with either 4xABVD or 2xBEACOPPesc + 2xABVD and consolidating involved field radiotherapy (30 Gy). All survivors in ongoing remission at least 1 year after treatment and younger than 40 years at diagnosis (females) or 50 years at diagnosis (males) were asked for participation in our prospective fertility study (Behringer et al. 2012). In the present analysis of radiotherapy sequelae we evaluated the levels of Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) as surrogate parameters of gonadal functioning. The effects of IF-RX-infra versus supradiaphragmatic radiotherapy (IF-RX-supra) were tested in a multiple regression model with adjustment for age, gender and chemotherapy. Results. FSH and LH levels of 274 female and 247 male survivors were analyzed. Of these, in total 21 patients (4%), 6 women and 15 men, had received IF-RX-infra. The adjusted log values of FSH and LH were significantly higher in patients who had received IF-RX-infra compared to IF-RX-supra (FSH p= 0.0006, LH p= 0.0127). The magnitude of the IF-RX-infra effects were comparable with the toxic effects of 2 cycles of BEACOPPesc. Age, chemotherapy and the interaction of age and gender proved to be additional significant factors. Whether IF-RX-infra resulted in hormone levels which indicate infertility depended highly on age and gender as well as the applied chemotherapy regimen. Females elder than 30 years and treated with BEACOPPesc had the worst hormonal outcome. Cave: as tumor sites and sites of radiotherapy are identical in this study, the following conclusion presupposes without any testable option that infradiaphragmal tumors do not per se cause the observed hormonal differences. Conclusion. This study indicates a significant influence of infradiaphragmatic involved field radiotherapy on gonadal hormone levels. Thus, involved field radiotherapy of infradiaphragmatic tumor sites may cause infertility, especially in females elder than 30 years and treated with BEACOPPesc.

P166
SCREENING FOR CORONARY ARTERY DISEASE AFTER MEDIASTINAL IRRADIATION IN HODGKIN LYMPHOMA SURVIVORS USING COMPUTED TOMOGRAPHIC ANGIOGRAPHY: PHASE II STUDY OF INDICATION AND ACCEPTANCE

Daniëls LA,[1] Krol ADG,[1] de Graaf MA,[2,6] Scholte AJHA,[2] van 't Veer MB,[3] Putter H,[4] de Roos A,[5] Schalij MJ,[2] Creutzberg CL[1]

[1]Departments of Clinical Oncology; [2]Departments of Cardiology; [3]Departments of Hematology; [4]Departments of Medical Statistics and Bio-informatics; [5]Departments of Radiology,Leiden University Medical Center, Leiden, The Netherlands; [6]The Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands

Background. Cardiovascular diseases are the most common non-malignant cause of death in Hodgkin Lymphoma (HL) survivors, especially after mediastinal irradiation. We investigated the role of CT coronary angiography (CTA) as a screening tool for coronary artery disease (CAD) in asymptomatic HL survivors, related CTA findings to exercise testing and subsequent interventions, and evaluated health-related quality of life (HRQoL) and acceptance of screening. Methods. Patients were eligible if at least 10 years disease free and treated with mediastinal radiotherapy. All patients were screened with CTA, ECG and exercise tests. Primary endpoint was significant CAD (>50% stenosis) on CTA. Screening was considered to be indicated for testing in a larger population if ≥12% of all scanned patients would need revascularisation. HRQoL was evaluated both at baseline and after completing the screening protocol by means of the EORTC QLQ-C30, the INFO-25, the Fatigue Assessment Scale (FAS) and a self designed questionnaire to specifically address acceptance of screening. Results. Fifty-two patients were included, 48 patients underwent CTA. Median age was 47 years, time since HL diagnosis 21 years and median dose of mediastinal radiotherapy was 36 Gy. Significant CAD on CTA was found in 20% (N=9), and after coronary angiography confirmed in 11% (N=5). Additionally, two patients were treated with optimal medical therapy. 96% of the patients participated in the HRQoL part of the study, the response rate after screening was 85%. Mean rating for general quality of life and health were both 72 points out of 100. Overall, 77% of the patients reported symptoms of fatigue. Visiting the cardiac outpatient clinic and undergoing CTA was perceived cumbersome by 10% and 20% respectively. The majority (90%) was content with participating in screening, although 25% perceived the emphasis that was placed on possible late effects of treatment as bothersome. Conclusions. Prevalence of significant CAD among HL survivors is high, while asymptomatic even in the presence of life-threatening CAD. Acceptance of screening is high, regardless whether CTA showed abnormalities or not. This might justify screening by CTA in asymptomatic HL survivors who underwent mediastinal radiotherapy, but needs to be evaluated in a larger cohort.

P167
COMPARISON OF RITUXIMAB IN THE FIRST AND SECOND LINE TREATMENT IN LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA

Mocikova H,[1] Pytlik R,[2] Stepankova P,[3] Michalka J,[4] Raida L,[5] Markova J,[1] Koren J,[2] Belada D,[3] Kral Z,[4] Kozak T[1]

[1]Dept. of Clinical Hematology, University Hospital Kralovske Vinohrady, Third Faculty of Medicine, Charles University in Prague, Czech Republic; [2]First Medical Dept.–Clinical Dept. of Haematooncology, First Faculty of Medicine and General Teaching Hospital, Charles University in Prague, Czech Republic; [3]Fourth Internal Clinic of Hematology, Charles University, Faculty of Medicine and University Hospital, Hradec Kralove, Czech Republic; [4]Dept. of Internal Medicine and Hematooncology, University Hospital, Brno, Czech Republic; [5]Dept. of Hemato-Oncology of the Faculty of Medicine and Dentistry Palacky University Olomouc, Czech Republic

Background. Strong CD20 expression in lymphocyte predominant Hodgkin lymphoma (LPHL) suggests the feasibility of rituximab in the treatment of this disease. Low toxcity and high efficacy were reported in LPHL patients treated with rituximab, however, it is unclear whether patients benefit from early treatment with this drug. Therefore, the aim of this study was to compare the time from diagnosis to second relapse in patients treated with rituximab in the first and second line therapy. Patients and Methods. Overall 23 LPHL patients (13 treated with rituximab in the first line and 10 treated with rituximab in the second line treatment) were analysed. Median age of patients was 33.2 years. Characteristics of patients (gender, clinical stage, B symptoms, risk factors and combination of rituximab with chemotherapy and/ or radiotherapy) did not differ significantly between both groups. Survival of patients was calculated using Kaplan-Meier method and differences of survival between subgroups with log-rank test. Results. Median follow-up of the whole group was 51.3 months (rituximab in the first line 32.1 months and rituximab in the second line since diagnosis 86,9 months and since the first relapse 19.8 months). The 5-year overall survival rate of the whole group was 100%. None of the patients treated with rituximab in the first line relapsed and only one patient relapsed after rituximab in the second line treatment. There was no statistical difference in the time from diagnosis to second relapse between both groups (p=1.0). Histologic transformation (HT) to diffuse large B-cell lymphoma was not observed in this group of 23 patients. Conclusions. The time from diagnosis to second relapse did not differ between patients treated with rituximab in the first and the second line treatment. The prognosis of LPHL is excellent and it is feasible to wait with the rituximab treatment until the relapse.
Supported by the Research project P 27/2012 awarded by Charles University in Prague, Third Faculty of Medicine, Prague, Czech Republic

P168
SURVIVAL AFTER HIGH DOSE THERAPY WITH AUTOLOGOUS STEM CELL SUPPORT FOR ADULT RELAPSED OR REFRACTORY HODGKIN'S LYMPHOMA IN NORWAY–A NATIONAL MULTICENTER STUDY

Smeland K,[1] Kiserud CE,[1] Lauritzsen GF,[2] Fosså A,[2] Østenstad B,[2] Kolstad A,[2] Fagerli UM,[3], Fluge Ø,[4] Maisenhølder M,[5] Loge JH,[1] Kvaløy S,[2] Holte H[2]

[1]National Resource Center for Late Effects, Department of Oncology, Oslo University Hospital; [2]Department of Oncology, Oslo University Hospital; [3]Department of Oncology, St. Olav's Hospital; [4]Department of Oncology, Haukeland University Hospital; [5]Department of Oncology, University Hospital of North Norway

Aim. To investigate survival after high dose therapy with autologous stem cell support (HDT) for relapsed/refractory Hodgkin's lymphoma (HL) compared to age- and gender matched controls, and analyse cause of death. Methods All adult patients (≥18 years) treated with HDT for relapsed/refractory HL in Norway 1987-2008 were included. Date and cause of death were obtained from Statistics Norway and linked with clinical data from each hospital. Observation time was estimated from HDT to death or cut-off on December 31 2011. Crude cumulative probabilities for survival were calculated by Kaplan-Meier method, and groups compared with log-rank tests. Five age- and gender matched controls per patient were drawn from the general Norwegian population, and risk for death among HL patients compared to controls were analysed using the Cox proportional Hazard method. Results. In total, 149 HL-patients have been treated with HDT in Norway until 2008. Median age at HDT was 33 years (range 18-64) and 59% were men. Total body irradiation and high dose cyclophosphamide (TBI) was used as high dose regimen in the first 15 patients (10%), whereas 147 (90%) received chemotherapy only (BEAM). Ninety-seven patients (65%) were alive at cut-off with median observation time 116 months. Only 2 patients died within the first 100 days after HDT. The 10- and 15-year overall survival was 64% (95% CI: 56%-72%) and 60% ((95% CI: 50%-69%). Compared to controls the mortality risk was 19 times higher (HR 19; 95% CI: 11-33) (figure 1). Among the HL patients, there was no significant difference in survival between genders or high dose regimens . Cause of death was HL for 30 (60%), NHL for 9 (18%), other haematological malignancies for 3 (6%), heart disease for 2 (4%), and other causes for 6 (12%) patients. Conclusions. HDT has been used for HL since 1987, with only a few cases per year until it was established as standard therapy in the mid-1990s. The survival after HDT for HL in Norway is good, and comparable with other published reports. HL was the most common cause of death.

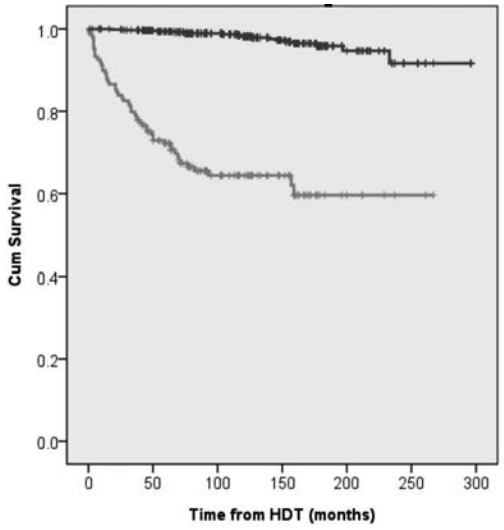

Figure 1: Overall survival after HDT for Hodgkin's lymphoma in green (n=149) versus age- and gender matched controls in blue (n=745). HR 19 (95% CI: 11-32), p<0.001.

P169
PROGNOSTIC SIGNIFICANCE OF CD20 EXPRESSION AND EPSTEIN-BARR VIRUS (EBV) ASSOCIATION IN CLASSICAL HODGKIN'S LYMPHOMA

Elsayed AA,[1,2] Asano N,[3] Ohshima K,[4] Izutsu K,[5] Kinoshita T,[6] Nakamura S[1]

[1]Dept. of Pathology and Clinical Laboratories, Nagoya University Hospital, Nagoya, Japan; [2]Dept. of Pathology, Faculty of Medicine, Mansoura University, Mansoura, Egypt; [3]Dept. of Clinical Laboratory, Nagoya University Hospital, Nagoya, Japan; [4]Dept. of Pathology, Kurume University School of Medicine, Fukuoka, Japan; [5]Dept. of Hematology, Toranomon Hospital, Tokyo, Japan; 6Dept. of Hematology and Cell Therapy, Aichi Cancer Center, Nagoya, Japan

Background/Purpose. Hodgkin and Reed-Sterberg (HRS) cells of classical Hodgkin lymphoma (CHL) show various phenotypic characteristics, being mostly of B-cell phenotype. However, some cases show T-cell/cytotoxic molecule (CM) phenotype on HRS cells which adversely affects the prognosis. Here, we investigated the clinicopathological significance of CD20 expression and EBV-association in CHL. Design and Methods. CD20 expression and EBV positivity (by EBER in situ hybridization) was investigated in 389 CHL patients. None of them showed expression of T/Cytotoxic molecule (CM) phenotype. Results. The patients of this study consisted of 125 females and 262 males with median age of 48 years. They included 74 CD20-positive cases (19%) (median age, 56 years; male-to-female ratio, 1.64) and 315 CD20-negative cases (81%) (median age, 45 years; male-to-female ratio, 2.22). EBV-positive cases comprised 44% of our series (n=173) in contrast to 216 EBV-negative cases (56%). Compared to patients with CD20-negative CHL, CD20-positive cases showed a significantly older age at onset (P=.018) and a higher association with EBV (61% *vs* 41%, P=.002). Five-year overall survival (OS) rate for CD20-positive and CD20-negative cases were 75% and 79% respectively (P=.872). The international prognostic index (IPI) could stratify the prognosis of CHL in this analysis; however, some other unique factors, including EBV positivity (but not CD20 positivity), presence of B symptoms, and thrombocytopenia in addition to elevated lactate dehydrogenase (LDH) and performance status >1 were identified as independent prognostic factors for OS. We thus attempted to construct a new prognostic model with these 5 prognostic factors. We classified patients into 3 risk groups using the following terms: low risk, 0 or 1 adverse factor; intermediate risk, 2 or 3 factors; high risk, 4 or 5 factors. This novel prognostic model could stratify the prognosis of CHL patients (P<.0001). The five-year OS for low-risk, intermediate-risk and high-risk groups was 91%, 66% and 36% respectively (P<.0001). Conclusion. IPI was still useful for prognostication of CHL, and other factors, not included in IPI, such as EBV positivity, presence of B symptoms, and thrombocytopenia, also significantly affected prognosis. Examination of EBV association in CHL is recommended as a routine pathologic practice especially in East Asian countries.

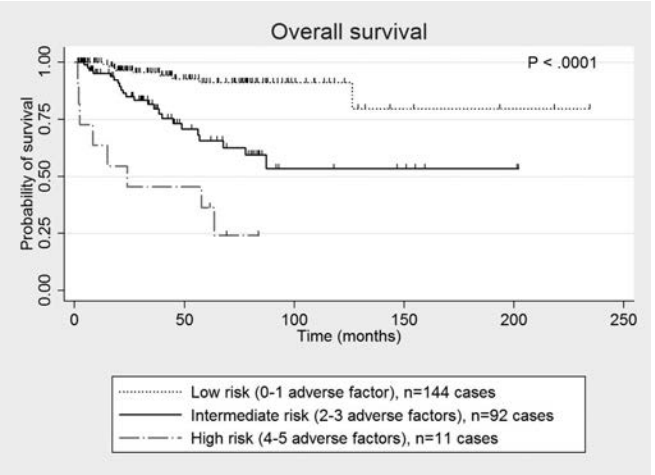

Figure 1.

P170
THE ADDITION OF LYMPHOCYTE/MONOCYTE RATIO (LMR) TO THE INTERNATIONAL PROGNOSTIC SCORE FOR HODGKIN LYMPHOMA IDENTIFIES LOW RISK PATIENTS WITH ADVERSE PROGNOSIS

Tadmor T,[1] Bari A,[2] Marcheselli L,[2] Aviv A,[3] Pozzi S,[2] Liardo EV,[2] Cox MC,[4] Giraffa M,[4] Cascavilla N,[5] Attias D,[1] Ferri P,[2] Sacchi S,[2] Federico M,[2] Polliack A[6]

[1]Division of Hematology, Bnai-Zion Medical Center, The Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [2]Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy; [3]Hematology–Oncology Unit, Emek Medical Center, Afula, Israel; [4]Department of Hematology, AO Sant'Andrea, La Sapienza University, Rome, Italy; [5]Department of Oncology-Hematology, IRCCS Hospital Casa Sollievo della Sofferenza, S. Giovanni Rotondo, Foggia, Italy; [6]Department of Hematology, Hadassah University Hospital and Hebrew University Medical School, Jerusalem, Israel

Most patients with Hodgkin lymphoma (HL) have an excellent prognosis and can be cured with chemo/radiotherapy. However,the existence of different histopathological subtypes and the variable biological and clinical features indicate that HL is a heterogeneous entity. Disease diversity is related to surrounding inflammatory cells, which play a role in prognosis. Thus it is relevant to recognize parameters that may reflect clinical and biological disease patterns and help to stratify patients. The current prognostic parameter for HL,the international prognostic score (IPS), relates to advanced disease, while consensus is lacking regarding early stage disease. The study evaluated the prognostic significance of absolute monocyte count (AMC) and lymphocyte/monocyte ratio (LMR) in classical HL. Medical records of patients treated between 1988-2011 in Italy and Israel were reviewed. We analyzed whether AMC and LMR could serve as prognostic values for overall survival (OS) compared to prognostic parameters as: age, gender, stage, albumin and hemoglobin, white blood cells and lymphopenia. Cut-off values were chosen using the maximum log rank test and c-Harell. The cohort included 371 patients, median age 35 years (range 17-79), 48% males, 19% stage IV and 31% had IPS score of 3-7. Median follow-up was 6.9 years (range 0.2-20) and 5-years OS was 91%. Monocytosis defined >600/mm3 and LMR cut-off was 3.5. The 10 years progression free survival (PFS) for patients with monocytes >600/mm3 and LMR<3.5 was 62% and 67% respectively, compared to 78% and 85% in the group with monocytes <600/mm3 and LMR>3.5 (p value: 0.032 and 0.005, respectively). In multivariate analysis:LMR and IPS maintained their prognostic significance in terms of 10 years PFS and OS (HR of 2.37 and 3.5). The addition of LMR to the IPS, divided the low risk patients (IPS:0-2) into 2 subgroups: one with "very low risk" of progression and another with prognosis and OS similar to those of patients with IPS 3-7. In Conclusion. LMR<3.5 was identified as an independent negative prognostic factor in patients with HL, with impact on PFS and OS. The addition of LMR to IPS was able to split the IPS " low risk" patients in a subgroup with less favorable prognosis.

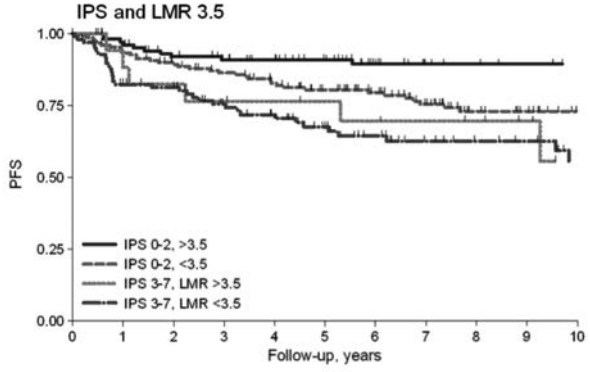

Figure 1. Progression free survival by IPS and LMR 3.5

P171
RADIATION PULMONARY COMPLICATIONS IN HODGKIN`S LYMPHOMA PATIENTS AS RESULT OF RADIOTHERAPY ALONE OR CHEMO-RADIOTHERAPY INVOLVING MEDIASTINAL IRRADIATION TO DIFFERENT TOTAL TUMOR DOSES

Danilenko A, Shakhtarina S, Afanasova N, Pavlov V

Medical Radiological Research Center, Obninsk, Russia

Objective. to study immediate and late pulmonary complications in Hodgkin`s lymphoma (HL) patients treated with radiotherapy alone or combined chemo-radiotherapy involving mediastinal irradiation to the total tumor doses (TTD) 20-30-40 Gy. Materials and Methods. the study included 491 initial HL patients without consequent relapses. In 1968-1997 treatment was given to 299 patients including 180 patients treated with radiotherapy alone and 119 patients treated with chemo-radiotherapy. In all cases TTD 40 Gy was administered to mediastinum. In 1998-2008 years 192 patients received chemo-radiotherapy involving mediastinal irradiation to TTD 20-30 Gy. Patients were 14-66 years old with median 25 years to time of treatment. Classical and digital radiograms were analized as well as linear and digital chest tomograms taken at the time of administering TTD 20 Gy, after completing mediastinal irradiation, and in 3, 12, 24, 36, 48, 60 months after completion of the treatment program. Acute and late radiation pulmonary complications were evaluated and systematized according LENT-SOMA scale. Results. Radiation pulmonitis was registered in 56 of 180 (31,1%) patients given radiotherapy alone (mediastinal TTD 40 Gy); 41 of 119 (34,4%) patients given chemo-radfiotherapy (mediastinal TTD 40 Gy);33 of 192 (17,2%) patients given chemo-radiotherapy (mediastinal TTD 20-30 Gy). Radiation pulmonary fibrosis was found in 171 of 180 (95%) patients given radiotherapy alone to the TTD 40 Gy; in 92 of 119 (77%) patients after combined therapy using TTD 40 Gy; 77 of 193 (38%) patients after combined therapy using TTD 20-30 Gy. The incidence rate of Grade I fibrosis was 61,7%, 57,9%, 35,4%,respectively; Grade 2-17,2%, 18.5%, 2,6%, respectively; Grade 3-16,1%, 0,9%, and no cases, respectively. Conclusions. Lower TTD (20-30 Gy) of mediastinal irradiation correlated with lower incidence of acute and late radiation pulmonary complications and lower intensity of lung fibrosis.

P172
SECOND NEOPLASMS IN YOUNG ADULTS FOLLOWING TREATMENT OF CHILDHOOD HODGKIN LYMPHOMA

Kruseova J, Ganevova M, Cepelova M, Luks A, Krol L, Malis J, Kabickova E, Churackova M, Stary J

Department of Pediatric Haematology and Oncology, University Hospital in Motol, Prague, Czech Republic

Objective and Rationale. Today more than 90% of children and adolescents with Hodgkin lymphoma can be cured by combined modality treatment, however in the long term follow up some of these patients experience one of the most serious late effects–development of secondary neoplasm. Materials and Methods. We have evaluated the occurence of second neoplasms in long term survivors after Hodgkin lymphoma treatment in childhood. We included 440 patients treated between January 1979 and December 2011 at the Department of Pediatric Haematology and Oncology, University Hospital in Motol. We have identified second neoplasms in twenty-eight of these patients (6,3%). Diagnosis was made by clinical symptoms in 53% of cases and in 47% at regular visit at the late effects department. There were seventeen males and eleven females. All these patients received combined chemotherapy and radiotherapy. The median time to diagnosis of secondary neoplasm (SN) was 15,9 years (range, 2,12 to 27,63 years). Second neoplasms were: 14 thyroid carcinomas, 5 soft tissue sarcomas, 4 colorectal carcinomas, 3 breast carcinomas, 1 acute lymphoblastic leukemia and 1 myelodysplastic syndrome. All patients except one received treatment for secondary malignancy. Outcome: nineteen patients are alive in first complete remission after SN, nine patients died (32,1%), including four patiens with soft tissue sarcomas, three patiens with carcinomas and both patiens with hematological malignancies (MDS, ALL). Conclusion. Follow up even many years after primary treatment may help in early recognition of secondary malignancies in long term survivors with opportunity of achieving good treatment results. Supported by MH CZ–DRO, University Hospital Motol, Prague,Czech Republic 00064203

P173

THE BREAST CANCER AFTER RADIOTHERAPY DATASET (BARD): AN INITIATIVE TO IMPROVE SCREENING FOR BREAST CANCER IN A HIGH RISK COHORT OF FEMALE HODGKIN LYMPHOMA SURVIVORS IN ENGLAND

Radford J,[1] Howell S,[2 3] O'Hara C,[4] Goode V,[5] Vaughan K,[6] Davies S,[7] Cowan R,[8] Swerdlow A[8]

[1]The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [2]The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [3]Public Health England (Northwest), Manchester, UK; [4]The Christie NHS Foundation Trust, Manchester, UK; [5]The University of Manchester, Manchester, UK; [6]Teenage Cancer Trust, London, UK; [7]The Christie NHS Foundation Trust, Manchester, UK; [8]The Institute of Cancer Research, London, UK

Introduction. Female survivors of Hodgkin lymphoma who received radiotherapy involving breast tissue under age 36 are at increased risk of breast cancer. Since 2003, national guidelines have recommended these women undergo annual breast screening starting 8 years after treatment or from age 25 whichever is later. In 2009 we showed that penetration of screening into this at-risk population was poor (Howell S et al, British Journal of Cancer, 2009). In addition, anecdotal evidence suggests that appointments for screening are not always issued in a timely way and/or require repeat referrals from the treating oncologist or family physician. These factors limit the effectiveness of screening and generate anxiety for at-risk women. Methods and Results. To address these issues we have established a national breast cancer after radiotherapy dataset (BARD), hosted at Public Health England (Northwest) in Manchester and funded by Teenage Cancer Trust. BARD comprises contact details for women irradiated pre-2003 and identified as part of a recall exercise undertaken in 2003, those irradiated 2003-2009 identified from cancer registries/radiotherapy centre records and finally women irradiated 2009-2013 and beyond identified from the nationally mandated radiotherapy dataset. The names of women irradiated under age 30 and requiring screening will be forwarded annually to the NHS Breast Screening Programme (NHSBSP) that will then issue a screening appointment at a local breast screening centre. For women irradiated 30-35 whom NHSBSP is not currently commissioned to screen, BARD will send a letter to the family physician prompting them to refer for screening. Conclusions. For the first time BARD brings together a cohort of women in England at high risk of breast cancer following radiotherapy to breast tissue during treatment for Hodgkin lymphoma under age 36. In collaboration with NHSBSP, BARD will facilitate the timely issue of screening appointments and improve the efficiency and reliability of screening and the user experience. Evaluation of the screening protocol, trends in breast cancer incidence as radiotherapy practice evolves and primary research into radiation induced breast cancer will also be possible. Discussions around extending the scope of BARD to other countries in the UK are underway.

P174

CLINICAL AND RADIOLOGICAL MANIFESTATIONS OF PULMONARY TOXICITY IN HODGKIN`S LYMPHOMA PATIENTS TREATED WITH CHEMOTHERAPY AND RADIOTHERAPY TO TOTAL TUMOR DOSES 20-30 GY

Shakhtarina S, Danilenko A, Afanasova N, Pavlov V

Medical Radiological Research Center, Obninsk, Russian Federation

Objective. To study pulmonary changes in Hodgkin`s lymphoma (HL) patients during and after chemo-radiotherapy using lowered radiation total tumor doses (TTD). Materials and Methods. 192 initial HL patients treated with chemo-radiotherapy involving mediastinal irradiation to TTD 20-30 Gy. Ages: 15-68 (median-27) years. According to chemotherapy and TTD the following groups were defined: I-COPP+RT 20-22Gy (34 pts), II-ABVD+RT 24-30 Gy (125 pts), III-BEACOPP+RT 30 Gy (33 pts). Results. During chemotherapy in 49 of 192 (25,5%) radiography showed pathological pattern of lung structure due to enlarged and increased in number lung vessels surrounded with denced intersticial tissue up to the vessels of IV-V order. Pathological process was of diffuse bilateral type, "air" bronchograms were ansent. Eight of 49 (16,3%) patients showed focal or confluent pulmonary infiltration, 3 (6,1%) patients had denced interlobular pleura, intersticial septs. Radiological signs of cytostatic impact: in Group I-6 of 34 (17,6%) patients; Group II-36 of 125 (28,8%); Group III-7 of 33 (25,5%). Diffuse intersticial changes of pulmonary stroma were seen seen in all groups of patients; focal or confluent pulmonary infiltration was only seen in Group II patients. Clinical manifestations of pulmonaru toxicity were also found in patients of Group II only (4 of 125; 3,2%). Fibrotic pulmonary changes due to cytostatic impact were not found. Radiological signs of short-term radiation changes in lungs were registered in 61 of 192 (31,8%) patients: Group I-11 of 34 (32,3%); Group II-40 of 125 (32%); Group III-10 of 33 (30,3%). Late complications-in 73 of 192 (39%) patients: Group I-10 of 34 (29,4%); Group II-47 of 125 (37,6%), Group III-16 of 33 (48,5%). Grade I fibrosis was predominating (68 0f 192; 35,4%) while Grade 2 fibrosis was found in 5 (2,6%) patients. Conclusion. radiological signs of pulmonary toxicity due to cytostatics were found after COPP, ABVD, BEACOPP. Clinically significant-after ABVD only. Incidence rate of short-term and late radiation pulmonary toxicity as result of mediastinal irradiation to TTD 20-30 Gy was lower than that from literature data concerning 40 Gy

P175

FERTILITY IN MALE PATIENTS WITH HODGKIN LYMPHOMA TREATED WITH BEACOPP REGIMEN

Smardova L,[1] Crha I,[2] Michalka J,[1] Kral Z,[1] Janikova A,[1] Charouzkova J,[1] Mayer J[1]

[1]Department of Internal Medicine, Hematology and Oncology, University Hospital Brno and Masaryk University, Czech Republic; [2]Department of Obstetrics and Gynecology, University Hospital Brno and Masaryk University, Czech Republic

Introduction. BEACOPP regimen is currently the standard treatment of advanced stage Hodgkin lymphoma (HL). However, its administration is associated with a higher risk of adverse effects, including impaired fertility due to containment of several gonadotoxic agents. Methods. We evaluated the impact of BEACOPP regimen on fertility status of 23 patients with advanced stage HL. The median age was 26 years (20-37). Most patients were in clinical stage IIB with risk factors (N=11), followed by the group of patients in stage III (N=8) and patients in stage IV (N=4). All patients were treated with 6-8 cycles of BEACOPP baseline (N=6) or escalated (N=17). For all patients were performed semen analysis and measurement of hormonal levels of gonadotropic hormones (follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone) before and after treatment. Results. Only 1 patient had normozoospermia and 22 patients had dysspermia before treatment. For all patients we found normal levels of gonadotropic hormones and testosterone. After treatment azoospermia was observed for all patients (the median time of semen examination was 24 month). For 20/23 (87%) patients was found FSH elevation (13.1 to 35.8 IU/l), for 5/23 (21%) patients LH elevation (9.2 to 15.0). After treatment, testosterone levels were normal for all patients. 6 patients (26%) used previously frozen sperm samples to attempt in vitro fertilization, in case of 4 patients it was successfull (healthy children were born 2-8 years after treatment). Conclusion. Male patients with HL are at high risk of infertility after treatment with BEACOPP regimen. Before starting treatment sperm cryopreservation should be offered to every patient. FSH levels probably correlate with spermatogonial damage after treatment.

P176

COMBINATION OF FERTILITY PRESERVATION STRATEGIES IN YOUNG WOMEN WITH RECENTLY DIAGNOSED HODGKIN LYMPHOMA

Smardova L,[1] Huser M,[2] Michalka J,[1] Zakova J,[2] Kral Z,[1] Crha I,[2] Janikova A,[1] Krizova L,[1] Mayer J,[1] Ventruba P[2]

[1]Department of Internal Medicine, Hematology and Oncology, University Hospital Brno and Masaryk University, Czech Republic; [2]Department of Obstetrics and Gynecology University Hospital Brno and Masaryk University, Czech Republic

Introduction. One of the most common long term consequences of chemotherapy is infertility due to the destruction of gonadal cells. The aim of this study is to describe the clinical management and outcomes of currently available fertility preservation techniques in a set of 154 female patients with Hodgkin lymphoma. Methods. Patients in reproductive age with newly diagnosed Hodgkin lymphoma were offered embryo or oocyte cryopreservation, ovarian tissue cryopreservation and the administration of GnRH analogues during chemotherapy. Results. During study period (2004-2009), 154 young female patients were

offered fertility preservation counseling. Patient's average age was 29.4 years. The majority of women were nuliparas or primiparas at the time of diagnosis. All referred patients were individually consulted regarding their risk of fertility impairment or loss due to planned gonadotoxic chemotherapy. The optimal approach was chosen on a strictly individual basis and was depended on the type of planned treatment, time available till the onset of treatment, the patient's age, and whether the patient has a partner. Administration of GnRH analogues (N=123, 79,9%) and ovarian tissue cryopreservation (N=16, 10,4%) were the most commonly used fertility preservation strategies. In 20 cases (12,9%), combination of several fertility preservation techniques was preferred in individually selected patients. In these cases, administration of GnRH analoques during chemotherapy was combined with one of the cryopreservation strategies. Conclusion. Combination of fertility preservation techniques gives young cancer patients the best chance for future fertility and should be concentrated in specialized centers.

P177
NEW PROGNOSTIC SCORE BASED ON BCL-6 EXPRESSION AND IPS STRONGLY PREDICTS SURVIVAL IN PATIENTS WITH HODGKIN LYMPHOMA

Antic D,[1,2] Andelic B,[1] Milic N,[3] Durašinovic V,[1] Todorovic M,[1,2] Bila J,[1,2] Vukovic V,[1] Jelicic J,[1] Mihaljevic B[1,2]

[1]Clinical Center Serbia, Clinic for hematology; [2]Medical Faculty, University in Belgrade; [3]Institute for medical statistic and informatic, Medical faculty, University in Belgrade, Belgrade, Serbia

Introduction. Biological factors like p53, pRb, bcl-6 and Ki67 may contribute to malignant transformation and may be of prognostic relevance. Aim: The aim of this study was to evaluate whether the expression of p53, pRb, bcl-6 and Ki67, could be important predict factors for outcome of patients with HL. Methods. Between October 2001 and June 2003, 40 de novo patients with a confirmed diagnosis of Hodgkin lymphoma were studied. Immunohistochemical analysis was performed on paraffin-embedded lymph node specimens using monoclonal antibodies. Also, in all patients risk was assessed by International Prognostic Score (IPS) and patients were subsequently treated with ABVD and BEACOPP chemotherapy regimens and followed up for a minimum of 10 years. Results. In our group 25 patients were treated with ABVD while 15 received escalated BEACOPP. 10-years overall survival (OS) was 76,3% and 36 (90%) patients achieved complete remission. Patients with low risk based on IPS score had significantly better survival than intermediate/poor risk patients (134 *vs* 91, respectively, p=0.005). Expression of p53, pRb and Ki67 did not affect response to therapy and survival significantly. Regarding to bcl-6 expression patients were divided in two subgroups; patients with bcl-6 expression in >20% cells had significantly longer mean OS of 122 months while patients with bcl-6 expression in ≤20% cells had mean OS of 87 months (p=0,037). Bcl-6 expression was an independent survival predicting factor in multivariate analysis together with the IPS (p=0,041 and p=0,022, respectively). Aggregate bcl-6-IPS score improved IPS prognostic stratification for the interemediate and high risk patients' by adding information on bcl-6 expression (132 *vs* 113 *vs* 64 months for low, intermediate and high risk score, respectively, p<0.001). New bcl6-IPS score retained his prognostic significance in multivariate analysis (p<0,001;RR=4,670; 95% CI 1,675-13,022). Conclusions. Cell cycle regulatory molecules including p53, pRb, bcl-6 and Ki67, have different level of expression in patients with HL, but we found that only bcl-6 expression had influence on the outcome. Aggregate bcl-6-IPS score improved standard prognostic stratification for the high and intermediate risk patients.

P178
ACUTE PULMONARY TOXICITY OF BLEOMYCIN-INCIDENCE AND RISK FACTORS IN A SERIES OF HODGKIN LYMPHOMA (HL) PATIENTS TREATED IN A SINGLE CENTER

Santos J, Carvalho S, Esteves S, Gomes da Silva M

Instituto Português de Oncologia de Lisboa Francisco Gentil, Portugal

Introduction. Bleomycin may cause acute pulmonary toxicity (BPT), with potentially irreversible consequences on lung function and impact upon treatment continuation. Epidemiological and treatment factors (sex, age, G-CSF, smoking, previous lung disease) may increase the risk of BPT. Aim: to evaluate the incidence, risk factors and clinical course of BPT in patients with Hodgkin lymphoma (HL) receiving ABVD. Methods. retrospective unicenter study in HL patients treated between 2010 and 2011. BPT was defined as 1) clinical and imagiologic pneumonitis, without an infectious cause, and with a decreased lung diffusion capacity (DLCO), or 2) at least one of the above criteria, leading to bleomycin discontinuation and/or treatment with corticosteroids. Risk factors were evaluated with the Chi square test, Fisher exact test, and Wilcoxon test, as appropriate. Results. 65 patients were analyzed, 57% male, median age 28 years (range 15-86): 26,2% had early favorable disease, 21,5% early unfavorable disease and 50,8% advanced disease (1,5% not assessed), according to GHLSG. Median number of ABVD cycles was 6 and 24,6% received mediastinal radiotherapy. Overall response rate was 94%. BPT occurred in 16 patients (24,6%): only 1 fulfilled all criteria. Bleomycin was discontinued in 9 patients, of whom 6 also received corticosteroids; the remaining 7 were treated with corticosteroids and kept on ABVD; 4 patients developed pulmonary fibrosis grade 2 to 5. Compared to patients without BPT, patients with BPT were older (median 36 versus 26 yo, p=0,077) and mainly female (68,5% versus 34,7%, p=0,017). Smokers and non-smokers had a similar incidence of BPT (p=0,528), as well as patients exposed (51%) or not to G-CSF (p=0,943). The cumulative dose of bleomycin and the DLCO, evaluated before treatment (in 57% in non-BPT patients and 87,5% BTP patients), were not different between the 2 groups (p=0,081 and p=0,197 respectively). Conclusions. the incidence of BPT was similar to what has been reported and was moderate to severe in 25% of patients, leading to a change in treatment in 56%. In this series, BPT was more frequent in women and the incidence appeared to increase with age. Prospective studies are needed with larger numbers of patients to identify populations at risk.

P179
TESTICULAR FUNCTION ASSESSMENT IN YOUNG MEN TREATED FOR HODGKIN'S LYMPHOMA DURING CHILDHOOD AND ADOLESCENCE

Moryl-Bujakowska A,[1] Balwierz W,[1] Malek A,[2] Sztefko K[3]

[1]Department of Pediatric Oncology and Hematology, Polish-American Institute of Pediatrics, Jagiellonian University Medical College, Krakow, Poland; [2]Department of Clinical Biochemistry, Children's University Hospital in Krakow, Poland; [3]Department of Clinical Biochemistry, Polish-American Institute of Pediatrics in Krakow, Jagiellonian University Medical College, Poland

Introduction. of modern methods of combined therapy allows the cure more than 90% of children and adolescents with Hodgkin's lymphoma. However, the intensive treatment carries the risk of late complications including gonadal dysfunction in men and women. In this report preliminary results of testicular function assessment in young men after Hodgkin's lymphoma therapy are presented. Testicular function was evaluated in 29 men [age: 5.0-18.2 (median 14.5) years, and 18.0-26.3 (median 22.8) years at the beginning of treatment and the end of observation, respectively] treated between 1.01.1999 and 31.12.2008 in Department of Pediatric Oncology and Hematology PAIP JU-MC in Krakow, according to PGP-HD-97 protocol. Multidrug chemotherapy (MOPP given alternatively with B-DOPA) combined with low-dose involved-field radiotherapy (15-25 Gy) was used in 25 men, and in 4 other men-chemotherapy only. Therapy was completed in all analyzed patients. Physical examination, Tanner stages of pubic hair and genital development were recorded as well as the plasma levels of follicle stimulating hormone (FSH), luteinizing hormone and testosterone were measured in all patients. Testicular volumes were measured in 18 men. The study was conducted between 1.01.2009 and 31.12. 2011. All men reached Tanner stages of pubic hair and genital development appropriate for their age. In all patients 207 measurements of hormones levels were performed. At least one abnormal result of measurements was found in 17/29 (58.6%) of men. The most frequent abnormality was the increased level of FSH (in 15 patients; 46.4% of FSH measurements). Abnormal results of measurements were found in 15/24 (62.5%) patients who received 6-8 chemotherapy cycles and in 2/5 patients treated with 3-5 cycles. Within the group of 17 patients with abnormal results eight men previously received radiotherapy of subdiaphragmatic region. Semen analysis was performed in two men and revealed azoospermia. Initial results of reproductive system assessment indicate the impairment of testicular function depending on intensity of treatment. Further observation and repeated gonadal function tests (including semen analysis) are needed in young men with completed Hodgkin's lymphoma

treatment. These studies are essential especially for young people who intend to have children.

P180
PROTEINURIA IN HODGKIN'S LYMPHOMA, IS IT AN UNDERESTIMATED FINDING?

Salihoglu A,[1] Senel TE,[2] Ozbalak M,[2] Elverdi T,[1] Gulturk E,[1] Eskazan EA,[1] Cem Ar M,[1] Ongoren S,[1] Baslar Z,[1] Aydin Y,[1] Tuzuner N,[3] Soysal T,[1] Ferhanoglu B[1]

[1]Istanbul University Cerrahpasa Medical Faculty, Hematology Department Turkey; [2]Istanbul University Cerrahpasa Medical Faculty, Internal Medicine Turkey; [3]Istanbul University Cerrahpasa Medical Faculty, Pathology, Turkey

Background. Renal manifestations of classical Hodgkin's lymhoma (cHL) at initial diagnosis including glomerulonephritis (minimal change, membranous, focal segmental glomerulosclerosis, proliferative, immunoglobulin A associated), amyloidosis and nephrotic syndrome are rare. Proteinuria can develop after remission of cHL heralding disease relapse. The aim of this study was to present clinical and laboratory features of cHL patients (pts) with proteinuria. Methods. Retrospective review of medical records from all consecutive pts diagnosed with cHL and treated between January 2003 and December 2012 was performed. Pts with positive dipstick testing for albumin on presentation were further evaluated. Results. Among 328 consecutive pts, urinalysis was performed in 181 (55%) on initial presentation. 15 pts (8.2%) (12 males, 3 females, median age 51 (16-77) years) with proteinuria found on a dipstick urinalysis were identified and analyzed. Median follow-up was 36 months. 60% of pts had mixed cellularity subtype, 60% of pts had early and 40% had advanced stage disease. B symptoms were present in 73% of pts. Edema was found only in pts with 4+ proteinuria. Creatinine was normal in 80% of the pts and 78% had hypoalbuminemia. Among the 4 patients with trace albuminuria 3 had underlying conditions such as atherosclerosis, diabetes mellitus and hypertension. 4 pts had 4+ proteinuria on dipstick screening. In 3 of these, nephrotic range proteinuria occurred simultaneously with cHL diagnosis. In one patient nephrotic syndrome heralded a late relapse (20 years after first cHL treatment at another center) of the disease. 2 of these patients underwent kidney biopsies revealing AA-type amyloidosis and focal segmental glomerulosclerosis (FSGS). 3+ proteinuria was caused by renal vein thrombosis in one patient. In two pts, pleural and pericardial effusions presented a challenge for treatment and 2 of 4 pts with nephrotic range proteinuria died during the treatment course (sudden cardiac death and pneumonia). 80% of the patients with proteinuria achieved complete remission, 1 patient underwent autologous transplantation. Conclusion. Urinalysis is mostly not a part of the diagnostic work-up in cHL. Data obtained in the present study showed that urinalysis should not be neglected at the time of diagnosis. Pts with proteinuria should receive special attention.

P181
THE PROGNOSTIC IMPACT OF LYMPHOCYTE/MONOCYTE RATIO, ABSOLUTE LYMPHOCYTE COUNT AND SUBSETS OF NATURAL KILLER CELLS IN PERIPHERAL BLOOD IN HODGKIN LYMPHOMA

Mocikova H, Palickova M, Spacek M, Markova J, Kozak T

Department of Clinical Hematology, University Hospital Kralovske Vinohrady, 3rd Faculty of Medicine, Charles University in Prague, Czech Republic

Background. Absolute lymphocyte/monocyte ratio (ALC/AMC) ≥1.1 was reported as prognostically significant in Hodgkin lymphoma (HL) at diagnosis and the absolute count of NK cells <80x10^9/L was predictive of no response and of a shorter event-free survival in diffuse large-B cell lymphoma. Significance of natural killer (NK) subsets (CD56dim CD16+, CD56bright CD16dim, CD16+CD56+CD94+CD244-) is not clear. Patients and Methods. We analyzed the ALC/AMC ratio (<1.1 *vs* ≥1.1), absolute lymphocyte count (<1.0 *vs* ≥1.0x10*9/l), NK subsets (CD56dim CD16+, CD56bright CD16dim, CD16+CD56+CD94+ CD244-), T cells (CD4+, CD8+), B cells (CD19+) in peripheral blood of 68 HL patients and their impact on progression-free (PFS) and overall survival (OS). Measurements of blood cell counts and multi-parameter flow cytometric analysis were used to aquire the data. The median age was 39 years and the median follow-up 12.8 months. Results. The median PFS and OS of the whole group was not reached. The median of ALC/AMC ratio was 2.22 (range 0.46-25.04). The mean and median of absolute lymphocyte count (ALC), NK subsets, T and B cells are summarized in Table 1A. Patients with the ALC/AMC ratio ≥1.1 experienced better PFS but not OS compared to patients with the ALC/AMC ratio <1.1 [Hazard ratio (HR)= 0.136, 95% CI (0.034-0.545)), p = 0.005; HR=0.256, 95%CI (0.042-1.557)), p=0.139, respectively]. The ALC <1.0x10^9/l was a poor prognostic factor for OS but not for PFS [(HR=1.782, 95%CI (0.1022-3.105), p=0.042, HR=1.259, 95%CI (0.729-2.176), p=0.409, respectively]. The receiver operating characteristics (ROC) curve analyses failed to identify the cut-off value of the NK subsets (CD56dim CD16+, CD56bright CD16dim, CD16+CD56+ CD94+CD244-), T cells and B cells related to OS (Table 1B), possibly due to the low absolute numbers of these cells in our group of patients and short follow-up. Conclusions. Our data confirm that ALC/AMC ratio ≥1.1 is associated with a better PFS and the absolute lymphocyte count<1.0x10^9/L is a poor prognostic factor for OS in HL. NK subsets were not proved to predict survival due to the low absolute counts of these cells. Supported by Research project P 27/2012.

Table 1.

Table 1A

	Mean x10^9/l	Median x10^9/l	95%Confidence Interva	Range x10^9/l
Absolute lymphocyte count	1.77	1.44	1.50 - 2.04	0.38 - 5.76
CD3+	1.31	1.02	1.09 - 1.52	0.27 - 5.11
CD3+CD4+	0.77	0.63	0.61 - 0.92	0.07 - 3.49
CD3+CD8+	0.50	0.38	0.39 - 0.61	0.08 - 3.33
CD3-CD56+	0.22	0.19	0.19 - 0.26	0.03 - 0.75
CD3-CD56-CD16+	0.033	0.025	0.024 - 0.042	0.001 - 0.175
CD3-CD56++CD16-	0.003	0.002	0.002 - 0.004	0 - 0.031
CD3-CD56+CD16-	0.005	0.003	0.004 - 0.007	0 - 0.034
CD3-CD56++CD16+	0.005	0.003	0.003 - 0.008	0 - 0.063
CD3-CD16+CD56+CD94+CD244-	0.129	0.103	0.104 - 0.154	0 - 0.422
CD19+	0.19	0.10	0.06 - 0.31	0.01 - 4.47

Table 1B

	Cut-off value	Sensitivity	Specificity	AUC (95% CI)
CD3+	4.0895	0.4	1	0.625 (0.264 - 0.986)
CD3-CD56-CD16+	0.026	0.6	0.549	0.384 (0.093 - 0.676)
CD3-CD56++CD16-	0.0015	0.6	0.51	0.482 (0.123 - 0.842)
CD3-CD56+CD16-	0.0125	0.4	0.941	0.498 (0.079 - 0.917)
CD3-CD56++CD16+	0.01	0.4	0.922	0.610 (0.297 - 0.923)
CD3-CD16+CD56+CD94+CD244-	0.1365	0.8	0.627	0.602 (0.392 - 0.812)
CD19+	0.1155	0.8	0.444	0.570 (0.281 - 0.859)

P182
LATE ADVERSE EFFECTS OF PREMATURE MENOPAUSE IN FEMALE HODGKIN LYMPHOMA SURVIVORS: DESIGN OF A COHORT STUDY

Krul IM,[1] Opstal-van Winden AWJ,[1] Schagen SB,[1] Zijlstra JM,[2] Appelman Y,[3] Lambalk CB,[4] Lips PTAM,[5] van Dulmen-den Broeder E,[6] Hauptmann M,[7] Krol ADG,[8] Aleman BMP,[9] van Leeuwen FE[1]

[1]The Netherlands Cancer Institute, Amsterdam, Division of Psychosocial Research and Epidemiology, The Netherlands; [2]VU University Medical Center, Amsterdam, Department of Haemato-oncology, The Netherlands; [3]VU University Medical Center, Amsterdam, Department of Cardiology, The Netherlands; [4]VU University Medical Center, Amsterdam, Department of Obstetrics and Gynaecology, The Netherlands; [5]VU University Medical Center, Amsterdam, Department of Endocrinology, The Netherlands; [6]VU University Medical Center, Amsterdam, Department of Pediatric Oncology, The Netherlands; [7]The Netherlands Cancer Institute, Amsterdam, Department of Epidemiology and Biostatistics, The Netherlands; [8]Leiden University Medical Center, Leiden, Department of Radiotherapy, The Netherlands; [9]The Netherlands Cancer Institute, Amsterdam, Department of Radiotherapy, The Netherlands

Background. Hodgkin lymphoma (HL) has become the prototype of a curable malignancy. However, young survivors are faced with an increased morbidity due to long-term effects of treatment. Both chemotherapy (CT) and radiotherapy (RT) may induce premature menopause at a very young age, which can have a great impact on quality of life (QoL) as it results in infertility as well as menopausal symptoms. Moreover, a premature menopause has been associated with a reduced bone mineral density (BMD) and an increased risk of cardiovascular disease (CVD) and neurocognitive dysfunction. So far, most stud-

ies on these conditions have been conducted in women with an early natural or surgery-induced menopause with short follow-up times. In this study we will examine the long-term effects of a CT- and/or RT-induced premature menopause on BMD, cardiovascular status, neurocognitive function and QoL in female HL survivors. Methods. Cross-sectional measurements will be performed within an existing cohort of female HL survivors. Women treated for HL in three large hospitals between 1965 and 2005 at ages 15-39 years will be invited for a visit to a survivorship care outpatient clinic. Participants will be asked to complete a questionnaire, provide a blood sample and to undergo several medical and neurocognitive tests. Multivariate regression analyses will be used to compare the outcomes of women who developed premature menopause with those who did not. Results. This study will increase knowledge about the BMD, cardiovascular status and neurocognitive function in long-term female HL survivors with a CT- and/or RT-induced premature menopause. It will also provide insight into the influence of these long-term effects on quality of life. Conclusions. Results of this study will lead to the identification of those HL survivors who are at increased risk for osteoporosis, CVD and neurocognitive dysfunction due to premature menopause as a consequence of their former treatment. This provides the opportunity to timely refer high-risk women for interventions in order to reduce morbidity and enhance QoL. Moreover, women who will experience premature menopause in the future can be better informed about potential long-term effects.

P183
PREDICTIVE FACTORS OF RESPONSE IN TUNISIAN ADULT HODGKIN LYMPHOMA

Kacem K,[1] Zriba S,[2] Ghédira H,[2] Yahyaoui Y,[1] Mansouri R,[1] Dridi M,[1] Hadj Mansour M,[1] Manai Z,[1] Zarrouk M,[1] Ben Neji H,[1] Ben Abdennebi Y,[1] Jeddi R,[1] Aissaoui L,[1] Belhadj Ali Z,[1] Ben Abid H,[1] M'Sadek F,[2] Ben Lakhal R,[1] Meddeb B[1]

[1]Clinical Hematology Department of Aziza Othmana of Tunis; [2]Clinical Hematology Department of Military Hospital of Tunis, USA

Purpose. Study of prognostic factors in HL population treated in two centers according to national protocol HL-2008. Patients and Methods. 173 patients were included and prospectively analyzed for response and outcome. Chemotherapy regimen was ABVD for early stages and escalated BEACOPP for advanced disease and stage II with IMT> 0.35. Complete response (RC) rate was of 82%. At 3 years, OS, EFS, RFS were respectively 90%, 75%, and 95%. In localized disease RC, OS, EFS, and RFS were respectively 86%, 95.5%, 84% and 95.5%. predictive factors of response was albumin<30g/l (p=0.04) and IMT> 0.35 (p=0.001). In addition to these factors, refractoriness (p= 0.009) and *VS*> 30+B (p=0.015) significantly influence OS and EFS. RC, OS, EFS, RFS were 80%, 86%, 69%,and 86% in advanced stages.In multivariate analysis predictive factors for response were SPI>2 (p=0.01), lyphopenia< 600 (p=0.001), stage IV (p=0.036), hepatic localization (p=0.04). For EFS, predictive factors were SPI>2, lymphopenia, stage IV, male sex and expression of CD20 (p=0.05). peripheral bulky disease and baseline WBC> $15x10^9$/L (p=0.003) significantly influence RFS while OS was significantly influenced by remission status at the end of treatement (p<0.0001), bone marrow infiltration , bulky mediastinal disease, expression of CD20, age> 45, and male sexe. Conclusion. Our results were in accordance with literature.

P184
CASE REPORT OF A PATIENT WITH HODGKIN LYMPHOMA AFTER TREATED WITH TNF ALFA INHIBITOR BECAUSE OF PSORIASIS AND PSORIATIC ARTHRITIS AND OVERVIEW OF THE LITERATURE

Páyer E,[1] Gál A,[1] Szegedi A,[2] Barna S,[3] Illés A[1]

[1]Institution of Medicine, [2]Department of Dermatology, [3]Scanomed Ltd,University of Debrecen, Hungary

TNF alfa inhibitors means milestone in treatment of chronic inflammatory diseases, however tumors, especially lymphomas may be more frequent in these patients. We riport about a 30-year-old patient presented with psoriasis vulgaris and psoriatic arthritis in 1998. It was treated with azathioprin, methotrexate and after progression infliximab from Jan 2009 to Jan 2011. In Dec 2010 cervical lymph node enlargement was detected on the right side, and histological analysis of bioptic sample proved Hodgin lymphoma, lymphocyte rich type. By the staging PET/CT Ann Arbor stage was II/A. ABVD treatment was started. After 2 cycles interim PET/CT was performed. On the right side the lymphoma disappeared, but on the left side of the neck new lymph node and tonsillary activity was showed which seemed to be an infection, thus ABVD was continued, and antibiotic therapy was added. After 6 cycles of ABVD PET/CT was performed again which showed complete metabolic remission. His treatment was completed with radiotherapy on the right side of cervical and supraclavicular region (32.2 Gy). Restaging PET/CT showed complete metabolic remission also and the patient is well up to this day. However psoriasis and arthritis worsened, which means treatment challange. This case raises two main questions. First of all, are there lymphomas or other hematologic malignacies really more frequent in patients treated with TNF alfa inhibitors? On the other hand, how can we treat the inflammatory diseases after succsessful treatment of hematologic malignacy?

Authors Index

surname, page number