11th International Symposium on Hodgkin Lymphoma

ABSTRACT BOOK

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**Abstract Book for the 11th International Symposium on Hodgkin Lymphoma**

**Immunotherapy - Biomechanisms**

**T004 (0051)  EXPRESSION OF PD-1 AND PD-L1 INCREASE IN MULTIPLE CONSECUTIVE BIOPSIES IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA**

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**Background:** High expression of programmed death receptor 1 (PD-1) and its ligand (PD-L1) by leukocytes in primary classical Hodgkin lymphoma (cHL) is associated with inferior outcome. However, it is unclear how expression varies during disease progression, and in the event of relapse. Our aim was to study PD-1 and PD-L1 in consecutive biopsies from untreated (reflecting the natural course) and treated (reflecting influence of treatment/relapse) cHL patients.

**Patients and Methods:** We screened pathology registers covering 3500 cHL patients, to identify patients that had removed a lymph node for other reasons prior to their cHL diagnose, and found 87 cases in three referral pathology centers in Sweden. These 87 biopsies were reviewed retrospectively and after review 11 of those patients had their benign lymph node biopsy reclassified as cHL. All those patients were untreated between the first and the diagnostic biopsy and designated as the untreated group. In addition, we identified thirty patients that had a primary and a relapse biopsy, designated as the treated. The paired biopsies were immunostained to detect PD-1+ and PD-L1+ leukocytes, and PD-L1+ tumor cells. Differences in expression between biopsies were analyzed using Wilcoxon signed-rank test.

**Results:** In the untreated, 8 (73%) of 11 cases had an increased proportion of PD-L1+ leukocytes in biopsy 2 compared to biopsy 1, although none of the markers were statistically significantly different when biopsies 1 and 2 were compared (Figure 1). In the treated, 19 (63%), 22 (73%), and 18 (60%) of 30 cases had increased proportions of PD-1+ leukocytes, PD-L1+ leukocytes and PD-L1+ tumor cells, respectively. When primary and relapse biopsies were compared, expression of PD-L1+ leukocytes (p = 0.04), PD-L1+ leukocytes (p = 0.005) and PD-L1+ tumor cells (p = 0.009) was significantly higher in the relapse biopsies (Figure 1).

**Conclusions:** Our findings show that PD-1 and PD-L1 expression increases in relapsed cHL, most likely due to primary treatment with chemotherapy and radiotherapy, which could have implications regarding treatment with PD-1 inhibition. In the untreated group an indication of up-regulation of the number of PD-L1+ cells in the microenvironment with time was seen, but did not reach statistical significance.

![Figure 1: Graphs showing expression of PD-1 and PD-L1 in untreated and treated groups.](image)

Our studies demonstrated that trabectedin: had a potent antitumor activity in cHL cells, with IC50 ranging from 0.17 to 0.5 nM; induced DNA damage resulting in G2/M cell cycle arrest; induced necroptosis and increased the generation of reactive oxygen species. Trabectedin was active also in the presence of mesenchymal stromal cells (MSCs), which have been shown to play a role in chemotherapy resistance.
Treatment of cHL cells with subtoxic concentrations of trabectedin decreased: NF-κB activity; CCL5, CCL17/TARC, IL-6, IL-13, M-CSF and TGF-β secretion; the capability of cHL-conditioned medium (CM) to induce the migration of monocyes, MSCs, and lymphocytes; the reprogramming/tumor-education of monocyes (E-monocytes) towards immunosuppressive macrophages, characterized by increased IDO and PD-L1 expression, the secretion of IL-10, TGF-β, and TARC, and the inhibition of the proliferation of activated lymphocytes. Trabectedin exerted a moderate synergistic activity with gemcitabine, but not with cisplatin, doxorubicin or vinorelbine. The combination with the CCR5-antagonist Maraviroc, found to increase cell killing mediated by B lymphocytes reprogramming chemotherapeutic agents as doxorubicin, enhanced the cytotoxic effects of trabectedin in cHL, especially in L-540 cells, decreasing the IC50 of trabectedin-mediated cell killing by up to 2-fold.

In vivo, trabectedin (50 μg/Kg) led to a more than 40% tumor growth reduction of L-540-derived tumor xenograft and inhibited monocyes tumor infiltration, without weight loss.

In conclusion, since the present challenges are to find new drugs or less toxic drug combinations, as well as counteract the formation of an immunosuppressive tumor microenvironment, this study offers a preclinical rationale for the use of trabectedin in the treatment of refractory/relapsed cHL.

**T007 (0099) PD-L1+ AND IDO-1+ TUMOR-ASSOCIATED MACROPHAGES PREDICT SURVIVAL IN PRIMARY CLASSICAL HODGKIN LYMPHOMA**

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**Background:** Tumor microenvironment (TME) and immune escape have a major impact on pathogenesis and survival in classical Hodgkin lymphoma (cHL). Particularly, high tumor-associated macrophage (TAM) content associates with poor outcome. Here, we aimed to identify TAMs and their immunophenotypes, and translate the findings into survival of cHL patients.

**Experimental Design:** We collected clinical data and formalin-fixed paraffin-embedded tumor samples from 134 cHL patients, and used multiplex immunohistochemistry (miHC) and computerized image analysis to examine macrophage markers (CD68 and CD163), Hodgkin Reed-Sternberg (HRS) cell marker (CD30), and indoleamine 2,3-dioxygenase 1 (IDO-1). CD68, CD163, CD274 (PD-L1), and IDO-1 mRNA levels were measured utilizing the Nanostring platform.

**Results:** The male/female ratio was 46%/54%, and the median age 30 years (range 16–83). Thirty-two (24%) patients were 45 years or older, 105 (78%) had nodular sclerosis subtype, and 76 (57%) stage IIB-IV disease. At the median follow-up of 54 months (range 7 to 229), 31 (23%) patients had relapsed and 11 (8%) died, 7 (64%) of the deaths being related to cHL. Five-year recurrence free survival (RFS), disease-specific survival (DSS) and overall survival (OS) rates were 78%, 93% and 90%, respectively.

**Table.** Cox univariate regression analysis showing association of cell proportions (analyzed as continuous variables) with survival

<table>
<thead>
<tr>
<th>PD-L1+</th>
<th>IDO-1+</th>
<th>IDO-1+ Tumor-Associated Macrophages</th>
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**Conclusions:** The findings implicate PD-L1+ and IDO-1+ TAMs as prognostic factors for survival and as potential novel targets for immunoncology drugs in patients with cHL.

**P001 (0015) HODGKIN'S VARIANT OF RICHTER TRANSFORMATION IN THE CZECH REPUBLIC**

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Background: Transformation of B-cell chronic lymphocytic leukemia (B- CLL) to Hodgkin lymphoma (HL) is a rare event. Optimal management of these patients (pts) is not established. This retrospective analysis summarizes diagnostics, treatment and prognosis of 10 pts with Hodgkin's variant (HV) of Richter syndrome in the Czech Republic.

Patients and Methods: Initial treatment of 7 pts with B CLL included chemotherapy in combination with rituximab and 3 pts were treated with chlorambucil. HV of Richter syndrome was diagnosed in 10 pts (8 males) in the Czech Republic between 1996 and 2017. Median duration since diagnosis of B CLL till diagnosis of HV was 8.4 years (range 2.6 – 16.5). Median age at diagnosis of HV was 68 years (range 54 – 83). Identical clonal IgH rearrangement (VH7/DH1/JH6) from initial B CLL tissue and from HV cells was confirmed in only one patient, frozen tissues from other pts were either insufficient or unavailable. Seven pts with HV were treated with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) including 2 pts in combination with rituximab. Another 3 pts received COPP (cyclophosphamide, vincristine, procarbazine, and prednisone). Involved field radiotherapy of 30Gy was used in 2 pts after chemotherapy.

Results: After treatment of Richter transformation to HV a complete remission was achieved in 3 pts, partial remission in 3 pts and progression in 4 pts. Only 4 pts are alive: 3 in longstanding complete remission and one in partial remission. Overall 6 pts died (3 in progression, one treatment toxicity, one solid tumour, one cause unknown). Median overall survival since diagnosis of B CLL was 207 months and since diagnosis of HV was 42 months.

Conclusion: Current treatment of Richter transformation to HV based on chemotherapy is not sufficient and these pts should be enrolled into clinical trials with new drugs.

This work was supported by grant AZV 16-29857A Ministry of Health of the Czech Republic and Research project Q28 Progres and Q40/08 Progres awarded by Charles University in Prague, Third Faculty of Medicine, Prague, Czech Republic

P002 (0061) DEVELOPMENT OF AN α-CD30 BISPECIFIC ANTIBODY IMMUNOTHERAPY FOR HODGKIN LYMPHOMA

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Hodgkin Lymphoma (HL) is highly treatable, but 15-25% of patients have refractory disease or relapse. Chemotherapy resistant disease is challenging to treat: novel therapeutic strategies are needed for this subset of patients. A recent approach to HL immunotherapy is CD30 targeting with brentuximab vedotin, an FDA approved α-CD30 antibody-drug conjugate (ADC). The efficacy of antibody therapy is based on target, epitope, and affinity. One of our objectives is to develop novel α-CD30 antibodies with varying binding properties. We will then generate anti-CD30/anti-CD3 bispecific antibodies (bi-mAbs) and CARs for clinical development. Bispecific CD30/CD3 antibodies provide conceptual advantages over naïve antibody therapies by possibly increasing effectiveness and reducing potential side effects associated with conjugated cytotoxic compounds in ADC therapy.

Methods: We generated 15 anti-human CD30 hybridoma cell lines by immunization of mice with purified recombinant huCD30-GST protein that we made. Five hybridomas were selected for further analyses. All candidates showed specific binding to CD30 by flow cytometry and ELISAs, and were characterized by DNA and protein sequencing. Our purified CD30 antibodies were then heteroconjugated with anti-huCD3 antibodies for in vivo/in vitro analyses. Our conjugated antibodies bind both tumor cells and T cells. Subsequent in vitro assessments will test their ability to trigger target cell death. For in vivo studies, CD30 bi-mAbs will be administered to C57BL/6 mice, or pre-incubated with human T cells and administered to NRG mice bearing eGFP/Luciferase-expressing huCD30+ lymphoma grafts. In vivo treatment efficacy will be monitored by overall mouse survival and tumor growth/regression, tracked by bioluminescent imaging.

Results: Characterization studies showed that 4 of our antibodies bound to a similar CD30 epitope, while a 5th bound a separate site. Both epitopes are distinct from that bound by brentuximab vedotin. Characterization of antibody affinity and analyses of biological and cytotoxic effects of each antibody is underway.

Conclusion: We developed bi-mAbs that target unique CD30 epitopes and allow us to prepare bispecific CD30/CD3 antibodies. The addition of anti-CD3, will potentially enhance immune response to the tumor. Ultimately, we aim to test our optimized bi-mAb in clinical trials, with the goal of improving survival for HL patients with relapsed/refractory disease.

P003 (0157) MICROSATELLITE AND CHROMOSOMAL INSTABILITY CONSTITUTE TWO MECHANISMS THAT INDEPENDENTLY LEAD TO GENOMIC INSTABILITY IN HODGKIN LYMPHOMA

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Background: Mechanisms underlying genomic instability as well as primary transforming events of Hodgkin lymphoma (HL) are still obscure. Here, we have investigated the putative contributions of microsatellite and chromosomal instability, respectively, to pathogenesis of HL.

Materials and Methods: We have investigated seven HL cell lines (five Nodular Sclerosis (NS): L428, HDLM2, LS40, LS91 and SUP-HD, two Mixed Cellularity (MC): L1236 and KMH2) and peripheral blood lymphocytes from 123 HL patients (100 SN-HL and 23 MC-HL). Microsatellite instability (MSI) was assessed by PCR. Chromosomal instability and telomere dysfunction were investigated by FISH. DNA repair mechanisms and radiation sensitivity were studied by transcriptome and molecular approaches.

Results: In the cell lines, we observed high MSI in L428 (4/5), KMH2 (3/5), and HDLM2 (3/5), low MSI in LS40, LS91, and SUP-HD1, and none in L1236. NS-HL cell lines showed telomere shortening, associated with alterations of nuclear shape. Small cells were characterized by telomere loss and deletion, resulting in chromosome fusion, large nucleoplasmic bridges, and breakage/fusion/bridge (B/F/B) cycles, and thus to chromosomal instability. The MC-HL cell lines showed substantial heterogeneity of telomere length. Intra-chromosomal double strand breaks induced dicentric chromosome formation, high levels of micromonoclonal formation, and small nucleoplasmic bridges. B/F/B cycles induced complex chromosomal rearrangements. Transcriptome analysis confirmed the differences in the DNA repair pathways between the NS and MC cell lines. Finally, a NS-HL cell line exhibited high radiation sensitivity compared to a MC-HL cell line. In accordance with our findings on HL cell lines, we have detected telomere dysfunction also in circulating lymphocytes from NS-HL patients as well as high telomere heterogeneity in MC-HL patients.

Conclusion: In NS-HL mononuclear cells, loss of telomere integrity may present the first step in the ongoing process of chromosomal instability. Perhaps NS-HL is associated with genetic defects in telomere replication and extension. On the basis of our data, MSI was identified as an additional mechanism for genomic instability in HL. MSI could be exploited for developing novel therapies and personalized treatment. MSI-cancers may constitute excellent candidates for immune checkpoint inhibitors.
**Biography and Microenvironment**

**T001 (0006) Ck2a is OVEREXPRESSION, ACTIVE AND TARGETABLE WITH SILMISERTIB IN CLASSICAL HODGKIN LYMPHOMA**

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**Introduction:** Most patients with Hodgkin lymphoma (HL) are cured with first line therapy however, treatment of relapsed patients still represents an unmet medical need requiring the development of new effective drugs. Ck2 is a pleiotropic kinase consisting of 2 catalytic (a) and 2 regulatory (b) subunits that sustains cancer signaling cascades through the activation of NF-κB, PI3K and STAT pathways. Despite Ck2 has been extensively studied in non-Hodgkin lymphomas (NHL), this protein has not yet been investigated in HL. Considering that NF-κB, PI3K and JAK-STAT pathways are key players in HL, it is likely that Ck2 might have a role in the pathogenesis of this disease.

**Methods:** Experiments were performed and replicated at least for five times employing 4 HL cell lines (L-428, L-540, KM-H2 and HDML-1) cultured in RPMI for 24 h, 48 h and 72 h with or without the Ck2 inhibitor silmitasertib. Ck2a, Ck2b, RelA-Serine (S)529, RelA, PARP, AKT-S473, AKT, STAT3-S727, STAT3 and tubulin expression levels were evaluated by western blot analysis (WB). Apoptosis was assessed by Annexin V/Propidium iodide (AV/PI) assay and PARP cleavage by WB. Immunohistochemistry (IHC) for Ck2 and Ck2 was performed on formalin fixed paraffin embedded sections of lymph-nodes from patients with HL, as well as indolent and aggressive NHL. Data were considered statistically significant when p values were <0.05.

**Results:** By WB and IHC we found that all the 4 HL cell lines expressed higher levels of Ck2a, but not of Ck2b, as compared with normal B lymphocytes. These data were confirmed by IHC on primary lymph-node derived from patients with HL (n = 15), showing that Ck2a but not Ck2b was highly expressed in Reed-Sternberg cells. No clinical data correlated with Ck2a or Ck2 expression. This dichotomy between a and b subunits was not observed in follicular or high-grade NHL (p < 0.01). In order to evaluate the activity of Ck2, we performed WB analysis of the phosphorylation status of Ck2a substatres. AKT, RelA and STAT3 were constitutively phosphorylated in HL at their activatory S-residue (S473, S529, and S727 respectively). Treatment of HL cell lines with silmitasertib caused down-regulation of AKT-S473, time and dose-dependent apoptosis (p < 0.01).

**Conclusions:** We demonstrated that Ck2 is overexpressed, active and induces key pro-survival signals in HL. Chemical inhibition with silmitasertib was able to induce apoptosis of HL cell lines. These preliminary data suggest that Ck2 could play a pivotal role in HL.

**T008 (0050) GENOTYPING CIRCULATING TUMOR DNA OF PEDIATRIC HODGKIN LYMPHOMA PATIENTS TO DETERMINE PATHOGENIC MECHANISMS AND MONITOR THERAPY**

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We used hybrid capture based targeted next generation sequencing of 106 genes and genomic regions frequently affected by mutations and translocations in B cell lymphomas to detect somatic variants in circulating cell free DNA in 20 patients with Hodgkin lymphoma. Somatic variants, including 11 translocation breakpoints, were detected in 69 of 94 samples with 1-13 variants per sample and allele frequencies from 1-36%. Fragments of clonalotypic VH-DH-JH rearrangements were captured from 16 samples. For all 22 variants, 5 translocation breakpoints and 5 VH-DH-JH rearrangements of 16 cases tested an origin from Hodgkin-Reed-Sternberg (HRS) cells could be demonstrated. Compared to genomic DNA from biopsies and blood cells ccfDNA was superior for detection of HRS genomic variants. Genes involved in JAK/STAT signalling, NFKB regulation, antigen presentation and PIK3 signalling were most frequently affected. 9 of 11 translocations involved SOCS1 and all caused SOCS1 inactivation. EBV status or histological subtype was not related to amounts of circulating tumor DNA. Analysis of the VH-DH-JH rearrangements revealed an origin from germinal center experienced but unselected B cells. Amount of tumor DNA in pre-therapy ccfDNA was related to metabolic tumor volume but not to stage or early response to chemotherapy. In consecutive ccfDNA samples of 19 patients responding to chemotherapy all 61 variants fall already after the first cycle below the detection limit and remained there in all further 34 samples from later time-points. In contrast, in 3 poor-responding cases mutations remained detectable, at least after the first or second chemotherapy cycle. ccfDNA of pediatric Hodgkin lymphoma is thus a suitable source to determine pathogenic mechanisms and monitor therapy already at early timepoints.

**T009 (0083) CIRCULATING TUMOR DNA AS A BIOMARKER FOR THE NONINVASIVE GENOTYPING AND MONITORING OF CLASSICAL HODGKIN LYMPHOMA**

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**Introduction:** Circulating tumor DNA (ctDNA) analysis has an emerging diagnostic role in multiple malignancies including lymphomas. In classical Hodgkin lymphoma (cHL), where malignant Reed Sternberg (RS) cells are rare and typically require microdissection from archival tissues, ctDNA could enable noninvasive genotyping of somatic single nucleotide variants (SNVs) and somatic copy number alterations (SCNAS).

**Methods:** 24 subjects with cHL from Stanford were studied, including 16 (67%) early stage and 8 (33%) advanced disease. Plasma samples were sequenced with CAPP-Seq (Newman et al Nat Biotech 2016), using a panel informed by tumor biopsies. cHL status was confirmed by previously analyzed subjects, including 121 DLBCL, 157 BMBCL, 93 DLBCL, 157 BMBCL.

**Figure 1:** A) tumor DNA levels from lymphomas of various histologies. B) tumor DNA level correlates with MTX in cHL, DLBCL, and NSCLC. C) tumor DNA is higher per unit MTV in cHL than in NSCLC. D) REL-I copy number alterations are more frequently detected in plasma of cHL patients than in DLBCL patients.
**T010 (0113) CLINICAL VALIDATION OF AN EXTRACELLULAR marker for cHL patients.**

**Results:** The median pretreatment ctDNA level in cHL was 212 hGE/mL (22–1918), corresponding to a median variant allele level of 2.8% (0.3–13.6) (Fig 1A). Pretreatment ctDNA levels in cHL were significantly correlated with total metabolic tumor volume (MTV) (Spearman = 0.615, p < 0.01) (Fig 1B) but not with other common clinical characteristics. Surprisingly, despite the lower tumor purity of RS cells in cHL than malignant B-cells in DLBCL, the relationship between ctDNA and PET/CT MTV in cHL was highly similar to that of DLBCL. Specifically, cHL and DLBCL were indistinguishable for the ratio between ctDNA and MTV (mean ctDNA/MTV of 2.1 vs 1.5 hGE/mL per cm^3 tumor, p = 0.0007) and both were significantly higher than that of NSCLC (Fig 1C).

Using our method for detecting SCNAs in ctDNA, we noninvasively genotyped PD-L1 gains in 47% of cHL patients, significantly more frequently observed than in DLBCL patients (p = 0.02) (Fig 1D) (Jin et al ASH 2017). When assessing minimal residual disease (MRD) detection in simulated cHL ctDNA samples of various purities, we found a lower detection limit of 0.0046%, with 100% sensitivity at ctDNA levels above 0.01%.

**Conclusions:** ctDNA levels in cHL are higher than expected based on tumor purity, with pre-treatment levels similar to DLBCL, and allows for reliable genotyping of cHL at diagnosis or relapse. Assessment of MRD with ctDNA in cHL demonstrates a remarkably low detection limit. These findings support the role of ctDNA as a noninvasive biomarker for cHL patients.

**PO04 (0011) ARRAY-BASED DNA METHYLOME ANALYSES OF CLASSICAL HODGKIN LYMPHOMA**

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**Results:** DNA methylation changes were identified in 69% of cHL samples. The median number of significantly differentially methylated regions (DMRs) per patient was 234 (range 4–10,128) and the median number of DMRs per locus was 17 (range 1–39). The most frequent methylation changes were hypermethylation of H3K27me3 and hypomethylation of H3K4me3. The most frequent targets of hypermethylation were constant regions and exons, while the most frequent targets of hypomethylation were introns and gene bodies. The most frequently hypermethylated gene was CCND1, while the most frequently hypomethylated gene was CCNE2. The most frequently hypermethylated CpG was CPG000011110, while the most frequently hypomethylated CpG was CPG000011111.

**Conclusion:** DNA methylation analyses of cHL samples identified a high number of differentially methylated regions (DMRs) and gene bodies. These findings may provide new insights into the pathogenesis and therapeutic targets of cHL.

**References:**

THE ROLE OF TCF3 IN CLASSICAL HODGKIN LYMPHOMA

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Introduction: TCF3 is a transcription factor, which plays an important role in the development of normal B and T cells. Activity of TCF3 can be inhibited by the ID2 and ABF-1 proteins that both are highly expressed in classical Hodgkin Lymphoma (cHL). Lower TCF3 levels or activity might contribute to the aberrant B-cell phenotype in cHL. This is in line with previous analyses showing that the expression of the TFs PU.1 and EBF themselves is drastically reduced in cHL which correlates with the hypermethylation of the respective promoters. Our analyses, thus, further support the notion that epigenetic processes play a major role in B-cell-specific gene silencing in cHL.

Methods: The effect of modulating TCF3, ID2 and ABF-1 on growth of cHL cell lines L428, L1236 and KM2 was assessed in a GFP competition assay. For TCF3 overexpression an empty vector control was used as a negative control. For knockdown of TCF3, ID2 and ABF-1 two shRNA constructs were made and a non-targeting shRNA was used as negative control. All constructs contained a GFP gene, and the effect on cell growth was determined by measuring the GFP+ cell percentage in a mixed population over a period of three weeks. Gene expression profiling was performed to identify cHL specific downstream targets for TCF3.

Results: Endogenous levels of TCF3 were significantly decreased in cHL cell lines compared to germinal center (GC) B cells. Endogenous levels of the two main inhibitors of TCF3, ID2 and ABF-1, were significantly increased in cHL cell lines compared to GC B cells. TCF3 overexpression was validated at the mRNA and protein level and induced a strong negative effect on cell growth in all three cHL cell lines, with a 50% reduction in GFP+ cells in six days. Knockdown of TCF3 or ID2 did not affect growth of cHL cell lines. ABF-1 knockdown had a negative effect on cell growth in 2 cHL cell lines, with a 50% reduction in GFP+ cells in 20 to 27 days. Knockdown of ABF-1 in KM2H cells did not affect cell growth. Using a 2-fold cut-off criterion and a p-value of ≤0.05 we identified 143 and 18 differentially expressed genes upon ABF-1 knockdown in L428 and L1236 cells.

Conclusion: Ectopic overexpression of TCF3 had a strong negative effect on cell growth in all cHL cell lines, suggesting a pro-apoptotic and/or anti-proliferative role for TCF3 in cHL. Downregulation of ABF-1, resulting in a functional restoration of TCF3 also had a negative effect on cell growth. Inhibition of ID2 had no effect in cHL cell lines, consistent with its overall low expression levels. A variable number of genes responded to ABF-1 knockdown in the two cHL cell lines. We are currently analyzing the functions and involved pathways of the TCF3-regulated genes to further understand the role of TCF3 in cHL.

Abstract Book for the 11th International Symposium on Hodgkin Lymphoma

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1Hospital Universitario de Salamanca, Salamanca, Spain, 2CIBERONC tumores hematológicos, Spain

Introduction: Hodgkin Lymphoma (HL) is a germinal centre B lymphocyte-derived neoplasia, but its genetic characterization remains complicated due to the small proportion of malignant cells in the tumour (cHL). Exportin-1 (XPO1) is an NPC export protein that is overexpressed in many malignancies. Recently, a mutation hotspot in this gene (p.E571K) has been described in primary mediastinal diffuse large B-cell lymphoma (PMBL) and HL.

In this study, we assessed XPO1 E571K mutation in tumour tissue by droplet-based digital PCR (ddPCR) and investigated correlation with clinical and biological characteristics. Methods: We evaluated samples from 89 adult HL patients at diagnosis. XPO1 E571K mutation was analyzed by ddPCR using custom Taqman® primers and probes (Camus, Haematologica 2016) on a QX200 ddPCR platform (BioRad, Hercules, CA, USA). PCR reaction was performed on a C1000 Touch Thermal Cycler (BioRad Laboratories). We defined the limit of blank/specificity (LoB) of the technique analyzing 21 wild type (WT) samples from healthy donors. Limit of detection was established using a dilution curve of mutated DNA (U-H01 cell line). Statistical analyses were carried out with IBM SPSS Statistics Software.

Results: A cutoff of 0.1% was established by the LoB of the technique (E571 mutation vs. WT), and sensitivity was 0.0085% in the dilution curve. We detected the presence of XPO1 E571K mutation in 26 cases (29%), median mutation burden was 0.57% (range 0.1–10.4%). Characteristics of mutated and unmutated patients are summarized in Table 1. No main differences between both groups were detected, but patients with XPO1 E571K mutation were slightly older (p = 0.042) and more likely to present with Ann Arbor stages III-IV (p = 0.008). Of note, 70% of cases with Ann Arbor stages III-IV were mutated (p = 0.01). This was confirmed by the Hasenclever index distribution, with 42% vs. 20% mutated patients among Hasenclever ≥3 vs. <3, respectively (p = 0.048). Interestingly, XPO1 E571K mutation was detected in all histologic subtypes, excepting two cases with Lymphocytic Depleted subtype. No significant differences were found in response, progression-free survival and overall survival.

Conclusion: ddPCR is a sensitive and specific technique for determining XPO1 E571K mutation in biopsy samples of patients with HL.

This mutation is present in 29% of cases. -Presence of the mutation is correlated with advanced age, III-IV stages and abdominal involvement. No correlation was found with prognosis.

Table 1: Clinical and biological characteristics of mutated vs. unmutated patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Mutated (%)</th>
<th>Unmutated (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;40</td>
<td>40 (81%)</td>
<td>11 (84%)</td>
<td>0.32</td>
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<tr>
<td></td>
<td>≥45</td>
<td>22 (76%)</td>
<td>12 (83%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>Lymphocyte predominant Classical HL</td>
<td>7 (50%)</td>
<td>4 (100%)</td>
<td>0.0006</td>
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<tr>
<td></td>
<td>Mixed cellularity</td>
<td>22 (56%)</td>
<td>12 (56%)</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>Nodular sclerosis</td>
<td>51 (50%)</td>
<td>15 (30%)</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte-depleted Lymphocyte-rich</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td>I-II</td>
<td>30 (53%)</td>
<td>7 (70%)</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>III-IV</td>
<td>25 (47%)</td>
<td>15 (59%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hasenclever</td>
<td>&lt;3</td>
<td>35 (53%)</td>
<td>7 (70%)</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>21 (47%)</td>
<td>13 (62%)</td>
<td>0.048</td>
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<tr>
<td>ECOG</td>
<td>&lt;1</td>
<td>22 (44%)</td>
<td>3 (22%)</td>
<td>0.19</td>
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<tr>
<td></td>
<td>≥2</td>
<td>20 (46%)</td>
<td>10 (50%)</td>
<td>0.008</td>
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<tr>
<td>Abdominal involvement</td>
<td>Yes</td>
<td>34 (44%)</td>
<td>15 (53%)</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>36 (44%)</td>
<td>17 (50%)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

-Percentage of patients with E571K mutation in lymphocytic depleted subtype. No significant differences were found in response, progression free survival and overall survival.

Table 1: Clinical and biological characteristics of mutated vs. unmutated patients.
**P007 (0043)**  **TARC IMMUNOHISTOCHEMISTRY IN THE DIAGNOSIS OF CLASSICAL HODGKIN LYMPHOMA**

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**Introduction:** Thymus and activation regulated chemokine (TARC or CCL17) is produced in high amounts by Hodgkin and Reed-Sternberg (HRS) cells and is largely responsible for the attraction of CD4+ T cells into the tumor micro-environment of classical Hodgkin lymphoma (cHL). In recent years, TARC has gained attention as a clinically useful biomarker as it has shown to be a sensitive tumor cell marker in serum. TARC can also be detected in diagnostic tissue by immunohistochemistry (IHC). We here aim to define a role for TARC IHC in the diagnostic and research setting of cHL.

**Methods:** TARC IHC was introduced as a routine staining in June 2014 at the department of Pathology of the University Medical Center Groningen, a tertiary referral center in the Netherlands. Briefly, after heat induced antigen retrieval (Ultra CC1), slides were incubated with a polyclonal goat-anti-human TARC antibody (1:800, R&D Systems, Minneapolis, MN) in an automated stainer (Ventana Benchmark). The staining was used for all new cHL cases for correlation with serum levels and in select cases of reactive lymphadenopathies and non-Hodgkin lymphomas, in which HRS-like cells were present. In 2017, all cases that had been stained for TARC until December 2016 were retrospectively selected.

**Results:** A total of 98 cases were retrieved and reviewed. Of 56 cHL cases, 54 (96%) showed medium to strong TARC expression in the HRS cells. In only 2 of these cases a minority of tumor cells was stained positive. In general, TARC staining was almost exclusively seen in tumor cells and only very occasionally in dendritic cells. In the vast majority of these cHL cases TARC was much more specific in pin-pointing HRS cells than CD30. A weak TARC staining in a minority of the tumor cells was seen in 3/3 primary mediastinal B cell lymphomas, 4/4 grey zone lymphomas, 2/7 (partially anaplastic) diffuse large B-cell lymphomas, 1/8 T-cell and histiocytic rich diffuse large B-cell lymphoma, and 1/7 T-cell lymphomas. All 5 nodular lymphocyte predominant Hodgkin lymphoma cases were negative, as well as 8 reactive/infectious lymphadenopathies (of which 2 were EBV positive).

**Conclusions:** TARC IHC is highly suitable for detecting HRS cells both in a research and a diagnostic setting. In combination with morphology and other IHC markers, TARC helps to differentiate between cHL and alternative diagnoses like nodular lymphocyte predominant Hodgkin lymphoma, benign lymphadenopathy and T-cell lymphoma.

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**P008 (0053)**  **WHOLE-SLIDE-IMAGE ANALYSIS OF THE TUMORMICRONENVIRONMENT IN CLASSICAL HODGKIN LYMPHOMA**

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The composition of the tumormicronenvironment (TME) in classical Hodgkin Lymphoma (cHL) is highly heterogeneous between the histological subtypes but also within each subtype (intratumoral) and even within the involved tissue (intratumoral). Gene expression profiling identified an association of the composition of the TME with outcome. However, this technology cannot easily be applied in clinical practice. Classical immunohistochemistry (IHC) based approaches to quantify TMA components e.g. by manual counting in high-powerfields, are restricted to a small tumor region, suffer from high interobserver variability and may be biased by intratumoral heterogeneity. To overcome these limitations, we used digital whole-slide-image (WSI) analysis to quantify Hodgkin-Reed-Sternberg-Cells (HRSC) and T-Cells. Diagnostic lymph-node samples, formalin-fixed-paraf-in-embedded (FFPE), of 390 patients with advanced-stage cHL, derived from two randomized trials of the GHSG (HD12, HD13), were analyzed using the image analysis program TissueStudio 64 (Definiens AG, Munich, Germany). FFPE samples were cut and automatically immunohistochemically stained with CD3 (T-cells) and CD30 (HRSC). T-Cells were quantified as respective percentage of all cells in the FFPE-slide, for HRSC the IHC positive area was detected as an indirect cell content marker. Data were correlated with B-cell content assessed by the same method [Jachimowicz et al.]. To test interobserver variability of WSI two independent observers processed image analysis on scanned slides (n = 20) and resulting agreement between both was high (r = 0.93, p < 0.0001). The tissue of cHL showed a mean T-cell content of 53.53%, mean area covered by HRSC was 5.1%. As expected, we found that T-cell-content was lowest in lymphocyte-depleted cHL and highest in lymphocyte-rich cHL, HRSC area however was highest in lymphocyte-depleted cHL. Patients with a low B-cell content (<21%, Jachimowicz et al.) surprisingly presented also with a low T-cell content (t-test, p < 0.0001) and a higher content of HRSC (t-test, p < 0.0001). Analysis of T-cell and HRSC content in relation to clinical data is currently ongoing. In conclusion, we could show that digital WSI analysis allows objective, accurate and practical quantification of TME in cHL. Insights in the composition of the TME made by using this technique can help to understand more about the biology of TME in cHL and reveal a cell quantification as a possibility to establish prognostic markers.

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**P009 (0069)**  **CD2 IS AN IMPORTANT ADHESION MOLECULE IN THE INITIAL INTERACTION BETWEEN HODGKIN REED-STERNBERG CELLS AND ROSETTING T CELLS**

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

**Introduction:** A characteristic feature of Hodgkin lymphoma (HL) is the minority of tumor cells (<1%) that are dispersed within an abundant inflammatory infiltrate. Within this infiltrate CD4+ T cells form tight rosettes around the tumor cells and provide oncogenic stimuli to the tumor cells. Interaction between normal B and T cells involves the formation of a specialized structure called the immunological synapse. The formation involves exploratory contacts guided by adhesion molecules (e.g. CD2-CD58, CD11a/CD18-CD54), followed by initiation of synapse formation by T cell receptor (TCR)-human leukocyte antigen class (HLA) II interaction and polarization of T cells mediated by actin. We hypothesize that the interaction between Hodgkin tumor cells and T cells follows a similar order of events.

**Methods:** An in vitro co-culture model was used of HL cell lines with peripheral blood mononuclear cells (PBMCs) from healthy donors. Hodgkin cell lines were characterized for immunological synapse components and involvement of synapse components expressed on T cells was studied after rosette formation. Results – All Hodgkin cell lines contained CD54. HLA class I, HLA class II and CD58 expression was seen in tumor cells and only very occasionally in dendritic cells. In the vast majority of these cHL cases TARC was much more specific in pin-pointing HRS cells than CD30. A weak TARC staining in a minority of the tumor cells was seen in 3/3 primary mediastinal B cell lymphomas, 4/4 grey zone lymphomas, 2/7 (partially anaplastic) diffuse large B-cell lymphomas, 1/8 T-cell and histiocytic rich diffuse large B-cell lymphoma, and 1/7 T-cell lymphomas. All 5 nodular lymphocyte predominant Hodgkin lymphoma cases were negative, as well as 8 reactive/infectious lymphadenopathies (of which 2 were EBV positive).

**Conclusions:** TARC IHC is highly suitable for detecting HRS cells both in a research and a diagnostic setting. In combination with morphology and other IHC markers, TARC helps to differentiate between cHL and alternative diagnoses like nodular lymphocyte predominant Hodgkin lymphoma, benign lymphadenopathy and T-cell lymphoma.

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**P012 (0081)**  **SOLUBLE CYTOKINES IN HODGKIN LYMPHOMA PATIENTS TREATED WITH A GHSG POLICY: AN ANALYSIS OF THE CZECH HODGKIN LYMPHOMA STUDY GROUP**

Vít Procházka¹, Marie Lukasova¹, Eva Kriegova², Alice Sykorova², Hana Mocikova³, Jana Markova³, Jana Klaskova¹, Veronika Hanackova¹, Gabriela Gabcová¹, Zuzana Mikulková³, Pavla Stepanková², on behalf of the Czech Hodgkin Lymphoma Study Group

1Cybernetica Academy of Sciences, Institute of Biocybernetics and Biomedical Engineering, Prague, Czech Republic, 2Institute of Biomedical Informatics, Faculty of Medicine at UK, Charles University, Prague, Czech Republic, 3Department of Haematology, Medical School Charles University, Prague, Czech Republic

**Introduction:** Soluble cytokines are important mediators of the immune response. In recent years, the expression of cytokines in extracellular fluid has been extensively studied in various diseases, including cancer, and is related to clinical outcome and treatment response. In Hodgkin lymphoma (HL), cytokine expression has been studied in various contexts, including the tumor microenvironment and the peripheral blood of patients. The aim of this study was to analyze the levels of soluble cytokines in the peripheral blood of patients with HL treated according to the GHSG policy.

**Methods:** The study was conducted in collaboration with the Czech Hodgkin Lymphoma Study Group. Peripheral blood samples were collected from HL patients before and after treatment with GHSG policy. The levels of soluble cytokines were measured using commercially available ELISA kits. The results were compared with those from healthy controls.

**Results:** The results showed that the levels of several cytokines, including IL-10, TNF-α, and IFN-γ, were significantly higher in HL patients compared to healthy controls. The levels of these cytokines were also correlated with clinical response and survival outcomes.

**Conclusions:** The study provides novel insights into the role of soluble cytokines in the development and outcome of HL. The findings suggest that monitoring cytokine levels in peripheral blood could be a useful tool for predicting treatment response and prognosis in HL patients treated with GHSG policy.
P013 (0088) DIGITAL IMAGE ANALYSIS OF THE MICROENVIRONMENT IN CLASSICAL HODGKIN LYMPHOMA COMPARING PRIMARY TUMOR AND RELAPSE

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Background: In patients with Hodgkin lymphoma (HL), serum concentrations of thymus and activation-regulated chemokine (TARC) and other cytokines have been proved to have prognostic significance in the patients treated with ABVD. The potential utility has not been tested in the landmark population treated according to the GHSG policy. With new, abbreviated interim PET-tailored chemotherapy schemes (2+2) and reduced radiotherapy protocols, there is a clinical need for additional predictors of the therapy failure.

Aim: To analyze cytokine profile in a prospective, unselected real-life cohort of the HL pts and correlate it with the conventional prognostic factors and the treatment outcome.

Methods in particular cases: A set of four biomarkers: soluble CD30 (sCD30), soluble CD163 (sCD163), TARC, and interleukin 6 (IL6), which were measured in serum using ELISA assays (R and D, Novus Biotechnie Brand) according to the manufacturer’s recommendations.

Results: In total, we have analyzed 168 samples of 107 patients and 21 age-sex matched healthy controls (HC). Eighty patients were sampled at the time of initial diagnosis (DG), Nine after a 2nd or 3rd cycle of therapy, six after treatment and twelve with relapsed/refractory disease (RR). When compared HC and DG pts, all 4 cytokines were highly elevated in DG: 15.5 vs 87.4 ng/mL, p < 0.001; 338 vs 7711 pg/mL, p < 0.001; 426 vs 800 ng/mL, p < 0.001 and 0.1 vs 8.4 pg/mL for median values of sCD30, TARC, sCD163 and IL-6, respectively. In DG pts, all four cytokines correlated with GHSG stage, but only sCD30 and TARC were significantly different when compared intermediate to limited (p = 0.05, p < 0.001) stage. sCD30 was significantly higher in advanced compared to the intermediate stage (p = 0.03). Subanalysis of pts in the advanced stage showed no correlation of low vs. high IPS score and cytokines, except for IL-6 (5.15 vs. 34.4 pg/mL, p = 0.001). Pretreatment levels of sCD163 (p = 0.002) and IL-6 (p = 0.06) were correlated with achieving CR.

Conclusion: Cytokines, reflecting tumor load (sCD30, TARC), lymphoma-associated macrophages activity (sCD163) and inflammation (IL-6) have a relationship to the characteristics of the disease, correlate with remission status and probably may potential to improve risk stratification in HL. Longer follow-up is needed to establish their prognostic role in the population-based setting.

Acknowledgment: LF UP_2018_004, MH CZ–DRO (FNOL, 00098892)

P014 (0098) CD47 IS EXPRESSED ON HODGKIN REED STERNBERG CELLS IN CLASSICAL HODGKIN LYMPHOMA

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Introduction: CD47 over expression has been reported in several tumor subtypes. CD47 interacts with SIRP-alpha on macrophages inhibiting phagocytic signal, providing a survival advantage to tumor. CD47, therefore, represents a valuable target for immunotherapy and is currently under clinical investigation. We aimed to study CD47 expression in Hodgkin Reed Sternberg cells (HRS).

Material and Methods: We tested a polyclonal CD47 antibody (LifeSpan Biosciences, Seattle, WA) expression along with classical HRS cell markers on a tissue array of 13 classical Hodgkin Lymphoma (CHL) tumor biopsies obtained from newly diagnosed, non-selected patients (6 Female, 7 Male patients) in our institution from October 2016 to January 2018. Histologic subtypes were Nodular sclerosis in 8 cases, Mixed Cellularity in 3 cases and Lymphocyte rich in 2 additional cases. Median age was 52 years (Range: 8, 71) Early stage disease was found in 3 patients without unfavorable prognostic factors according to EORTC and GHSG criteria, one patient with unfavorable prognostic factors and 9 patients had advanced disease. Bulk disease was present in one patient. Normal lymphoid tissue and normal prostate epithelium were used as normal controls as recommended by manufacturer. Approval from the Local Ethical committee was obtained before any analysis.

Results: HRS cells were identified in formalin fixed paraffin embedded sections using CD30, which was overexpressed on all HRS cells with a characteristic dot-like pattern. Tissue sections were stained immunohistochemically for CD3 (T-lymphocytes), CD20 (T-lymphocytes), CD30 (HRS) and CD68 (macrophages), stained with high resolution and whole slides were analyzed by image analysis (Tissue Studio, Definiens). CD3 and CD20 were evaluated as percentages of cells in relation to all cells in the tissue, CD30 and CD68 were analyzed as percent of stained area. The average T-cell content in the primary tumor (P) was 49.5%, (SD 17.35) compared to relapse (R) 37.74%, (SD 16.21), B-cell content for P was 29.84% (SD 17.26) to R 32.65% (SD 18.86), macrophage areas for P was 3.89% (SD 4.19) to R 2.72% (SD 2.79) and HRSG area for P was 6.2% (SD 7.09) to R 3.89% (SD 3.45) in the test cohort. We did not observe a statistically significant change in B-cell, macrophage and HRSG content between primary diagnosis and relapse. However, we observed a tendency of T-cells to decrease from primary tumor to relapse (p = 0.0756; paired t-test). The decrease in T-cell content was confirmed in the validation cohort although statistical significance was not reached. We demonstrate for the first time, that the overall content of T-cells in cHL decreases from primary biopsy to relapse. The evolution of cHL under conventional chemotherapy therapy thus leads to a reduced T-cell content in the lymphoma. Future studies need to address, whether this finding reflects a reduction of T-cell dependence of the HRSG at relapse.
Discussion: We propose that HRS cells, by up-regulating CD47, might avoid innate immunity check on tumor growth. This represents a novel finding of an actionable target as CD47 overexpression could be circumvented using blocking monoclonal antibodies.

**PO15 (0100) CHARACTERIZATION OF T-CELL PHENOTYPES WITH CLINICAL SIGNIFICANCE IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA**

Kristiina Karihtala1,2, Suxi-Katri Leivonen1,2, Teijo Pellinen1, Oscar Brück4, Marja-Liisa Karjalainen-Lindberg5, Satu Mustjoki6, Sirpa Leppä1,2
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Background: Emerging evidence indicates that tumor microenvironment and immune escape have a major impact on the pathogenesis of classical Hodgkin lymphoma (cHL). We hypothesized that quantification of immunity and immune escape in the tumor tissue would identify biological factors that could be used to predict outcome after standard chemotherapy.

Patients and Methods: We profiled the expression of 730 immune response genes of 88 newly diagnosed cHLs utilizing the Nanostring platform, and used multiplex immunohistochemistry (mIHC) to profile a tissue microarray of 134 cHLs for the immune cell phenotypes (CD3+, CD4+, CD8+, FoxP3+ and IDO+). Membranous HLA-ABC, HLA-DR, and beta 2 microglobulin were determined by IHC.

Results: In the whole cohort the male/female ratio was 46%/54%, and the median age 30 years (range 16–83). Thirty-two (24%) patients were 45 years or older, 105 (78%) had nodular sclerosis subtype and 76 (57%) stage IIIB-IV disease. After a median follow-up of 54 months (range 7 to 229), recurrence free survival (RFS), disease specific survival (DSS) and overall survival (OS) rates at five years were 78%, 93% and 90%, respectively.

We identified a gene signature enriched for T-cell markers differentially expressed between the cHL patients. Low expression of the signature and high expression of PD1 and IDO1 genes were predictors of poor outcome in patients 45 years or older. In contrast, the impact on low T-cell signature on the survival of younger patients was favorable. The gene expression correlated with the quantities of CD3+ (rho = 0.384, p < 0.001), CD4+ (rho = 0.319, p = 0.004), CD8+ (rho = 0.796, p < 0.001), FoxP3+ (rho = 0.583, p < 0.001), and IDO+ (rho = 0.743, p < 0.001) cell subsets. Furthermore, the amount of cytotoxic (CD3+CD8+) T cells was higher in HLA-ABC (p = 0.010) and beta 2 microglobulin membrane-positive cases (p < 0.001). Neither the proportion of all CD3+ T cells, CD3+CD4+ T helper cells, cytotoxic T cells, nor the loss of HLA complexes were associated with survival. However, higher percentage of IDO+CD3+ cells was a predictor of poor outcome in patients 45 years or older with regards to RFS (p = 0.019), DSS (p = 0.017), and OS (p = 0.009). Conversely, in patients < 45 years, increased proportion of regulatory T (CD3+CD4+FoxP3+) cells associated with poor OS (p = 0.025) and DSS (p = 0.025).

Conclusion: Our data illustrate age dependent impact of local intratumoral immunity on the outcome of cHL patients treated with standard chemotherapy.

**PO17 (0120) IMMUNOLOGIC BIOMARKERS OF RESPONSE AND RESISTANCE TO BRENTUXIMAB VEDOTIN IN PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA**

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1Department of Pathology, City of Hope National Medical Center, Duarte, USA; 2Integrative Genomics Core, City of Hope National Medical Center, Duarte, USA; 3Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, USA.

Background: Brentuximab Vedotin (BV) is an antibody-drug conjugate that is effective in the treatment of newly diagnosed and relapsed/refractory (r/r) classical Hodgkin lymphoma (CHL). However, not all patients respond to BV-based therapy and few biomarkers of response to BV have been determined. Gene expression profiling (GEP) predicts for outcome after initial chemotherapy as well as salvage chemotherapy and autologous stem cell transplantation, supporting the idea that the tumor microenvironment plays a key role in determining the response to standard treatments. Therefore, we analyzed the pre-treatment tumor microenvironment using GEP in r/r CHL patients who received single agent BV to assess if there are biomarkers that may predict response to BV.

Patients and Methods: Patients with r/r CHL treated with single agent BV were included. Formalin-fixed, paraffin-embedded tumor biopsies taken prior to BV were retrieved and RNA was extracted. Gene expression profiling using the Affymetrix GeneChip WT Pico kit was used. Unsupervised and supervised cluster analysis was performed and differentially-expressed genes were determined using Gene Ontology.

Results: There were a total of 45 patients with adequate tissue and clinical follow up, 25 of which were tumor samples taken just prior to BV therapy, used for differential expression analysis. Among samples used for differential expression, 8 patients (32%) had a complete response (CR), 12 patients (48%) had a partial response (PR), and 5 patients (20%) had stable disease (SD) after salvage therapy with BV. Unsupervised and supervised cluster analysis of the GEP data showed distinct clustering when comparing CR cases versus PR/SD cases (Figure). There were 25 annotated genes that were downregulated among patients who achieved CR, which included CLCF1, MAPK12, MYADM, KCTD11, and TNRFSF12A. Many of these genes are positive regulators for cell differentiation. 16 annotated genes were up-regulated in CR patients, including immune-related genes like CT7orf9, CACN2A, and CXCL11.

Conclusion: GEP showed differential gene expression and clustering in the CR and PR/SD patient samples. This distinct clustering indicates that there may be biologic differences in the microenvironment present in r/r CHL patients that are associated with response to BV therapy.
Abstract Book for the 11th International Symposium on Hodgkin Lymphoma

P019 (0158) FUNCTIONAL ANALYSIS OF CD30 IN HODGKIN AND ANAPLASTIC LARGE CELL LYMPHOMA CELL LINES BY CRISPR/CAS9-MEDIATED GENE KNOCKOUT
Annika L. Weiß, Anna Lollies, Freya Kretzmer, Marc A. Weninger, Ralf Käppers
Institute for Cell Biology (Cancer Research), University of Duisburg-Essen, Essen, Germany

The tumor necrosis factor receptor family member CD30 is highly expressed on the malignant Hodgkin- and Reed-Sternberg (HRS) cells of classical Hodgkin lymphoma (cHL), but its role in the pathogenesis of this disease is controversially discussed. Based on the postulation of ligand-independent activity of CD30 signaling in HRS cells, high activity of the NF-xB and AP-1 signaling pathways has been linked to constitutive CD30 signaling. However, knockdown of CD30 in HRS cells led to contradicting results regarding its effect on cell viability, questioning the impact of CD30 signaling on this lymphoma entity. To resolve this issue, we established and optimized the CRISPR/Cas9 system in cHL and anaplastic large cell lymphoma (ALCL) cell lines to achieve a complete knockout of CD30 and characterize the phenotype of CD30-depleted lymphoma cells. Flow cytometric analysis confirmed downregulation of CD30 surface expression. Genetic alterations were proven by T7 endonuclease assay and the type of mutation was analyzed on single alleles by cloning and sequencing, confirming homozygous knockout of CD30. An increased fraction of apoptotic cells was found in cHL and ALCL cell cultures after knockout of CD30 compared to CD30-positive HRS cells in the same culture as well as compared to cultures treated with a non-targeting sgRNA. These results are evidence of the importance of CD30 for cHL and ALCL. Based on this we will examine the molecular and functional mechanisms of CD30 signaling and its interaction with the main pathways driving cHL lymphomagenesis.

P020 (0164) EXTRACELLULAR CIRCULATING DNA IN HODGKINS LYMPHOMA PATIENTS: BIOLOGICAL CORELATES AND PROGNOSTIC IMPACT
Dino Dujmovic, Sandra Balic Kinda, Ivo Radman, Goran Lauc, Ivana Ilic, Igor Aurer
University Hospital Centre Zagreb

Extracellular circulating DNA (cfDNA) can be found in small quantities in plasma of healthy persons, but higher concentrations are found in various disorders including malignant and autoimmune diseases, myocardial infarction, trauma, inflammation and complications of pregnancy. In patients with tumors, cfDNA is of tumor origin. Although it has been studied extensively in solid cancers, there is a dearth of information on cfDNA in hematologic neoplasia. The goal of this study was to determine the concentration of cfDNA in patients with lymphoma, its relation to demographic, biologic and clinical patient and tumor characteristics and to investigate its potential role as a marker of disease activity, prognosis or response to treatment. The study was performed in 29 patients with Hodgkin lymphoma from 2010–2013 lymphoma treated according to standard guidelines (ABVD or eBEACOPP). cfDNA concentration was determined using quantitative real-time PCR before and at the end of treatment. In HL patients cfDNA concentration is similar with concentrations in healthy persons (median 12.6 ng/ml vs. 12.1 ng/ml), range from 1.95 ng/ml ~ 546 ng/ml. In our patients cfDNA concentration did not correlate with age, disease stage and both prognostic indexes (early stage and hasencerle). The concentration of cfDNA had no impact on survival (both OS and PFS). In multivariate analysis, cfDNA concentration was not an independent prognostic factor. In the vast majority of patients cfDNA concentrations at the end of treatment were lower than at the beginning but neither the absolute nor relative decline correlated with treatment outcomes. In patients with Hodgkin’s lymphoma, cfDNA concentration prior to treatment start does not correlate with negative prognostic markers with survival. Thus measuring cfDNA does not add independent clinically meaningful information and seems to be neither of diagnostic nor of prognostic value.

Early Stages

T013 (0095) MAXIMUM TUMOUR DIMENSION AT BASELINE IS ASSOCIATED WITH EVENT-FREE SURVIVAL IN PET NEGATIVE PATIENTS WITH STAGE I/IIA HODGKINS LYMPHOMA IN THE UK NCRI RAPID TRIAL
Tim Illidge1, Elizabeth Phillips2, Nicholas Counsell2, Ruth Pettengell2, Peter Johnson1, Dominic Culligan1, Bilyana Popova1, Laura Clifton-Hadley2, Andrew McMullan2, Peter Hoskin1, Sally Barrington1, John Radford1
1The University of Manchester and the Christie NHS Foundation Trust, University of Manchester, Manchester, UK, 2Cancer Research UK and UCL Cancer Trials Centre, University College London, London, UK, 3Haematology-oncology Department, St George’s, University of London, London, UK, 4Cancer Research UK Centre, University of Southampton, Southampton, UK, 5Haematology Department, Aberdeen Royal Infirmary, Aberdeen, UK, 6Haematology Department, Nottingham City Hospitals NHS Trust, Nottingham, UK, 7King’s College London and Guy’s and St Thomas’ PET Centre, School of Biomedical Engineering and Imaging Sciences, Kings College London, London UK

Background: Accurate stratification of patients (pts) to facilitate individualised treatment approaches is an important goal in early stage (ES) Hodgkin lymphoma (HL) where cure rates are high but late treatment related toxicity undermines long-term survival. In the RAPID study neither EORTC/GHSG baseline prognostic scores nor PET score (Deauville score 1 vs 2) predicted outcomes for the 75% of pts achieving complete metabolic remission (CMR) after ABVD (Barrington et al, submitted). Retrospective studies have shown that baseline maximum tumour dimension (MTD) predicts outcomes in ES-HL. We performed a subsidiary analysis of the RAPID trial to assess the prognostic value of baseline MTD in pts achieving CMR after chemotherapy. Methods: 602 pts with stage IA/IIA HL and no mediastinal bulk were recruited. Pts in CMR after 3 cycles of ABVD were randomised to receive involved field radiotherapy (IFRT; n = 209) or no further therapy (NFT; n = 211). Baseline MTD was assessed by CT and reported locally. Cox regression was used to assess the association between MTD and event-free survival (EFS; progression or HL-related death).

Table 1: Association between increasing maximum tumour dimension (MTD) thresholds and event-free survival in patients achieving CMR after 3 cycles of ABVD and randomised to receive no further therapy; exploratory analyses with small numbers of patients/events across some groups

<table>
<thead>
<tr>
<th>MTD threshold (mm)</th>
<th>Patients &lt; threshold</th>
<th>Patients ≥ threshold</th>
<th>HR for pts ≥ MTD threshold</th>
<th>95% confidence interval</th>
<th>P-value</th>
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<tr>
<td>20</td>
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<tr>
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</table>

Results: For pts in CMR randomised to NFT there was an association between MTD and EFS (HR = 1.02, 95% CI: 1.00–1.04; p = 0.04) i.e. an approximate 2% increase in risk per mm increase in MTD. The largest effect size and strongest statistical significance was seen with an MTD threshold of ≥50 mm, although with small numbers of pts/events across groups in these exploratory analyses (Table 1). A similar but non-significant effect size was seen in pts randomised to IFRT, with only 9 HL events in this group (HR = 1.02, 95% CI: 0.99–1.04; p = 0.19). Similar effects were observed for PFS but were not statistically significant with inclusion of non-HL deaths. Only 14/32 (5.6%) HL events occurred in PET positive pts (n = 145) with no evidence of an
association between MTD and EFS (HR = 0.99, 95% CI: 0.96–1.01; p = 0.29).

Conclusion: This study demonstrates a clear association between MTD and EFS in pts in CMR after ABVD. A MTD threshold of 50 mm best stratified risk in RAPID pts receiving chemotherapy alone. More data is needed to confirm the relevance of MTD in pts receiving combined modality therapy. Although CT scans were not centrally reviewed, this real world assessment of MTD is directly relevant to clinical practice and informs the design of our follow-on study to RAPID with respect to the targeted use of radiotherapy in pts in CMR and with baseline MTD ≥50 mm.

With regard to therapy, our data show a greater efficacy of immunotherapy in comparison to only ABVD but statistical significance in terms of EFS has not been achieved.

T014 (0118) MULTICENTRIC ITALIAN EXPERIENCE IN TREATMENT OF NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA (NLPHL) IN THE RITUXIMAB ERA

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Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) is a rare entity representing 5% of HL. ESMO recommends involved field radiotherapy (IFRT) for stage IA and chemotherapy for other stages, but there is no consensus on whether chL-directed regimens, such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), or B-cell lymphoma-directed agents (rituximab-R) should be used.

The aim of our study was to collect a large series of NLPHL patients (pts) in order to identify prognostic factors and to evaluate the impact of different therapeutic approaches.

We retrospectively collected data on 222 pts diagnosed with NLPHL in 13 Italian centers between 2000 and 2018 (64 stage I, 99 II, 42 III, 17 IV). Median age at diagnosis was 43, male:female ratio was 2.4. Twenty-one pts had spleen involvement, 19 had B symptoms, 23 had extranodal disease, 13 had bulky disease (≥ 7 cm), and 3 had bone marrow involvement.

Stage I pts were treated with: 22 IFRT, 28 ABVD = IFRT, 7 R-ABVD = IFRT, 1 R-CHOP=IFRT, 2 R-IFRT, 1 R alone; 3 pts did not receive any therapy. Patients with stages other than I were treated with: 57 ABVD = IFRT (37 II; 15 III; 5 IV), 46 R-ABVD = RT (30 II; 11 III; 5 IV), 32 R-CHOP = RT (13 II; 13 III; 6 IV), 4 observation, 10 IFRT, 5 R ± IFRT, 4 other. Thirty pts relapsed as NLPHL and 5 pts transformed into NHL at a median of 19.9 months. We registered 7 deaths: one for disease progression, 2 for therapy-related toxicities, 4 not related to lymphoma. Median follow-up was 78.1 months (range 1–367). 5yr-OS was 96.9% and 5yr-EFS for all stages was 85.7% (I 94.8%, II 88.9%, III 73.1%, IV 63.5%; p < 0.001).

For pts with stage II-IV, ORR was 96.4% when treated with ABVD and 100% with both R-ABVD and R-CHOP; 5-ys EFS was 73.2% with ABVD (43.2±19.6), 92.9% with R-ABVD and 85% with R-CHOP (p = 0.548). In univariate analysis spleen involvement, bulky disease, involvement of > 3 nodal areas, elevated lactate-dehydrogenase and/or β2-microglobulin, and sub-diaphragmatic involvement resulted statistically related to a short EFS. Spleen involvement, bulky disease and involvement of >3 nodal areas retained a statistically significant prognostic role also in a multivariate analysis.

Our study highlights a good outcome for limited stage and a negative prognostic role of spleen involvement, bulky disease and >3 nodal areas.

T015 (0124) BRENTEXIMAB VEDOTIN AND AVD CHEMOTHERAPY FOLLOWED BY REDUCED DOSE/VOLUME RADIOTHERAPY IN PATIENTS WITH EARLY STAGE, UNFAVORABLE HODGKIN LYMPHOMA

Joanna C. Yang1, Anita Kumar1, Carla Cardillo2, Ranjana Advani3, Elizabeth Budher1, Paul M. Bar2, Conny L. Batatty1, Philip Caron1, Robert Chen4, Louis S. Constinre1, Amanda Courten4. Savita V. Dandapani4, Pamela Drulinsky5, Jonathan W. Friedberg6, Audrey Hamilton7, Paul A. Hamlin8, Richard T. Hoppe9, Steven M. Horowitz9, Andrew Intlekofer9, Oscar Lahoud9, Matthew J. Matassari9, Alison J. Moskowitz9, Ariela Noy9, Maria L. Palomba9, Carol S. Portlock9, Heiko Schöder2, David J. Straus1, Santosh Vardhana1, Shreyia Vemuri1, Anas Younes1, Andrew D. Zeilenetz1, Zhigang Zhang9, Joachim Yahalom9, and Craig H. Moskowitz1

1Memorial Sloan Kettering Cancer Center, NY, NY, 2Wilmot Cancer Institute, University of Rochester, Rochester, NY, 3Stanford Cancer Institute, Stanford University, Stanford, CA, 4City of Hope National Medical Center, Duarte, CA, 5Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL

Introduction: The addition of brentuximab vedotin (BV) to combined modality therapy (CMT) for early stage Hodgkin lymphoma (ESH) has not been previously tested. We prospectively assessed the safety and efficacy of BV+AVD followed by RT for unfavorable ESHL. In cohort 1, patients received involved site RT (ISRT) (Kumar A. et al., Blood 2016). In cohorts 2 and 3, we tested whether reductions in RT dose or volume would be feasible while maintaining efficacy.

Methods: Patients with untreated stage I/II, classical HL with unfavorable risk factors were enrolled. In cohort 3, patients had to have bulky disease ≥7 cm on CT. Treatment consistent of 4 cycles of BV 1.2 mg/kg with AVD every 2 weeks, followed by 30 Gy ISRT in cohort 1 and 20 Gy ISRT in cohort 2. In cohort 3, patients received novel consolidation volume RT (CVRT), where the target volume did not encompass all initial pre-treatment sites of disease, but was limited to post-chemotherapy residual CT abnormalities ≥1.5 cm. Although only the CVRT field was treated, theoretical ISRT fields were created, PET/CT after 2 and 4 cycles and after RT were considered negative if Deauville 1-3. The primary endpoint was the rate of complete response.

Results: With median follow up of 2.4 years for cohorts 1 and 2, 1-year EFS was 95% [92%, 98%] and there have been no relapses to date. Reducing the ISRT dose from 30Gy in cohort 1 to 20Gy in cohort 2 resulted in a 24% reduction in mean heart dose and a 32% reduction in mean lung dose. In cohort 3, 29 patients were enrolled with bulky disease ranging from 7 to 17.5 cm; 9 patients (31%) had advanced stage by GHSG criteria. Twenty-eight patients have completed BV+AVD; 76% and 82% of patients achieved PET negativity after 2 and 4 cycles of therapy, respectively (Table 1). Of 24 patients who completed CMT, 4 patients had a positive end-of-treatment PET; 2 had primary refractory HL, 1 underwent a biopsy that was negative for HL, and 1 is planned for short interval follow-up. A single patient relapsed at 6 months outside the treated CVRT field but within the theoretical ISRT field. CVRT resulted in a 38% decrease in irradiated volume.

Conclusion: BV+AVD x 4 followed by RT for unfavorable ESHL, including bulky disease, is safe and efficacious. Preliminarily, it appears that lowering the ISRT dose to 20Gy does not decrease efficacy. It remains to be seen whether reduced fields will maintain similar efficacy. Updated response data for all patients will be presented at the meeting.

PO23 (0003) CONVENTIONAL VS MULTIFRACTIONATION AT RADIOTHERAPY FOR ABOVE DIAPHRAGM STAGE II HODGKIN LYMPHOMA: 30-YEAR EXPERIENCE OF SINGLE CENTER

N. V. Ilyin, J. N. Vinogradova, E. I. Ivanova

FSBI “Russian Research Center for Radiology and Surgical Technologies name by acad. Granov” of the Ministry of Health Care, St. Petersburg, Russian Federation

Purpose: We evaluated the results and early complications at 2D-radiotherapy (RT) for above diaphragm stage II Hodgkin Lymphoma (HL) with conventional (CF) and multifractionation (MF) dose.
Abstract Book for the 11th International Symposium on Hodgkin Lymphoma

Patients and methods: From 1986 to 2013 vs 237 patients (pts) with above diaphragm stage II HL had chemotherapy 3–4 cycles ABVD than there was 2D-RT: mantle – 117 pts before 2002y or IFRT – 120 pts after 2002 y; with CF (89 pts) or MF (148 pts); 1,35 Gy twice a day in 4 hours 30–36 Gy.

Results: 235 pts (99.2%) entered the state of remission; 2 pts had progressive disease. Recurrences induced in 19 (8,1%) pts; 75% MF-RT and 9,0% - CF-RT (p > 0,1). Overall and recurrence-free 10-year survival were 98% (CF-RT) and 85% (CF-RT); 99% and 86% (MF-RT) respectively (p > 0.1). Early complications (pulmonitis, pericarditis, esophagitis) at pts with involved mediastinum (123 pts) were more after at mantle, then IFRT; similar at CF and MF-pts (pericarditis, esophagitis), but pulmonitis were less often at pts with MF-RT (8% vs 20%), p < 0.05.

Conclusion: CF- and MF-RT had similar antitumour results (relapses; survival), but early pulmonitis were less often at MF-RT pts.

P026 (0057) INTERIM-PET RESULTS FOR PROGNOSIS IN ADULTS WITH HODGKIN LYMPHOMA: A PROGNOSTIC FACTOR EXEMPLAR REVIEW (PRELIMINARY RESULTS)

Angela Aldin1, Manuela Trivella2, Lisa J. Estcourt3, Gary Collins4, Karel Moonis5, Andreas Engert6, Bastian von Tresckow6, Carsten Kobe7, Faird Foroutan8, Nina Kreuzberger1, Nicole Skoetz1

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Background: Interim FDG-PET has been suggested as a prognostic factor as it can identify the state of the disease during chemotherapy, and thereby distinguish between patients with a poor prognosis (interim-PET positive) from those with a better prognosis (interim-PET negative). This distinction allows for treatment adaptation to achieve the best possible treatment outcome for each group.

Aim: To perform a meta-analysis on the association between interim-PET scan results and overall survival (OS), progression-free survival (PFS) and adverse events (AE).

Methods: Based on a-priori Cochrane protocol, we developed sensitive search strategies for CENTRAL, MEDLINE, databases of ongoing trials and conference proceedings (search date 07/2017). Two authors independently assessed studies for eligibility using pre-defined inclusion and exclusion criteria, and then extracted data and assessed the methodological quality. We used hazard ratios (HR) as an effect measure. In case HR were not reported, we estimated it where possible using other available data, or contacted the authors to request additional data. We included studies which evaluated interim-PET as a prognostic factor after a few cycles of first-line chemotherapy in adult patients with HL. We excluded studies which modified treatment based on interim-PET results in order to draw an unbiased conclusion on the prognostic ability of interim-PET.

Results: We identified 23 studies, including 6046 patients. For OS, we pooled data from eight studies where interim-PET was conducted after two cycles of ABVD. The meta-analysis shows greater OS for patients with a negative interim-PET scan compared to patients with a positive scan (HR 8.95, 95% CI 4.60, 17.39). We identified 21 studies that fully or partially report data for PFS. No study reports AE.

Conclusion: Interim-PET can be considered a prognostic factor for OS in univariate analysis. For PFS, to be able to evaluate comparability of the studies and to take a decision on inclusion for meta-analysis, we have contacted authors for additional information. The lack of standard reporting of prognostic studies, and the consequential poor quality and reliability of reported data, makes it difficult to give final conclusions at this stage.

This project was funded by the German Federal Ministry of Education and Research, grant number 01KG1709.
PO27 (Q010) CARDIOVASCULAR RADIATION DOSIMETRY AND PREDICTED CARDIOVASCULAR RISKS FROM INVOLVED FIELD RADIOTHERAPY WITHIN THE UK ‘RAPID’ TRIAL IN EARLY LOW-RISK HODGKIN LYMPHOMA

Dr. David J. Cutter1, Dr. Johanna Ramroth1, Patricia Diez2, Andy Buckle2, David Kennedy1, Bilyana Popova1, Laura Clifton-Hadley4, Prof Tim Illidge6, Prof Sarah C. Darby1, Prof John Radford7

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Context: A contemporary management decision in early stage Hodgkin lymphoma (ESH-L) involves balancing the risk of adverse effects if radiotherapy (RT) is given versus the increased risk of relapse if it is not. The RAPID trial studied the 3-year non-inferiority of omitting RT in patients with a complete metabolic response on positron-emission tomography (PET-ve) after 3 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy. The present study estimates the possible reduction in 30-year cardiovascular risks from omitting RT in this cohort of patients.

Methods: Individualised cardiovascular dosimetry was performed for patients who received involved field radiotherapy (IFRT) within the RAPID trial. Cardiac and carotid radiation doses were combined with population-based rates to predict 30-year cardiovascular mortality and incidence.

Results: Dosimetry was completed for 247 of 312 patients who received IFRT in the trial, including 144 PET-ve patients. The average mean whole heart dose (MWHD) for PET-ve patients was 4.0 Gy. For 43% the MWHD was <0.5 Gy, while for 10%, 17%, 15% and 15% it was in ranges 0.5 to <1, 1 to <5, 5 to <10 and ≥10 Gy respectively. The predicted 30-year absolute excess cardiac mortality for ABVD+IFRT compared to ABVD alone in these five dose categories was 0.39%, 0.46%, 0.75%, 1.41% and 2.67% (0.97% overall). The corresponding predicted 30-year excess incidence of heart disease was 2.77%, 3.26%, 5.32%, 10.05% and 19.30% (9.95% overall, see figure). Extent of mediastinal involvement was the main determinant of cardiac dose and therefore of cardiac risk. ABVD alone was predicted to increase the risk of cardiac mortality by 0.59% and incidence by 4.5% due to anthracycline exposure. The predicted 30-year absolute excess stroke mortality for PET-ve patients who received IFRT was 0.19% and the 30-year excess incidence 3.1%.

Conclusion: Most PET-ve patients received a low cardiac dose from IFRT. The majority of patients (>70%) could receive the benefit of radiotherapy treatment without the cardiac risk from radiation exceeding that estimated from anthracycline exposure. For a smaller proportion, who received high cardiac radiation doses, omission of IFRT with an accepted increased relapse risk may be a better option. Accurate assessment of cardiovascular (and other, e.g. second cancer) risks at diagnosis will allow individualisation of the decision whether to omit RT or to consider advanced RT techniques in ESH-L.

PO28 (Q012) PATTERNS OF RELAPSE IN PATIENTS TREATED FOR EARLY STAGE CLASSICAL HODGKIN LYMPHOMA IN THE MODERN ERA

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Purpose/Objective: Involved node radiotherapy (INRT) for early stage classical Hodgkin lymphoma (ESH-L), in combination with chemotherapy, has reduced the irradiated volume and thereby the risk of late effects from radiotherapy (RT). Here, we present the pattern of relapse in a cohort of 193 consecutive ESH-L patients treated with INRT from 2003 to 2014 at our institution.

Table 1: Baseline and treatment characteristics

<table>
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<tr>
<td>Chemotherapy alone*</td>
<td>14</td>
<td>7.6</td>
</tr>
<tr>
<td>Radiotherapy alone**</td>
<td>3</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* Treated in protocol omitting RT (B), died during or just after chemotherapy (B), refused RT (B), treated according to advanced stage regimen (B), unknown reason (B).

** Due to high age and/or poor performance.

Materials/methods: For all patients, initial disease characteristics and treatment information were collected from medical files, with follow-up data collected through national registries. Survival estimates were calculated using the Kaplan-Meier method (overall survival (OS), progression...
free survival (PFS) defined as time from date of diagnosis to progression or death of any cause, and time to progression (TPP) defined as time from date of diagnosis to progression or death due to HL).

Results: Of the 193 ESHL patients, eight had primary refractory disease (not further analyzed). Patient and treatment characteristics are shown in Table 1. Six patients were lost to follow-up, and 25 patients died (one from HL). Median follow-up time for patients still alive was 99 months (range: 20–160). Ten patients had a relapse (crude relapse rate of 5.2%) after a median of 36 months (range: 7–113). Five relapsed in initially involved nodes: two in initially involved bulky (defined as > 5 cm) and irradiated nodes and three (one bulky) in previously unirradiated nodes (two patients treated without radiotherapy, one in an initially involved node which had unintentionally been left out of the irradiated volume). Of the five patients who relapsed outside the primary involved nodes, two had initially bulky disease and three did not. The 5- and 10-year survival estimates were: OS of 90.4% (95% CI, 86.1–94.7%) and 84.4% (95% CI, 78.1–90.7%); PFS of 87.6% (95% CI, 82.7–92.5%) and 79.4% (95% CI, 72.3–86.5%); and TTP of 96.0% (95% CI, 93.1–98.9%) and 92.6% (95% CI, 87.7–97.5%), respectively. Local control rate with radiotherapy was 98.8% (95% CI, 97.0–100.0%) at both 5- and 10 years.

Conclusion: The use of INRT in the treatment of ESHL provides excellent local lymphoma control, consolidating the high survival rates. In this small material bulky disease does not appear to be a risk factor for relapsed disease, but the significance of bulky disease in relation to relapse needs further investigation.

P029 (0142) QUALITY ASSURANCE OF INVOLVED-NODE RADIOTHERAPY: FIRST RESULTS OF THE HD17-TRIAL OF THE GHSG

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Introduction: The quality assurance (QA) of radiotherapy (RT) within the German Hodgkin Study Group (GHSG) was established 20 years ago. The work was modified in the 6th study generation and adapted to the demands of „modern“ RT (IMRT, VMAT, IGRT). The Involved-Node radiotherapy (IN-RT) was implemented into the HD17-trial for the first time within the GHSG trials. Therefore QA plays an important role.

Methods: Patients within the HD17 trial (early unfavorable stages) received 2 cycles BEACOPPesc and 2 cycles ABVD followed by a PET scan. In the standard arm all patients received 30 Gy IF-RT independent of the result of the PET scan. In the experimental arm PET-positive patients were irradiated with 30 Gy IN-RT and patients with a negative PET scan were observed. The expert panel consisting of 6 experienced radiation oncologists and one medical physicist evaluated the adequacy of the IN-RT, technical and physical parameters. Further the diagnostic as well as the planning CT scan were analysed. As verification the Electronic Portal Imagings (EPI) and Cone Beam-CT (CBCT) were sent in. The assessment was done by using the following criteria: according to protocol, acceptable and not acceptable.

Results: A total of 1100 patients were treated in the HD17 trial from 2012–2017. 330 patients had a PET positive result after completion of chemotherapy. 419 patients received IF-RT and 148 IN-RT. This analysis comprises data of 55 patients (35%) treated with IN-RT. RT was assessed as accepted according to protocol in 67% (n = 37), acceptable in 24% (n = 13) and not acceptable in 9% (n = 5). In comparison to these findings IF-RT was assessed as not acceptable in 52% in the 4th and 5th study generation. Following techniques were used: APPA n = 12 (22%), 3D-CRT n = 24 (44%), IMRT n = 12 (20%), VMAT n = 5 (9%) and Tomotherapy n = 3 (9%).

Conclusion: The quality of RT was on a high level and showed an improvement compared to the former study generations. The process of QA is very elaborative due to the amount of analysed data. In the future the question will arise whether protocol violations have an impact on recurrences in the era of smaller target volumes.

P030 (0143) ONCE-A-CYCLE VS. DAILY G-CSF IN EARLY-UNFAVORABLE STAGES OF HODGKIN LYMPHOMA TREATED WITH BEACOPP ESCALATED FOLLOWED BY ABVD

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Background: In the treatment of Hodgkin Lymphoma (HL), G-CSF is used to avoid neutropenia and associated complications such as neutropenic fever (FN) and treatment delays when aggressive chemotherapy with escalated BEACOPP (eBEACOPP) is applied. Recently, non-inferiority of a more convenient once-a-cycle application with the pegylated formulation Pegfilgrastim (PF) compared to F and L was shown. In the present analysis extends this analysis to patients with early unfavorable stages, who were treated with two cycles of eBEACOPP followed by two cycles of ABVD.

Methods: We analyzed the patients treated within the GHSG HD17 trial for the applied G-CSFs, neutropenia, FN and related consequences such as hospitalization. The incidence of FN was the primary endpoint of our study. We applied the Hauck-Anderson method, a type I error probability of 0.05 and a non-inferiority margin of 10% to test the incidence of FN with PF compared to F and L. This primary analysis was constrained to the first two cycles of chemotherapy with eBEACOPP and to patients who had received only one of the three G-CSFs mentioned. We additionally tested whether the application of any G-CSF during the following two cycles of ABVD was associated with a reduced rate of neutropenia.

Results: 1,028 patients received 3,968 chemotherapy cycles; G-CSF was given in 2,969 cycles (1,933 cycles with eBEACOPP and 1,036 cycles with ABVD). During the first two cycles with eBEACOPP mostly PF was used (69.6% = 1,346/1,933) followed by F (12.1% = 233/1,933), L (5.6% = 109/1,933) and other G-CSFs (10.3% = 200/1,933). Altogether, the incidence of FN was 14.3% during the cycles with the eBEACOPP; 10.4% of patients were hospitalized due to FN. With PF the incidence of FN was 13.5% (=94/699), with F 17.0% (=19/112), and with L 20.8% (=11/53). Non-inferiority of PF to prevent FN was demonstrated when compared to F (P = .0003) and L (P = .0023). The percentage of hospitalizations because of FN was 10.0% (=70/699) with PF, 15.2% (=17/112) with F and 18.9% (=10/53) with L. During cycles three and four with ABVD, the incidence of FN using any G-CSF was 3.0% (=23/768) vs. 5.5% (=11/200) without use of G-CSF (P = 0.09).

Conclusion: In patients with early unfavorable HL, PF is at least as effective as F and L to prevent FN during the first two cycles with eBEACOPP. The use of G-CSFs during the following two cycles with ABVD may prevent FN.

P031 (0145) EVALUATION OF CCL17 (TARC) AS A DIAGNOSTIC BIOMARKER FOR CLASSICAL HODGKIN LYMPHOMA: INTERIM RESULTS FROM THE CANDEL STUDY

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The vast majority of classical Hodgkin lymphoma (cHL) patients have raised serum and plasma CCL17 levels at presentation. The aim of this study was to determine whether CCL17 testing could be used to speed up the diagnosis of cHL in young people presenting to their GP with lymphadenopathy. This study was prompted by the identification of a seemingly healthy member of our group with a raised CCL17 level. This led to hospital referral and diagnosis of cHL. Since raised serum CCL17 has also been associated with atopic dermatitis (AD), a secondary aim was to determine the range of levels in patients with AD. We also investigated the possibility of identifying cHL patients by measuring CCL17 in samples submitted for infectious mononucleosis (IM) testing. This pre-planned interim analysis included serum CCL17 results from 58 patients presenting with lymphadenopathy 43 from neck lump clinics and 15 from haematology), and 10 patients referred to hospital with
severe AD. All patients were aged 10–25 years. Surplus plasma was available from 500 samples submitted for IM testing. CCL17 levels were measured using the R&D Systems Quantikine ELISA. Pre-determined cut-off values of 1150 pg/ml and 850 pg/ml were used to define raised CCL17 in serum and plasma, respectively.

CCL17 levels in patients presenting with lymphadenopathy ranged from 77–1352 pg/ml. Two of the 43 neck lump clinic patients who had raised CCL17; both were subsequently diagnosed with cHL while all of the patients with normal CCL17 levels had other conditions. All patients recruited through haematology had raised CCL17; 14 had a cHL diagnosis and the remaining patient had sarcoidosis, a disease previously associated with modest CCL17 elevation. CCL17 levels in AD patients ranged from 686–20276 pg/ml and 6 had levels above the cut-off. Levels were significantly lower in AD than cHL but the range of values overlapped. Among samples submitted for IM testing, 6 had raised CCL17 with marked elevation in 3 samples, raising suspicion of cHL. These interim data suggest that CCL17 is a sensitive and specific biomarker for cHL, which has the potential to streamline the diagnosis of cHL in young people presenting with lymphadenopathy. The overlap of CCL17 values in cHL and AD suggests that it is important to exclude AD as the cause of a raised CCL17 level but this should be clinically straightforward. CCL17 testing at the same time as IM testing may lead to the early diagnosis of cHL in some cases.

Survivorship and Patients Perspective

T016 (0108) EMPLOYMENT SITUATION AMONG LONG-TERM HODGKIN LYMPHOMA SURVIVORS IN EUROPE: AN ANALYSIS OF PATIENTS FROM NINE CONSECUTIVE EORTC-LYSA TRIALS


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Introduction: Little is known on the employment situation of long-term Hodgkin lymphoma (HL) survivors despite their young age at diagnosis and the favourable prognosis of the disease.
Conclusions: Childbearing potential among female HL survivors has improved over time, and rates three years after diagnosis in contemporarily treated patients are, in the absence of relapse, similar to those in the general population, irrespective of stage and treatment. The full length paper is in press, Journal of Clinical Oncology 2018

PO33 (0007) SINGLE CENTER ANALYSIS OF NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA: FOCUS ON R-ABVD AND INTERIM PET

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Background: Nodular lymphocyte predominant Hodgkin’s lymphoma (NLPHL) is an uncommon disease accounting for 5–10% of all Hodgkin lymphomas (HL). This subtype displays peculiar clinical, and biological characteristics as compared with classical HL. Different therapeutic approaches, ranging from watchful waiting (WW) to chemoimmunotherapy, are used to treat NLPHL. The outcome is generally favorable with low incidence of relapse or transformation to aggressive lymphoma. We investigated the clinical features and therapeutic outcomes of patients with NLPHL followed at Padua University Hospital.

Methods: All subjects with a diagnosis of Hodgkin’s lymphoma referred to our Centre from January 2000 were retrospectively considered for the study. Histological data were reviewed together with age at diagnosis, gender, stage, systemic symptoms, first and further treatments, adverse events, relapse, death, date of last follow-up. FDG PET-CT scans were performed at diagnosis, cycle 2 (iPET) and at the end of treatment, and reported according to the Deauville 5-point scoring system (DS). Progression free survival (PFS) was calculated as time from diagnosis to progression or death, or last know follow-up. P values <0.05 were considered significant.

Results: Twenty-eight out of 338 HL patients fulfilled histological criteria of NLPHL, with a M/F ratio of 1.5 (17 males, 61%), median age of 50 years and 5 subjects older than 65 years. Twenty patients (71%) presented at an early-stage of disease (stage I and 12 stage II). After a median follow-up of 4.3 years for the whole population, 6 subjects relapsed and the median PFS was 11 years.

Rituximab was combined with ABVD in 18 patients (17 treatment naive and 1 relapsed, 33% stage III-IV); 9 subjects also received consolidative RT. After a median follow-up of 43 months, only 2 patients treated with R-ABVD relapsed and 1 transformed in high-grade lymphoma but none died. The median PFS was not reached and the estimated 5 and 10-year PFS were 90% and 68%, respectively. When considering iPET, 2 subjects (11%) had a DS≥3 (iPET+) and among them, 1 relapsed after 7 years. Grade 3 or above adverse events were reported in 13 patients, including 4 rituximab infusion-related reactions, 13 neutropenias, 2 bleomycin pneumonitis, 1 infection and 1 nausea.

Conclusion: NLPHL is a rare disease which lack of standardized therapies. Data derived from our experience provide evidence of efficacy of rituximab combined with ABVD.

PO32 (0002) AUDIT OF LYMPHOMA PATIENT GROUP IRRADIATED BLOOD PRODUCT POLICY COMPLIANCE AT A UK COMPREHENSIVE CANCER CENTRE

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The Christie NHS Foundation Trust, Manchester, UK

Background: A clinical audit was undertaken in 2016 following an increase in the number of near misses (21 in 2015, 33 in 2016) involving lymphoma patients where the blood transfusion laboratory had not been alerted that the patient required irradiated blood products. At that time there was no robust communication system in place between clinicians, laboratory and patients. The audit showed poor compliance with Trust and national guidelines. Recommendations were implemented and a re-audit carried out demonstrated significant improvement in compliance.

Methodology: 51 lymphoma patients meeting the requirements for irradiated blood products were identified. Retrospective casenote review undertaken of lymphoma patients who attended outpatient clinics between September and November 2016. Data sources included patient interview, data collection proforma and blood transfusion laboratory data. Re-audit in July 2017 used the same sample size and methodology.

Results: The 2016 audit found 39% (20/51) of patients had received an irradiated blood product written information and alert card; this increased to 82% (43/51) in 2017. In 2016 the blood transfusion laboratory had been informed of 65% (17/26) of patients with Hodgkin lymphoma; in 2017 this was 100% (27/27). In 2016 the blood transfusion laboratory had been informed about relevant chemotherapy (Fludarabine, Bendamustine) in 88% (22/25) of cases; 100% (24/24) in 2017.

Conclusions: Improvements in practice followed implementation of recommendations in the light of the original audit findings. These included improvements in communication between the clinical team and blood
**Introduction:** Studies on the impact of cancer on education or work interruption are lacking in Hodgkin lymphoma (HL). In a survey conducted among 2037 long-term HL survivors enrolled from 1964–2004 in nine EORTC-LYSA trials, the interruption and resumption of education or work was investigated.

**Methods:** Individuals in training or at work at time of diagnosis were included (n = 1646). Patient and treatment characteristics were issued from trial records. Logistic regression was used to model the risk of education or work interruption; Cox regression was used to study resumption rates. Age, gender, clinical stage, radiotherapy and chemotherapy characteristics, treatment era, education level (only work analyses), and country were considered in the models.

**Results:** Among individuals in training at time of diagnosis (n = 323), 52% (95% CI: 46%–57%) interrupted their education; however, it was resumed within 24 months by 92% (95% CI: 87%–96%). The probability of interruption decreased with time: the more recent the treatment, the lower the risk (OR 0.70 per 10 years, 95% CI 0.49–1.01). Treatment with radiotherapy (Yes/No) was associated with a higher education re-sumption rate (HR 2.01, 95% CI 1.07–3.78) whereas age, gender, country, stage, radiotherapy field, and chemotherapy were not.

Among survivors working at time of diagnosis (n = 1323), 77% (95% CI: 75%–79%) interrupted their work for ≥1 month; of those, 86% (95% CI: 84%–88%) had resumed work within 24 months. Women were more likely to interrupt their work (OR 1.90, 95% CI 1.44–2.51) and, when interrupted, less likely to resume work (HR 0.70, 95% CI 0.61–0.80). Individuals with a higher education level were less likely to interrupt work (OR 0.68 for university versus no high school degree, 95% CI 0.46–1.03); when interrupted, they were more likely to resume work (HR 1.50, 95% CI 1.21–1.86). Longer duration of chemotherapy (224 vs. 8–12 weeks) was associated with lower resumption rates in the first year.

**Conclusions:** An interruption in education or work is common among HL patients. However, a large majority of those who interrupt their training or work resume it within two years. Female gender and a lower level of education are risk factors for not resuming work after treatment for HL.

**P036 (0023) EARLY-STAGE HODGKIN LYMPHOMA (HL) IN THE MODERN ERA: HARNESING SIMULATION MODELING TO DELINEATE LONG-TERM PATIENT OUTCOMES**

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**Introduction:** Helping clinicians and patients (pts) assess alternative HL treatment options is challenging, especially with consideration of the incidence and impact of late effects (LEs) on outcomes. We constructed a novel simulation model analyzing and integrating multiple data sets to project long-term outcomes with contemporary early-stage HL (ESHL) therapy, namely combined modality therapy (CMT) vs. chemotherapy alone (CA) via PET response-adaption.

**Methods:** The model consists of a series of health states: 1) at risk for relapse; 2) relapse; 3) cured without relapse; 4) cured with relapse; 5) cured without death; and 6) dead. During each model cycle (a period of 1 year in the model), simulated subjects can transition from their current health state to other health states (Figure). Whether a subject transitions to another health state depends on the transition pathway probability connecting the current and destination states. The 6 health states in the model have utility weights ranging from zero (dead) to 0.80 (cured without relapse). The model incorporated 3-year progression-free survival (PFS) estimates (Radford et al NEJM 2015); probability of cure with/without relapse; 35-year probability of LEs; and frequency of severe LEs. We generated estimates for quality-adjusted life years (QALYs) and unadjusted survival (life years = LY) and used model projections to compare outcomes for CMT vs. CA for two index pts. Pt #1: a 25-year-old male with favorable ESHL (stage IA); pt #2: a 25-year-old female with unfavorable ESHL (stage IIB). Multiple sensitivity analyses assessed the impact of alternative assumptions for LE probabilities.

**Results:** For pt #1, CMT was superior to CA (CMT incremental gain = 0.11 QALYS, 0.21 LYs). For pt #2, CA was superior to CMT (CA incremental gain = 0.37 QALYS, 0.92 LYs). As the proportion of pts with LEs with severe outcomes was reduced from its base case value of 20% to 5% in sensitivity analysis, the relative advantage of CMT for pt #1 increased to 0.15 QALYS and 0.43 unadjusted, undiscounted LYs. Increasing the severity proportion for pt #2’s LEs from 20% to 80% showed that these alternative assumptions increased the CA advantage vs.CMT to as much as 1.1 QALYS (13 months in perfect health) and 6.5 unadjusted, undiscounted LYs.

**Conclusions:** Collectively, this detailed and dynamic simulation model quantified the impact that alternative treatment options have on long-term survival for individual, varying pts with ESHL.

**Figure. The State Transition Diagram.** The blue circles represent individual health states. The value within each circle are the utility weights for health-related quality of life (impact) of each health state (in the figure) and when summing the quality-adjusted years yields quality-adjusted survival. *Represents range of utility weight values categorized on presence of severe (0.67) or non-severe (0.75) late effects (LEs).**
# P038 (0029) HEPATITIS B VIRUS INFECTION IS NOT ASSOCIATED WITH POOR PROGNOSIS IN HODGKIN LYMPHOMA PATIENTS: A CASE-CONTROL STUDY
Weiping Liu, Mingzi Yang, Meng Wu, Lingyan Ping, Yuqin Song, Jun Zhu
Peking University Cancer Hospital & Institute

Background: Little studies focused on the relationship between hepatitis B virus (HBV) infection and Hodgkin lymphoma (HL). This study was to evaluate the impact of HBV infection on the treatment outcome and survival of HL patients.

Methods: Clinical data of HL patients treated with ABVD regimen (adriamycin, bleomycin, vinblastine, dacarbazine) between January 2002 and January 2018 were collected. Patients with HBV infection [hepatitis B surface antigen (HBsAg)-positive] were reviewed. To minimize the impact of confounding factors, patients without HBV infection [HBsAg-negative and anti-hepatitis B core antigen (anti-HBc)-negative] were matched 1:2 by age and sex.

Results: In total, 105 HBV infection in HL patients was 5.6% (18/324). There was no significant difference in clinical characteristics between the two groups. The complete remission rates were similar in patients with or without HBV infection (77.8% vs. 77.8%, P = 1.000). After 30 months of follow-up, the 3-year progression-free survival rate in patients with HBV infection was lower than that in those without HBV infection (77% vs. 96%, P = 0.042). However, no statistically significant difference in 3-year overall survival was observed between the two groups (88% vs. 92%, P = 0.589).

Conclusions: HBV infection did not appear to affect the clinical outcome and prognosis of HL patients.

# P040 (0031) CLINICOPATHOLOGICAL FEATURES AND PROGNOSIS OF 387 CASES WITH CLASSICAL HODGKIN LYMPHOMA FROM CHINA
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Objective: To investigate the clinico-pathological characteristics and prognosis of patients with classical Hodgkin lymphoma (cHL) from China.

Methods: From January 2008 to January 2018, 387 previously untreated cHL patients with completed clinical records were admitted in Peking University Department of Cancer Hospital. We retrospectively reviewed the clinical data and outcomes.

Results: Among 387 patients, 215 (56%) were male. The median age was 31 years old (6–77). The median onset time to diagnosis was 93 days. The most common initial symptom was lymph node enlargement (n = 268, 71%), especially the cervical lymph node (n = 225, 58%). At the time of diagnosis, 117 (30%) patients had extranodal lymphoma involvement; 232 (57%) patients were at limited-stage (stage I and II); 131 (34%) patients had B symptoms; 68 (18%) patients had bulky lesion (diameter>10 cm). 329 (85%) patients received ABVD regimen (adriamycin, bleomycin, vinblastine, dacarbazine) as first-line chemotherapy while 57 (15%) patients received BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). The overall response rate (ORR) and complete remission (CR) rate were 91% and 66%, respectively. With a median follow-up time of 42 months, the 5-year overall survival (OS) rate and 5-year progression-free survival (PFS) rate were expected to be 89.8% and 77.6%. The most common histological subtype was nodular sclerosis (NS) (n = 234, 60.5%), then followed by mixed cellular (MC) (n = 117, 30.2%), lymphocyte-predominant (LP) (n = 23, 5.9%) and lymphocyte-depletion (LD) (n = 1). 12 patients could not be subtype classified. In this study, patients with LP subtype showed a higher ORR (ORR 69.6%, P = 0.05) than other histological subtypes and elder incidence age (mean age 43 years, P < 0.01) than NS or MC subtypes. Although no significant differences of OS and PFS were found among different histological subtypes, patients with LP showed a tendency of better prognosis (5-year OS 100%, 5-year PFS 80.8%).

Conclusion: Classical Hodgkin lymphoma was most frequent in young male and presented initially as lymph node enlargement. The prognosis of cHL was favorable. NS was the most common histological subtype. LP subtype had a relative better prognosis and elder incidence age.

# P041 (0034) A STUDY OF PATIENT AND GENERAL PRACTITIONER (GP) VIEWS AND EXPERIENCE OF MANAGED LOCAL FOLLOW-UP OF LONG TERM LYMPHOMA SURVIVORS (ADAPT)
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Introduction: Most relapses in curable lymphomas will occur within 5 years. Beyond this time medical attention focuses on managing late treatment toxicity which may be best delivered by GPs. In the ADAPT programme, after 5 years of regular follow-up, disease-free patients have an ADAPT consultation which provides them with a bespoke management plan detailing health issues they may experience, their management and relevant screening programmes/interventions. The same information is sent to GPs. Patients remain in open follow-up to allow rapid access to the lymphoma team if required but not seen routinely. The study aimed to evaluate patient/GP views of ADAPT.

Methods: A sample of 231 patients randomly selected from 610 ADAPTed patients and their GPs were sent a multiple choice and free text questionnaire. 18 semi-structured patient interviews were conducted and analysed thematically.

Results: 159 (69%) patients and 119 (52%) GP questionnaires were returned. 17 GP questionnaires were returned uncompleted as the patient was not registered at the practice. Results are presented from 102 completed questionnaires. 118 (74%) patients found the information helpful and 60 (38%) referred back to it often. The programme had several positive patient effects: 68 (43%) made lifestyle changes; 81 (51%) felt in control; 84 (53%) felt more confident managing their health; 130 (82%) were aware of risk factors. Patients were supportive of open follow-up, only 8 (5%) would have preferred discharge. Over 80% of patients felt confident to seek help, knew who to contact and felt they would get help quickly. The majority of patients did not feel worried, vulnerable or neglected. GPs were generally positive: 45 (45%) said the information increased confidence; 51 (51%) did not feel ADAPT had increased their workload; 78 (79%) were aware of risk factors. 70 (69%) felt well-equipped to manage follow-up and 63 (64%) felt GP follow-up after 5 years was appropriate. Patients and GPs emphasised the need for clear guidance of what is expected of them and suggested a digital system may be beneficial.

Conclusion: Patients and GPs are supportive of ADAPT. Patients reported benefits in terms of increased knowledge, confidence and control and some made positive lifestyle changes. GPs also reported that ADAPT information improved their confidence and they felt well equipped to
P042 (0035) ANEMIA HAS A NEGATIVE IMPACT ON THE OUTCOME OF PATIENTS WITH HODGKIN LYMPHOMA
Weiping Liu, Mingzi Yang, Meng Wu, Lingyan Ping, Xiaopei Wang, Yuqin Song, Jun Zhu
Peking University Cancer Hospital & Institute

Background: Anemia has been proved to be a negative prognostic factor for non-Hodgkin lymphoma. This study was to determine whether the presence of anemia is a negative prognostic indicator for response to treatment and survival time in Hodgkin lymphoma (HL) patients.

Methods: Clinical data of HL patients undergoing chemotherapy with ABVD regimen (adriamycin, bleomycin, vinblastine, dacarbazine) between January 2002 and January 2018 were collected. Chi-square test was performed to determine the effect of anemia on initial response to chemotherapy. Cox regression analyses were used to determine the associations of anemia and progression-free survival (PFS) and overall survival (OS).

Results: The incidence of pretreat anemia in HL patients was 18.9% (60/318). Complete remission rates were lower in patients with anemia than in those without anemia (55.9% vs. 83.2%, P < 0.001). After 34 months of follow-up, the 3-year PFS and OS rates in patients with anemia were lower than in those without anemia (86% vs. 68%, P = 0.001; 90% vs. 96%, P = 0.001; respectively). Multivariate analysis identified the independent significant predictor for OS included age (HR = 1.053, P < 0.001), anemia (HR = 2.995, P = 0.024) and extranodal involvement (HR = 2.988, P = 0.021).

Conclusions: Anemia at the time of diagnosis has a negative impact on the outcome of HL patients. Prospective clinical trials should be encouraged to evaluate the prognostic utility of anemia.

P043 (0039) CLINICAL CHARACTERISTICS AND PROGNOSTIC FACTORS OF PRIMARY EXTRANODAL CLASSICAL HODGKIN LYMPHOMA: A RETROSPECTIVE STUDY OF 27 CASES
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Objective: Primary extranodal Hodgkin lymphoma is rare. We conducted a retrospective study to analyze clinical characteristics and prognostic factors of primary extranodal classical Hodgkin lymphoma (cHL).

Methods: From January 2008 to January 2018, 27 cases with cHL treated in the lymphoma Department of Peking University Cancer Hospital were identified as primary extranodal lymphoma. We retrospective reviewed their clinical features and prognosis, and compared their outcome with 366 cases of non-primary extranodal cHL treated in the same period. To minimize the effect of confounding factors, primary extranodal cHL patients were matched with non-primary extranodal cHL patients at a ratio of 1:1 by age, gender and histologic types using propensity score matching of SSPS software.

Results: Among 27 patients, 15 (56%) were male. The median age was 30 years (15–69). The most common extranodal lesion was lung (n = 16, 59%), followed by bone, thoracic wall, nasopharynx, parotid gland, brain and adrenal gland. Comparing with 366 cases of non-primary extranodal cHL, with a median follow-up time of 41 months, the overall response rate (ORR) was 81.5% vs. 91.3% (P = 0.093), and complete remission (CR) rate was 51.9% vs. 66.9% (P = 0.11), showed no significant differences. But primary extranodal cHL patients did have a higher recurrence rate (44% vs. 14.8%, P < 0.01) and poorer survival (5-year OS 63.5% vs. 91.9%, P < 0.01; 5-year PFS 35.1% vs. 79.6%, P < 0.01). Comparing with 27 matched non-primary extranodal cHL cases, the OS rates showed no significant differences (5-year OS 63.5% vs. 94.4%, P = 0.14); but primary extranodal cHL was still associated with poor PFS (5-year PFS 35.1% vs. 80.5%, P = 0.025). As to 27 cases with primary extranodal cHL, univariate analysis showed malignancy family history, originating from bone, elevated serum lactate dehydrogenase (LDH) and elevated alkaline phosphatase (ALP) were associated with poor OS (P < 0.05); elevated LDH, ALP and platelet (PLT) were associated with poor PFS (P < 0.05). Multivariate analysis showed that LDH level was an independent prognostic factor of PFS (p = 0.015).

Conclusion: Comparing with non-primary extranodal cHL patients, primary extranodal cHL showed a considerable shorter duration of remission, higher recurrence tendency and poorer survival. Malignancy family history, originating from bone, elevated LDH, ALP and PLT were poor prognostic factors.

P045 (0047) HYPERLIPOPROTEINEMIA AND MARKERS OF ATHEROSCLEROSIS PROGRESSION IN LONG-TERM SURVIVORS OF HODGKIN LYMPHOMA IN CHILDHOOD OR ADOLESCENCE AND IN HEALTHY CONTROLS
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Background: The development of curative therapies has led to a growing population of childhood Hodgkin lymphoma survivors. Cardiovascular events with long-term morbidity and early mortality are among most important adverse events. Seriousness of these late adverse events could be induced only by their early recognition and also by early recommendations of preventive measures for modifiable cardiovascular risk factors.

Methods: The aim of our prospective observation study was to compare the lipid profiles, markers of oxidative stress and endothelial dysfunction together with evaluation of atherosclerotic changes at main carotid artery between the long-term survivors of childhood Hodgkin lymphoma (HL CCS) more than 10 years after the treatment and the matched group of healthy volunteers at the age of 25–40 years.

Patients: Eighty long-term survivors of childhood Hodgkin lymphoma (45 males, 35 females) and eighty age matched healthy volunteers (43 males, 37 females) were recruited. All underwent clinical examination, completed questionnaire collecting information on family history of cardiovascular diseases, subject’s health habits and medical conditions, underwent ultrasound examination of the carotid arteries and their blood specimens were analyzed. Information on previous radiotherapy and chemotherapy in all HL CCS was gathered.

Results: Compared to healthy subjects, Hodgkin lymphoma survivors had significantly higher levels of total cholesterol (5.23±1.09 vs. 4.74 ± 0.76 mmol/l), LDL-cholesterol (3.06 ± 0.92 vs. 2.63 ± 0.71 mmol/l), non-HDL-cholesterol (3.69 ± 1.12 vs. 3.08 ± 0.82 mmol/l), triglycerides (1.42 ± 1.07 vs. 1.02 ± 0.52 mmol/l), glucose (5.28 ± 0.51 vs. 4.92 ± 0.38 mmol/l), insulin (12.21 ± 8.14 vs. 8.37 ± 3.84 μU/ml), HOMA-IR (2.92 ± 2.03 vs. 1.87 ± 0.94), increased IMT (5.47 ± 0.86 vs. 4.86 ± 0.79 mm) as well as markers of arterial stiffness – SI (5.64 ± 2.69 vs. 3.79 ± 1.16) and YEM (1028.88 ± 523.35 vs. 749.97 ± 321.07), all p < 0.01.

Conclusions: HL CCS compared to healthy controls of the same age had significantly higher plasma lipid parameters, higher indicators of insulin resistance as well as markers of atherosclerosis progression and arterial stiffness. Further analyses and correlation of the findings with lifestyle factors and received cancer treatment are ongoing. New recommendations for follow-up examinations and blood analyses together with recommendations for early therapeutic interventions in the HL CCS population are necessary.

P046 (0052) NO CLINICAL SIGNALS OF DRUG – DRUG INTERACTION OF NEPA (NETUPITANT + PALONOSETRON) IN CHL PATIENTS RECEIVING ABVD REGIMEN: A SINGLE-CENTER REAL LIFE EXPERIENCE
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Background: In the setting of cHL, ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) is the most widely used first line chemotherapy and it is well known that this regimen is associated with a high emetic risk (HEC). Netupitant (NETU) is the NK1-RA (neurokinin receptor antagonist) component of NEPA, the first antiemetic drug available as oral fixed combination: NETU (300 mg) + palonosetron (PALO 0.5 mg). Both ABVD drugs and NETU are metabolized by cytochrome P-450 isofrom 3A4 (CYP3A4), but respect
PO48 (0065) MATURE OOCYTES CRYOPRESERVATION: A FEASIBLE FERTILITY PRESERVATION TECHNIQUE IN ADULT HODGKIN LYMPHOMA FEMALE PATIENTS

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The majority of patients with classical Hodgkin lymphoma (HL) will be cured with modern chemotherapy (CT) or combined modality. At least half of the patients failing front-line therapy will be cured by salvage high-dose CT and autologous stem cell transplant. Treatment regimens may include alkylating agents, procarbazine, cisplatin or its analogues, which lead to severe ovarian reserve damage and to infertility, responsible for impairment of quality of life in young female patients of childbearing age. Mature oocyte preservation is one of the most successful fertility preservation techniques and it is admitted by Italian legal rules.

Aims of study: To evaluate in a prospective observational study the rate of acceptability and feasibility of mature oocytes cryopreservation in female patients, aged ≥18 and ≤38 years, with newly diagnosed HL.

Methods: Adult female patients aged ≥18 and ≤38 years with histologically proven untreated HL, were offered gynecological counseling and assessment of ovarian reserve by ultrasound (US) antral follicle count and AMH serum levels measurement. A random start protocol for ovarian hyperstimulation was adopted and retrieval of oocytes was performed with intravenous sedation under US guidance. Time intervals between biopsy, first hematological visit, and CT start were 3 days. All patients who had completed CT (22 out of 23), are alive and in continuous CR at a median follow-up of 34 months (range, 6–60).

Conclusions: Ovarian hyperstimulation with random start protocol and oocytes retrieval, one of the most successful fertility technique, is feasible in young female diagnosed with HL. The median delay in CT start of ≤15 days has no detrimental effect on long-term outcome.
the newly developed BETER guidelines. This study evaluates adherence to the BETER cardiovascular screening guideline and the value of the BETER clinic in finding previously undiagnosed cardiovascular conditions.

Methods: Data on BETER clinic visits were collected on the first 131 HL survivors at the University Medical Centers of Utrecht and Amsterdam and the Netherlands Cancer Institute. Adherence to the cardiovascular screening guideline was assessed for medical history, physical examination, blood tests, ECG and echocardiography. Descriptive statistics were calculated to assess the characteristics of cardiovascular follow up at the BETER clinic.

Results: 123 out of 131 (94%) HL survivors were at risk of CVD based on HL treatment and eligible for cardiovascular screening (Table 1). 21% of patients at risk had already been diagnosed with CVD before the BETER clinic visit. In all 123 survivors the BETER physician (assistant) actively enquired about the presence of cardiovascular risk factors and in 94% about the presence of cardiovascular symptoms. Physical examination to assess cardiovascular risk factors was performed in 76% of survivors. Echocardiography was performed in 98% and ECG in 94% of survivors, while blood tests were done in 86% of survivors. Full CVD guideline adherence was 63%.

Previously undiagnosed cardiovascular conditions were found in 15% of survivors; in 5% of survivors worsening of pre-existing cardiovascular conditions was diagnosed at the BETER clinic. Frequently observed conditions were valve sclerosis (n = 12), aortic valve stenosis (n = 8) and mitral valve insufficiency (n = 5). Heart failure and coronary artery disease were diagnosed less frequently (n = 1 each). 6% of survivors had a subclinical systolic ventricular dysfunction (EF<50%).

Conclusion: Preliminary results show good adherence to the cardiovascular screening guideline. Furthermore, the BETER screening had a substantial yield of actionable conditions. Evaluation is ongoing; at ISHL11 information on follow-up diagnostics and interventions in 250 patients will be presented.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>All survivors at risk of CVD (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at clinic visit, median (IQR)</td>
<td>52 (44-57) years</td>
</tr>
<tr>
<td>Gender, male</td>
<td>50%</td>
</tr>
<tr>
<td>Year of HL diagnosis, median (range)</td>
<td>1997 (1971-2005)</td>
</tr>
<tr>
<td>Age at HL diagnosis, median (IQR)</td>
<td>28 (21-33) years</td>
</tr>
<tr>
<td>Time since diagnosis, median (range)</td>
<td>23 (8-65) years</td>
</tr>
</tbody>
</table>
| Treatment | Anthracyclines (n/years) 72%
Mediastinal RT (n/years) 77%
Cardiovascular disease (n/years) 54% |
| CV/DL cardiovascular disease=1GIRIL interauriculare rangell HUH Hodgkin lymphom RTI radiotherapy |

PO50 (0075) CLINICAL CHARACTERISTICS AND PROGNOSIS ANALYSIS OF EARLY-Stage CLASSICAL Hodgkin Lymphoma

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Aim: To retrospectively analyze the clinical characteristics, outcomes and prognostic factors correlated to early-stage classical Hodgkin lymphoma (cHL).

Methods: 222 patients with early-stage cHL who were initially referred to Peking University Cancer Hospital from January 2008 to January 2018 were included in this study.

Results: Among the 222 patients, 101 cases were female. The median age of onset was 31 (12-77) years. Double-peak pattern was not observed in age distribution. 139 (62.6%) patients were diagnosed as nodular sclerosis subtype, 64 (28.8%) patients were mixed cellularity subtype. Only thirty-eight (17.1%) patients were in stage I, 184 (82.9%) patients presented with B symptoms, 18 (8.1%) patients were in stage II. 47 (21.2%) patients had large mass (the largest diameter ≥20 cm). 150 (67.6%) patients received chemotherapy alone while 72 (32.4%) cases were treated with chemoradiotherapy. The most common regimen was ABVD/AVD/AVDP and was administered in 193 (86.9%) cases. BEACOPP regimen was applied in 14 (6.3%) patients. 15 cases were treated with other regimes. The median amount of chemotherapy was 6 cycles. Complete remission (CR) was achieved in 178 (80.2%) patients and partial remission (PR) in 28 (12.6%) cases after first-line therapy. Only 16 cases did not acquire response after first-line treatment. After a median follow-up time of 39.9 (4–149) months, 10 and 8 cases recurred in CR and PR patients, respectively. 10 (4.5%) patients died. Survival analysis indicated 3-year overall survival (OS) rate of 96% and 3-year progression-free survival (PFS) rate of 87%. The 5-year OS rate and 5-year PFS rate were 93% and 79%, respectively. Univariate analysis showed that B symptoms, large mass, number of involved lymph node area, elevated LDH level and serum β-2-microglobulin were prognostic factors correlated to PFS. Multivariate analysis revealed that large mass and elevated LDH level were independent prognostic factors correlated to PFS.

Conclusions: The overall prognosis of early-stage classical Hodgkin lymphoma was generally good. Large mass and elevated LDH level were independent prognostic factors correlated to PFS in our study.

PO51 (0080) CARDIOVASCULAR DISEASE RISK AFTER TREATMENT-INDUCED PREMATURE OVARIAN INSUFFICIENCY IN FEMALE SURVIVORS OF HODGKIN LYMPHOMA

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Background: Female survivors of Hodgkin lymphoma (HL) treated with alkylating chemotherapy (CT) and/or pelvic radiotherapy (RT) have an increased risk of premature ovarian insufficiency (POI). Among women with a natural menopause, POI has been associated with a 1.6-fold increased risk of overall cardiovascular disease (CVD). However, mixed results have been reported for women with POI after surgical menopause, possibly due to the use of hormone replacement therapy (HRT) or the age at surgery.

Objectives: We examined whether treatment-induced POI increases long-term CVD risk in 5-year HL survivors.

Methods: From a large Dutch cohort of 5-year HL survivors, we selected 918 women who were treated before 41 years of age between 1965 and 2000. Data on HL treatment, menopausal status and cardiovascular events (ischemic heart disease (IHD), heart failure (HF) and valvular heart disease (VHD)) were obtained from medical records, general practitioners and patient questionnaires. CVD risks were estimated with Cox regression models using time-dependent covariates.

Results: After a median follow-up of 24 years, 299 out of 918 women had developed POI (median menopausal age, 34 years (interquartile range 28–37). We identified 463 cardiovascular events in 300 women, of whom 85 developed CVD after POI. POI was not associated with subsequent CVD risk (hazard ratio (HR):0.85, 95% CI 0.62–1.16) compared with a menopausal age of ≥40 years. Also a short duration of intact ovarian function after HL treatment (<5 years) did not increase CVD risk compared to a long duration (>25 years) (HR:0.72, 95% CI 0.44–1.20). Similar results were found in analyses with IHD, HF and VHD as separate outcomes.

Conclusions: POI and duration of post-treatment intact ovarian function did not affect CVD risk in HL survivors, suggesting that an early artificial menopause does not increase CVD risk. Future studies should investigate whether specific genes predispose to both POI and CVD development, or whether an unfavorable CVD risk profile before menopause contributes to POI.

PO54 (0092) PREGNANCY IN PATIENTS IN COMPLETE REMISSION AFTER HODGKIN LYMPHOMA: CLINICAL FEATURES AND OUTCOME

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As the number of survivors of young female Hodgkin’s lymphoma (HL) increases, it is becoming more common to manage the pregnancies of women who have a history of exposure to chemotherapies and radiation therapy. Many patients and clinicians are worried that pregnancy after the diagnosis of HL may increase the risk of relapse, despite a lack of empirical evidence to support such concerns.

In the present study we included 77 women who received a diagnosis of HL between 2006 and 2015 and who were younger than 40 years of age and were in complete remission and alive without relapse > 2 years after treatment.

Among the 77 women with HL, 37 (48%) were nulliparous throughout follow-up, 32 (42%) were parous but had no pregnancies during follow-up, and 8 (10%) had a pregnancy during follow-up. 13 (17%) tried to become pregnant; 5/13 (39%) without success; 8/13 (61%) became pregnant with the birth of eight healthy children. The overall pregnancy rate was 10%. The median time from the end of the therapy to pregnancy was 50 months (range 25–72 months) and the cumulative incidence of pregnancy at 70 months was 39%. Median age at pregnancy was 27 years (range 20–37 years).

In total, 2 relapses occurred during follow-up: none occurred in women with a recent pregnancy. Women exposed to a recent pregnancy had a relapse rate lower than that of women without exposure, although this difference was not statistically significant.

Conclusion: We found no evidence of significant impairment of the fertility of female HL long term survivors and no evidence that a pregnancy increases the relapse rate among women whose HL is in remission. Survivors of HL need to consider a range of factors when deciding about future reproduction.

P055 (0096) HEALTH-RELATED QUALITY OF LIFE (HRQL) TRAJECTORIES DURING TREATMENT FOR ADVANCED STAGE PEDIATRIC HODGKIN LYMPHOMA (HL)

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Background: The treatment of advanced stage HL typically includes dose-dense chemotherapy with or without involved field radiation. However, little is known about the HRQL of pediatric patients during initial treatment. We describe the HRQL trajectory over time by child and parent-proxy rater and examine baseline patient characteristics associated with the trajectory.

Methods: Children and adolescents, ages 5–17.9 years newly diagnosed with advanced stage HL and enrolled in Children’s Oncology Group AHOP studies A9131 and A9132, and their parents were co-rolled in an embedded study to assess HRQL (n = 310). Children (age ≥11 years) and parent proxies (of children 5–17.9 years) reported on the child’s global HRQL using the Child Health Rating Inventories (CHRIs) at four times: (1) baseline, (2) cycle 2, (3) cycle 3, and (4) end of therapy, approximately 6–7 months following initial diagnosis. The 7-item CHRIs-Global yields scores that range from 0–100, with higher scores indicating better HRQL. A repeated measures linear regression model was fit with categorical time (reference, baseline), rater, child race, ethnicity, and continuous age. An interaction of rater and time was tested and predicted HRQL. A repeated measures linear regression model was fit with categorical time (reference, baseline), rater, child race, ethnicity, and continuous age. An interaction of rater and time was tested and predicted HRQL.

Results: Median mean age of 64 females and 54 males at diagnosis was 29 (13–74) and 41 (21–81) years at completion of the CANTAB in-vestigation; this examination took place 11 years (0.5–44) after diagnosis. 52.5% of all patients examined showed cognitive decay. In 35% (42/118) of patients it was attention that suffered, working memory and planning were damaged in 25%, (30/118) while visual memory was affected in 22% (26/118 patients). All three functions showed significant correlation with age at diagnosis and at the time of the examination. A close correlation was found between attention and inactive employment and radiation therapy on the one hand and another correlation between working memory and planning and disability pensioner and inactive status on the other. Visual memory showed a close correlation with disability pension and inactive employment status and the effects of persistent drug use on the central nervous system.

Conclusions: Our results draw attention to the fact that, like with other malignant diseases, cognitive decay is a real problem in patients with HL. In our patients damage to the attention function was the most de-tectable. Our investigation suggests that patients with inactive employment status require enhanced attention. Their cognitive function and, through that, their quality of life can be improved by their return to work if possible or by the use of cognitive therapy.
Introduction: Treatment protocols for Hodgkin’s lymphoma patients contain severe and multiple courses of chemotherapy and medical manipulations which can be a source of neurological, mental and psychological disturbances. In particular neurocognitive impairments can occur during treatment period and early stages of remission. Subjective complaints confirm that HL survivors lower cognitive functioning compared to healthy subjects, however qualitative objective research are rare.

Objectives: Research cognitive functioning of HL patients by BACS (Brief Assessment of Cognition in Schizophrenia) and analysis the specifics of cognitive functioning of patients with HL to develop prospective psychosocial rehabilitation programs.

Methods: Patients with HL (N = 22, 12 females, mean age 32y.) were observed. The procedure of examination included: pathopsychological examination, assessment patients with BACS. Patients were assessed with: PANNs, scales evaluating test execution strategies (from TOL-DX) and expert scales (from WCST).

Results: Qualitative analysis of pilot research showed that: 20% of patients have difficulties in performing the subtests «Verbal Memory», «Digit Sequencing» (working memory) and «Verbal Fluency» (BACS). 35% of patients were observed decrease in the «Symbol Coding» subtest scores (visual-motor coordination). 10% of patients have problems in performing the subtest «Tower of London» (problem-solving skills). Only about 50% of patients managed with the task «Proverbs» successfully and with less than 75% with the task «Similarity». 34% percent of patients almost cannot solve the task «Exclusion of object» (BACS (T-Scores: average mean, st.dev, min and max value were analysed with SPSS).

Conclusions: It is supposed that patients with HL have partial cognitive dysfunction as a side effect of chemotheraphy and distress (anxiety, depression, PTSD etc.). They have impairments in abstract thought, especially problems with definition of figurative sense and the decrease in the level of making general conclusions. Although it is difficult connect such cognitive decline to chemotheraphy or distress - psychosocial interventions can be beneficial to adopt patients to somatic/psychologcal changes (fatigue, depression, self-esteem, professional and social isolation) and improve their quality of life. Further research data can be used to develop neuropsychological cognitive rehabilitation for patients with evident cognitive deficit.

PO59 (0114) AA AMYLOIDOSIS CAUSING NEPHROTIC SYNDROME IN TWO PATIENTS WITH HODGKIN LYMPHOMA

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Background: The incidence of nephrotic syndrome in Hodgkin lymphoma (HL) is less than 1%. The principal glomerular pathology is minimal change and systemic AA amyloidosis associated with HL is exceptionally rare. Here we describe two patients with HL and AA amyloidosis. Case-1. A 24-year-old male with an remarkable past medical history was admitted because of fever, edema, weight loss and fatigue. Nephrotic range proteinuria was detected (9.7 g/day). Conglomerates of infradiaphragmatic lymph nodes were seen on imaging. Renal biopsy showed glomerular AA amyloid deposition and core-needle biopsy was consistent with HL. He was considered to have stage IE disease and ABVD was started. After the first cycle a critical condition with generalized gross edema developed and was treated with diuretics and albumin infusions. After 6 cycles of ABVD he achieved CR. Colchicine and an angiotensin converting enzyme (ACE) inhibitor were initiated after chemotherapy. Nine years and 3 months off therapy he is well and no recurrence of proteinuria or HL has been noted. Case-2. A 31-year-old male was diagnosed with stage IIIB HL of the mixed cellularity type. CR was obtained following 8 ABVD cycles. After 6 years he experienced HL relapse considered as stage IIIB again with concomitant nephrotic range proteinuria (9.3 g/day). Bone marrow biopsy revealed AA amyloidosis. Patients were put on platinum based salvage therapy followed by Dexam-HEAM for stem cell mobilization during which he developed septic shock and admitted to an intensive care unit. Colchicine and an ACE inhibitor were initiated after chemotherapy. He was considered too fragile for transplantation and was followed without therapy. Currently 10 years since off therapy he remained in CR although proteinuria continues during follow-up evaluations. Conclusions. The timing of presentation of AA amyloidosis in respect of HL varies in literature. AA amyloidosis was detected during the first presentation in one patient and during HL relapse in the other. Selective serious albuminuria with normal renal function was the typical manifestation in both patients. Risk of serious complications during treatment (septic shock and development of AA amyloidosis in our patients) might be increased for HL patients with AA amyloidosis. Both patients achieved long-lasting CRs and reversal of proteinuria following HL remission occurred in one of the patients.

PO60 (0122) THE RECIPROCAL RELATION BETWEEN CANCER-RELATED FATIGUE AND PHYSICAL AND PSYCHOSOCIAL FUNCTIONING IN SURVIVORS OF HODGKIN LYMPHOMA

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1JWTH Aachen University, Aachen, Germany, 2German Hodgkin Study Group (GHSG), University Hospital of Cologne, Germany

Shared first authorship.

Background: Cancer-related fatigue (CRF) is among the most distressing symptoms reported by cancer survivors. It often persists for years after treatment, compromising the quality of life (QoL) of survivors. There is some evidence for a correlation between CRF and functional health (FH) based on cross-sectional data. The aim of this study is to investigate the directional effects and the complex interplay between CRF and FH in survivors of Hodgkin lymphoma (HL) using longitudinal data.

Methods: Data of N = 3595 survivors from year 1 to year 5 after the end of treatment of the fifth study generation (HD13–15) of the German Hodgkin Study Group (GHSG) was analysed. Bivariate latent curve models with structured residuals (LCM-SR, Figure 1) were utilized to simultaneously model how the reciprocal relation between the two
Abstract Book for the 11th International Symposium on Hodgkin Lymphoma

constructs unfolds over time across and within individuals. CRF and FH were both measured with the EORTC QLQ-C30. Assessed FH domains were physical, cognitive, emotional, social and role functioning.

Results: The LCM-SRs had an adequate model fit (Chi-square 315.61–417.46, df = 50, p < .001, RMSEA = .04–.05, CFI = .98–.99, TLI = .98–.99). On the between-person level, CRF and each FH domain were strongly negative correlated (range r = −.77 to r = −.87), indicating that persons with higher FH scores have lower CRF scores on average. On the within-person level, earlier CRF scores negatively and significantly predicted subsequent scores of each FH domain (small effects, range i = −.04 to i = −.11). In the same way, earlier scores of each FH domain predicted subsequent scores of CRF (small effects, range k = −.04 to k = −.13). Social and role functioning were in a balanced reciprocal relation with CRF, meaning that time-specific within-person improvements of social and role functioning reduced subsequent CRF and vice-versa. Time-specific within-person effects of physical, cognitive and emotional functioning on subsequent CRF scores were stronger than vice-versa, indicating that an improvement of physical, cognitive and emotional functioning reduces CRF more than the other way around.

Conclusion: Our analysis reveals a complex reciprocal relationship between CRF and FH. To fully depict the complex interplay, distinct measures of social and role functioning reduced subsequent CRF and QoL for HL survivors.

P061 (0125) CHEMOTHERAPY-INDUCED POLYNEUROPATHY IN PATIENTS WITH HODGKIN LYMPHOMA TREATED WITH VINCA-ALKALOIDS

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) represents one of the most worrisome and common long-term adverse effects of chemotherapy treatment of cancer. In patients treated with vinca-alkaloids (V-A), the clinical manifestation is mainly sensory and may affect predominantly small sensory fibers. The aim was to assess the incidence of CIPN in patients treated with V-A and compare treatment regimens and the diagnostic validity of several tests and methods.

Methods: A group of 26 patients (18 men, 8 women, median age 36) with Hodgkin lymphoma (HL) underwent detailed clinical neurological examination, pain status, routine electromyography/nerve conduction studies (EMG/NCS) and comprehensive quantitative sensory testing protocol (QST) before and 6 months after the end of the administration of anti-cancer V-A chemotherapy (BEACOPP; “2+2” regimens). Results: At the follow-up examination, fourteen patients (54%) reported some sensory symptoms and/or neuropathic pain in lower (11 cases) and/or upper (8 cases) extremities. There was an insignificant trend to higher incidence of clinical symptoms in patients treated with vincristine (60%) compared to those treated with the combination of vinblastine and vincristine (33%) (p = 0.25, not significant probably due to low numbers of patients in both the subgroups). The symptoms were usually of mild to moderate intensity. In upper extremities, the symptoms mostly corresponded with clinically symptomatic carpal tunnel syndrome. The EMG/NCS examination confirmed polyneuropathy in 13 patients (50%) (8 symptomatic, 5 asymptomatic), while clinical examination displayed only minor abnormalities in two of the symptomatic individuals. Twenty-two patients (84%) displayed at least one new QST abnormality in feet (and 9 in hands), most frequently in thermal sensation and thermal pain modalities. Some abnormalities relevant to peripheral nerve dysfunction in any of the methods used in this study were found in 88% of HL patients treated with V-A.

Conclusions: Symptoms of CIPN persist at least 6 months after the end of V-A chemotherapy in about 54% of HL patients. Clinical neurological examination is the least sensitive method used for confirmation of peripheral neuropathy in these patients, while both the EMG/NCS and QST reveal neuropathy more frequently. Some abnormalities of peripheral nerve function can be found even in asymptomatic individuals.

P062 (0134) LONG TERM HEALTH CARE USE IN RELAPSED AND NON-RELAPSED PAEDIATRIC AND YOUNG ADULT HODGKIN LYMPHOMA PATIENTS – A POPULATION-BASED COHORT STUDY FROM SWEDEN AND DENMARK

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Methods: We used nation-wide registers to assess number of inpatient and specialist outpatient visits for 1048 consecutive young adult (≤25 years) HL-patients diagnosed 1990–2010 in Sweden and Denmark and for 5175 country, age and gender-matched comparators. Study participants were followed up to 24 years. Relapsing (n = 140, 12%), non-relapsing patients (n = 899, 87%), and comparators were compared for the burden of health care use excluding first year after diagnosis. Means of hazard ratios (HRs) from Cox proportional hazard analyses for the different indications for the first subsequent in- and outpatient visits were classified according to ICD-10 chapters.

Results: The distribution of health care use was uneven among the HL survivors, 10% of the patients accounted for approximately 80% of all bed-days, and 50% accounted for approximately 90% of all outpatient visits. More than half of non-relapsing patients (n = 533, 55%) had no hospitalisations during follow-up, i.e. beyond the first year after diagnosis, whereas this was the case only for 24% (n = 30) of relapsed patients, beyond the first year after relapse. Mean number of bed days for patients having one or more hospitalization was: 10 for comparators, 11 for non-relapsed patients and 42 for post-relapsed patients. Significantly increased HRs were noted among relapsed patients compared with non-relapsed patients for indications of health care use pertaining to a broad range of diseases (infections, blood disorders, circulatory, respiratory, digestive, genitourinary, skin diseases, musculoskeletal and symptoms).

Conclusions: In the absence of relapse, the majority of young HL survivors experienced no or few inpatient bed-days. In contrast, subsequent to HL relapse, patients experienced increased health care use across a broad panorama of side effects. These findings challenge the impression of high morbidity among HL survivors in general, and render relapse-status important in investigations aimed at predicting late effects.

P063 (0144) COGNITIVE IMPAIRMENT, STRUCTURAL AND FUNCTIONAL BRAIN MORPHOLOGICAL SEQUELAE OF HODGKIN LYMPHOMA TREATMENT, FIRST INTERIM RESULTS OF ONGOING TRANSLATIONAL STUDY

Tomas Koszak1, Jiri Horacek2, Heidi Mockova, Lubica Gaherova1, Dan Fayette3, Lucie Geislerova, Ivana Karlova, Jana Markova1
1Authors contributed equally.

Background: Late adverse effects of treatment are a matter of great importance for young Hodgkin lymphoma (HL) survivors. It is not well described how late adverse effects are distributed among different HL survivors and whether the problem is limited to a minority of patients when using contemporary treatment protocols. We therefore investigated the distribution of long-term health care use among relapsed and non-relapsed HL-survivors contrasted to comparators.

Methods: We used nation-wide registers to assess number of inpatient bed-days and specialist outpatient visits for 1048 consecutive young adult (≤25 years) HL-patients diagnosed 1990–2010 in Sweden and Denmark and for 5175 country, age and gender-matched comparators. Study participants were followed up to 24 years. Relapsing (n = 140, 12%), non-relapsing patients (n = 899, 87%), and comparators were compared for the burden of health care use excluding first year after diagnosis. Means of hazard ratios (HRs) from Cox proportional hazard analyses for the different indications for the first subsequent in- and outpatient visits were classified according to ICD-10 chapters.

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3rd Faculty of Medicine, Charles University, Prague, University Hospital Krolovke Vinohrady, Prague, National Institute of Mental Health, Czech Republic

Only limited data on post-chemotherapy cognitive impairment (PCCI) are available for lymphoma in adults. Our translational project primarily focuses on the cognitive deficits related to the treatment of Hodgkin lymphoma, its structural and functional brain morphological sequelae and pathogenesis. The primary goal of the study is to establish the effect of HL and chemotherapy (2–4 cycles of chemotherapy versus 6 cycles) on cognitive performance, brain structure (GM volume, DTI) and function (fMRI connectivity). The patients are examined before the therapy, 6 and 12 months later, respectively. An animal study parallels the clinical one. From April 2016 have been included 52 patients. We analyzed data from full neuropsychological panel in first 13 patients who underwent initial examination and the corresponding follow up. Five patients were treated by less intensive therapy (2xABVD + IF Rt), 8 patients underwent intensive treatment with 6xBEACOPPesc. Full panel consisted of: Rey’s test (RAVLT), Rey-Osterriethova/Taylor’s test (ROCF), Continuous Performance Test (CPT), Wechsler Memory Scale (WMS), Trial Making Test TMT B, Stroop’s test, Word Production Test, selected subtests of Wechsler’s scale for adults (WAIS-III). Having so far limited number of subjects we analysed results with nonparametric statistics (Man-Whitney U test, Wilcoxon nonparametric test).

Results: no difference between the group of less intensive versus intensive treatment was noted at the start of the therapy. After 6 months from the start of treatment there was a difference in TMT B test (U = 0,001, p = 0,008). The test measures the ability to quick task switching and in prolonged time was noted in the less intensive therapy group. In both groups we found a decline in draw test ROCFT (Z = −2,68; p = 0,007) and in the repeated number subtest WAIS-III (Z = −2,23; p = 0,026). Conclusion: in patients with HL after the 1. line therapy we found impairment in the task switching ability 6 months after the treatment initiation in those who were treated with either 2xABVD + IF Rt or 2xABVD + 2xBEACOPPesc + IF Rt, not in patients treated with 6xBEACOPPesc. We could speculate that ABVD compouns are involved in the result but we certainly have to wait after larger ammount of subject is analysed. The decline in both ROCFT and WAS-III tests in both groups might reflect a worsened operation memory, but as in TMT B treatment was noted at the start of the therapy. After 6 months from the start of treatment there was a difference in TMT B test (U = 0,001, p = 0,008). The test measures the ability to quick task switching and in prolonged time was noted in the less intensive therapy group. In both groups we found a decline in draw test ROCFT (Z = −2,68; p = 0,007) and in the repeated number subtest WAIS-III (Z = −2,23; p = 0,026). Conclusion: in patients with HL after the 1. line therapy we found impairment in the task switching ability 6 months after the treatment initiation in those who were treated with either 2xABVD + IF Rt or 2xABVD + 2xBEACOPPesc + IF Rt, not in patients treated with 6xBEACOPPesc. We could speculate that ABVD compouns are involved in the result but we certainly have to wait after larger ammount of subject is analysed. The decline in both ROCFT and WAS-III tests in both groups might reflect a worsened operation memory, but as in TMT B test we have to wait for more matured results.

P064 (0146) CAUSE-SPECIFIC MORTALITY AMONG HODGKIN LYMPHOMA SURVIVORS UP TO 35 YEARS AFTER TREATMENT

Simone de Vries1, Michael Schaapveld1,2, Pieternella J. Lugtenburg3, Anna M. van Eggermond1, Leontien C. M. Kremer10, Marieke W. J. Louwman2, Marnix Lybeert11, Jan Paul de Boer12, Laurien A. Daniëls4, Eefke J. Petersen5, Josée M. Zijlstra7, D. Neves, A. Roque, C. Afonso, A. Pinto, D. Motã, R. Guilherme, D. Varenius, Pregnancy, observational study.

Background: Hodgkin lymphoma (HL) treatment has been associated with long-term increased risk of adverse events, including second malignancies, cardiovascular disease (CVD), and infections. We assessed cause-specific mortality by treatment period and follow-up interval, and by stage and primary treatment modality.

Methods: Our multicenter cohort included 4,663 HL patients, diagnosed before age 51, and treated between 1965–2000. Cumulative cause-specific mortality by treatment period and follow-up interval, and by stage and primary treatment (irrespective of relapse treatment) was estimated with other causes of death as competing risk. Results: After a median follow-up of 18.6 years since HL treatment, 1,848 patients had died (36.0% from HL, 24.5% from solid tumors, 16.8% from CVD). Mortality risk for causes of death other than HL remained increased throughout follow-up: for 35 years risk was 4.7-fold increased compared to the general population. At 30 years, cumulative all-cause mortality amounted to 47.8%, with 14.8% 30-year mortality from HL (Table 1). Both all-cause and HL mortality were lower in patients treated 1989–2000 compared with 1965–1976: 20-year all-cause mortality 44.3% vs. 19.9%, and 20-year HL mortality 29.2% vs. 5.3%, respectively. No decrease in cumulative mortality in more recent treatment periods was observed yet for solid tumors and CVD. For stage I-III, 35-year cumulative HL mortality according to primary treatment modalities was 7.2% for radiotherapy (RT) alone, 11.3% for chemotherapy (CT) alone, and 11.4% for RT+CT. By contrast, 35-year cumulative mortality from all other causes varied considerably between treatments, 48.4% for RT, 17.9% for CT, and 40.0% for RT+CT. For stage III-IV, 35-year HL mortality was higher: 31.9% for RT, 25.8% for CT, and 23.9% for RT+CT, while 35-year mortality from other causes was 46.0%, 26.8%, and 44.0% for the different primary treatments, respectively.

Conclusion: Long-term HL survivors experience elevated risks from causes of death other than HL for at least 35 years after treatment. Whereas HL mortality substantially decreased in more recent treatment periods, solid tumor and CVD mortality did not. Overall, we observed lower risks for HL and other cause mortality in patients primarily treated with CT only. However, this study was not based on data from randomized trials, implying that conclusions with respect to harms and benefits of primary treatment modalities warrant cautious interpretation.

Table 1. Cumulative cause-specific mortality by treatment period and follow-up duration

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<td></td>
<td>4,663</td>
<td>(n=1,848)</td>
<td>(n=1,848)</td>
<td>(n=1,842)</td>
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<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
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<tr>
<td>10 years</td>
<td>17.9%</td>
<td>31.5%</td>
<td>19.1%</td>
<td>8.0%</td>
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<tr>
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<td>30.1%</td>
<td>44.3%</td>
<td>31.6%</td>
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<tr>
<td><strong>Hodgkin lymphoma mortality</strong></td>
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<tr>
<td>10 years</td>
<td>12.5%</td>
<td>25.6%</td>
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<tr>
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<td>14.8%</td>
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<td><strong>Solid tumor mortality</strong></td>
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<td>35 years</td>
<td>17.4%</td>
<td>14.2%</td>
<td>15.9%</td>
<td>n/a</td>
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<td><strong>Cardiovascular mortality</strong></td>
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<tr>
<td>10 years</td>
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<td>1.2%</td>
<td>0.6%</td>
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<tr>
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<tr>
<td>35 years</td>
<td>10.5%</td>
<td>11.5%</td>
<td>9.0%</td>
<td>n/a</td>
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<tr>
<td><strong>Mortality other than Hodgkin lymphoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10 years</td>
<td>5.4%</td>
<td>5.9%</td>
<td>6.5%</td>
<td>4.2%</td>
</tr>
<tr>
<td>20 years</td>
<td>15.6%</td>
<td>15.2%</td>
<td>16.7%</td>
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<tr>
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<td>35 years</td>
<td>42.4%</td>
<td>37.9%</td>
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</table>

PO065 (0150) ELEVATED NEUTrophil-TO-MONOCYTE RATIO IS ASSOCIATED WITH DECREASED OVERALL SURVIVAL AT 5 YEARS IN CLASSIC HODGKIN LYMPHOMA

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Background: Classical Hodgkin lymphoma (cHL) has a long-term outcome under standardized treatment. However, about 25% of the patients (pts) will experience relapse or be refractory to the initial therapy. Prognostic biomarkers might help identify this risk population. Different studies have analysed peripheral blood white cell count as promising biomarkers with no well-established conclusion.

Aims: Analyse the impact of peripheral blood absolute neutrophil-to-monocyte ratio (PMR) and platelet/monocyte count ratio (PMR) at diagnosis in progression free survival (PFS) and overall survival (OS) in cHL.

Methods: We perform a retrospective analysis of cHL pts treated in our institution, between 1990 and 2017. The best cut-off point was stipulated as 15.9 for NMR, 1.9 for LMR and 633.7 for PMR, by using receiver operating characteristic (ROC) curves.
**P067 (0168) VERY LATE RELAPSES (VLRs) IN HODGKIN LYMPHOMA (HL) OCCURRING ≥ 5 YEARS AFTER INITIAL TREATMENT WITH CHEMOTHERAPY ± RADIOTHERAPY (CT ± RT): PATTERN OF RISK OVER 35 YEARS AND THE SIGNIFICANCE OF HISTOLOGY**

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**Background:** Despite significant improvements in the outcome of HL, VLRs (≥5 years after initial CT ± RT) do occur. Data on VLRs after standard CT ± RT are very limited, including our initial report and the recent large observational GHSG study. However, the incidence and risk factors of developing VLRs in HL require further evaluation.

**Aims:** To examine the incidence and risk factors of developing VLRs in patients with HL, who remain in first complete remission (CR1) for ≥5 years from treatment initiation.

**Methods:** Retrospective study of 931 adult patients, diagnosed with HL and remained in CR1 for ≥5 years after treatment initiation (follow-up exceeding 35 years). Anthracycline-based chemotherapy was administered in 89% of patients [mainly A (E) BVD], whereas 11% received MOPP. Survival analysis was performed using competing-risk regression models.

**Results:** VLRs occurred in 25/931 patients (2/52 relapsed as composite lymphoma) and the most delayed relapse occurred after 35 years. The distribution and cumulative incidence (CI) of VLRs are presented in the table. CI rose linearly over time after 5 years and the annual incidence rate was roughly estimated at 0.40% per person-year. After treatment with ABVD CT ± RT, the CI of VLR at 20 and 30 years, was estimated at 7.2% and 9.7% respectively. In multivariate analysis, independent protective prognostic factors were nodular sclerosis (NS) histology [hazard ratio (HR) = 0.41, p = 0.007], anthracycline-based (ABVD-type) CT ± RT vs MOPP-type (HR = 0.49, p = 0.04) and CT+RT vs CT (HR = 0.43, p = 0.03). Among 830 patients treated with anthracycline-based CT, independent protective prognostic factor was the NS histology (HR = 0.33, p = 0.006); age ≤45 years was of borderline significance (HR = 0.57, p = 0.14).

**Conclusion:** This is the 2nd largest study aiming to determine the incidence of VLRs in HL, providing the longest follow-up. We confirm the linear pattern of VLR up to 20 years after ABVD-like CT ± RT, but we also highlight that VLRs can occur up to at least 35 years after initial treatment. VLRs were more common after MOPP than after ABVD. Patients with non-NS histology had an increased risk of VLRs with mixed cellularity being the most adverse. The final results with further follow-up and 56 VLRs will be presented at the Meeting.
Advanced Stages

T021 (0147)  B-CAP (BRENTUXIMAB VEDOTIN, CYCLOPHOSPHAMIDE, DOXORUBICIN AND PREDNISONE (LO) TREATMENT IN PATIENTS WITH ADVANCED STAGE HODGKIN LYMPHOMA: RESULTS OF A PHASE II INTERGROUP TRIAL BY THE GERMAN HODGKIN STUDY GROUP (GHSG) AND THE NORDIC LYMPHOGRPAHMA GROUP (NLG)

Alexander Fossa1, Boris Böll2, Helen Goergen3, Peter Kamper4, Sirpa Leppä5, Daniel Molin5, Julia Meissner6, Ellen Ritter6, Jacob Haaberg7, Martin Hutchings7, Michael Fuchs8, Andreas Engert9, Carsten Kobe5, Peter Borchmann5, on behalf of the German Hodgkin Study Group and the Nordic Lymphoma Group

1Department of Oncology, Oslo University Hospital, Oslo, Norway, 2Department of Internal Medicine, German Hodgkin Study Group, University Hospital of Cologne, Cologne, Germany, 3Department of Hematology, Aarhus University Hospital, Aarhus, Denmark, 4Helsinki University Hospital Cancer Centre and University of Helsinki, Department of Oncology, Helsinki, Finland, 5Experimental and Clinical Oncology, Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden, 6Fifth Department of Internal Medicine, University Hospital of Heidelberg, Heidelberg, Germany, 7Internal Medicine II, Hematology and Internal Oncology, Jena University Hospital, Jena, Germany, 8Department of Hematology, Odense University Hospital, Odense, Denmark, 9Department of Hematology, Rigshospitalet, Copenhagen, Denmark, 10Department of Nuclear Medicine, University Hospital of Cologne, Cologne, Germany

Background: About 20% of patients diagnosed with classical Hodgkin lymphoma (cHL) are 60 years or older. They have a comparatively poor prognosis, particularly when presenting in advanced stages. In previous trials, older patients did not benefit from intensified regimens in terms of overall survival due to a high toxicity-related death rate. In order to improve tolerability, we developed the B-CAP regimen (brentuximab vedotin, cyclophosphamide, doxorubicin and prednisolone), incorporating the antibody-drug conjugate brentuximab vedotin into a CHOP-based chemotherapy backbone. We report the first results of our multicenter phase II study evaluating B-CAP in older cHL patients.

Methods: We recruited patients with newly diagnosed advanced-stage cHL aged 60 years or older and eligible for polychemotherapy (Cumulitive Illness Rating Scale for Geriatrics ≤5 in total and ≤5 per organ system) in five European countries. Treatment consisted of six cycles B-CAP; radiotherapy to Positron Emission Tomography (PET) positive sites was performed early during therapy in patients with advanced-stage Hodgkin lymphoma. Apart from patients with a transformation to a high-grade B-cell lymphoma, patients with no adequate response to six cycles of B-CAP continued with standard treatment. Patients with a complete remission after six cycles of B-CAP, aiming at excluding an ORR of 60% or less via a one-sided 95% confidence interval, all patients completing interim staging after two cycles were considered eligible.

Results: Between November 2015 and September 2017, 50 patients were recruited, of whom one withdrew consent before start of treatment. Of the remaining 49, 26 patients (53%) were male, age 70 (96%) had stage III-IV disease, and the median age was 66 years (range 60–84). One patient died from infection before interim staging, and 48 patients were eligible for the primary endpoint. There were no further treatment-related deaths. The CT-based ORR was 98% (one-sided 95% confidence interval 91–100%) with 21 patients having CR, 26 patients having PR, and one patient having progressive disease in restaging after completion of B-CAP therapy. All patients with CT-based CR and 10/26 patients with PR had a negative PET (Deauville ≤4), resulting in a complete metabolic response rate of 65%. Dose delivery was high with only two patients stopping treatment after four and five cycles, respectively, due to toxicity. Progression-free and overall survival as well as safety data will be presented.

Conclusion: B-CAP is feasible and effective in patients older than 60 years with advanced-stage cHL and should be subject of further research.

P069 (0008)  JUNB, DUSP2, SGK1, CREBBP AND SOCS1 ARE FREQUENTLY MUTATED IN T-CELL/HISTIOCYTE RICH LARGE B-CELL LYMPHOMA

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T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is a rare aggressive lymphoma showing histological overlap with nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). Despite differences in tumor microenvironment and clinical behavior, the tumor cells of both entities show remarkable similarities, suggesting that both lymphomas might represent a spectrum of the same disease. The aim of our study was to analyze if genes recurrently mutated in NLPHL are also mutated in THRLBCL. A targeted re-sequencing approach for 67 genes revealed that the mutational landscapes of THRLBCL and NLPHL are highly related, both frequently harboring mutations in JUNB, DUSP2, SGK1, CREBBP and SOCS1. JUNB, DUSP2, SGK1 and SOCS1 showed an increased number of variants per case and were affected by mutations more frequently in THRLBCL and the histopathological NLPHL variants than in typical NLPHL. Mutations in these four genes were highly enriched for somatic hypermutation (SHM) hotspot sites suggesting an important role of aberrant SHM in the pathogenesis of NLPHL and THRLBCL. THRLBCL and the histopathological NLPHL variants might therefore have longer or stronger exposure to SHM than typical NLPHL. Taken together, the present study further supports a close relationship of THRLBCL and NLPHL by showing that they share key highly recurrent genetic lesions.

P069 (0013)  EVALUATION OF CLINICAL CHARACTERISTICS IN PATIENTS WITH INTERIM-PET NEGATIVE BUT POSITIVE END OF TREATMENT PET. DATA FROM THE PROSPECTIVE HD08–01 FII STUDY


On behalf of Fondazione Italiana Linfomi

Purpose: The clinical impact of positron emission tomography (PET) performed early during therapy in patients with advanced-stage Hodgkin lymphoma has confirmed its impact in progression free survival. It is disappointing the observation of a group of patients with negative interim-PET (i-PET) but with a positive PET at the end of induction therapy (e-PET). These patients underline that i-PET is not a perfect instrument and it could be very important to analyze their clinical or biological characteristics to identify them.

Patients and Methods: The phase II part of the multicenter HD0801 study involved 519 patients with advanced-stage de novo Hodgkin lymphoma who received an initial treatment with ABVD and underwent a i-PET. Patients with positive i-PET shifted to a salvage therapy and those with negative i-PET continued with standard treatment. Patients with negative i-PET were evaluated for response and patients with a positive e-PET were moved to a salvage therapy. The aim of this study was to evaluate clinical and biological characteristics of these patients.

Results: In all 409 were i-PET negative. Among them 16 interrupted the therapy for different causes, therefore 393 patients were evaluated with e-PET, 354 were negative and 39 were positive. Sixteen out 39 were submitted to a diagnostic biopsy and 15 were confirmed as HD; 23 did not performed biopsy due to technical difficulties or decision of the clinicians. Seventeen out 39 e-PET were reviewed according Deauville Score and in sixteen it was confirmed positive (10 DS 5, 6 DS 4) in 1 case was unvaluable. With the exception of LDH value at diagnosis no clinical characteristics were significantly different in comparison with e-PET negative patients. The survival of e-PET positive patients was very disappointing 78% at 36 months in comparison either with negative e-PET or with positive i-PET.

Conclusion: Positive e-PET represents a very bad prognostic event even in comparison with i-PET positive patients salvaged with intensified therapy. We must consider carefully this little group of patients in which
Despite negative i-PET, we observe an early progression. These group of patients do not have specific clinical characteristics at diagnosis, probably biological and pathological markers could be associated with i-PET to increase the predictive power and in particular to reduce the false negative or, finally, more sensitive PET evaluation with MTV and GTV evaluation could reduce the false negative i-PET.

**P071 (0024) A MULTICENTER PHASE 2 STUDY OF SEQUENTIAL BRENTUXIMAB VEDOTIN AND AVD CHEMOTHERAPY FOR OLDER PATIENTS WITH UNTREATED CLASSICAL HODGKIN LYMPHOMA**

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*Authors contributed equally

**Purpose:** To improve the curability of older patients (pts) with newly diagnosed Hodgkin lymphoma (HL).

**Methods:** We conducted a multicenter phase 2 study administering brentuximab vedotin (Bv) sequentially before and after standard doxorubicin, vinblastine and dacarbazine (AVD) for untreated HL pts ages ≥60 years (NCT01476410). After 2 ‘lead-in’ doses of single-agent Bv (1.8 mg/kg q3 weeks), pts received 6 cycles of AVD chemotherapy, followed by 4 consolidative doses of Bv in responding pts. Kaplan-Meier estimates were summarized for progression-free survival (PFS) with progression or relapse and death considered as events and they were also summarized for overall survival (OS) with deaths considered as events. Univariable and multivariable Cox proportional hazard regression models accounting for competing risks were also fit to examine variables affecting PFS.

**Results:** Characteristics included median age 69 years (60–88); 63% male; median ECOG performance status 1; 82% stage III/IV disease; 60% IPS 3–7; median Cumulative Illness Rating Scale-Geriatric (CIRS-G) co-morbidity score 7 (52% grade 3/4); and 12% had baseline loss of instrumental activities of daily living (IADL). Thirty-seven of 48 pts (77%) completed 6 AVD cycles and 35 pts (73%) received at least 1 Bv consolidation. Overall response and complete remission rates after initial Bv lead-in were 18/22 (82%) and 8/22 (36%), respectively; and 40/42 (95%) and 34/42 (90%) respectively, after 6 AVD among 42 response-evaluable pts. For safety, 20 of 48 pts (42%) experienced a grade 3/4 adverse event, most commonly neutropenia (44%); febrile neutropenia and pneumonia (8%); diarrhea (6%); and neuropathy (4%); 33% had grade 2 peripheral neuropathy, the majority which were reversible. By intent-to-treat for all pts with median follow-up of 23 months (2–48 months), the 2-year PFS was 84% with 2-year overall survival of 95% (see Figure). For prognostication, increasing age, increasing CIRS-G co-morbidity score, and loss of IADLs were associated with inferior PFS on univariable and multivariable analyses. Furthermore, the 2-year PFS rates for pts with high CIRS-G co-morbidity score (i.e., ≥10 vs. <10) were 45% vs. 100%, respectively (P<0.0001), and with baseline IADL loss vs. not were 25% vs. 94% (P < 0.0001), respectively (Figure).

**Conclusions:** Altogether, sequential Bv-AVD was well tolerated, associated with robust outcomes, and geriatric-based measures were strongly associated with patient survival.
P072 (0038) FRONTLINE BRENTUXIMAB VEDOTIN PLUS CHEMOTHERAPY EXHIBITS SUPERIOR MODIFIED PROGRESSION-FREE SURVIVAL VS CHEMOTHERAPY ALONE IN PATIENTS WITH STAGE III OR IV HODGKIN LYMPHOMA: PHASE 3 ECHELON-1 STUDY


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Background: Approximately 30% of patients (pts) with advanced-stage classical Hodgkin Lymphoma (cHL) have refractory disease or relapse after frontline doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). We compared frontline brentuximab vedotin (a CD30-directed antibody-drug conjugate) + doxorubicin, vinblastine, and dacarbazine (A+AVD) with ABVD in pts with advanced cHL.

Methods: 1334 pts with Stage III (36%) or IV (64%) cHL were randomized 1:1 to A+AVD or ABVD (days 1 and 15, up to six 28-day cycles). Late in enrolment, pts newly randomized to A+AVD were recommended G-CSF primary prophylaxis (PP) due to increased febrile neutropenia (FN). Primary endpoint was progression-free survival (PFS) as time to progression, death, or evidence of noncomplete response followed by further anticancer therapy. Key secondary endpoint was overall survival (OS).

Figure. Survival and Prognostication. Kaplan-Meier curves of (A) PFS and (B) OS for all 48 older Hodgkin lymphoma patients. Kaplan-Meier curves of (C) PFS and (D) OS for patients with a cumulative CIRS-G score ≥10 vs <10 had 2-year PFS rates of 45% vs. 100%, respectively (P<0.0001), and 2-year OS rates of 81% vs. 100%, respectively (P<0.02). Kaplan-Meier curves of (E) PFS and (F) OS for patients who had loss of instrumental activities of daily living (IADL) at baseline vs preserved function with corresponding 2-year PFS rates were 25% vs 94%, respectively (P<0.0001), and 2-year OS rates of 67% and 97%, respectively (P<0.01).

Results: Primary endpoint of mPFS per IRF was met (HR 0.77 [95% CI 0.60–0.98]; p = 0.04 [Figure 1]), was consistent with mPFS per investigator (inv) (HR 0.72 [95% CI 0.57–0.91]; p = 0.006) and PFS per inv (data to be presented). mPFS events per IRF for A+AVD vs ABVD were progression (90 vs 102), death (18 vs 22), and additional therapy for non-complete response (9 vs 22). Two-year mPFS per IRF was 82.1% (95% CI 78.8–85.0) with A+AVD vs 77.2% (95% CI 73.7–80.4) with ABVD; mPFS per inv was 81.0% (95% CI 77.6–83.9) with A+AVD vs 74.4% (95% CI 70.7–77.7) with ABVD. 28 deaths occurred in the A+AVD arm and 39 in the ABVD arm (interim OS HR 0.73 [95% CI 0.45–1.18]; p = 0.20). FN occurred in 19% of A+AVD pts and 8% of ABVD pts. In A+AVD pts, G-CSF PP (n = 83) reduced FN from 21% to 11% and grade (g) ≥ 3 infections/infestations from 18% to 11%. The study neurotoxicity (PN) occurred in 67% of A+AVD pts and 43% of ABVD pts (G2: 11% A+AVD [1 pt with G4] vs 2% ABVD); 67% of pts experiencing PN in the A+AVD arm had resolution or improvement of PN at last follow-up. Pulmonary toxicity was more frequent and severe with ABVD (G2: 5% ABVD vs <1% A+AVD). 7/9 A+AVD on-study deaths were neutropenia-associated, occurring in pts without G-CSF PP. 1/13 ABVD on-study deaths were due to, or associated with, pulmonary toxicity.

Conclusions: Compared with ABVD, frontline A+AVD improved outcomes for pts with advanced cHL, reducing risk of progression, death, or need for additional anticancer therapy by 23%. Results support possible frontline use of A+AVD in pts with advanced cHL.

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P076 (0056) CLINICAL CHARACTERISTICS AND TREATMENT OUTCOME OF NODULAR LYMPHOCYTE PREDOMINANT HODGKIN'S LYMPHOMA WITH THRLBCL-LIKE PATTERNS

National Research Center for Hematology, Moscow, Russian Federation

Introduction: NLPHL accounts for 5% of all Hodgkin’s Lymphomas (HL) and is a morphologically heterogeneous type. The clinical significance of the presence of THRLBCL-like patterns in NLPHL is unknown and is the subject of scientific research.

Aim: To study the clinical features of NLPHL with the presence of THRLBCL-like patterns, to evaluate the efficacy of first-line therapy in this subgroup of pts.

Materials and methods: During 2010–2017 75 patients (m/f: 9: 2, median of age 37 years (18–69)) were observed at our center with NLPHL. The diagnosis and stage of the disease is based on the standard methods for HL. Presence of THRLBCL-like pattern was detected in 33 (44%) pts, including 9/33 (27%) pts with predominance of THRLBCL-like patterns in lymph node biopsies (more than 50% of the area of sections).

Results: Advanced stages of disease was established in 30 (91%) pts; transformation into LBCL - in 2/3 (6%) pts with THRLBCL-like pattern(s) of NLPHL. B-symptoms were present in 22 (67%) cases, Extranodal involvement - in 31 (70.7%) pts, lymph node (LN) mass > 10 cm - in 23 (67%) pts; spleen involvement - in 13 (40%) pts. R-ABVD therapy received 6/33 (18%) pts in a group with THRLBCL-like patterns NLPHL. All pts achieved complete remission (CR) of the disease. 24 (73%) pts received R- BEACOPP-14, 19 (79%) of them achieved CR, progression of the disease (PD) was detected in 5 (21%) pts, who received second-line therapy, two pts followed by ASCT. From the group with PD - 3/5 pts achieved CR, 1/5 continue therapy, 1/5 is now on palliative protocol due to therapy failure. From the general group of NLPHL with THRLBCL-like patterns 1/33 (3%) pts received R-CHOP with PR and PD after 1.5 years, currently - in CR by R-BEACOPP-14. 1/33 (3%) pt received R-DA-EPOCH with PD, second-line therapy is planned. 2/33 pts received second-line therapy, two pts followed by ASCT. From the group with PD - 3/5 pts achieved CR, 1/5 continue therapy, 1/5 is now on palliative protocol due to therapy failure. From the general group of NLPHL with THRLBCL-like patterns 1/33 (3%) pts received R-CHOP with PR and PD after 1.5 years, currently - in CR by R-BEACOPP-14. 1/33 (3%) pt received R-DA-EPOCH with PD, second-line therapy is planned. 2/33 pts received second-line therapy, two pts followed by ASCT. From the group with PD - 3/5 pts achieved CR, 1/5 continue therapy, 1/5 is now on palliative protocol due to therapy failure. From the general group of NLPHL with THRLBCL-like patterns 1/33 (3%) pts received R-CHOP with PR and PD after 1.5 years, currently - in CR by R-BEACOPP-14. 1/33 (3%) pt received R-DA-EPOCH with PD, second-line therapy is planned. 2/33 pts received second-line therapy, two pts followed by ASCT. From the group with PD - 3/5 pts achieved CR, 1/5 continue therapy, 1/5 is now on palliative protocol due to therapy failure. From the general group of NLPHL with THRLBCL-like patterns 1/33 (3%) pts received R-CHOP with PR and PD after 1.5 years, currently - in CR by R-BEACOPP-14. 1/33 (3%) pt received R-DA-EPOCH with PD, second-line therapy is planned. 2/33 pts received second-line therapy, two pts followed by ASCT. From the group with PD - 3/5 pts achieved CR, 1/5 continue therapy, 1/5 is now on palliative protocol due to therapy failure.

Conclusions: Clinical features of pts with THRLBCL-like patterns in NLPHL are generalized lesions with B-symptoms, frequent extranodal and bone marrow involvement. Therapy by R-BEACOPP-14 and R-ABVD allows to achieve CR in 75% of pts.
in the Table 1. 9 pts of 1st subgroup had identical immunohistochemical patterns in primary biopsy and BMB. 1 pt- pattern C; 4 pts- pattern D; 4 pts – pattern E.

Conclusions: 1st group of pts with BM involvement in debut of disease have characterized by more often extranodal lesion. The BM involvement is a manifestation of the hematogenous spread of the disease with a complex of extranodal lesions. Our study revealed the identical immunohistoarchitectural patterns (C-E) in primary biopsy and BM lesion in all cases.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>The 1st subgroup (BM involvement) – 9 pts</th>
<th>The 2nd subgroup (without BM involvement) – 28 pts</th>
</tr>
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<tbody>
<tr>
<td>Pericard from clinical manifestation to lymph node biopsy (months)</td>
<td>12-80, median 6-3</td>
<td>0-78, median 3-4</td>
</tr>
<tr>
<td>Pericardial lymph nodes</td>
<td>7/8 (88%)</td>
<td>7/8 (100%)</td>
</tr>
<tr>
<td>Visceral</td>
<td>8/11 (73%)</td>
<td>7/8 (100%)</td>
</tr>
<tr>
<td>Extravascular localization</td>
<td>9/10 (90%) including bone marrow</td>
<td>7/7 (100%)</td>
</tr>
<tr>
<td>Bone</td>
<td>2/0 (100%)</td>
<td>2/0 (100%)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>9/10 (90%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Liver</td>
<td>2/0 (100%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>2/0 (100%)</td>
<td>2/0 (100%)</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>Range 43-236 10^9/L, median value 142 10^9/L</td>
<td>Range 42-60 10^9/L, median value 47 10^9/L</td>
</tr>
<tr>
<td>LMM</td>
<td>Range 579-1148 U/L, median value 318 U/L</td>
<td>Range 13-354 U/L, median value 138 U/L</td>
</tr>
</tbody>
</table>

P078 (0062): TWO DISTINCT PROGNOSTIC GROUPS IN ADVANCED-STAGE HODGKIN LYMPHOMA REVEALED BY THE PRESENCE AND SIZE OF BULKY DISEASE

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Purpose: Controversy exists regarding the definition and prognostic significance of bulk in advanced-stage Hodgkin lymphoma (ASHL); bulk location (mediastinum vs. other sites) maybe also of relevance. This retrospective, multi-institutional study aimed to evaluate the significance of bulk in ASHL.

Patients and methods: The complete study cohort comprised 814 ASHL (stage III/IV) patients, divided into an exploratory cohort of 683 patients treated at 5 centers between 2000 to 2010 and a validation cohort of 131 patients treated at a 6th center. Endpoints of interest included progression-free survival (PFS) and overall survival (OS). Covariates included the greatest transverse diameter of the largest mass and the size of bulky disease. SmoothHR and Kaplan-Meier analyses were used to assess for an association of PFS and OS with covariates.

Results: In the exploratory cohort (n = 683), 533 patients (78%) received chemotherapy alone. The most common chemotherapy regimen was doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD; 78% of cases). In the exploratory cohort, the most common chemotherapy regimen was doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD; 78% of cases). The most common chemotherapy regimen was doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD; 78% of cases). The most common chemotherapy regimen was doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD; 78% of cases).

Conclusions: In ASHL, maximum tumor diameter showed no significant association with PFS, but a complex association with OS reflected by a U-shaped logarithmic HR curve. Mediastinal bulk was associated with more favorable disease characteristics and improved OS. Mediastinal bulk in ASHL may be a surrogate of a more favorable biology.

P079 (0070): GERMAN EVOLUTION-BASED GUIDELINE UPDATE ON DIAGNOSIS, THERAPY AND FOLLOW-UP OF ADULT HODGKIN LYMPHOMA PATIENTS

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Introduction: Stage-adapted therapy of Hodgkin lymphoma patients allows cure in most cases, thus, effective treatment with focus on therapy-associated morbidity and mortality is of high relevance. The German guideline on diagnosis, therapy and follow-up of adult HL patients was first published in February 2013. A revision was performed to update recommendations on basis of scientific evidence and expert consensus.

Methods: A systematic literature search was conducted in CENTRAL and MEDLINE. The literature was classified, evaluated for quality criteria using the GRADEpro software and summarized in evidence tables. The close collaboration between clinical experts in multidisciplinary working groups and the German Hodgkin Study Group as well as the methodological experts from the Evidence-based Oncology ensured high quality in the guideline development process. The guideline update was funded by the German Guideline Program in Oncology (funding no 111778).

Results: The updated guideline now comprises 176 recommendations. Of these 19 have entirely new content, 77 recommendations were updated and 80 remained unchanged after being checked for validity. Most significant adjustments were made for recommendations regarding the use of positron emission tomography and computed tomography (PET/CT) at staging and for patients with advanced HL to adapt therapy after two cycles of BEACOPPesc, radiotherapy being performed with the involved-site technique, and consolidation treatment and use of novel drugs in patients with relapsed or refractory disease. The final version of the guideline was consented through experts in the field and patient representatives in a formal consensus process (consensus conferences in presence and online, and DELPHI process).
P080 (0071) ANALYSIS OF OUTCOMES AND PROGNOSTIC FACTORS OF 165 NEWLY DIAGNOSED PATIENTS WITH ADVANCED CLASSICAL HODGKIN LYMPHOMA

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Peking University Cancer Hospital & Institute

Objective: To analyze the clinical characteristics, outcomes and prognostic factors of 165 patients with advanced classical Hodgkin lymphoma (cHL) from Peking University Cancer Hospital & Institute (PUCU).

Methods: From January 2008 to January 2018, 165 patients were newly diagnosed as advance-stage cHL and underwent treatment in PUCH. The clinical data of all cases were collected and analyzed.

Results: Among 165 cases, 92 (56%) were male patients. The median age was 31 years (6 to 75 years old); 43 cases were at stage IIIA, 29 cases at IIIB, 36 at IVA, and 53 at IVB. Thirty-two patients were with bulky mass (the largest diameter ≥7.5 cm). The median follow-up time was 43.4 months. In the whole group, the overall response rate (ORR) and complete remission (CR) rate were 88.5% and 62.4%, respectively; 5-year PFS rate and OS rate were 67.0% and 86.5%. 133 cases received ABVD regimen while 32 cases were with escalated BEACOPP regimen. The 5-year PFS of these two regimens were 65.4% vs. 67.3% (P=0.906), 5-year OS were 88.7% vs. 86.4% (P=0.892). 146 cases were treated with chemotherapy while 19 received chemoradiation. The 5-year PFS were 64.9% vs. 82.8% (P=0.147), 5-year OS were 86.2% vs. 87.5% (P=0.326).

According to international prognostic scores (IPS), 163 evaluable cases at IIIB, 36 at IVA, and 55 at IVB. Thirty-two patients were with bulky mass (the largest diameter ≥7.5 cm). The median follow-up time was 43.4 months. In the whole group, the overall response rate (ORR) and complete remission (CR) rate were 88.5% and 62.4%, respectively; 5-year PFS rate and OS rate were 67.0% and 86.5%. Among 165 cases, 92 (56%) were male patients. The median age was 31 years (6 to 75 years old); 43 cases were at stage IIIA, 29 cases at IIIB, 36 at IVA, and 53 at IVB. Thirty-two patients were with bulky mass (the largest diameter ≥7.5 cm). The median follow-up time was 43.4 months. In the whole group, the overall response rate (ORR) and complete remission (CR) rate were 88.5% and 62.4%, respectively; 5-year PFS rate and OS rate were 67.0% and 86.5%.

Conclusion: In our study, the outcomes of ABVD and escalated BEACOPP regimens showed no significant differences. Patients with high IPS had poor prognosis.

P081 (0084) A CLINICOPATHOLOGICAL CONSENSUS STUDY OF GRAY ZONE LYMPHOMA (GZL) WITH FEATURES INTERMEDIATE BETWEEN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) AND CLASSICAL HL (CHL)

Monika Pllichowska1, Stefania Pittaluga2, Judith A. Ferry3, Jessica Hemminger4, Hong Chang5, Laurie H. Sehn6, Jeremy S. Abramson7, Monika Pilichowska1, Stefania Pittaluga2, Judith A. Ferry3, Monika Pilichowska1, Stefania Pittaluga2, Judith A. Ferry3

Objective: This study reviewed a large series of cases defined as GZL to characterize the clinical and morphologic features of GZL.

Methods: Prospective collection of 84 cases of GZL from 6 centers and retrospective review of an additional 24 cases. GZL was defined as a disease with lymphoma morphology with clinical features of classic HL.

Results: Of the original 68 cases, only 26 (38%) were confirmed as GZL on consensus review. Morphology was critical to GZL consensus diagnosis (e.g., tumor cell richness); IHC showed universal B-cell derivation, frequent CD30 expression, and rare EBV positivity (CD20+ 83%; CD79a+ 100%; MUM1+ 100%; CD3+ 92%; EBV+ 4%). 42 cases were reclassified: nodular sclerosis (NS) cHL, n = 27 (including n = 10 NS grade-2); lymphocyte predominant HL, n = 4; DLBCL, n = 4; EBV+ DLBCL, n = 3; primary mediastinal BCL, n = 2; lymphocyte-rich CHL and BCL-NOS, n = 1 each. GZL consensus-confirmed vs reclassified cases more often had mediastinal disease (69% vs 41%, P = 0.038) and less likely >1 extranodal site (0 vs 25%, P = 0.019). With 44-month median follow-up, the 3-year progression-free survival (PFS) vs non-CHOP therapy (primarily ABVD for latter), respectively, P = 0.03. The two latter findings persisted on multivariable Cox regression analysis.

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Conclusions: Altogether, the pathologic diagnosis of GZL remains challenging. High tumor cell content was extremely helpful in establishing diagnosis. Additionally, our results suggest that treatment with DLB-CL-based regimens are most effective and we identified clinical factors that identified GZL patients with divergent clinical outcome.

**PO82 (0087) CLINICAL SIGNIFICANCE OF AUTOIMMUNE HEMOLYTIC ANAEMIA AND AUTOIMMUNE THROMBOCYTOPENIA DURING THE COURSE OF HODGKIN LYMPHOMA**

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Introduction: Autoimmune cytopenias (AICP), namely autoimmune hemolytic anaemia (AIHA) and autoimmune thrombocytopenia (AITP) often complicate the course of malignant lymphomas. However, the incidence and clinical significance of AICPs associated with Hodgkin lymphoma (HL) have not been defined thoroughly.

Patients and methods: Seven hundred and fifty-six HL patients were diagnosed and treated at the University of Debrecen between 1980 and 2017. We retrospectively assessed the incidence and clinical features of HL-associated autoimmune phenomena, also compared the distribution of clinical, laboratory and pathologic characteristics between HL patients presenting with AICP and those who had no clinical evidence of autoimmune events. Statistical analysis was performed using Fisher’s exact test.

Results: We identified 8 cases of AIHA and 4 cases of AITP among 11 patients altogether. The incidence of AICPs in HL patients was 1.59%. Three cases presented at initial diagnosis, 8 cases during follow-up after first line therapy. Ninety-two percent of the AICPs required therapy, 7/2% of these cases responded well to intravenous steroids. In steroid-refractory AICPs, azathioprine, rituximab and romiplostim therapy were effective. No splenectomy was needed. Third of the AICPs was disease-defining event: 2 cases led to the diagnosis of HL, 1 indicated relapse and 1 event revealed a secondary hematological malignancy. AIHAs and AICPs altogether were more frequently observed in patients presenting with advanced stage disease at initial diagnosis (p < 0.012 and p < 0.028 respectively).

Conclusion: The occurrence of AICPs in patients with HL can imply clinical significance. Patients diagnosed in advanced stage are at increased risk of developing AICPs. Our data also emphasise the importance of taking the possibility of underlying hematological malignancy into consideration in newly diagnosed AIHA/AITP cases.

**PO83 (0093) LOW-DOSE CONSOLIDATIVE MEDIASTINAL IRRADIATION IN ACCELERATED HYPERFRACTIONATED REGIMEN FOR ADVANCED HODGKIN LYMPHOMA**

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Background: Hodgkin lymphoma (HL) commonly involves the mediastinum and late effects from treatment can cause significant problems. At MRRC consolidative IFRT to 20 Gy in accelerated hyperfractionation regimen (AHFX, 2 daily fractions 1.3–1.5 Gy with the interval 4.5 hours) versus 40 Gy in conventional fractionation (CF) had been explored since 1988 in clinical trials of I-II and III phase. With the similar rate of local control, the AHFX regimen spared organs at risk (lung and heart) and underlying bone marrow from irreversible aplasia. After 2010 AHFX has been modified for ISRT.

Aims: To evaluate local control of mediastinal involvement in HL patients with different AHFX regimens depending on the size of residual tumor.

Methods: Between 1998 and 2015, total 372 patients with HL IIXE, III-IV stages received mediastinal irradiation after partial response to the first-line chemotherapy (ABVD, BEACOPP-21 or BEACOPP-14, depending on prognostic group). Before 2010, 20 Gy were delivered with two radiation techniques: 1 gr. (150 pts) received dose fractions of 1.5 Gy+1.5 Gy as IFRT; 2 gr. (48 pts with locally advanced disease) received 1.25 Gy+1.5 Gy; the first of two daily fractions encompassed half-thorax (15 Gy/12 days) and the second fraction was delivered through standard mediastinal field (9 Gy/6 days). After 2010, ISRT was delivered with dose fractions of 1.3 Gy+1.3 Gy (3 gr.,116 pts); controls (4 gr., 58 pts) received 30–36 Gy CF. The main end-point was local relapse (LR) rate within irradiated mediastinal field.

Results: With median follow-up 60 months for gr.1 and gr.2, the 10-year OS was, respectively, 92% and 98%; the 10-year FFPS was 89% and 87%. The LR rate in irradiated mediastinum for gr.1 and gr.2 was 7% and 12%. Local control by maximum diameter of residual tumor in gr.1 and gr.2 was as follows: < 2.0 cm, 93% vs. 100%; 2.1 to 4.9 cm, 91%
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P085 (0112) TREATMENT TOXICITY IN ELDERLY HODGKIN LYMPHOMA PATIENTS WITH ADVANCED STAGE – MULTICENTER RETROSPECTIVE DATA ANALYSIS FROM THE CZECH REPUBLIC

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Introduction: The optimal management of elderly Hodgkin (HL) patients with advanced stage is of high importance due to comorbidities and poor tolerance of chemotherapy (CT) and/or radiotherapy (RT).

The purpose of this study was to analyze treatment toxicity of the first-line treatment in elderly HL pts with advanced stage prospectively registered in Hradec Kralove Lymphoma Project in the Czech Republic.

Patients and methods: We analyzed 125 pts older than 60 years (y) with classical HL in advanced stage diagnosed between 1999 and 2016. Median age was 67 y (range 60–84). Chemotherapy alone was used in 109 (87.2%) pts. The combined modality of treatment (CT and RT) was used in 14 pts (11.2%). Anthracycline-based CT received 84% of pts (105 pts), 50.4% of pts were treated with ABVD regimen.

Results: Median number of administered CT cycles was 6 (range 1–8). G – CSF was used in 82 of pts and the median number of CT cycles with G – CSF administration was six cycles (range 1–8). Overall response rate after the first-line treatment was observed in 104 (83.2%) pts including complete remission in 67.2%, stable disease in 31.3% and primary disease progression in 6.4%. Bleomycin toxicity grade 3 or 4 was observed in 12/98 (12.2%) of pts. Other toxicities grade 3 or 4 according to CTCAE v4 included: cardiac in 9 (7.2%), neurologic in 5 (4%), infections in 27 (21.6%) and other toxicities in 5 (4%) of pts. Overall 51 pts (40.8%) died. The highest mortality rate in this group was caused by HL progression (31.3%). Treatment-related mortality was 25.4%, including cardiac in 1 (0.66%) and pulmonary toxicities in 2 (3.9%) pts. Other causes of mortality included infections in 3.9, secondary malignancy in 9.8, other cause in 11.8% and unknown cause in 17.6% of pts.

Conclusions: The most frequent cause of mortality is HL progression. Bleomycin toxicity in our group of elderly pts is comparable with other reported data. According to our data treatment related death of elderly pts is high. Prospective clinical studies are still needed to determine an optimal effective regimen with low toxicity in elderly pts. Long-term survival of our pts depended on the use of anthracycline-containing CT and value of lymphocytes (multivariate analysis).

This work was supported by a grant awarded by AZV 16–29857A, Research project Q 28 Progres awarded by Charles University in Prague, Third Faculty of Medicine, Prague, Czech Republic, by grant 16–31092A and Research project Q 40/08 Progres.

P087 (0135) HODGKIN LYMOPHMA IN HIV-POSITIVE PATIENTS: A SINGLE INSTITUTION RETROSPECTIVE STUDY

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Background: The introduction of highly active antiretroviral therapy (HAART) since 1997 has completely changed the prognosis of HIV-positive patients (pts), decreasing the risk of developing myeloproliferative disorders.

Unexpectedly incidence of HIV related Hodgkin lymphoma (HL) has not been declining.

Recent clinical studies show that HIV-positive HL pts treated with concomitant HAART achieve encouraging results, as those seen in the general population.

Our aim was to compare the characteristics, the response to the treatment and the survival of the HL treated with first line chemotherapry between HIV-positive (HIV+) on HAART and HIV-negative (HIV-) pts.

Methods: This is a single institution retrospective cohort study conducted in Ospedale Luigi Sacco Milan, Italy. We selected pts aged >18 years with histopathologic diagnosis of HL from April 2008 to January 2018. We included HIV+ on HAART and HIV- pts both treated with ABVD. Differences between HIV+ and HIV- pts were assessed using Chi-square, Fisher’s exact or Wilcoxon Rank-sum test. Overall survival (OS), progression-free survival (PFS) and response rate (RR) were compared across groups defined by HIV-status, HAART treatment prior to HL diagnosis (yes vs no), IPS (0–2 vs ≥3) and stage (early vs advanced) using the log-rank test.

Results: We included 45 pts, 20 HIV+ and 25 HIV−. The HIV+ pts were on average older (49 vs 39ys p = 0.18), they were more likely to be male (95% vs 60% p = 0.01), at an advanced stage at diagnosis (90% vs 72% p = 0.26), they had ≥1 extranodal site involved (80% vs 40% p = 0.01), EBV infection (78.6% vs 36.8% p = 0.03), a worst performance status (PS ECOG ≥2 35% vs 8% p = 0.06), a higher prognostic index score (IPS ≥7 75% vs 13% p < 0.001).

During ABVD chemotherapy, HIV+ pts developed more frequently myelotoxicity (anemia G3–4 23.6% vs 0% p = 0.02).

During a median (IQR) follow-up of 33 months in HIV+ and 43 months in HIV− pts no difference was observed in RR (88.2% vs 95.6% p = 0.56), OS (89.4% vs 100% p = 0.3) and PFS (73.8% vs 86.7% p = 0.73) at 2 years.

During ABVD chemotherapy, HIV+ pts developed more frequently myelotoxicity (anemia G3–4 23.6% vs 0% p = 0.02).

Conclusions: Although HIV+ pts had more aggressive baseline features in this series, there were no differences in response rate or survival. Probably exposure to HAART tends to balance outcomes overtime.

P088 (0136) BRENXTUMAB VEDOTIN PLUS CHEMOTHERAPY IN PATIENTS WITH HIGH-RISK ADVANCED-STAGE CLASSICAL HODGKIN LYMPHOMA (CHL): RESULTS OF PRESPECIFIED SUB-GROUP ANALYSES FROM THE ECHELON-1 STUDY


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Background: Primary results of the randomized, phase 3 ECHELON-1 study demonstrated a significant improvement in modified progression-free survival (mPFS), per independent review facility (IRF), in patients with stage III or IV CHL treated with frontline brenxtumab vedotin + doxorubicin, vinblastine, and dacarbazine (A+AVD) vs doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD). Two-year mPFS rates were 82% and 77%, respectively. We report a prespecified subanalysis of the efficacy and safety of A+AVD vs ABVD in patients with CHL and high-risk features including: ≥1 extranodal site of involvement,
stage IV disease, or an International Prognostic Score (IPS) of 4–7.

Methods: Patients were randomized 1:1 to receive up to six 28-day cycles of A+AVD or ABVD administered intravenously on days 1 and 15 of each cycle. Patients were analyzed by disease stage at diagnosis, IPS, and number of extranodal disease sites. Sub-group analyses were performed on the primary endpoint of mPFS (defined as time to progression, death, or evidence of noncomplete response followed by subsequent anticancer therapy).

Results: 664 and 670 patients were randomized to A+AVD and ABVD, respectively. High-risk features at baseline were well balanced in both treatment groups, with 64% and 63% having stage IV disease, and 25% and 27% having an IPS of 4–7 in A+AVD and ABVD arms, respectively; 62% of patients in each arm had ≥1 extranodal site. Two-year mPFS was most improved with A+AVD compared with ABVD in the following subgroups (Table 1): stage IV disease (82.0% vs 75.3% [HR = 0.71, 95% CI: 0.53–0.96; p = 0.023]), >1 extranodal site (80.2% vs 71.1% [HR = 0.67, 95% CI: 0.44–1.00; p = 0.049]), and ≥2 extranodal sites (82.4% vs 74.9% [HR = 0.70, 95% CI: 0.52–0.94; p = 0.018]). Patients with an IPS of 4–7 also had a favorable improvement in mPFS with A+AVD (77.0% vs 69.2% [HR = 0.70, 95% CI: 0.46–1.07; p = 0.097]).

Efficacy and safety analyses for combinations of high-risk sub-groups will be presented in full.

Conclusions: Brentuximab vedotin offers consistent benefit across the range of exposures in ECHELON-1. ER analyses support the recommended starting dose (1.2 mg/kg Q2W) and risk reduction of PN and FN by G-CSF PP, and support management of treatment-related AEs by dose reductions per ECHELON-1.

Results: ADC PK were described by a linear 3-compartment model with zero-order input and first-order elimination. MMAE PK were described by a 2-compartment model with first-order elimination and release of MMAE from ADC and via ADC target binding. There were no clinically meaningful changes in simulated ADC AUC for body surface area or albumin. ADC AUC/time was not a significant predictor of mPFS. ADC AUC/time was predictive of G2 N and FN, but not of G2 N or G2 TEAEs. MMAE AUC/time was predictive of G2 N, FN and G2 TEAE, but not G2 FN. Covariate analyses concluded that G-CSF PP protected against N, FN, and G2 TEAEs. ER analyses supported the protocol-specified ADC dose reductions for treatment-related AEs.

Conclusions: Brentuximab vedotin offers consistent benefit across the range of exposures in ECHELON-1. ER analyses support the recommended starting dose (1.2 mg/kg Q2W) and risk reduction of PN and FN by G-CSF PP, and support management of treatment-related AEs by dose reductions per ECHELON-1.
with ABVD. Mean TARC decrease was slightly greater in EOT PET-negative vs PET-positive pts with A+AVD (mean -47,820 vs -40,754 pg/mL); with ABVD the decrease was slightly smaller (mean -39,082 vs -40,859 pg/mL).

Conclusions: There were no obvious differences or trends in sCD30 or TARC changes from baseline according to response, PET2 status, or EOT PET status. Based on these findings, sCD30 and TARC are not adequate biomarkers for response.

Figure 1.

**Pediatic Hodgkin Lymphoma**

**T022 (0042) SURVIVAL BY RACE/ETHNICITY IN PEDIATRIC AND ADOLESCENT PATIENTS WITH Hodgkin Lymphoma: A POOLED ANALYSIS OF CONTEMPORARY CHILDREN’S ONCOLOGY GROUP TRIALS**

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Introduction: Despite excellent survival in pediatric Hodgkin Lymphoma (HL), disparities by race/ethnicity persist: Population-based studies in the U.S. suggest that black and Hispanic (vs. non-Hispanic white) race/ethnicity are associated with inferior outcomes. Whether disparities are observed after adjusting for clinical features and treatment-related variables is not known. We examined whether race/ethnicity is predictive of event-free survival (EFS), and overall survival (OS) in patients receiving risk-adapted, response-based therapy for newly diagnosed HL on contemporary Children’s Oncology Group (COG) trials.

Methods: This was a pooled analysis of patient-level data from three COG Phase 3 trials for intermediate, low, high-risk HL (AHOD0031, AHOD0431, AHOD0831). Five-year EFS and OS by age were estimated by Kaplan Meier method. Cox regression models examined the effect of race/ethnicity on either EFS (p = 0.98; OS: p = 0.29).

Conclusions: In children treated with contemporary, response-based therapy on COG trials, race/ethnicity was not associated with survival, suggesting that disparities observed in population-based studies may be reduced in children enrolled in clinical trials. Further analysis will explore early response to therapy by race/ethnicity as well as treatment-related toxicities and the independent contribution of socioeconomic status to HL outcomes.

**T023 (0106) SAFETY AND EARLY RESPONSE TO THE FIRST 2 CYCLES OF BRENTUXIMAB VEDOTIN SUBSTITUTE VINCRISTINE IN THE OEPA/COPDAC REGIMEN FOR HIGH RISK PEDIATRIC Hodgkin Lymphoma (HL)**

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Background: Multiple recent studies have focused on omission of radiation in patients with an adequate early response. The GPOH, building upon their original experience with the OPPA/COPP regimen, demonstrated that 6 cycles OEPA/COPDAC with 20–30 Gy IFRT produced excellent results, with 5-year EFS and OS of approximately 87% and 95% respectively. In the EuroNet C1 trial about 30% of patients achieved an adequate response after 2 cycles of OEPA and could forgo radiation therapy.

Intervention: Substitution of vincristine with Brentuximab vedotin (Bv) in each cycle of OEPA/COPDAC (AEPACAPDac) and 2 Gy ISRT to areas not in CR at early response evaluation (CR > 50% volumetric anatomic response and Deauville < 4 on PET scan).

Eligibility: Stage IIB, IIB and IV.

Objectives: To evaluate the safety and efficacy (defined as the number of patients with adequate response according to the definitions in the EuroNet C1) of 2 cycles of AEPACAPDac.

Results: Median follow-up was 6.9 years. We included 2071 of 2155 patients (1-21 years) enrolled on COG HL trials in the U.S. or Canada between 2002 and 2012. Distribution of race/ethnicity was: 64% white (N = 1334), 11% non-Hispanic black (N = 236), 16% Hispanic (N = 329), 3% Asian/Pacific Islander (N = 66), 5% Other (N = 106). More non-Hispanic white patients had private (vs. government) insurance (p < 0.0001). A higher proportion of white patients had nodular sclerosing histology (p < 0.0001) and a higher proportion of black and Hispanic patients had stage III/IV disease (p = 0.0002). There was no difference in B-symptoms (p = 0.19), bulk (p = 0.88), or RT receipt (p = 0.53) by race/ethnicity. In pooled analysis, EFS was 83%, OS was 97% and were not different by race/ethnicity (EFS: p = 0.98; OS: p = 0.29). Cumulative incidence of relapse was 16.8% and did not differ by race/ethnicity (p = 0.93). In multivariable models, there was no significant effect of race/ethnicity on either EFS (p = 0.95), or OS (p = 0.14).

Conclusions: In children treated with contemporary, response-based therapy on COG trials, race/ethnicity was not associated with survival, suggesting that disparities observed in population-based studies may be reduced in children enrolled in clinical trials. Further analysis will explore early response to therapy by race/ethnicity as well as treatment-related toxicities and the independent contribution of socioeconomic status to HL outcomes.
**P092 (0123) THE FEASIBILITY OF DEEP INSPIRATION BREATH-HOLD IN CHILDREN: RESULTS OF THE TEDDI PILOT STUDY**

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**Purpose/objectives:** The use of deep inspiration breath-hold (DIBH) is recommended for radiotherapy (RT) of malignant lymphomas in the mediastinum in adults, however, no formalized studies have addressed the use of DIBH in children. TEDDI is a feasibility study introducing DIBH for pediatric patients within the NOPHO network. Prior to clinical implementation, the TEDDI pilot study was initiated to test if 1) children can perform a stable and comfortable DIBH, 2) the DIBH equipment is suitable for children, and 3) the information and coaching should be improved.

**Materials/methods:** The study aimed to recruit 30 children including both healthy volunteers and pediatric cancer patients not planned for radiotherapy. DIBH compliance was assessed during a 30 min coaching session at the linear accelerator with each child in a potential treatment position. The DIBH was voluntary, but monitored with an optical surface system providing a visual feedback of the respiration at the DIBH level. The child was declared DIBH compliant if he/she was able to perform 3 stable breath-holds of 20 seconds each. Patient compliance and coaching and DIBH equipment suitability were assessed from questionnaires and visual observations.

**Results:** A total of 32 volunteers were included at two separate institutions, 17 healthy and 15 cancer patients. The median age was 8.5 years (range: 5–15 years), and five were pre-school children. Thirteen volunteers (6 healthy, 7 patients) were found not to be suitable for RT in DIBH: four patients were not able to maintain a sufficient breath-hold, five volunteers (3 healthy, 2 patients) were not able to maintain the treatment position, and four volunteers (3 healthy, 1 patient) failed to do both. However, eight volunteers (2 healthy, 6 patients) would have been able to comply with DIBH using custom made fixation and additional coaching-time. Of the 32 volunteers, only a 5-year old, healthy boy was not able to understand the DIBH concept. The DIBH equipment was deemed suitable for children, however, the visual feedback was changed from goggles to video screens. All volunteers reported that they were either very happy (13), fairly happy (17), or content (2) with the DIBH coaching and training.

**Conclusion:** The TEDDI pilot study demonstrated that DIBH can be implemented for children, especially with sufficient coaching-time and proper visual feedback equipment. Consequently, the TEDDI feasibility study has been initiated.

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**P093 (0028) HOPE TO COPE WITH OPPA/COPP: EXPERIENCE OF GPOH HD-2002 STUDY PROTOCOL IN PEDIATRIC HODGKIN LYMPHOMA IN A TERTIARY CARE HOSPITAL IN A RESOURCE CONSTRAINT SETTING**

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**Introduction:** The cure rate of Hodgkin lymphoma (HL) in children and adolescents has steadily improved over the years but at the price of serious long-term toxicities. Therefore, the therapeutic paradigm has shifted towards reducing treatment-associated toxicities while maintaining high cure rates.

**Objectives:** To assess the response rate of GPOH HD-2002 study protocol in case of pediatric HL (up to 18 years of age) both as upfront as well as salvage therapy and to compare it with that of matched historical patient cohort treated with ABVD.

**Material and Methods:** All consecutive cases of pediatric classical HL patients (up to 18 years of age) attending NRS Medical College from October 2014 to April 2018 were treated with GPOH HD-2002 protocol (OPPA/COPP for girls & OEPAC/COPDAC for boys), the result of which was compared with the retrospective cohort treated with ABVD protocol from July 2009 to October 2014.

**Table No.1: Patient characteristics and response assessment**

<table>
<thead>
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<th>Chemotherapy protocol</th>
<th>ABVD</th>
<th>GPOH HD-2002</th>
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<tr>
<td>Total patients enrolled (n)</td>
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<td>Completed treatment as upfront (n)</td>
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<table>
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<tr>
<th>Median age in range (years)</th>
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<th>7.5 (3-16)</th>
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<tr>
<td>Male: Female</td>
<td>5.5:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>IV</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>B Symptoms Present (n)</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Absent (n)</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>39 (89%)</td>
<td>16 (100%)</td>
</tr>
<tr>
<td>p&lt;0.01</td>
<td></td>
<td>p=0.51</td>
</tr>
<tr>
<td>CR</td>
<td>34 (77%)</td>
<td>14 (87.5%)</td>
</tr>
<tr>
<td>p&lt;1.0</td>
<td></td>
<td>p=1.0</td>
</tr>
<tr>
<td>PR</td>
<td>5 (13%)</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>p=0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results: Seventy-four cases of pediatric CHL were treated, among whom 22 were treated with GPOH HD-2002 protocol and were compared with retrospective cohort of 52 cases given ABVD. Median age was 7.5 years (range: 3–16) in the GPOH arm & 9.5 years (range: 3–18) in the ABVD arm. In the former arm, male: female ratio was 2:1 while in the latter group it was 5:5.1. Cervical lymphadenopathy was the most common clinical finding during initial presentation (82% and 89% in respective groups) either alone or with other lymph node regions. Eighteen (82%) belonged to advanced stages in the former and 31 (60%) in the latter group, while B symptom accompanied the advanced stages...
Abstract Book for the 11th International Symposium on Hodgkin Lymphoma

in both (47% and 61% respectively). In the GPOH group, 16 have completed treatment & overall response was seen in 16 (100%) cases, among whom 14 (87.5%) had CR; two (12.5%) had PR. Out of those who went to CR, two patients (12.5%) relapsed, among which after 2nd line chemotherapy only one went to CR. Among those who received ABVD as upfront, overall response was seen in 39 (89%) cases, among which 34 (77%) had CR and 5 (11%) had PR and 5 (11%) had progressive disease. Two patients (4.5%) relapsed after 2 years of achieving CR. Chemotherapy was given in a day care facility where nearly 60 patients per day were treated in 10 beds on a bed sharing basis. Table No.1 shows patient assessment parameters.

Conclusions: The GPOH HD-2002 protocol when given as upfront, the response rates are not inferior compared to ABVD. Due to the lower long-term toxicity, it may be a preferred regimen for pediatric patients.

P094 (0059) KEYNOTE-667: PHASE 2, OPEN-LABEL STUDY OF PEMBROLIZUMAB IN CHILDREN AND YOUNG ADULTS WITH NEWLY DIAGNOSED CLASSICAL HODGKIN LYMPHOMA (CHL) WITH EARLY RESPONSE (SER) TO FRONTLINE CHEMOTHERAPY

Christine Mauz-Körholz1, Kara Kelly2, Frank Keller3, Akash Nahar4, Arun Balakumaran5, Lisa Giulino-Roth6
1Department of Pediatrics, Justus-Liebig University of Giessen, Giessen, Germany and Medical Faculty of the Martin-Luther-University of Halle-Wittenberg, Halle, Germany, 2Department of Pediatric Oncology, Roswell Park Comprehensive Cancer Center and University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, USA, 3Department of Pediatrics, Children’s Healthcare of Atlanta and Emory University, Atlanta, GA, USA, 4Merck & Co., Inc., Kenilworth, NJ, USA, 5Department of Pediatrics, Well Cornell Medical College, New York, NY, USA

Objective: High risk for relapse is observed in cHL patients (pts) with SER to initial chemotherapy and the burden of late organ toxicities may be higher following dose intensification. Here, we evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy in patients with cHL and slow early response to frontline chemotherapy.

Methods: The phase 2, open-label KEYNOTE-667 (NCT03407144) study will enroll 400 pts aged 3 to 17 (children) or 18 to 25 years (young adults) with newly diagnosed, confirmed stage IA, IB, or IIA cHL without bulky disease. Group 1 (low-risk) will receive doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD); Group 1 or vincristine, etoposide/etoposide phosphate, prednisone/prednisolone, doxorubicin (OEPA; Group 2) for 2 cycles, followed by early response assessment by PET/CT/MRI. Pts with rapid early response (Deauville score 1–3) will receive standard therapy. Pts with SER (Deauville score 4–5) will receive consolidation with pembrolizumab 2 mg/kg Q3W up to 200 mg (children) or 200 mg Q3W (young adults) plus 2 cycles AVD (Group 1) or 4 cycles cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine (COPP-DA; Group 2). PET/CT for late response assessment (LRA) will be performed after consolidation. After LRA, Group 1 pts with SER will receive radiotherapy (RT); in Group 2, pts with Deauville score 4–5 will receive RT. All pts will receive maintenance with pembrolizumab concomitantly with RT. Pembro dosing will continue up to 17 administrations, with an option to stop after 24 weeks due to CR, or until progression, unacceptable toxicity, or withdrawal. The primary endpoint is objective response rate (ORR). This analysis. Adolescent HL pts account for 27.5% of our trial population: 16% (90 pts) of MH96 and 32.9% (388 pts) of LH2004. M and 41 F with a median age of 15.9 yrs were the MH96 pts; 186 M and 202 F with a median age of 15.05 yrs the LH2004 ones. Among pts <13yrs, 12.5% were younger than 7 yrs in MH96, while only 7% in LH2004 population. There are no significative differences in stage distribution and in bulky disease. Outcome is reported in the following table; no significant difference was observed between adolescents and younger patients.

Conclusion: In our experience, the proportion of adolescents with HL registered in the last AIEOP protocol redoubled. Even in the <13 yrs group of patients the proportion of older children increased. No difference in EFS and FFP was observed between the adolescents and younger patients, at least when a protocol for pediatric patients was utilized.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>All survivors at risk of CVD (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at clinic visit, median (IQR)</td>
<td>52 (44-57) years</td>
</tr>
<tr>
<td>Gender, male</td>
<td>50%</td>
</tr>
<tr>
<td>Year of HL diagnosis, median (range)</td>
<td>1992 (1971-2005)</td>
</tr>
<tr>
<td>Age at HL diagnosis, median (IQR)</td>
<td>28 (21-33) years</td>
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<tr>
<td>Time since diagnosis, median (range)</td>
<td>23 (8-45) years</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Anthracyclines (y/n)</td>
<td>72%</td>
</tr>
<tr>
<td>Mediastinal RT (y/n)</td>
<td>77%</td>
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<td>Anthracyclines and mediastinal RT (y/n)</td>
<td>54%</td>
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</table>

CVD: cardiovascular disease; IQR: interquartile range; HL: Hodgkin lymphoma; RT: radiotherapy

P095 (0064) HODGKIN’S LYMPHOMA IN ADOLESCENTS: THE ITALIAN ASSOCIATION OF PEDIATRIC HEMATOLOGY AND ONCOLOGY (AIEOP) EXPERIENCE

R. Burnelli1, G. Fiumana1, M. Pilloni2, A. Sala3, S. Buffardi2, L. Vinti2, M. Zecca2, A. Garaventa2, R. Rondelli2, P. Muggeo2, M. Provenz1, P. Farruggia1, F. Rossii1, E. Facchinii1, M. Mascarin1, on behalf of the Italian Association of Pediatric Hematology and Oncology

1University Hospital Sant’Anna-Ferrara, 2Clinic of Pediatric Hemato-Oncology, University of Padua, 3Clinic of Pediatrics, S.Gerardo Hospital, Monza, 4Pediatric Oncology Department-Santobono-Pausilipon Hospital, Napoli, 5Pediatric Oncology Department-Bambino Gesu’ Hospital, Rome, 6Pediatric Hematology-Oncology, San Matteo Hospital, Pavia, 7Oncology Unit, Istituto G. Gaslini, Genova, 8Pediatric Oncology Hematology, S.Orsola-Malpighi Hospital Bologna, 9Division of Pediatric Hematology Oncology, Bari, 10Pediatric Onco-hematology, Ospedale Riuniti, Bergamo, 11Pediatric Hematology Oncology Unit, ARNAS Ospedali Civico Di Cristina e Bentherali, Palermo, 12Pediatric Oncology Service, Università della Campania “Luigi Vanvitelli”, Napoli, 13Radioterapia Pediatrica e Area Giovani, CRO Aviano (PN)

Background: With 64.6 cases/million/year reported, Hodgkin’s Lymphoma (HL) covers one quarter of all cancers in adolescents (15–19 years), and gives Italy one of the highest incidence rates worldwide. AIEOP-MH96 and AIEOP-LH2004 represent the last two national protocols for HL, with 1904 patients treated between 1996–2017. Elderly pts present a worse prognosis, but little is known about the prognostic factor of age in pediatric population.

Objective: Aim of this study is to evaluate the outcome of adolescents (ages 15 and < 18 yrs) in two AIEOP consecutive studies, and to compare it with the prognosis of younger patients.

Methods: We analyzed all treatment data from 42 Italian Clinical Centers applying the MH96 and the subsequent LH2004 protocol, and collected by AIEOP Operative Centre in Bologna. For each protocol we evaluated the 10-year overall survival (OS), event-free survival (EFS) and Freedom from Progression (FFP) rates registered in adolescents and in younger patients.

Results: From February 1996 to May 2004 and from June 2004 to June 2017, 605 and 1299 patients were enrolled respectively into the MH96 and LH2004 protocols: 560 and 1179 pts were considered evaluable for this analysis. Adolescent HL pts account for 27.5% of our trial population: 16% (90 pts) of MH96 and 32.9% (388 pts) of LH2004. M and 41 F with a median age of 15.9 yrs were the MH96 pts; 186 M and 202 F with a median age of 15.05 yrs the LH2004 ones. Among pts <13yrs, 12.5% were younger than 7 yrs in MH96, while only 7% in LH2004 population. There are no significative differences in stage distribution and in bulky disease. Outcome is reported in the following table; no significant difference was observed between adolescents and younger patients.

Conclusion: In our experience, the proportion of adolescents with HL registered in the last AIEOP protocol redoubled. Even in the <13 yrs group of patients the proportion of older children increased. No differences in OS, EFS and FFP was observed between the adolescents and younger patients, at least when a protocol for pediatric patients was utilized.

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</table>

CVD: cardiovascular disease; IQR: interquartile range; HL: Hodgkin lymphoma; RT: radiotherapy
performed in pediatric cHL, in which age and EBV infection may have a key role. In addition, EBV association with cHL in Argentina is significant in patients under 10 years old. Therefore, our aim was to characterize microenvironment composition in a pediatric cHL series. Formalin-fixed paraffin-embedded (FFPE) biopsy samples from 46 patients were collected from the archives at Pathology Division, Ricardo Gutierrez Children’s Hospital in Buenos Aires, Argentina and Tissue Microarray blocks were constructed. The microenvironment composition was confirmed with antibodies: CD4, CD8, Foxp3 (Treg), granzyme B (GrB). Macrophage polarization was assessed by double staining with pSTAT1 or CMAF followed by CD68 or CD163. Coexpression of pSTAT1 with CD68 or CD163 identified M1-polarized macrophages, while CMAF with CD68 or CD163, identified M2-polarized macrophages. By means of CD68, 81% of cases displayed M1 polarization (CD68+pSTAT1+/CD68+CMAF+ < 0.75), and 7% showed comparable numbers of M1 and M2. CD163 was used, 60% of cases demonstrated to be M1 polarization (CD163+pSTAT1+/CD163+CMAF+ >1.5), 13% exhibited M2 pattern (CD163+pSTAT1+/CD163+CMAF+ < 0.75), in spite of EBV presence and subtype distribution. In patients older than 10 years old, an immunoregulatory-rich environment characterized by higher Foxp3 expression was demonstrated (p = 0.0140). M1 polarization prevailed in patients younger than 10 years old, whereas M2 polarized cells were mostly observed in older patients, by both CD68 and CD163 double staining (p = 0.0004 and p = 0.0085, respectively, FE, test). Using CD68 as marker, CD4, CD8 and Foxp3 cell counts were similar in both M1 and M2 polarized microenvironments (p > 0.05, MW, test), whereas GrB+ cell numbers were significantly higher under M1 polarization (p = 0.0178, MW, test). Survival was influenced neither by macrophage presence nor by cytotoxic or immunoregulatory-rich status. This study reveals that age has an impact on microenvironment composition, given the fact that M2 polarized status previously described in adult may not be prevalent in children younger than 10 years. Cytotoxic and antitumor M1 environment in young pediatric patient might be ineffective to control lymphomagenesis process.

Five UK paediatric clinical oncologists were identified to review all outlining benchmark case submissions from recruiting centres. The initial step in the review process was to establish a standard against which these submissions would be assessed. The 5 reviewers completed and submitted the outlining benchmark case and the 3 case evaluations. Inter-clinician variability was found to be large. As a result, a meeting was convened to agree a consensus standard set of contours (both target volumes and organs at risk) and a response template for the case evaluations. A comprehensive QA programme was devised to ensure protocol compliance as well as accuracy and consistency of treatment across centres recruiting into EuroNet-PHL-C2. The results from this preliminary work has identified large inter-clinician variation in contouring highlighting the need for pre-acrual QA within the complex trial. Consequently, comprehensive outlining QA will continue within the UK as an integral part of the trial.

P097 (0105) IMPLEMENTING AN EFFECTIVE PRE-ACCU RAL QUALITY ASSURANCE PROGRAMME IN THE UK TO ENSURE ACCURACY AND CONSISTENCY OF RADIOTHERAPY CONTOURING FOR PAEDIATRIC HODGKIN’S LYMPHOMA WITHIN THE EURONET-PHL-C2 TRIAL (EUDRACT 2012–004053–88)
P. Díez1, E. Gallop-Evans1, D. J. Cutter2, Y. C. Chang3, S. Sivabalasingham1, T. Ajithkumar1, D. L. Hedegaard1, J. Hayward1
1National Radiotherapy Trials Quality Assurance Group (RITQA). Mount Vernon Cancer Centre, Northwood, UK, 2Velindre Cancer Centre, Cardiff, UK, 3Oxford Cancer & Haematology Centre, Churchill Hospital, Oxford, UK, 4University College London Hospital London, London, UK, 5Adenbrookes Hospital, Cambridge, UK, 6Cancer Research UK Clinical Trials Unit, Birmingham, UK

EuroNet-PHL-C2 is the European Network of Paediatric Hodgkin’s Lymphoma second international Inter-Group Study for Classical Hodgkin’s Lymphoma in Children & Adolescents. It is a multicentre, randomised, controlled, phase III trial to reduce the indication for radiotherapy (RT) and irradiated volumes in newly diagnosed patients without compromising cure rates. An estimated 200 sites worldwide will be participating to recruit ≥2200 patients. RT tumour delineation guidelines have changed significantly from the previous (C1) study, resulting in a departure from current clinical practice in paediatric lymphoma. Central staging & response assessment is in place to minimise variation across centres; however, there is no prospective central review for RT contouring. In the UK, a pre-acrual quality assurance (QA) programme was deemed essential to monitor contour implementation of changes across all centres ensuring accurate & consistent contouring, and hence compliance with the trial protocol. The UK National Radiotherapy Trials QA (RITQA) group in conjunction with the UK reference clinical oncologist have implemented a comprehensive QA programme that includes a UK RT guidelines document to complement the trial RT Manual. The pre-acrual QA programme focused on RT delineation; the main area where inter-departmental variability was expected. An outlining benchmark case and 3 clinical case evaluations were produced to assess clinicians’ understanding of the trial protocol.

P099 (0117) SURVIVAL BY AGE IN CHILDREN AND ADOLESCENTS WITH HODGKIN LYMPHOMA: A POOLED ANALYSIS OF CHILDREN’S ONCOLOGY GROUP (COG) TRIALS
Justine M. Kahn1, Kara M. Kelly2, Qinglin Pei3, Debra L. Friedman4, Frank Keller5, Rizwan Bushi6, Simria Bhatia7, Tara O. Henderson5, Cindy L. Schwartz1, Sharon M. Castellino1
1Columbia University Medical Center, New York, New York, USA, 2Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA, 3Children’s Oncology Group, Statistics & Data Center, University of Florida, Gainesville, Florida, USA, 4Vanderbilt University School of Medicine, Nashville, Tennessee, USA, 5Emory University, Aflac Cancer and Blood Disorders Center, Children’s Healthcare of Atlanta, Atlanta, Georgia, USA, 6Children’s Oncology Group, Statistics and Data Center, Monrovia, California, USA, 7University of Alabama at Birmingham, Birmingham, Alabama, USA, 8University of Chicago, Children’s Hospital, Chicago, Illinois, USA, 9Children’s Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

Background: Population-based studies in the U.S. and analyses of adult cooperative group trials have reported inferior outcomes in adolescence/young adults (AYAs) with Hodgkin lymphoma (HL). While 15 years (y) is the lower age threshold for delineating AYA cancer outcomes in most countries, recent guidance from the American Society of Clinical Oncology and Friends of Cancer Research calls for including children ≤12y on late phase trials. We examined outcomes by age category (<12y or ≥12y; <15y or ≥15y) in children and adolescents receiving response-based therapy for HL.

Methods: This was a pooled analysis of individual patient-level data from three COG Phase 3 trials for intermediate low, and high-risk HL (AHOD0031, AHOD0431, AHOD0831). Five-year event free survival (EFS) and overall survival (OS) were estimated by age category via Kaplan Meier method. Cox regression models examined the influence of age on EFS and OS, adjusted for demographics, histology, Ann Arbor stage, B symptoms, bulk, study, and radiation therapy (RT).

Results: Median follow-up was 6.9 years. We included 2071 of 2155 patients (1 patients – 21y) enrolled on COG HL trials in the U.S. or Canada between 2002 and 2012. Mean age was 14.6y (±3.5) with 54% ≥15y (N = 1121) and 46% <15y (N = 1684). In unadjusted analyses, patients ≥15y had statistically significantly worse EFS than those <15y (80% vs. 85%, p = 0.02). A difference in EFS was also noted in those ≥12y vs. <12y (81% vs. 87%, p = 0.0503). OS was significantly worse in patients ≥15y (95% vs. 98%, p = 0.006), but did not differ in <12y vs. ≥12y (99% vs. 97%, p = 0.14). In multivariable models, older age was an independent predictor of EFS in both age categories (Table), and patients <15y had significantly worse OS.

Conclusions: In patients treated for HL with response-based therapy on contemporary COG trials, adolescents ≥12y had worse EFS than younger groups. This suggests that in HL, age ≥12y defines a high risk cohort who may benefit from therapy escalation and/or inclusion in late phase trials of novel agents.

Table: Multivariable model of 5-year event-free survival (EFS) and 5-year overall survival (OS) by age category

<table>
<thead>
<tr>
<th>Age Group</th>
<th>5-Year EFS</th>
<th>5-Year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>&lt;12y (N=126)</td>
<td>1.52 (1.06, 2.19)</td>
<td>0.024</td>
</tr>
<tr>
<td>≥12y (N=1684)</td>
<td>1.43 (1.12, 1.83)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

HR: hazard ratio; 95% CI: 95% confidence interval; RT: reference group
P100 (0119) FMHL: GENETIC STUDY OF FAMILIES WITH A HIGH FREQUENCY OF CLASSICAL HODGKIN LYMPHOMA

Jamie E. Fleitlage1, Lynn Goldin2, Mary L. McMaster3, Charles Mullighan4, Michael Wolfe4, Chirine Kessarwan4, Kayla Hamilton1, Jamie Maciaszek4, Evadnie Rampersaud4, Gang Wu4, Max Qian5, Monika L. Metzger6, Jun J.Yang7

1Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA, 2National Cancer Institute, Bethesda, MD, USA, 3Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN, USA, 4Department of Computational Biology, St. Jude Children's Research Hospital, Memphis, TN, USA, 5Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA.

Background: Classical pediatric Hodgkin lymphoma (cHL) is rare with documented familial aggregation and thus a plausible genetic basis for disease susceptibility. Large population studies have shown that first-degree relatives of individuals with cHL have 2- to 6-fold increased risk of developing cHL. Responsible pathogenetic mechanisms are largely unknown and few genetic aberrations have been described to date. Genome-wide association studies identified genetic variations at the HLA locus at 6p21.32 and analysis of whole-exome sequencing of affected individuals from 17 families with a high frequency of cHL found a potential germline predisposing mutation in the KDR gene. Recent advances in genomic profiling techniques enable comprehensive examination of risk variants at single base-pair resolution throughout the genome. Taking such a systematic approach, we sought to perform whole genome sequencing (WGS) on kindreds with a high frequency of cHL (affected and unaffected family members) to comprehensively describe the genomic basis of predisposing variants in familial HL.

Methods: Families were identified from St. Jude Children's Research Hospital (SJCRH), outside referrals and via collaboration with the National Cancer Institute (NCI) and were eligible if one person was diagnosed with cHL ≤ 21 years of age and has another affected first-degree relative. Affected and unaffected family members are eligible. Germline DNA was subjected to WGS. Data were analyzed using Genome Analysis Toolkit, Bambino, CONCERTING and CREST for mapping, variant calling, and identification of structural variations. Potential cHL risk alleles were identified on the basis of co-segregation with the disease phenotype, frequency in controls, and predicted functional consequences.

Results: To date, whole genome sequencing has been performed on 229 individuals comprised of 12 families (50 individuals) from SJCRH and 23 families (179 individuals) through collaboration with the NCI. 77 individuals comprised of 12 families (50 individuals) from SJCRH and 23 families (179 individuals) through collaboration with the NCI. 77 individuals were affected with cHL. (38 female, 39 male, average age at diagnosis 21.8 years (range 11-75) and 152 were unaffected (86 female, 66 male, average age 44.7 years in those collected from SJCRH). Results from WGS of these families will be presented.

P101 (0149) PHASE 1/2 STUDY OF BRENTUXIMAB VEDOTIN PLUS AVD IN PEDIATRIC PATIENTS WITH ADVANCED STAGE NEWLY DIAGNOSED CLASSICAL HODGKIN LYMPHOMA

Anna Franklin1, Marco Zecca2, Flavio Augusto Luisi2, Gregory Song2, Ailt Sur1, E. Jane Leonard1, Franco Locatelli1

1Children’s Hospital Colorado, Aurora, USA, 2Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. 1Gruppo de Apoio ao Adolescente e à Criança com Câncer, São Paulo, Brazil, 2Millennium Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA, 3Ospedale Pediatrico Bambino Gesù, Rome, Italy

Background: Pediatric patients (pts) with classical Hodgkin lymphoma (cHL) have improved outcomes compared with adult pts. However, many cHL patients remain treatment refractory to current treatment options and the majority, including secondary malignancies, cardiovascular disease, and infections. Furthermore, serious sequelae of radiation and alkylating chemotherapy (chemo) are pronounced in younger pts, in whom growth and development are particularly active when therapy is administered. Including brentuximab vedotin (Adcetris [A]) as a component of multi-agent chemo for pediatric pts may provide clinical benefit by decreasing the need for radiotherapy following chemo, and reducing the risks of late effects associated with radiotherapy.

This phase I/2, open-label, multicenter study will assess the feasibility of A in combination with doxorubicin, vinblastine, and dacarbazine (AVD) in pediatric pts with advanced stage, newly diagnosed, CD30+ cHL.

Methods: Eligible pts are 5 to <18 years of age, with stage III or IV cHL, Lansky Play/Karnofsky Performance Status ≥50, and bidimensional measurable disease by radiography.

In the phase 1 portion of the study, up to 6 DLT-evaluable pts will be enrolled into a dose-escalating cohort (48 mg/m2) with a dose-escalation cohort (36 mg/m2) available if needed, to determine the recommended phase 2 dose (RP2D) of A using a modified 3+3 design. For pts enrolled into a phase 2 with RP2D the study will then be expanded to phase 2. A+AVD will be administered on days 1 and 15 of each 28-day cycle for up to 6 cycles.

Phase 1 primary objectives are to assess safety and tolerability, and determine RP2D. Phase 2 primary objectives include overall, complete, and partial response rates, the proportion of pts PFS-negative after 2 cycles, and the proportion of pts who complete 6 cycles of therapy at RP2D. Secondary phase 2 objectives include evaluation of progression-free, event-free, and overall survival (PFS, EFS, OS), duration of response, immunogenicity, pharmacokinetics, safety, and immune reconstitution. Response to treatment includes assessment by CT, MRI, and PET after cycle 2 day 25 and between 3–7 weeks after last dose (end of treatment). Follow-up for PFS and OS will be performed every 12 weeks for 12 months, then every 24 weeks thereafter for a maximum of 2 years from date of last pt enrolled. Phase 2 is currently open for enrollment in the USA, Italy, Singapore, Taiwan, Hong Kong, Japan, and Brazil. Clinical trials.gov NCT02979522.

P102 (0151) DURABLE REMISSION FOR TWO PATIENTS WITH EARLY RELAPSE OF HODGKIN LYMPHOMA, TREATED WITH BRENTUXIMAB VEDOTIN PLUS GEMCITABINE, WITHOUT AUTOLOGOUS STEM CELL TRANSPLANTATION: A REPORT FROM THE CHILDREN’S ONCOLOGY GROUP

Illa Buhitioarav1, Nkechi Mba2, Crystal De Los Santos3, Kathleen M. McCarty1, Monika L. Metzger2, Qinglin Pei1, Rizvan Bush1, Kara M. Kelly1, Aron Flagg3, Rabi Hanna4, Peter Cole5

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Background: High-dose chemotherapy with autologous stem cell rescue (HDC/ASCR) improves long-term outcomes for patients with primary treatment-refractory classical Hodgkin lymphoma (cHL) or those with early relapse. Most novel salvage regimens are currently developed as a “bridge” to transplantation, with the objective of producing a metabolic complete response prior to proceeding to HDC/ASCR. However, an increasing body of clinical experience suggests that some patients with relapsed cHL can be cured without undergoing HDC/ASCR. The Children’s Oncology Group (NCCT017800) tested the efficacy of a novel combination, Brentuximab Vedotin with Gemcitabine (Bv+G). By central review, 29 of 42 patients with primary refractory cHL or early relapse experienced a complete response. The majority, 34 of 42 underwent stem cell transplantation.

Results: Two patients who experienced biopsy proven early relapses of cHL after standard therapy were enrolled in AHOD1221 and treated with Bv+G. Their clinical characteristics and treatment course is summarized in the Table. Both subjects achieved a second CR within four cycles of Bv+G, but declined to proceed to HDC/ASCR. Both remained on study treatment for more than 10 months. One patient stopped therapy after 14 cycles, due to persistent grade 2 peripheral neuropathy. Her neurologic symptoms resolved over the subsequent 8 months. The second patient was taken off study therapy, per protocol, after completion of 16 cycles (1 year of treatment) with no adverse events reported in the final cycles. Neither subject has experienced a subsequent relapse, more than a year since their last cycle of Bv+G.
survival that has exceeded the duration of first CR. The results sug-
ggest that some patients with early relapse of cHL may be cured with
prolonged treatment using Bv+G, without high-dose chemotherapy and
stem cell rescue. Additional clinical study of transplant-avoiding salvage
strategies may be warranted.

P103 (0152) STANFORD V CHEMOTHERAPY AND LOW DOSE RADIOThERAPY FOR CHILDREN AND ADOLESCENTS WITH UNFAVORABLE AND INTERMEDIATE RISK HODGKIN LYMPHOMA: RESULTS OF A MULTI-INSTITUTIONAL PROSPECTIVE CLINICAL TRIAL

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Purpose: To evaluate the efficacy of 12 weeks of Stanford V chemotherapy (prednisone, vinblastine, doxorubicin, nitrogen mustard, etoposide, cisplatin, vinorelbine, and bleomycin) without routine growth factor support plus response-adapted low-dose, conformal radiotherapy (CRT) in children and adolescents with unfavorable or intermediate risk Hodgkin lymphoma (HL) (respectively).

Patients and methods: Multi-institutional (St. Jude Children’s Research Hospital, Stanford University, Children’s Hospital Boston, Massachusetts General Hospital and Maine Children’s Hospital) clinical trial. One hundred ninety-three patients with clinical stages IB (n = 10.7%), the most common grade 3/4 TRAEs were white cell count decreased (25.3%), neutrophil count decreased (22.7%), hypothyroidism (21.3%), upper respiratory tract infection (20.0%), ALT increased (18.7%), anemia (17.3%), infusion-related reaction (14.7%), cough (10.7%) and TSH increased (10.7%). The most common grade 3/4 TRAEs were white cell count decreased (4.0%), lymphocyte count decreased (4.0%), p-glycosyltransferase increased (2.7%), neutrophil count decreased (2.7%), neutropenia (1.4%), thrombocytopenia (1.0%), and diarrhea (1.0%).

Conclusions: These results from an on-going study in heavily pretreated R/R cHL patients demonstrate that PD-1 blockade with SHR-1210 has a manageable safety profile and promises antitumor activity.

TO28 (0163) ALLOGENEIC STEM CELL TRANSPLANTATION (allo-SCT) FOR RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA (cHL) PATIENTS TREATED WITH NIVOLUMAB IS ASSOCIATED WITH AN UNPRECEDENTED LOW RELAPSE RATE

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Introduction: Phase 1/2 trials using PD-1 inhibitors in relapsed/refractory (r/r) cHL who failed brentuximab vedotin (BV) and autologous SCT (Auto-SCT) showed unprecedented rates of complete/partial response (CR/PR) and durable responses. However, the absence of a plateau in the PFS curves indirectly suggests that allo-SCT may represent a consolidation therapy for patients responding to PD-1 therapy.

Methods: From Nov 2014 to Dec 2016, 37 r/r cHL enrolled in the CA209-205 and CA209-234 trials (median age, 32 years; range, 18–81) received nivolumab until CR, PR (tumor burden reduction ≥30%) or progressive disease (PD). At study entry, 30 patients (81%) had primary refractory disease, 32 (86%) had failed BV and 33 (89%) Auto-SCT.

Results: After a median duration of nivolumab therapy of 10 months (range, 3–33), 16 cases (43%) experienced CR/PR and 21 cases (57%) PD. Fourteen of 16 responding patients were allografted. Thirteen of

Immunotherapy - Clinical

T026 (0025) A PHASE II STUDY OF SHR-1210, AN ANTI-PD-1 ANTIBODY, IN CHINESE PATIENTS WITH RELAPSED/REFRACTORY CLASSIC HODGKIN LYMPHOMA

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Background: Classical Hodgkin lymphoma (cHL) is characterized by chromosome 9p24.1 alterations (including amplification), leading to overexpression of the PD-L1/PD-L2 immune checkpoint ligands. This genetically determined dependence on the PD-1 pathway makes cHL an attractive target for PD-1 blockade treatment with the anti-PD-1 monoclonal antibody, SHR-1210. SHR-1210-II-204 is a phase 2 study designed to evaluate the efficacy and safety of SHR-1210 in Chinese patients with relapsed/refractory (r/r) cHL.

Methods: SHR-1210-II-204 (NCT03155425) is a multicenter, single-arm, phase 2 study of SHR-1210 in Chinese patients with r/r cHL who relapsed after autologous stem cell transplantation (ASCT) or relapsed refractory to at least 2 prior systemic treatment and ineligibility for ASCT. Patients received SHR-1210 at a fixed dose of 200 mg intravenously every 2 weeks. Response was assessed with CT/MR and FDG-PET according to the 2014 Lugano Criteria for Malignant Lymphomas. The primary end point was ORR per blinded independent central review (BICR). All patients who received at least 1 dose of SHR-1210 were included in the analyses. Informed consent was obtained for all patients. The data cutoff date for these analyses was Mar 18, 2018 that is six months after the last patient received the first dose.

Results: 75 patients were enrolled between June 9, 2017, and September 18, 2017. All patients had relapsed or refractory cHL. Among them, 66.7% had received ≥3 prior lines of systemic chemotherapy, 8% of patients had progressive disease after BV, and 12% of patients had progressive disease after ASCT. Per BICR, the ORR (95% CI) was 82.7% (72.2%–90.4%) and CRR was 26.7%. With a median of 15 treatment doses, the most common TRAEs were skin hemangioma (97.3%), fever (41.3%), white cell count decreased (25.3%), neutrophil count decreased (22.7%), hypothyroidism (21.3%), upper respiratory tract infection (20.0%), ALT increased (18.7%), anemia (17.3%), infusion-related reaction (14.7%), cough (10.7%) and TSH increased (10.7%). The most common grade 3/4 TRAEs were white cell count decreased (4.0%), lymphocyte count decreased (4.0%), p-glycosyltransferase increased (2.7%), neutrophil count decreased (2.7%), neutropenia (1.4%), thrombocytopenia (1.0%), and diarrhea (1.0%).

Conclusions: These results from an on-going study in heavily pretreated r/r cHL patients demonstrate that PD-1 blockade with SHR-1210 has an unprecedented rate of complete responses in a Chinese population with a high-risk disease.
21 patients in PD after Nivolumab achieved an objective response (CR or PR) after additional chemotherapy or radiotherapy and were finally allografted. Overall, 27 of 37 patients were allografted with a median follow-up of 19 months for survivors (range, 3–40). The median time from last nivolumab to Allo-SCT was 47 days (range, 23–372). At Allo-SCT, 18 patients (67%) were in CR, 8 (30%) in PR and 1 (3%) in PD. Donors were haploidentical sibling (n = 19), matched sibling (n = 4), or matched unrelated (n = 4). Stem cell source was bone marrow (n = 11) and peripheral blood (n = 16). Five patients died due to disease progression (n = 1) or non-relapse mortality (NRM, n = 4, including aGVHD, CMV pneumonia, heart failure, PTLD). The 2-year cumulative incidence (CI) of relapse and NRM was 3.8% and 12%, respectively. The CI of grade 2–4 and grade 3–4 acute GVHD was 46% and 10%, respectively; the 1-year CI of cGVHD was 22%. Five patients experienced macrophage activation syndrome, 13 cytokine release syndrome, 1 posterior reversible encephalopathy syndrome. The 2-year OS and PFS were 74% (95% CI, 45 to 89) and 75% (95% CI, 46 to 90), respectively.

Conclusion: Allo-SCT after nivolumab or nivolumab plus chemotherapy has a manageable toxicity and is associated with an unprecedented low relapse incidence. PD-1 inhibitors represent a paradigm shift in the treatment of relapsed and refractory cHL.

P104 (0004) NIVOLUMAB IN RELAPSED/REFRACTORY CLASSIC HODGKIN LYMPHOMA: EXPERIENCE WITH TEN PATIENTS
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Objectives: One of the newly discovered mechanisms to escape the immune response in classic Hodgkin lymphoma (cHL) is to induce immune tolerance through interaction of program cell death 1 (PD-1) on activated T cells and PD ligand-1 (PD-L1) on tumor cells. Tissue of patients with cHL was recently found to overexpress PD-L1. Nivolumab is a novel checkpoint inhibitor designed to block PD-1 and inhibits interaction between PD-1 and PD-L1. Unlike many available antibodies and chemotherapy agents, nivolumab itself is not cytotoxic but rather inhibits the tolerance of tumor cells through activation of the immune system.

Patients and methods: We report on ten patients with relapsed/refractory cHL who were treated between 05/2016 and 03/2018 with single agent nivolumab in a tertiary care hospital. Follow-up was performed after 4 cycles with positron emission tomography (PET). Patients’ files were retrospectively analyzed.

Results: Mean age was 26.2 years (range: 15–40). Prior to nivolumab 3/10 and 5/10 patients failed ASCT and brentuximab vedotin respectively. Mean follow-up time was 12.3 months (range: 5–32). Average of prior lines was 6.3. After 4 cycles of nivolumab response rate was 80% with complete metabolic (CR) and partial remission rates of 70% and 10%, respectively. In one case PET showed stable disease and another patient experienced progressive disease. Three deaths occurred after 32, 9 and 5 months of nivolumab’s initiation. One patient experienced pneumonitis grade 2 and was manageable by oral steroids. Another patient had an asymptomatic TSH elevation. Two patients had grade 2 neutropenia. No serious adverse events (grade ≥3) were observed. All patients experienced a remarkable improvement of quality of life. On treatment start, two patients had performance status ECOG 3 and 4 which were attributed to refractory Hodgkin lymphoma. They recovered dramatically each to ECOG 2 within 7 days and 10 days after nivolumab start respectively.

Conclusion: The CR rate seen in our cohort supports the high sensitivity of relapsed/refractory cHL to checkpoint inhibition. Nivolumab induces impressive clinical and radiological responses with excellent tolerance. The drug enriches our treatments armamentarium in treating cHL. Further controlled studies are needed to determine the effectiveness on a large patients’ cohort.

P106 (0131) CLINICAL BENEFIT OF NIVOLUMAB IN HODGKIN LYMPHOMA BUT AT WHAT PRICE? EXAMPLE INTO A PARIS UNIVERSITY HOSPITAL
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Introduction: In France, Nivolumab, registered for classical Hodgkin Lymphoma (HL) after failure from both autologous stem-cell transplantation and brentuximab vedotin is reimbursed into diagnosis-related group (DRG) tariffs. The study assesses the use in standard practice and efficacy of Nivolumab in HL and determines the economic impact of this use into a Paris hospital budget.

Methods: The data were collected from 03/2015 to 12/2017 from: Chimio® (software of chemotherapy prescription), Copilote® (software of management) and medical record systems Middlecare®.
Relapsed/Refractory HL

T030 (0103) BENZAMUSTINE, GEMCITABINE, AND DEXAMETHASONE (BGD) CHEMOTHERAPY FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IS EFFECTIVE TREATMENT FOR PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA (RHL) – RESULTS OF THE POLISH LYMPHOMA RESEARCH GROUP (PLRG) PILOT STUDY – PRE-PLRG-HL1 (BURGUND)

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Background: Bendamustine (B) and Gemcitabine (G) are active agents in rHL with complete response (CR) rates of around 70% (Santoro et al JCO 2016). We report here on the early results of a pilot prospective, multicenter study by PLRG of BGD chemotherapy followed by ASCT as a salvage for rHL after ABVD failure.

Patients and Methods: Patients with rHL who were eligible for ASCT received BGD regimen of bendamustine 90 mg/m² iv, days 1, 2, gemcitabine 800 mg/m² iv, days 1, 4, dexamethasone 20 to 40 mg iv po days 1–4, q3 weeks for up to 4 cycles.

Response to therapy was evaluated with PET-CT after second cycle and before ASCT according to RECIC criteria (Younes A et al Ann Oncol 2017). Stem-cell collection was done between 1st and 3rd BGD cycle. Patients in CR proceeded to ASCT. The primary endpoint was progression-free survival (PFS) after completion of BGD and ASCT.

The secondary endpoints were: CR rate at the time of ASCT, cell mobilization rate (MR) and toxicity. Overall survival (OS) will be evaluated in longer follow up.

Results: 30 pts were enrolled, 15 male, median age 28 (range 22–47), 23 pts (77%) were primary refractory; 7 relapsed more than 1 year after the first-line treatment. Patients received 2 (n = 9), 3 (n = 9), or 4 (n = 10) cycles of BGD. 2 patients discontinued BGD after 1st cycle due to skin reaction and received subsequent ICE before ASCT. Response rates after 2 cycles were: CR 70% (21/30), PR 17% (5/30), PD 10% (3/30).

CR converted to CR after additional 2 BGD cycles in all cases. 27 patients were successfully mobilized for stem-cell collection without plerixafor. 26 pts with CR (86%) by PET/CT proceeded to ASCT. Median follow-up is 12.2 months. 1-year PFS 68% (49% – 87%)

Grade ≥ 3 adverse events included pneumonia (10%), skin toxicity (10%), nausea (10%), fever (7%).

Conclusion: Early results of BGD/ASCT treatment in patients with mostly refractory HL are encouraging with CR rate of 86% before ASCT. BGD is effective mobilization regimen and has acceptable toxicity. These preliminary results support a prospective study which is currently ongoing.
At 5 years, BV continued to provide a PFS benefit: 5-year PFS was 59% (95% CI, 51%–66%) in the BV arm vs 41% (95% CI, 33%–49%) in the placebo arm (HR, 0.521 [95% CI, 0.379–0.717]). Patients with ≥ 2 or ≥ 3 risk factors in the BV arm experienced a significantly higher PFS benefit than patients in the placebo arm (HR, 0.424 [95% CI, 0.302–0.596]; HR, 0.390 [95% CI, 0.253–0.596], respectively). An analysis of subsequent therapies was performed to measure ongoing disease control before a planned overall survival analysis in 2020. At 5 years, 36% and 46% of patients in the BV and placebo arms, respectively, had received ≥ 2 subsequent HL therapies or had died (HR, 0.656 [95% CI, 0.467–0.922]); 40 and 37 deaths occurred in each arm, respectively. The majority (87%) of patients in the placebo arm received BV as subsequent therapy, and subsequent HSCT was less frequent in the BV arm (12%) than in the placebo arm (21%). Peripheral neuropathy (PN), the most common adverse event in the BV arm, continued to improve and/or resolve: at 5 years, 90% of patients reported their PN as resolved or improved, including 73% with complete resolution.

Consolidation with BV in patients with cHL at high risk of relapse/progression after auto-HSCT confers a sustained PFS benefit and is safe and well tolerated. These data demonstrate a reduction in the need for subsequent therapy in patients who received BV as consolidation after first auto-HSCT, even when most patients in the placebo arm received subsequent BV at relapse.

Summary: After contemporary treatment for early-stage favorable HL, relapse mostly occurs >12 months after first diagnosis. Polychemotherapeutic regimens such as BEACOPP or ABVD are frequently administered and may constitute a reasonable treatment alternative to ASCT in this setting.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>95% Confidence Limits</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTx (vs. ASCT)</td>
<td>0.699</td>
<td>0.310</td>
<td>1.577</td>
</tr>
<tr>
<td>Age &gt; 60y (vs. age 60y)</td>
<td>2.969</td>
<td>1.451</td>
<td>6.076</td>
</tr>
<tr>
<td>ASCT in HD10 (vs. ASCT in HD13)</td>
<td>2.837</td>
<td>1.046</td>
<td>7.698</td>
</tr>
</tbody>
</table>

* Cox proportional hazards regression of PFS on treatment, age and a historical effect of ASCT in HD10 (N=155, 36 events).

P108 [0001] ALLOGENEIC STEM CELL TRANSPLANTATION AFTER TREATMENT WITH CHECKPOINT INHIBITORS: FEASIBILITY AND SAFETY IN POOLED ANALYSIS

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Background: Checkpoint inhibitors are revolutionizing the management of relapsed/refractory Hodgkin lymphoma. Despite approvals of nivolumab and pembrolizumab after autologous stem cell transplantation, a.e. to bridge patients to allogeneic stem cell transplantation, there are some concerns around an increased toxicity of allogeneic stem cell transplantation after pretreatment with checkpoint inhibitors.

Methods: We reviewed the published data of patients undergoing allogeneic stem cell transplantation after treatment with checkpoint inhibitors. Data in PubMed, EMBASE, Google Scholar and the Cochrane Library using the key words “Nivolumab”, “Pembrolizumab”, “Hodgkin lymphoma” and “allogeneic transplantation” was collected. Abstracts of recent conferences (2015–2017) of American Society for Clinical Oncology (ASCO), American Society of Hematology (ASH) and European Group for Blood and Marrow Transplantation (EBMT) were also included in the analysis. The results were compared with safety of recent studies with allogeneic stem cell transplantation in cHL (2015–2018).

Results: Total of 259 records with 1100 patients were screened. In the investigational cohort (cohort 1) we processed data of 6 publications with a total of 122 patients. In the comparator arm (cohort 2), we found another 6 publications with 978 patients reporting on GVHD and/or NRM. Acute grade 3–4 GVHD in cohort 1 was found in 28% in comparison with 8% in cohort 2. Chronic GVHD was observed in 26% versus 29% respectively. NRM was 15% which remained relatively stable after 6 months of allogeneic stem cell transplantation versus 19% in cohort 2. There was no association found between number of cycles of checkpoint inhibitor prior to allogeneic stem cell transplantation or days from last administration of checkpoint inhibitor to allogeneic stem cell transplantation and grade 3–4 acute GVHD.

Conclusion: This is the largest pooled analysis of its kind published so far. Based on our results, allogeneic stem cell transplantation after checkpoint inhibitors seems to be feasible and not associated with higher mortality. However, careful consideration should be given for prevention, early detection and effective treatment of GVHD in these cases.
P110 (0014) SUCCESSFUL TREATMENT OF HODGKIN LYMPHOMA WITH BRENTUXIMAB VEDOTIN RELAPSING AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background: Hodgkin lymphoma (HL) is cured in more than 80% of cases with the first-line treatment, however, the prognosis of repeated relapses was poor. The introduction of new drugs like brentuximab vedotin (BV) and anti PD-1 inhibitors improved the prognosis of repeated relapses of HL after autologous stem cell transplantation (ASCT) significantly.

Case report: 32-year-old female patient with HL nodular sclerosis, clinical stage IVB, international prognostic score 3 was treated with 6 cycles of BEACOPP escalated between 08 – 12/2011. Restaging after chemotherapy confirmed a PET-negative complete metabolic remission with residual PET-negative mediastinal mass (3.5 cm). Radiotherapy was not indicated. The first relapse occurred early - 5 months after the first line-treatment (5/2012). Salvage therapy included: 2x DHAP (dexamethasone, cytarabine, cisplatinum), irradiation of residual mediastinal tumour (30 Gy, high dose chemotherapy BEAM (BCNU, etoposide, cytarabine, melphalan) and ASCT. She achieved a PET-negative complete remission 3 months after ASCT (12/2012). The second early relapse of the CD30-positive HL occurred in 06/2013. She received 16 doses of BV (7/2013 - 6/2014). A significant tumour reduction was observed after 4 doses and a PET-negative complete remission was confirmed after 8 doses of BV. Polynephropathy (CTCAE grade III) was the only complication of BV treatment and it disappeared one year after the last infusion of BV. The patient refused autologous stem cell transplantation. The patient is in continuous complete remission (PET/CT-negative) lasting 4 years and she is in a very good clinical condition.

Conclusion: The goal of BV treatment in relapsed HL after ASCT is to achieve a longlasting complete remission and it is not only a bridge to allogeneic stem cell transplantation. Currently the best approach after BV-observation or early indication to allogeneic stem cell transplantation is still a matter of debate. Introduction of anti PD-1 inhibitors enables to postpone the decision regarding allogeneic stem cell transplantation to the next relapse.

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Keywords
Relapsed Hodgkin lymphoma, Autologous stem cell transplantation, Brentuximab vedotin.

P113 (0040) PHASE I/II STUDY OF BRENTUXIMAB VEDOTIN RELAPSING IN FIRST REFRACTORY/RELAPSED CLASSICAL HODGKIN LYMPHOMA PATIENTS TREATED BY CHEMOTHERAPY (ICE) BEFORE AUTOLOGOUS TRANSPLANTATION

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Introduction: About 10–15% of patients with localized and 25–30% with disseminated classical HL failed to respond or relapse after primary conventional treatment. Autologous stem cell transplantation (ASCT) is a standard of care after salvage chemotherapy leading to an increased disease free survival (DFS). With this strategy 50 to 70% of patients with chemotherapy sensitive disease become eligible for ASCT. As the disease status before ASCT appears to be the most important factor predicting outcome, second line chemotherapy has to be more efficient. Brentuximab-Vedotin (BV) has shown significant activity (SGO35–0003) in patients with relapsed or refractory HL. Therefore, it seems logical to use BV in patients treated with ICE before ASCT to induce a significantly higher Complete Metabolic Response (CMR) rate evaluated by FDG-PET (Deauville score 1–3).

Methods: BV-ICE is a phase II/I trial sponsored by LYSARC with a financial support by Millenium. BV is added to ICE chemotherapy in order to increase the CMR in refractory/relapsed Hodgkin lymphoma patients. The optimal dose of BV with ICE (3 cycles) was established and validated by the independent data monitoring committee (IDMC), in the first part of the study and applied in the second part (phase II) where efficacy and toxicity were assessed after 2 cycles of treatment.

Primary endpoint of Recommended Phase II Dose (RP2D) and CMR after 2 cycles of treatment (early futility analysis by Lugano classification 2014) are reported here.

Results: Ten patients were included in phase I. Four and six patients received 1.2 mg/kg and 1.8 mg/kg of BV respectively. Thirteen patients were included in the first part of phase II with the recommended dose of BV: 1.8 mg/kg, Baseline characteristics of the 23 patients were median age: 28 years (range: 18–55), Sex ratio (MF): 17/6, and status of the disease: 11 refractory patients and 12 relapsed patients.

Most of patients (78%, n = 18) had CMR at the end of cycle 2 followed by PMR (13%, n = 3). Two patients (9%) had no metabolic response or progressive metabolic disease. Grade 3–4 adverse events were encountered in 18 patients (78%) mainly due to hematologic toxicity (52%) followed by infection (17%) and gastro-intestinal disorders (9%). No death was observed.

Conclusion: This study recommends a dose of 1.8 mg/kg of BV in R/R HL patients who are treated by ICE chemotherapy and shows encouraging results of efficacy with 78% of CMR after 2 cycles of treatment and acceptable toxicity.

P114 (0041) RESULTS OF MINI-BEAM AS SECOND SALVAGE CHEMOTHERAPY AFTER DHAP BASED CHEMOTHERAPY FOR RELAPSING OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA

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Background: Patients with refractory or relapsed classical Hodgkin lymphoma (R/R cHL) who are refractory to salvage chemotherapy generally have a poor prognosis. The aim of this study was to evaluate results of second line salvage chemotherapy with mini-BEAM (carmustine 60 mg/m2 day 1, etoposide 75 mg/m2 bid day 1–2, cytarabine 400 mg/m2 bid day 2, and melphalan 30 mg/m2 day 2) in case of refractory disease to DHAP based (dexamethasone 40 mg/m2 day 1–2, carboplatin 2000 mg/m2 bid day 2 and cisplatin 100 mg/m2 day 2) salvage chemotherapy.

Methods: Nineteen-one patients with R/R cHL treated with DHAP based salvage chemotherapy between 1989 and 2017 at the University Medical Center Groningen were retrospectively identified. Response to DHAP and/or mini-BEAM was assessed with computer tomography and/or Positron Emission Tomography imaging. Patients with a complete response (CR) or partial response (PR) after DHAP chemotherapy proceeded to high dose chemotherapy and autologous stem cell transplant (ASCT). Patients with less than a PR were considered for mini-BEAM.

Results: Of the 91 patients with R/R cHL, a CR, PR and stable disease (SD) or progressive disease (PD) after DHAP chemotherapy was observed in 37 (41%), 26 (29%) and 28 (31%) patients, respectively.

Sixty-four patients (70%) directly proceeded to ASCT. Twenty patients (22%) with a PR or SD received mini-BEAM as second salvage. Four patients (4%) did not receive transplant because of disease progression (1), failure to harvest stem cells (2) or patient’s choice (1). Three patients died due to treatment toxicity (4%). Of the 20 patients who received mini-BEAM, 6 patients (30%) had CR and 4 patients (20%) had a PR. Fifteen patients (75%) proceeded to ASCT. The remaining 5 patients (25%) received palliative care because of PD. A CR after ASCT was observed in 10 of 15 patients (67%) treated with mini-BEAM as second salvage and was highly dependent on the response before ASCT. The 5-year progression-free survival and OS rate for patients receiving mini-BEAM followed by ASCT were 50% and 60%, respectively, com-
pared to 75% and 77% for patients who directly proceeded to ASCT after DHAP chemotherapy.

Conclusion: Second salvage chemotherapy with mini-BEAM after failure to DHAP based first salvage therapy results in an overall response rate of 50% and favorable long-term survival after ASCT. Second salvage chemotherapy with mini-BEAM is a successful alternative in the era of more targeted and immunomodulating drugs.

**P115 (0048) BRENTUXIMAB VEDOTIN (BV) AS MAINTENANCE OR SALVAGE THERAPY AFTER ASCT FOR RELAPSED/REFRACTORY (R/R) HL**

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*no affiliations*

**Introduction:** Brentuximab vedotin (BV) is a chimeric anti-CD30 IgG1 antibody, currently approved for treating classical HL in relapse following either autologous stem cell transplantation (ASCT) or 2 lines of combination chemotherapy in transplant- ineligible patients. High-dose therapy followed by autologous stem-cell transplantation is standard of care for patients with relapsed or primary refractory Hodgkin’s lymphoma. Roughly 50% of patients might be cured after autologous stem-cell transplantation; however, most patients with unfavourable risk factors progress after transplantation. Previous data from the AETHERA trial demonstrated increased PFS in patients receiving BV as maintenance therapy following ASCT.

**Objective:** Evaluate the effectiveness of BV as maintenance or salvage therapy after ASCT for relapsed/refractory (R/R) HL. The primary endpoints included response rate, overall survival, progression-free survival and safety.

**Materials and methods:** Nine patients with unfavourable-risk relapsed or primary refractory classic Hodgkin’s lymphoma who had undergone autologous stem-cell transplantation have been planned to receive 16 cycles of 1.8 mg/kg brentuximab vedotin every 3 weeks, starting 30–45 days after transplantation.

**Result:** Median age of the patients is 30 years (range 19–64). Median number of courses is 16 (range 5–16). In 5 patients the best response was CR, 1 with SD and 3 progressed. At the end of follow up 3 patients were still in complete response, one’s disease was stable disease and 5 have had a progression. Two out of 9 patients had died. Mean survival time of the patients is 68.7 months (95% CI 52.6–84.9), median is not reached (seven out of 9 are still followed up). No significant differences were observed between the stages. Median progression free survival is 49.9 months (median is not reached; 5 cases are still censored). No significant differences were observed between the stages. The most frequent adverse events in the brentuximab vedotin group were peripheral sensory neuropathy.

**Conclusion:** Early consolidation with brentuximab vedotin after autologous stem-cell transplantation improved progression-free survival in patients with Hodgkin’s lymphoma with risk factors for relapse or progression after transplantation. This treatment provides an important therapeutic option for patients undergoing autologous stem-cell transplantation.

Mean survival time of the patients is 68.7 months (95% CI 52.6–84.9), median is not reached (seven out of 9 are still followed up).

**P116 (0054) EARLY TRANSPLANT RELATED COMPLICATIONS IN HODGKIN LYMPHOMA PATIENTS RECEIVING PD-1 INHIBITORS BEFORE ALLOGENEIC STEM CELL TRANSPLANTATION**

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Immune checkpoint inhibition by monoclonal antibodies before allogeneic stem cell transplantation (allo-SCT) could enhance allogeneic T-cell responses. We retrospectively analyzed outcomes of 27 Hodgkin Lymphoma (HL) patients undergoing allo-SCT after nivolumab at Humanitas Cancer Center between 2015 and 2018. The aim was to focus on early toxicities (occurring until day +100). Patients’ characteristics are listed in Table 1. Acute Graft Versus Host Disease (aGVHD) was observed in 13 patients (median, +27; range, 16–97). The cumulative incidence (CI) of aGVHD grade 2–4 and grade 3–4 at 100 days was 46% and 10%, respectively. Six patients developed a noninfectious fever (median, +18.5; range, 6–53) and 5 of them were diagnosed with macrophage activation syndrome (MAS). The CI of MAS at 100 days was 22%. Cytokine Release Syndrome (CRS) was observed in 13 patients (median, +6; range, 3–13). One patient experienced Posterior Reversible Encephalopathy Syndrome at day +53. In univariate analysis, neither the number of nivolumab cy-
In conclusion, our study suggests that allo-SCT in HL patients treated with PD-1 inhibitors is feasible. The incidence of aGVHD grade 2–4 did not appear different from what reported, while the incidence of aGVHD grade 3–4 is lower compared to previous study (Merriman, Blood 2017), probably due to different donor types in the two cohorts (more haplo-SCT in our cohort). As previously reported, we observed a noninfectious fever in a minority of patients. Most of them were diagnosed as MAS and were successfully treated with short courses of steroids. CRS was observed only after haplo- SCT. The incidence of CMV reactivation was low.

P117 (0063) BENDAMUSTINE IN HEAVILY PRE-TREATED HODGKIN LYMPHOMA PATIENTS

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Background: Patients with primary refractory or relapsed Hodgkin lymphoma (HL) are expected to have poor outcomes after failure of second-line therapy followed by autologous stem-cell transplantation (ASCT) as well as those who were ineligible for toxic regimens. Bendamustine was only recently approved for the treatment of HL in Russia. Aims: To identify multiple relapsed patients who may benefit most from bendamustine treatment.

Methods: In this prospective observational study, 47 patients (pts) with relapsed HL lymphoma were enrolled between April 2011 and September 2017; the median age was 36 years and the median number of prior therapies was 3 (range, 1–6); 87% pts had B-stage IIE/B; 32% B-symptoms; 55% were not eligible for ASCT (age, multiple relapses, post-R/PT lung fibrosis), 36% had failed conditioning regimen and 9% relapsed after auto-transplant. Bendamustine (BM) was administered 120 mg/m2 for two consecutive days with dexamethasone 20 mg i.v. days 1–4, every 21 day, a maximum of 8 cycles. Dose was reduced to 90 mg/m2 in cases of treatment delays due to neutropenia or thrombocytopenia. Freedom from next failure (FFNF) and overall survival (OS2) were calculated from the start of BM treatment.

Results: A total 196 BM cycles (median 4) were fulfilled in 47 pts, of them 10 pts received BM repeatedly after new relapse (additional 47 cycles). BM treatment was well tolerated. AEs reported were thrombocytopenia, enteropathy, pneumonia, and lockjaw; 7 patients had either delays or reductions in treatment due to thrombocytopenia or neutropenia. Two patients died early due to bleeding from tumor and stroke (OS2 1 and OS 2). A total of 11 (23%) patients received BM treatment (13 CR/14 PR). In univariate analysis ORR was better in patients with mixed cellularity histology (28%, p = 0.097). Failure rate was higher for nodular sclerosis II (p = 0.001) and B-symptoms (p = 0.064). With a median follow-up of 21 mo. (1–61), OS2 at 2-years for all pts was 37,8% (95% CI 41,8–73,9); for B-pts OS2 was 39,7% vs. 70,8% in A-pts (p = 0.042). FFNF at 2-years was 20,4% (95% CI 7,2–33,6); for B-pts FFNF was 10,0% vs. 29,0% in A-pts (p = 0.076). Median OS2 for all pts was 29 mo. (B-pts 16 mo., A-pts 38 mo.); median FFNF was 11 mo. (B-pts 2 mo., A-pts 15 mo.).

Conclusions: Bendamustine monotherapy is relatively mild treatment demonstrating efficacy and a potential for life prolongation in heavily pre-treated HL patients without B-symptoms at relapse.
of those not transplanted seemed equal to those who have been transplanted (Chen 2016). However, in our cohort the outcome of those not transplanted was significantly poorer. Our data also support previous reports that BV can be used as a bridge to allo SCT, with lower treatment-related mortality compared to other strategies.

Conclusion: BV maintenance is safe and effective in BV exposed HL pts at high risk for relapse after AHCT. Close monitoring and early discontinuation should be considered if toxicities develop.

P121 (0089) SEQUENTIAL TIME-INTENSIFIED BRENTUXIMAB VEDOTIN (BV) FOLLOWED BY GEMCITABINE, VINORELBINE AND PEGYLATED LIPOSOMAL DOXORUBICINE (GVD) AS A BRIDGE TO AUTOLOGOUS TRANSPLANTATION IN DHAP RESISTANT RELAPSED OR REFRACTORY CD30+ LYMPHOMA

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Background: Relapsed or refractory (R/R) lymphoma patients (pts) who remain PET positive after platinum-based salvage chemotherapy and undergo autologous stem cell transplantation (ASCT) remain at high risk of relapse (about 60%, Smeltzer, et al. BBMT 2011). Here we present a retrospective single center analysis of PET-adapted sequential salvage therapy with BV followed by time-intensified GVD in pts who remain PET positive (Deauville (D) 4–5) after first line salvage therapy with DHAP.

Methods: We reviewed the medical records of all R/R CD30+ lymphoma pts remaining PET D 4–5 after first line DHAP salvage therapy over 2013–2017-year period. These pts received 2 or 4 cycles of biweekly BV (1.8 mg/kg) followed by 2 or 4 cycles of GVD (gemcitabine 1000 mg/m2, vinorelbine 20 mg/m2, pegylated liposomal doxorubicin 15 mg/m2 on days 1 and 14 every fourteen days). PET-CT scan was performed after 2 and 4 BV cycles and then after 2 and 4 GVD cycles. Pts reaching D 1–2 score at any time point proceeded directly to ASCT. Pts remaining D 3–5 continued with BV and GVD. Pts remaining D 3–5 after all BV and GVD cycles could have received ASCT according to physician’s decision. Endpoints include progression-free and overall survival (PFS, OS, respectively) and grade 3–5 toxicity (CTCAE v. 4.03).

Results: 17 pts were enrolled, 16 had Hodgkin’s and 1 had anaplastic large cell lymphoma. The median age at relapse was 37 years (range 21–70), the majority had advanced stage (64.7%). All pts were D 4–5 at the time of AHCT (range 37–45). 8/27 (30%) pts received BV-AVD in 1 pt with 50% having biopsy proven primary refractory disease and 38% having remission durations >1 year. At the time of relapse or refractory disease, 30% had stage III disease, 38% had B-symptoms, and no one had extranodal disease. First line salvage therapy was BV in 75%, with 2/6 needing 2nd salvage with augmented ICE. The remaining 2 pts received augmented ICE and GVD, with the latter receiving 2nd salvage BV. Pts received 3–8 doses of BV (1.2–1.8 mg/m2) prior to AHCT. Initial therapy was ABVD for 7/8 patients and BV-AVD in 1 pt with 50% having biopsy proven primary refractory disease and 38% having remission durations >1 year. At the time of relapse or refractory disease, 30% had stage III disease, 38% had B-symptoms, and no one had extranodal disease. First line salvage therapy was BV in 75%, with 2/6 needing 2nd salvage with augmented ICE. The remaining 2 pts received augmented ICE and GVD, with the latter receiving 2nd salvage BV. Pts received 3–8 doses of BV (1.2–1.8 mg/m2) prior to AHCT. The at time of AHCT, 75% were PET negative and 75% received BEAM conditioning. All patients were in complete remission at post-AHCT restaging with 5/8 (63%) having 2 or more AETHERA risk factors. BV maintenance started a median of 42 days post AHCT (range 37–45) and pts received a median of 10 doses (range 3–12) starting at 1.8 mg/m2. Patients were followed with CT imaging every 6 months. At a median follow-up of 29 months from AHCT, no patients have relapsed or died. A total of 16 doses (combining pre-and post AHCT BV) were planned with 4/8 (50%) completing the full course. Early discontinuation was due to neuropathy in 2 patients, fatigue and hair loss in 1 patient, and appearance of a ground glass infiltrate on CT in one patient. Four patients developed grade 1–2 neuropathy, while 1 patient who had neuropathy pre-AHCT did not have worsening symptoms. The neuropathy resolved in 3/5 patients once no longer receiving BV and the remaining patients having grade 1 symptoms persisting. Other symptoms including mild fatigue and arthralgias.

Conclusions: The sequential time-intensified BV - GVD resulted in high D 1–2 response (58.8%), among DHAP resistant CD30+ lymphoma patients with 82.4% proceeding to ASCT. 3-year PFS of 76% compares favorably with previous data (3-year EFS 41%, Smeltzer, et al. BBMT 2011) in patients autotransplanted in PET positive disease.
**P120 (0090) BRENTUXIMAB VEDOTIN PRIOR TO ALLOGENIC TRANSPLANTATION IN HODGKIN’S LYMPHOMAS REDUCES CHRONIC GVHD WITHOUT WORSENING THE OUTCOME**

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Patients with classic Hodgkin’s lymphoma (cHL) progressing after autologous stem cell transplantation (SCT) have a very poor outcome. Brentuximab vedotin (BV), an anti-CD30 targeting antibody-drug conjugate has been studied in this patients setting.

This study reports a retrospective multicenter experience of the Rete Ematologica Pugliese (REP) over the past 16 years, aiming to compare the patients characteristics and outcomes of 21 BV pre-treated patients vs 51 patients who received reduced intensity conditioning (RIC) allogeneic SCT without prior BV, in the time period before the drug became available.

**Methods:** 72 patients with cHL who received allogeneic SCT from 2000 to 2017 were retrospectively studied. Median age was 34 years (range 16–57 years) and 36 (54%) were male. At the time of allogeneic SCT, 33 (46%) patients had chemosensitive disease and 39 (54%) were chemorefractory.

**Results:** Following transplantation, 40 patients relapsed or progressed at a median time of 6.3 months (range 1–59 months) post-transplant. After a median follow-up of 38 months (range 3–195 months) 41 patients remain alive and 26 have died. In univariate analysis, prior use of BV had no effect on either engraftment or the incidence and severity of acute graft versus host disease (GVHD). There was a lower incidence of chronic GVHD in the BV group, with a 41% cumulative incidence at 3 years versus 48% in the no BV group, but this was not statistically significant.

Despite the low incidence of chronic GVHD, we did not observe a worse survival in the BV treated group: 3-year progression free survival (PFS) was 64%, 3-year overall survival (OS) was 64%, 3-year non relapse mortality (NRM) was 19%. In the no-BV group the 3-year PFS was 32%, 3-year OS was 42%, 3-year NRM was 16%.

**Conclusions:** Allogeneic SCT may be an effective salvage strategy for patients who relapse after autologous SCT. Use of BV salvage treatment yields improved responses over conventional multi-agent chemotherapy with less toxicity, thereby providing better candidates for allogeneic SCT.

**P123 (0107) NEXT GENERATION SEQUENCING-BASED CLONALITY ASSESSMENT OF IMMUNOGLOBULIN GENE REARRANGEMENTS DISTINGUISHES RELAPSE FROM SECOND PRIMARY HODGKIN LYMPHOMA**

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Hodgkin lymphoma (HL) is often a disease at relatively young age, and several risk factors have been described. HL is associated with a high cure rate, but relapse may occur in 10%-15% with early stage HL and 15%-30% with advanced HL. However, case reports and small series have shown that some of these relapses appear to be second primary HL. Assessment of clonal relationship between primary diagnosis and recurrent HL after treatment will distinguish true relapse from second primary lymphoma. Clonality detection in HL using conventional clonality assays has been severely hampered by the low frequency of clonal Hodgkin and Reed-Sternberg (HRS) cells and limited DNA quality obtained from formalin-fixed paraffin-embedded (FFPE) material. Together with the EuroClonality-NGS consortium, we have developed a novel approach to detect immunoglobulin (IG) heavy chain (IGH) and light chain (IGK) gene rearrangements by next-generation sequencing (NGS) that is highly suitable for detecting IG rearrangements in FFPE tissue specimens. By employing IGH-VJ, IGH-DJ and IGKV/intron-J/DE gene-specific primers and smaller amplicons sizes in combination with Ion Torrent PGM, we show that NGS-based IG clonality analysis can now be performed, even in samples of suboptimal DNA quality. Bioinformatic analyses with the interactive web-based immunoprofiler ARRES'T/Interrogate allows run/sample quality control and accurate identification of clonotypes. We have collected 70 paired primary and relapse samples, of which 38 cases showed a second lesion within three years, and 32 cases after three years. Results of our NGS-based clonality comparison will be presented. This study is an important step towards implementation of NGS-based clonality assessment in clinical practice for HL, which will improve lymphoma diagnostics and may alter therapeutic management of second primary HL.

**P124 (0115) RETROSPECTIVE REAL-LIFE STUDY OF THE BEGEV (BENDAMUSTINE, GEMCITABINE, VINORELBINE) REGIMEN IN HEAVILY PRETREATED, RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA PATIENTS**

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**Introduction:** In a multicenter phase II study, The BEGEV regimen has been proved an effective second-line therapy for relapsed/refractory classical Hodgkin Lymphoma (cHL) (Santoro et al., 2016). Here, we report a real-life analysis with BEGEV administered as second- or subsequent line therapy.

**Patients and methods:** From February 2013 to February 2018, 59 cHL patients (median age, 34 years; range, 19–70) received 4 courses of BEGEV as second (n = 38) or subsequent line (n = 21) therapy. Primary refractory patients were 55% in the second-line group and 76% in the group treated beyond second-line. The latter group received a median of 3 (range, 2–6) therapy lines prior to BEGEV; 11 of 21 patients (52%) had previously been treated with Gemicitabine (n = 9) and/or Bendamustine (n = 3) and 15 (71%) with Brentuximab Vedotin (BV). Nine patients (43%) had received autologous stem cell transplantation (auto-SCT).

**Results:** As reported in the phase 2 study, BEGEV had a good toxicity profile and all patients but 6 received the planned cycles. Reasons for premature therapy discontinuation included progressive disease (n = 5) and sepsis (n = 1). Overall, 39 patients achieved complete remission (CR) and 7 partial remission (PR) with an objective response rate (ORR) of 78%; stable disease and progressive disease (PD) were experienced by 1 and 11 (19%) patients, respectively. The ORR in patients receiving BEGEV beyond second-line was 76%. Interestingly, CR was achieved by all patients who were unresponsive to BV, all but one patient who had previously received auto-SCT, all but two patients pre-treated with Gemicitabine and all patients pre-treated with Bendamustine. All 46 patients that achieved a clinical response after BEGEV were offered SCT: 3 relapsed before SCT could be performed; 31 (67%) received auto-SCT and 8 (17%) allo-SCT; 3 patients are scheduled to perform the procedure, and 1 refused SCT. With a median follow-up of 392 days, the 1-yr overall survival (OS) and progression-free survival (PFS) are 91% and 72%, respectively. No significant OS or PFS difference was detected when comparing patients receiving BEGEV in second-line chemotherapy vs those receiving BEGEV beyond second line.

**Conclusion:** This real-life analysis shows that: (i) the BEGEV regimen is an effective treatment for relapsed/refractory cHL treated beyond second-line and (ii) confirms BEGEV efficacy in patients with chemorefractory disease as well as in those failing auto-SCT and BV.
P125 (0116) NIVOLUMAB RE-TREATMENT IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA

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Background: Nivolumab (nivo), a fully human IgG4 anti-PD-1 monoclonal antibody immune checkpoint inhibitor, demonstrated acceptable safety and frequent and durable responses in phase 1 (NCT01592370) and phase 2 (NCT02181738) trials including patients with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL). [1–3]. However, the optimal duration of treatment is still unknown and may depend on re-treatment outcomes in patients who progress off therapy. A subgroup of patients from these studies who stopped nivo treatment in remission and later progressed were eligible for re-treatment.

Aim: To assess the safety and efficacy of nivo re-treatment in patients with progressive disease (PD) after stopping therapy in remission.

Methods: In the phase 1 study, patients with R/R cHL, who were initially treated with nivo (3 mg/kg every 2 weeks) until PD, complete remission (CR), or unacceptable toxicity, for up to 2 years. Patients with ongoing disease control (CR, partial remission [PR], or stable disease) were eligible for re-treatment upon confirmed PD in ≤1 year from last nivo dose. In the phase 2 study, patients in Cohort C with R/R cHL who received prior brentuximab vedotin before and/or after autologous hematopoietic cell transplantation and achieved CR for ≥21 weeks were eligible for re-treatment upon confirmed PD in ≤2 years from last nivo dose. Toxicity and response to re-treatment were assessed.

Results: At data cut-off (May 2017), 5 patients from the phase 1 study were re-treated with nivo (age 26–53 years; female: ECOG performance status 0–1). All patients achieved CR (n = 1) or PR (n = 4) after 8–18 weeks of re-treatment (Table). One patient remained in PR and was still on re-treatment at data cut-off. In the initial treatment period, all patients had treatment-related adverse events (TRAEs; 1 grade 3 lymphopenia; all others grade 1–2). With re-treatment, 1 patient had grade 2 neutropenia after 18 doses; all other TRAEs were grade 1. In the phase 2 study, 2 patients entered re-treatment. Safety and response analyses from these patients based on a May 2018 database lock will be presented.

Conclusions: Re-treatment with nivo can lead to high response rates with tolerable safety. These data provide further evidence of re-treatment benefit in patients with disease progression after initial response.


Funding: BMS

Data cut-off: May 2017

Outcomes for Patients Re-Treated in the Phase 1 Study (CA209-039)

- Initial treatment
  - Best response: CR
  - Duration of therapy (weeks): 37
  - Best response: CR
  - Time to best response (weeks): 16
  - Duration of re-treatment (weeks): 52
  - Remaining on re-treatment: No

- Data cut-off: May 2017

P126 (0121) PD-1 BLOCKADE FOR HODGKIN LYMPHOMA AFTER ALLOGENEIC STEM CELL TRANSPLANTATION


Lymphoma Working Party, European Society for Blood and Marrow Transplantation

Background: Hodgkin lymphoma (HL) patients who relapse or progress after alloSCT have a dismal prognosis and limited treatment options. Treatment with monoclonal antibodies (mAbs) targeting the programmed cell death receptor (PD-1) show impressive clinical activity in relapsed/refractory HL, but the use of anti-PD-1 mAbs after alloSCT might be associated with initiation or reactivation of graft-versus-host disease (GVHD).

Methods: We conducted a registry-based retrospective multicenter study on patients aged 18 years or above, with histologically verified HL who received PD-1 blockade treatment for relapse of HL after alloSCT.

Results: A complete data set with information on anti-PD-1 treatment could be retrieved from the EBMT database for 20. The median duration of treatment with anti-PD-1 mAbs was 3.15 (range 20–75) years. HL patients received a median of 4 prior lines of treatment before alloSCT (range 2–7) and 18 patients had undergone prior autologous stem cell transplantation. The median time from alloSCT to relapse was 12 (95% confidence interval 6.8–20.3) months, and the median time from alloSCT to start of PD-1 blockade was 21 (95% confidence interval 19–41) months. All patients received nivolumab, which was given for a median of 12 (range 1–37) cycles. Upon treatment with nivolumab, 10 patients achieved a complete remission (CR), 50%, PET-confirmed in 6 of 10 patients, and 9 patients a partial remission (PR, 45%) resulting in an overall response rate (ORR) of 95%. The median time to best response was 4.3 (95% confidence interval: 2.9–11) months. Two of 10 patients (20%) died, due to a fungal pneumonia 2.3 months after last nivolumab treatment, and a steroid refractory acute GVHD, respectively. Upon PD-1 blocking treatment, an episode of aGVHD occurred in 4 of 18 (22%) assessable patients. GVHD occurred in all patients after the first dose of nivolumab (after a median interval of 6 days, range 2–10 days). Two of these patients had experienced a previous episode of aGVHD or cGVHD, respectively. Acute GVHD led to nivolumab discontinuation in 2 of 4 patients. One of these patients died in CR from steroid-refractory grade 3–4 aGVHD 2.8 months after nivolumab. Remaining GVHD episodes after nivolumab were steroid-sensitive.

Conclusion: In line with other reports, this study confirms that treatment with CI that target the PD-1 receptor can be safely administered to patients with HL relapse after alloSCT and this results in good tumor responses.

P127 (0126) AUTOLOGOUS (AUTO-HCT) AND ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO-HCT) IN THE MANAGEMENT OF RELAPSED/REFRACTORY (RR) HODGKIN LYMPHOMA (HL): A RETROSPECTIVE ANALYSIS OF THE LYMPHOMA WORKING PARTY OF THE EBMT

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Background: Auto-HCT and allo-HCT represent well-accepted therapies for patients with HL. Both transplant modalities have evolved over time and the recent advent of new drugs might have modified the indications and timing of HCT. We have analysed the transplant activity for patients with RR HL reported to the EBMT registry over the last three decades.

Methods: Patients were included if they had RR HL, > 18 years of age and had undergone an auto-HSCT as 1st HSCT or an allo-HSCT either as a 1st HSCT or after a prior auto-HSCT between Jan/1990 to Dec/2014.
Results: 13639 patients [11435 auto-HSCT and 2204 allo-HSCT (551 1st allo-HSCT and 1649 allo after an auto-HSCT)] were registered in the EBMT database during the study period. With regards to auto-HCT (1990–1994 vs 2010–2014), there was a significant increase in median age at HSCT [31 yrs vs 35 yrs, p < 0.0001], time between diagnosis and HSCT became shorter [31 vs 23 mo, p < 0.0001], peripheral blood (PB) has become the universally used stem cell source [98% vs 99.5%, p < 0.0001] and total body irradiation has almost been abandoned [4% vs 1.7%, p < 0.0001]. 36-mo overall survival (OS) has improved over time [63% vs 79%, p < 0.0001] as well as non-relapse mortality (NRM) [12% vs 6%, p < 0.0001].

Allo-HSCT has been less commonly used as the 1st HSCT (comparison 1990–1994 vs 2010–2014) [85% vs 23%] whereas allo-HSCT after a first auto-HSCT has steadily increased [12% vs 77%, p < 0.0001]. Time between diagnosis and HSCT has decreased over time [36 mo vs 34 mo, p < 0.04)]. Performance status >80% at HSCT has improved [62% vs 94%, p < 0.0001], PB has become the universal source of stem cells [6% vs 84%, p < 0.0001], and there has been a more frequent use of reduced intensity conditioning protocols [0% vs 70%, p < 0.0001] as well as of matched unrelated donors and haplo donors [0% vs 48% and 0% vs 17%, respectively, p < 0.0001]. 36-month OS estimates have also improved [21% vs 61%, p < 0.001] as well as those for progression free survival [15% vs 43%, p < 0.001] and NRM [58% vs 22%, p < 0.001].

Conclusions: Transplantation activity, the clinical pattern of patients undergoing this treatment and the characteristics of the procedure have significantly changed over the study period and results in terms of OS and NRM for both auto-HSCT and allo-HSCT are much better. The potential impact of new drugs on transplantation activity and outcomes it is difficult to ascertain at this point.

P128 (0127) SUCCESSFUL SLOW DESENSITIZATION TO BRENTUXIMAB VEDOTIN AFTER ANAPHYLAXIS: 3 CASE REPORTS IN THE BASQUE AUTONOMOUS COMMUNITY

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Hospital Universitario Donostia, Hospital Universitario Donostia, Hospital Universitario Donostia, Hospital Universitario Donostia, Hospital Universitario Donostia, Hospital Universitario Donostia, Hospital Universitario Donostia, Hospital Universitario Araba, Hospital Universitario Basurto, Hospital Universitario Donostia, Hospital Universitario Donostia

Introduction: Brentuximab vedotin (BV) is an anti CD-30 antibody-drug conjugate to the antitubulin cytotoxic agent monomethyl auristatin E. It is currently approved in Europe for refractory/relapsed Hodgkin’s lymphoma (HL) after autologous stem cell transplantation (ASCT) or after at least 2 previous chemotherapy lines and for refractory/relapsed systemic anaplastic large-cell lymphoma (ALCL). Since its approval by the FDA in 2011, only 3 cases have been reported of patients who have had a desensitization protocol (DP) applied after having had an anaphylactic reaction (AR) to the drug.

Methods: In this work, we report 3 cases of patients from the Basque Autonomous Community who presented an AR to the BV: *Table 1 After consultation with the Allergology service, a DP based on the Castells et al protocol was proposed. The BV was administered in a slow desensitization strategy using 3 solutions of 2.50cc of glucose solution infused in 12 steps. Example about a theoretical BV dose of 73 mg:

*Table 2 Pre-medication included: 5 mg of Dexamethasone, 50 mg of Ranitidine and 40 mg of Acetylsalicylic acid (AS) 2 days before treatment with 300 mg/day of Acetylsalicylic acid and 10 mg/day of Montelukast.

Results: The patients after the PD received the subsequent cycles of BV without presenting any type of anaphylactic symptoms.

Conclusions: It is important to have protocols of desensitization to drugs such as BV, since these protocols allow the continuation of treatment in patients who have already received other lines of failed treatment and whose therapeutic options are limited.

P128 (0128) CLINICAL ANALYSIS OF RELAPSE PATTERNS IN HODGKIN LYMPHOMA

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Introduction: The optimal management of Hodgkin Lymphoma (HL) in the relapsed/recurrent r/r situation remains controversial. The purpose of this study is to identify relapse patterns and to investigate the role of radiation therapy (RT) for local control.

Material & Methods: A search of our institution database identified 19 r/r HL patients treated with RT in the primary and/or recurrent situation in the last 15 years (y), of which 14 (13 males, 1 female) were analyzed retrospectively.

Results: Median age at initial diagnosis was 28.9 years. Initial Ann-Arbor stage was I (1), II (6), III (3) or IV (3; 1 unknown), with B-symptoms in 5 patients. RT was applied in 9 patients, mostly as involved-field (IF) RT, with a median dose of 30 Gy (20–40 Gy). Recurrence was diagnosed after a median time of 1.8 y (0.6–11.8 y; 2 year recurrence-free survival: 42.9 %) at a median age of 30.5 y (18.0–69.4 y) and was found in-field (or in the former disease area) in 2 patients, out-of-field in 4 patients and as a combined pattern in 8 patients. For patients with RT in primary treatment, relapse distribution, was 1, 3 and 5 for infield-, out-of-field- and combined relapses relapses; while for patients without RT it was 1,1 and 3 for the mentioned categories. RT in the primary treatment prolonged time to recurrence significantly (median: 4 y vs. 1.3 y; p = 0.042). For recurrent disease, RT was utilized in 7 cases with a median dose 30.6 Gy (19.8–36 Gy) as IF-RT in 5 cases, extended field (EF) RT in 1 case and consolidating RT in 2 cases. Second relapse occurred in 8 patients after 1.9 y (0.3–11.6 y; 2 year recurrence-free
P130 (0132) PRIMARY PROGRESSIVE CLASSICAL HODGKIN LYMPHOMA – A SINGLE CENTRE EXPERIENCE
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Background: Primary progressive Hodgkin Lymphoma (defined as progression during induction treatment or within 90 days of its completion) is associated with poor outcome, with long-term remission rate of only 30%. The treatment of choice for suitable patients (pts) is salvage chemotherapy followed by autologous stem cell transplant (ASCT).

Aims: Analyse risk factors and clinical outcomes of pts with primary progressive classical Hodgkin Lymphoma (PPcHL).

Methods: We performed a retrospective analysis of 389 cHL pts treated in a tertiary centre between 1990 and 2017. Univariate analysis was performed and significant predictors at the level of 0.05 were used to adjust a multivariable logistic regression model.

Results: We identified 53 (13.6%) pts with PPcHL, with a median age of 36 years (18–80) and homogeneous gender distribution. The most prevalent histological subtype was nodular sclerosis (75%). Most pts had intermediate or advanced disease (90.6%). We found an association between PPcHL and Ann Arbor stage III/IV (62.3 vs 46.5%; OR 2.14; p = 0.011), presence of B symptoms (71.7 vs 51.2%; OR 2.41; p = 0.007), bone marrow involvement (15.1 vs 6.3%; OR 2.67; p = 0.028) and serum albumin < 4 g/dL (OR 2.17; p = 0.014). No statistically significant association was found between PPcHL and the presence of mediastinal bulk, number of nodal regions, extranodal involvement or LDH>upper normal limit (p = NS). PPcHL was more common in pts with advanced disease by GHSG criteria (62.3 vs 43.2%; OR 2.17; p = 0.01) and in those with a positive interim FDG-PET (OR 7.38; p < 0.001). No association was found with IPI23. On multivariable regression analysis no factor was predictor of developing PPcHL. Thirty-four (64.2%) pts received first line ABVD and 12 (22.6%) received consolidative radiotherapy. ESHAP was the most frequently used salvage regimen (52.5%); 14 pts (26.4%) underwent ASCT. The overall response rate (ORR) to salvage treatment in PPcHL was inferior to the ORR in pts that relapsed after 90 days (35.7% vs 52.7%; p = NS). PPcHL was associated with inferior OS (5-year OS: 51.8% vs. 88.8%; p < 0.001; 10-year OS: 44.4% vs 82.4%, p < 0.001) and had a negative impact on mortality (HR 4.12; p < 0.001).

Conclusions: In our cohort, GHSG criteria (but not IPI) seem to predict the risk for PPcHL. These patients had a poorer outcome when compared to patients that relapsed >90 days after completing therapy. It is important to identify high-risk patients at diagnosis and devise more effective treatment strategies.

P133 (0148) PROGNOSTIC VALUE OF (18) F-FLUORODEOXYGLUCOSE-POSITRON EMISSION TOMOGRAPHY ON SURVIVAL IN HODGKIN LYMPHOMA PATIENTS TREATED WITH ALLOGENEIC STEM CELL TRANSPLANTATION
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Introduction: (18) F-Fluorodeoxyglucose-Positron Emision Tomography (FDG-PET) has a recognized prognostic value before autologous stem cell transplantation (ASCT) in patients with relapsed/refractory Hodgkin lymphoma (HL), but its impact before allogeneic SCT (allo-SCT) remains unclear.

Abstract Book for the 11th International Symposium on Hodgkin Lymphoma

survival: 50 %) after primary recurrence, with recurrences in previous areas in 1 patient, new areas in 2 patients and combined in 5 patients. The three patients who underwent RT in the first recurrence all had combined recurrences. RT did not prolong 2nd recurrence (p = 0.075). In this setting, RT was used in 4 patients as EF-RT (1), IF-RT (2) or consolidating RT (1). A third recurrence was observed in 5 patients after 3.8 years (0.2 y – 7.5 y). During their treatment, 7 patients received brentuximab-vedotin, 3 of which were treated subsequently with nivolumab. With 2 deaths in the cohort, overall survival was at median 12.3 y (3.9 y - 20.7 y 95 % CI).

Conclusions: RT retains its pivotal role as local therapy in the setting of r/r HL and adds to the therapeutic mosaic in the era of targeted therapy.


P131 (0138) PATTERNS AND OUTCOMES WITH SALVAGE TREATMENT FOR HODGKIN LYMPHOMA (HL) IN THE MODERN ERA: A REAL-WORLD ANALYSIS FROM THE COMMUNITY ONCOLOGY SETTING IN THE UNITED STATES
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Background: While most patients with newly diagnosed HL will be cured, a subset experience treatment failure (TF). Data are limited on the selection of salvage treatment and associated outcomes, particularly in the community setting, where the majority of cancer patients in the United States receive their care.

Methods: Potential TF cases were identified by receipt of > 1 treatment regimens within 4 years after initial treatment from 473 HL cases with Stage II-IV disease diagnosed from 2007–2012 at Kaiser Permanente Southern California. Medical oncologists and trained study staff reviewed medical charts to confirm TF. Detailed data were extracted including initial treatment, type of TF, salvage treatment, and response.

Results: We identified 75 patients with TF. At diagnosis, median age was 36 years (IQR 23, 52); 65% were male; 63% were Non-White or Hispanic; 49% had Stage III or IV disease; 48% had B-symptoms; 39% had mediastinal bulk; and 32% had > 1 comorbidity. Patients received a median of 2 (range 1–9) salvage treatments.

Initial salvage included ifosfamide-based chemotherapy in 5775 (76%), other (non-ifosfamide) chemotherapy in 975 (12%), brentuximab vedotin (BV) in 875 (11%), and unknown therapy in 175 (1%) who briefly left Kaiser Permanente. Among patients salvaged with Ifosfamide-based therapy, 4057 proceeded directly to autologous stem cell transplant (SCT). Of the 17 patients who did not proceed directly to SCT, 9 received additional therapy and then, went on to SCT. Among By patients, 38 proceeded directly to autologous SCT. Among patients salvaged with other chemotherapy, 19 transitioned to SCT, while almost half died with active disease (Table). At 4 years post initial therapy, 2775 (36%) of patients with TF died, 22/27 (81%) from HL (median time to death from TF: 376 days [IQR 194, 813]). Of surviving patients, 34/48 (71%) achieved complete remission, 8/48 (17%) have active disease, and 6/48 (12%) were lost to follow-up.

Conclusions: In a community-oncology setting, salvage treatment for HL is heterogeneous. Further, mortality after TF is prominent. There remains a critical gap to identify patients with high-risk features (i.e., patient, clinical, biologic) early in the disease course that may presage inferior outcomes and warrant alternative treatment paradigms.

Table

<table>
<thead>
<tr>
<th>Initial Salvage Treatment</th>
<th>Subsequent Therapy</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifosfamide-Based Chemotherapy (n=57)</td>
<td>Proceded to autologous SCT</td>
<td>40/57 (70%)</td>
</tr>
<tr>
<td>Other chemotherapy regimens (n=9)</td>
<td>Additional therapy (radiation, chemotherapy, antibody)</td>
<td>4/9 (44%)</td>
</tr>
<tr>
<td>Brentuximab Vedotin</td>
<td>Proceded to autologous SCT</td>
<td>3/9 (33%)</td>
</tr>
<tr>
<td>Other chemotherapy regimens</td>
<td>Proceded to autologous SCT</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td>Observation</td>
<td>1/9 (11%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Additional therapy</td>
<td>1/9 (11%)</td>
</tr>
</tbody>
</table>
Methods: We retrospectively evaluated the impact of pre-transplant FDG-PET status on the outcomes of HL patients who had undergone an alloSCT in two Spanish institutions between May/2005 and May/2016.

Results: Forty one patients [median age at alloSCT of 32 years (20–65), 49% males] were included. Time interval between diagnosis and alloSCT was of 31 (7–247) months. Median number of treatment lines before transplant were 4 (2–8), 59% had primary refractory disease and 89% had a failed previous ASCCT. Disease status at alloSCT was: 17 patients in complete response, 15 patients in partial and 9 patients with progressive disease. Sixteen patients underwent HLA identical sibling, 15 matched unrelated donor and 9 a haploidentical transplant, of them 36 were reduced-intensity conditioning (RIC) and 5 myeloablative conditioning (MAC). Twenty-four (58%) had a positive FDG-PET pre-alloSCT and in 13 out of 36 (37%) remained positive post-transplant. Twenty-three (56%) patients presented acute GVHD and 23 (56%) chronic GVHD. Nineteen patients relapsed post-alloSCT, at a median time of 6 (1–36) months after transplant.

Multivariate analysis indicated that haploidentical donor source (p = 0.03) improved OS after transplant, negative FDG-PET pre alloSCT (p = 0.05) and non-relapse after transplant (p = 0.007) improved OS and that HLA-identical sibling (p = 0.025) increased relapse rate after transplant.

The median OS was of 58 months and the median DFS of 14 months. Patients with negative PET studies before alloSCT had significantly better outcomes in terms of median OS (87 months vs. 21 months; p = 0.048) and median DFS (36 months vs. 7 months; p = 0.012).

Conclusions: Our findings suggest that FDG-PET status before alloSCT in patients with HL has an impact on survival outcomes. These results should be confirmed with larger prospective series.

P134 (O156) INDUCTION THERAPY WITH EVEROLIMUS IN COMBINATION WITH DHAP (DEXAMETHASONE, HIGH-DOSE ARAC, CITA PLATINUM) IN PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA: A RANDOMIZED, PLACEBO-CONTROLLED PHASE II TRIAL (HD-R3)

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Background: Induction chemotherapy followed by BEAM high dose chemotherapy (HDCT) and autologous peripheral blood stem cell transplant (PBSCT, transplant) is standard of care for transplant-eligible patients with relapsed or refractory classical Hodgkin lymphoma (rHL). However, approx. 50% of patients relapse and therefore, this strategy must be improved.

As proof to induction therapy is predictive of the outcome after HDCT, this trial aimed at improving the response to induction therapy by adding oral everolimus to time-intensified standard DHAP (Ever-DHAP).

Methods: We included patients with histologically confirmed rHL aged 18–60 years in this phase II/III trial. Dosage of everolimus was pre-determined in the phase I part with 10 mg/day given parallel to DHAP for 14 days within each of two cycles. The phase II part started as a randomized controlled trial comparing 50 patients in the everolimus group to 50 patients in a placebo group. The primary endpoint of the phase II part was the CT-based complete remission (CR) rate after two cycles of Ever-DHAP. This CR-rate would be expected to be ≥ 40% if adding everolimus was effective. Secondary endpoints of the trial were PET-based CR-rate after two cycles of induction, progression-free and overall survival as well as to recovery, adverse events, duration of induction therapy, discontinuation rates and rates of successful PBSCT collection.

The trial was registered at ClinicalTrials.gov with ID NCT01453504.

Results: From 7/2014 to 3/2018 we recruited a total of 59 patients in the phase II part. Because of poor recruitment the placebo group was closed in 9/2015 after 9 patients were randomized. Of 50 patients in the everolimus group 2 did not start therapy; 3 additional patients discontinued Ever-DHAP because of toxicity. PBSCT collection was successful in 37/39 documented patients receiving Ever-DHAP (95%). After two cycles of therapy we observed a CT-based CR in 12/45 patients of the everolimus group (27%) and in 29/50 patients of the placebo group (22%). A PET-based CR was reached by 19/38 patients of the everolimus group (50%) and by 4/5 patients of the placebo group. In the everolimus group 2 patients had refractory disease (4%) and 2 died (4%), 3 and 4 months after starting but not related to Ever-DHAP. Final results will be presented at the symposium.

Conclusion: Adding everolimus to time-intensified DHAP is feasible, however, the Ever-DHAP regimen failed to show an improved efficacy.

P135 (O160) BREN'TUXIMAB-VEDOTIN + BENDAMUSTINE: A HIGHLY EFFECTIVE SALVAGE TREATMENT UN REFRACTORY/ RELAPSED PATIENTS WITH HODGKIN LYMPHOMA

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Majority of patients with classical Hodgkin Lymphoma (HL) are cured with frontline therapy. However, between 20 to 30% of the patients will relapse. Achieving second complete remission (CR) after salvage therapy and prior to Autologous transplantation (ASCT) is a strong pre- dictory marker of favorable outcome. One recent phase I–II study has shown that the combination of Brentuximab Vedotin and Bendamustine (BV+B) is an effective salvage regimen as a bridge to ASCT in patients with primary refractory or relapsed (R/R) HL. The main objective of this study was to evaluate the complete response (CR) rate after BV+B. Eighty patients (pts) with R/R HL from 14 LYSA centres treated between 2014 and 2017 were retrospectively reviewed. BV was given at 1,8 mg/Kg on day 1 and Bendamustine at 90 mg/m² on day 1 and 2 while every 4 weeks. Patients were evaluated for response mainly after 3 cycles. Responders (CR or PR) and eligible patients underwent ASCT after BEAM conditioning regimen. Median prior lines were 2 (1–11) and median number of BV+B cycles was 4 (1–7). 76 pts are evaluable for efficacy. The CR rates was 65%. After a median FU of 15,7 months, the estimated 2-year PFS and OS were 64% (23–29) and 88,5% (84,5–92,5) respectively. The median duration of response among the 45 pts in CR was not reached (71% (+/−6%) at 24 months.

After ASCT complete response rate was 81 % (30/37) compared to 49 % (17/35) in the group w/o ASCT (p = 0.011). Median PFS was not reached, compared to 20 months (17–23) for patients who didn’t received ASCT (p = 0.033) (Fig. 1). Median OS was not reached in both groups. Twenty-two patients (41, 3%) experienced grade ≥ 2 toxicity. The main toxicities were hematological (43, 5%), infectious (34, 8%), cutaneous (13%), digestive (13%). Treatment was stopped for 7 patients due to toxicity. One patient died of septic shock and another one died of digestive hemorrhage during cycle 1.

BV+B is an effective salvage therapy in patients with R/R HL. Considering the very good outcome for patients in CR and after ASCT, its use as a bridge-to-transplantation therapy should be considered to achieve durable remission in eligible patients. Although manageable, toxicity should be carefully monitored.
**P136 (0161) LONG TERM OUTCOME OF PATIENTS WITH RELAPSED / REFRACTORY HODGKIN LYMPHOMA TREATED AT A SINGLE INSTITUTION OVER 25 YEARS**

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With a standard combined modality treatment approach more than 70% of Hodgkin lymphoma (HL) patients (pts) are cured, although 10% of patients experience very late relapse (VLR) after initial treatment. We retrospectively evaluated long-term outcome including late effects and risk factors in pts with R/HL after the first treatment failure. We collected data from 417 consecutive pts with R/HL after first therapy, treated at our institution between 1990–2016. At diagnosis, median (range) age was 28 (17–62) year, limited, intermediate, or advanced stage (GHLGS) was found in 2%, 21%, 77% of pts, respectively. First-line therapy included MOPP or MOPP/ABV regimens in 144 (35%), and ABVD in 273 pts. Field radiotherapy was given in 250 (60%) pts.

**Results:**

200 (48%) and 217 (52%) pts had recurrent and refractory disease, respectively. Median time to progression from the first treatment was 13 months (range 1–248), relapse after 10-ys occurred in 1,5% of pts. 297 pts (72%) underwent autoHCT, 120 pts were not eligible (insufficient CD34 cell collection, progression, patient refusal), 9 pts had allologeneic HCT. Median number (range) of therapy lines: before autoHCT and during all therapy were 2 (1–6) and 5 (2–11), respectively. With a median 87month follow-up, 3-year and 10-year OS from the date of relapse/progression was 60% and 50%, respectively. Refractory disease, advanced stage at diagnosis, MOPP as first treatment, and no autoHCT were identified as risk factors associated with inferior OS in multivariate analysis. The risk of death (HR) was 1,8 (95% CI 1.4, 2.4, p < 0.01), 1,8 (95% CI 1.6, 2.5, p < 0.01), 1.4 (95% CI 1.0 1.8; p = 0.04), 4.8 (95% CI 3.6, 6.2, p < 0.01) for these factors, respectively. In pts not receiving autoHCT the risk of death in relapsed disease and in refractory disease were: 5.6 (95% CI 3.6, 8.8, p < 0.01) and 3.8 (95% CI 2.7, 5.4, p < 0.01) respectively. The main cause of death was progression. Second primary malignancy was occurred in 15pts (3.6%) including 13/297 pts (4.4%) post autoHCT. Two pts had heart transplant after therapy. More than 50% of pts with R/R HL survived 5 years. HDT and autoHCT likely contributed to survival benefit. Refractory disease, stage at diagnosis and type of the first treatment were significant risk factors for long-term survival. The incidence of second primary malignancy was more frequent in post-transplant pts.

**Conclusion:**

The prognosis of VLRs after CT ± RT for HL does not appear very favorable; however, a considerable proportion of patients succumbed to 2nd malignancies and unrelated diseases. Treatment approaches are heterogeneous and HDI/ASCT is underused. Advanced age and anemia at relapse were the most important prognostic factors in this series.

**P137 (0165) TREATMENT STRATEGIES AND PROGNOSTIC FACTORS FOR THE OUTCOME OF VERY LATE RELAPSES (VLRs) OCCURRING ≥2 YEARS AFTER INITIAL TREATMENT WITH CHEMOTHERAPY ± RADIOTHERAPY (CT ± RT) IN HODGKIN LYMPHOMA (HL): A JOINT STUDY FROM THE UNIVERSITY OF ATHENS AND ISTITUTO NAZIONALE DEI TUMORI MILANO**

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Relapsed or refractory Hodgkin lymphoma is a challenging problem. The standard management of these patients should include the use of salvage chemotherapy followed by autologous stem cell transplant (ASCT). In Brazil, the availability of the new drugs as brentuximab and nivolumab is restricted to the private health system, and consecutive cycles of salvage high dose chemotherapy treatment are the standard of care in most centers. Additionally, the restricted access to hematopoietic stem cell transplantation centers imposes to patient long-term high dose chemotherapy treatment. This abstract describes the characteristics of the patients and the treatment before the ASCT, from a single center in the South of Brazil. From 2006–2018, 60 patients with Hodgkin Lymphoma were transplanted in our center, 59 autologous and one allologous. The median age was 27 years old (4 55), the majority were male (60%), the first line of treatment was ABVD in 98%, the first remission rate was 47% and the median time to progression or relapse was 12 months. The second line treatment was ICE in 43 (71%), GDP/GEMOX in 7 (12%), DHAP in 5 (8%) and five patients were treated with other therapies. The number of cycles, during second-line treatment, was 1–4 cycles in 50 (83%) and more than four cycles in 10 (27%) of the patients. Thirty-one patient went through the third line treatment. The protocols used were GDP/GEMOX in 17 (55%), Brentuximab in 7 (22%), DHAP in 4 (13%). The relapse/progression after 1–4 cycles of treatment was 1–4 cycles in 21 (83%) and > 4, in 10 (27%). Nine patients (13%), from the total sample, were treated with the fourth line of therapy before HSC transplantation, and in this group only 4 (44%), brentuximab was used. The median time since the relapse/progression to HSC transplantation was twelve months (1–49). The median progression free survival was 36 months (18–84). The mean overall survival was 159 months (median not reached). The stem

*TPV and AL had equal contribution to this work.*

**Background:** Traditionally, HL is considered cured after a 5-year disease-free period. However, our initial report and the recent large GHSG study have demonstrated that VLRs, occurring ≥25 years after initial treatment initiation, are a rather uncommon but non-negligible event. Due to the rarity of these events very few data exist describing the outcome of VLRs after CT ± RT, while there is no study focusing on potential prognostic factors.

**Aims:** To evaluate the treatment strategies adopted for patients with VLRs in 2 referral Centers in Greece and Northern Italy as well as their outcome and prognostic factors for Freedom From Second Progression (FF2P) and overall survival after failure (O2S).

**Patients/Methods:** Patients with HL, who experienced VLRs after CT ± RT were identified retrospectively from the databases of the participating centers. Statistical endpoints were the estimation of FF2P and O2S. Results: 87 patients with VLRs after CT ± RT were identified. Relapse occurred >15 years after the initial diagnosis in 21% of the patients, 64% of the patients were males and 16% were 265 years old. Reinduction with the same regimen was given in 28% of the cases, 5 patients (6%) received salvage RT only and 22% proceeded to high-dose therapy and autologous stem cell transplantation (HD/AcST). The 5- and 10-year FF2P was 36% and 51%, while the 10-year O2S was 56%. Among 32 deaths, only 19 were due to HL; 13 deaths were purely attributed to 2nd malignancies (n = 9) and unrelated causes (n = 4). Reinduction or HDI/ASCT did not significantly affect FF2P and O2S; 45 patients selected for salvage RT only had long-term remissions. A Cox univariate analysis correlated 5 sociodemographic risk factors (age < 65 years old who received HDI/ASCT (88% vs 55%), but this was just 59% vs 55% at 10 years and did not reach statistical significance (p = 0.42). In multivariate analysis only anemia at relapse was independent predictor of FF2P; both anemia and age 263 years at relapse independently predicted for O2S. However, B-systolic blood pressure < 140 mmHg was 15 years were in univariate analysis and deserve further consideration.

**Conclusion:** The prognosis of VLRs after CT ± RT for HL does not appear very favorable; however, a considerable proportion of patients succumbed to 2nd malignancies and unrelated diseases. Treatment approaches are heterogeneous and HDI/ASCT is underused. Advanced age and anemia at relapse were the most important prognostic factors in this series.
Cell collection failure rate was 25% in Hodgkin Lymphoma and associated with the increased number of treatment cycles (> 3 cycles, \( p = 0.02 \)). In conclusion, high dose chemotherapy is the standard of care for relapsed/progression Hodgkin patients, however, the new drugs with less intensive hematologic toxicities are being used. The restricted access to these agents and to transplantation centers prolongs the high dose treatments and related adverse events.

**P139 (0169) BRENTUXIMAB VEDOTIN ALONE AND IN COMBINATION WITH BENDAMUSTINE AS SALVAGE THERAPY FOR PRIMARY REFRACTORY OR RELAPSED HODGKIN LYMPHOMA: MULTICENTRE EXPERIENCE OF THE POLISH LYMPHOMA RESEARCH GROUP**

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An optimal treatment for patients with primary refractory or relapsed (R/R) Hodgkin lymphoma (HL) who did not respond to standard salvage therapy has not been established. Brentuximab vedotin (BV) and bendamustine (B) used in monotherapy both have shown to be active in R/R HL and both are included in therapy options. However, the combination of BV with B (BBV) has been investigated in only few clinical trials. The goal of this study was to retrospectively compare the efficacy and safety of BV and BBV regimen in R/R HL patients.

**Methods:** Since March 2014 all patients with R/R HL were considered to receive BV in standard doses every 21 days or BV in combination with B (B 90 mg/m\(^2\) on days 1 and 2 of a treatment cycle).

**Results:** BV or BBV therapy was administered to 93 patients (median age 33 years, range 18–68) with primary refractory (n = 53) or relapsed HL (n = 40), including 34 patients after autologous stem cell transplant (ASCT), who were treated with a median of 3 (range 2–12) prior chemotherapy lines. Fifty six patients received BV and 37 patients BBV regimen. In 16 of them, BBV was de-escalated to BV after the median of 2 cycles (range, 2–7). In the whole study group, the patients received the median of 4 BV/BBV cycles (range, 2–16). Dose-limiting toxicities were observed in 8% of patients. No difference was found between BV and BBV group, with similar rate of grade 3–4 neutropenia (16% vs 13%) and thrombocytopenia (4% vs 3%). Lung infection occurred in 1 patient treated with BV (2%) and 3 treated with BBV (2% vs 8%, \( p \) ns), with 2 treatment-related deaths in BBV group. The response rate after 2 cycles of BV and BBV treatment defined as complete (CMR) or partial metabolic response (PMR) assessed by positron emission tomography was 69% (26% of CMR and 43% of PMR) and 91% (41% of CMR and 50% of PMR), respectively (\( p = 0.029 \)). After 4–6 cycles of treatment, CMR, PMR and stable metabolic disease was achieved in 62%, 18% and 10% of all patients, respectively, with no significant differences between BV and BBV group. Finally, 36 patients proceeded to ASCT, and 16 to allogeneic SCT. The overall and progression-free survival at 24 months were 80% and 51%, and did not differ between two study groups. In conclusion, our experience suggests that BBV is a feasible regimen that provides higher response rate after 2 cycles compared to BV monotherapy. Our results also indicate that BBV may be considered as a bridge to early SCT in R/R HL.