Plasma vesicle-associated mirnas as therapy response biomarkers in hodgkin lymphom

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ABSTRACT BOOK

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αἷμα [haima] = blood
αἵματος [haimatos] = of blood
λόγος [logos]= reasoning

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Biology and Microenvironment

T004

ANALYSIS OF THE MUTATIONAL LANDSCAPE AND DYNAMICS IN HODGKIN LYMPHOMA USING NGS

E. Mata[1], A. Díaz-López[1], C. Montalban[1], R. Fernandez[2], C. Bellas[3], F. Burgos[4], M.J. Mestre[5], J. Menárguez[6], M. Provencio[7], C. Santonja[7], M.A. Piris[8], J.F. Garcia[1]

[1]MD Anderson Cancer Center, Madrid, Spain; [2]Hospital de Cabueñes, Gijon, Spain; [3]Hospital Puerta de Hierro, Madrid, Spain; [4]Hospital Severo Ochoa, Leganés, Madrid, Spain; [5]Hospital Universitario de Móstoles, Madrid, Spain; [6]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [7]Fundación Jiménez Díaz, Madrid, Spain; [8]Hospital Universitario Marqués de Valdecilla, Santander, Spain

Few studies have been aimed to the identification of driver mutations in classical Hodgkin Lymphoma (cHL), and only occasional gene mutations in members of the NF-kappaB and JAK/STAT pathways, and, more recently B2M, have been previously described. We analyzed 57 cHL tumor samples (FFPE) using massive parallel sequencing (Ion Torrent™ semiconductor technology). To increase coverage a previous tumor cell enrichment process by punch tissue cores from selected tumor-rich areas was implemented. In addition, we have also analyzed an independent group of 12 patients with primary refractory cHL (patients that did not achieve complete response after first line ABVD, or who presented with primary progressive disease), using the same methodology for NGS, but with an enrichment procedure based on laser microdissection of HRS cells (CD30+). Overall, the results show very high genomic heterogeneity with a range of 10-400 SN*Vs* per sample, most of them (~60%) missense type. We found a relatively large number of genes recurrently mutated at low frequency and only a few genes mutated in up to 15-20% of the patients, reflecting a high level of genomic instability in the neoplasm. Specific mutations in genes previously described in cHL (NFKBIA, TNFRSF14) and in diffuse large B-cell lymphomas (CARD11, STAT6, CREBBP, CMYB) were consistently found, as well as new SN*Vs* in genes not previously described (STAT6, BTK, NFKB2). Of note, we found high prevalence of mutations affecting BTK and the BCR pathway, suggesting some dependencies of active BCR signaling albeit the absence of BCR expression by HRS cells. Consistent with this interpretation, incubation of a panel of cHL cellular models with either Ibrutinib or AVL-292, selective-BTK inhibitors, *in vitro* constrains cell proliferation and causes cell death. Indeed, gene expression and GSEA analysis of the cHL HDML-2 cell line showed a similar basal BCR pathway activation levels than the HBL1 DLBCL cell followed by an intense inhibition after ibrutinib incubation. In conclusion, cHL is characterized by high genomic instability, including numerous mutations in genes related with B-cell function and specific signaling pathways. Pathogenic predictions of the different SN*Vs* identify potential driver mutations that can be associated with the pathogenesis of the disease and might represent new therapeutic targets.

T005

HIGH EXPRESSION OF PROGRAMMED CELL DEATH RECEPTOR 1 IN THE TUMOR MICROENVIRONMENT IS ASSOCIATED WITH INFERIOR EVENT FREE SURVIVAL IN CLASSICAL HODGKIN LYMPHOMA

P. Hollander[1,2], P. Kamper[3], K.E. Smedby[4,5], G. Enblad[1], J. Mortensen[3], R.-M. Amini[2], F. d'Amore[3], D. Molin[1,*], I. Glimelius[1,4,*]

[1]Experimental and Clinical Oncology, Department of Immunology, Genetics and Pathology; Uppsala University, Uppsala, Sweden; [2]Clinical and Experimental Pathology, Department of Immunology, Genetics and Pathology; Uppsala University, Uppsala, Sweden; [3]Department of Hematology, Aarhus University Hospital, Aarhus, Denmark; [4]Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [5]Hematology Center, Karolinska University Hospital, Stockholm, Sweden

**Shared last authorship*

Immune checkpoint inhibition targeting the programmed cell death receptor 1 (PD-1) pathway is a novel treatment approach in relapsed and refractory classical Hodgkin lymphoma (cHL). Use of PD1-inhibitors may be justified early on in selected patients if patients with high risk of treatment failure could be identified at the time of diagnosis. Our aim was to investigate the prognostic impact of PD-1 expression in tumor infiltrating lymphocytes in diagnostic cHL biopsies. Patients from Aarhus, Denmark (n=283) diagnosed 1990-2006 aged 15-86, and Sweden (n=132) diagnosed 1999-2002 aged 18-74 were included. The patients were mostly treated with chemotherapy (mainly ABVD) ± radiotherapy. Tissue microarray samples were available from 387 patients. Immunohistochemistry was used to detect PD-1 and the percentage of positive cells was estimated using a digital image analysis program. Fifty-seven patients (15%) presented with a high expression of PD-1, defined as ≥10% positive lymphocytes in the tumor microenvironment. Overall survival (OS) and event free survival (EFS) (treatment failure or death from any cause) were analyzed using log rank test and Cox proportional hazards regression. The median follow-up time was 10.8 years. Among patients with a high expression of PD-1 there were 29 (51%) events, and among those with a low expression 104 (32%) (Figure 1).

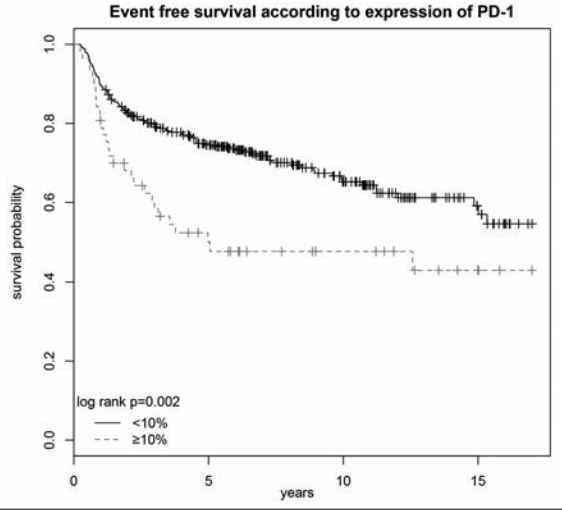


Figure 1.

A high PD-1 expression was associated with an inferior EFS (age-adjusted hazard ratio (HR)=1.69; 95% confidence interval (95%CI) 1.12-2.54), an observation which persisted also in a fully adjusted analysis (adjusted for age, albumin <40g/L, B-symptoms, bulky tumor, country, extranodal tumor involvement, sex, stage IIB-IV, and white blood cell count >15x10^9/L) (HR=1.80; 95%CI 1.19-2.90). High PD-1 was not significantly associated with worse OS. There was a weak correlation between high expression of PD-1 and intratumoral Epstein-Barr virus negativity (Spearman correlation coefficient 0.12, p=0.015), and nodular sclerosis histologic subtype (correlation coefficient 0.10, p=0.04). This is the first study to

show that high expression of PD-1 in the tumor microenvironment of cHL is associated with inferior EFS (fully adjusted multivariate analyses). Patients with high expression of PD-1 have a tumor permissive exhausted immune system and may therefore be more likely to experience treatment failure after conventional treatment regimens.

T006

THE AP-1 TRANSCRIPTION FACTOR BATF3 REGULATES MYC EXPRESSION AND IS REQUIRED FOR TUMOR CELL SURVIVAL IN CLASSICAL HODGKIN LYMPHOMA AND ANAPLASTIC LARGE CELL LYMPHOMA

A. Lollies[1], S. Hartmann[2], M. Schneider[1], T. Bracht[3], J. Arnolds[4], L. Klein-Hitpass[1], B. Sitek[3], M.-L. Hansmann[2], R. Küppers[1,*], M.A. Weniger[1,*]

[1]Institute of Cell Biology (Cancer Research), Faculty of Medicine, University of Duisburg-Essen, Essen, Germany; [2]Dr. Senckenberg Institute of Pathology, Goethe-University of Frankfurt, Medical School, Frankfurt am Main, Germany; [3]Medical Proteom Center, Ruhr-University Bochum, Bochum, Germany; [4]Department of Otorhinolaryngology, Faculty of Medicine, University of Duisburg-Essen, Essen, Germany

**Co senior authors*

The malignant cells in classical Hodgkin lymphoma (cHL) and anaplastic large cell lymphoma (ALCL) are characterized by deregulated transcription factor activity of several signaling pathways including constitutive active JAK/STAT and AP-1. Our group and others have performed gene expression profiling (GEP) of cHL and ALCL and identified BATF3, a member of the AP-1 transcription factor family, as one of the most up-regulated genes in cHL and ALCL cells. In the present study, up-regulated expression of BATF3 was confirmed at mRNA and protein level in cHL and ALCL cells. To assess BATF3 function, small hairpin (sh)RNA vectors against BATF3 were generated to downregulate BATF3 in lymphoma cell lines. Transduction experiments demonstrate that downregulation of BATF3 leads to reduced cell proliferation and induced apoptosis in cHL and ALCL cell lines. To identify BATF3-regulated targets in BATF3-knockdown cells, GEP was performed. GEP after BATF3 knockdown demonstrated a significant downregulation of known MYC target genes and immunoblot analysis confirmed downregulation of MYC in shBATF3-transduced cells. Chromatin-immunoprecipitation (ChIP) experiments demonstrated that BATF3 regulates MYC expression by binding to an AP-1 element present in the MYC promoter. To examine whether BATF3 activity was connected to the constitutive JAK/STAT activation in cHL and ALCL, we treated cHL and ALCL cell lines with the JAK2 inhibitor TG101348 and found decreased levels of BATF3 protein, suggesting that BATF3 is regulated by STAT factors. Additionally, activation of JAK/STAT signaling by interleukin stimulation induced BATF3 expression in cHL and ALCL cell lines. ChIP experiments validated STAT binding to the BATF3 promoter, indicating that STATs directly regulate BATF3 expression. In conclusion, we recognized a new oncogenic axis in cHL and ALCL and revealed a complex transcription factor network in which BATF3 links STAT signaling to MYC expression.

P024

INACTIVATION OF THE PUTATIVE UBIQUITIN-E3 LIGASE PDLIM2 IN CLASSICAL HODGKIN AND ANAPLASTIC LARGE CELL LYMPHOMA

K.D. Wurster[1,2], F. Hummel[1,2], J. Richter[3], M. Giefing[3,4], S. Hartmann[5], M.-L. Hansmann[5], S. Kreher[2], K. Köchert[1,2], D. Krappmann[6], W. Klapper[7], M. Hummel[8], S.-S. Wenzel[2], G. Lenz[9], M. Janz[1,2], B. Dörken[1,2,10], R. Siebert[3], S. Mathas[1,2,10]

[1]Max-Delbrück-Center for Molecular Medicine, Berlin, Germany; [2]Hematology, Oncology, and Tumor Immunology, Charité-Universitätsmedizin Berlin, Berlin, Germany; [3]Institute of Human Genetics, Christian-Albrechts University Kiel, Kiel, Germany; [4]Institute of Human Genetics, Polish Academy of Sciences, Department of Cancer Genetics, Poznan, Poland; [5]Dr. Senckenberg Institute of Pathology, University of Frankfurt, Medical School, Frankfurt, Germany; [6]Research Unit Cellular Signal Integration, Helmholtz Zentrum München für Gesundheit und Umwelt, Neuherberg, Germany; [7]Department of Pathology, Haematopathology Section and Lymph Node Registry, Christian-Albrechts University Kiel, Kiel, Germany; [8]Institute of Pathology, Charité-Universitätsmedzin Berlin, Berlin Germany; [9]Division of Translational Oncology, Department of Medicine A, University Hospital Münster, and Cluster of Excellence EXC 1003, Cells in Motion, Münster, Germany; [10]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

Apart from its unique histopathological appearance with rare tumor cells embedded in an inflammatory background of bystander cells, classical Hodgkin lymphoma (cHL) is characterized by an unusual activation of a broad range of signaling pathways involved in cellular activation. This includes constitutive high-level activity of NF- B, JAK/STAT, AP-1 and IRF transcription factors (TFs), which are physiologically only transiently activated. Here, we demonstrate that inactivation of the putative ubiquitin E3-ligase PDLIM2 contributes to this TF activation. PDLIM2 expression is lost at the mRNA and protein level in the majority of cHL cell lines and HRS cells of nearly all cHL primary samples. This loss is associated with PDLIM2 promoter methylation, altered splicing and, in rare cases, genomic alterations. Reconstitution of PDLIM2 in HRS cell lines inhibits proliferation, blocks NF- B transcriptional activity and contributes to cHL-specific gene expression. In non-Hodgkin B cell lines, siRNA-mediated PDLIM2 knockdown results in super-activation of TFs NF- B and AP-1 following PMA stimulation. Furthermore, expression of PDLIM2 is lost in anaplastic large cell lymphoma (ALCL), which shares key biological aspects with cHL. We conclude that inactivation of PDLIM2 is a recurrent finding in cHL and ALCL, promotes activation of inflammatory signaling pathways and thereby contributes to their pathogenesis.

P025

DETERMINATION OF THE MUTATIONAL LANDSCAPE OF PRIMARY HODGKIN AND REED/STERNBERG CELLS OF CLASSICAL HODGKIN LYMPHOMA

M. Schneider[1,2], C. Döring[1], J.C. Czeschik[3], A. Lollies[3], S. Hartmann[1], S. Rahmann[3], M.-L. Hansmann[1], R. Küppers[2]

[1]Dr. Senckenberg Institute of Pathology, Goethe-University of Frankfurt, Medical School, Frankfurt, Germany; [2]Institute of Cell Biology (Cancer Research), Faculty of Medicine, University of Duisburg-Essen, Essen, Germany; [3]Genome Informatics, Institute of Human Genetics, Faculty of Medicine, University of Duisburg-Essen, Essen, Germany

Despite recent advances in our understanding of classical HL (cHL) the pathogenesis of this disease is still largely unknown. For instance, only a few genetic aberrations in the tumor cells of cHL, the Hodgkin and Reed/Sternberg (HRS) cells, have been identified. In general, the analysis of HRS cells is hampered by the rarity of the HRS cells which usually comprises only about 1% of the tumor tissue. To better understand the pathogenesis of cHL and to identify new genes critically involved in this process, we developed a method to perform whole exome sequencing of microdissected HRS cells. So far 11 primary cHL cases were successfully sequenced. The successful validation of 16 of 21 selected mutations in HRS cells of three cHL cases by direct PCR with microdissected cells and Sanger sequencing showed the reliability of the analysis. In a preliminary analysis of the data, NFKBIE mutations were identified in three cases. Thus, NFKBIE mutations are a recurrent event in cHL.

P026

HODGKIN CELL-DERIVED EXTRACELLULAR VESICLES SHAPE FIBROBLAST ACTIVITY

T. Bösl, H.P. Hansen, A. Engert, E. Pogge von Strandmann

University Hospital of Cologne, Department of Internal Medicine I, Innate Immunity Group and German Hodgkin Study Group, Cologne, Germany

In Hodgkin lymphoma (HL) the malignant cells are greatly outnum-

bered by non-malignant immune cells supporting tumor growth and progression. Hodgkin Reed Sternberg (HRS) cells grow highly dependent on the microenvironment, which is actively shaped by a very complex cross-talk between the tumor cells and the reactive infiltrate. HRS cells secrete cytokines and angiogenic factors capable of recruiting and inducing the proliferation of surrounding cells to finally orchestrate their cellular microenvironment and to inhibit the development of an efficient antitumor immune response. Within this scenario, the role of extracellular vesicles (EVs) released by HRS cells which can communicate with other cells in trans has not been addressed yet. Recently, we demonstrated that E*Vs* released by HRS cells impact on the formation of a tumor supportive niche by stimulating IL-8 release. Here, we investigate the role of tumor cell-derived vesicles on fibroblast activity and thus their impact on creating a tumor favorable surrounding. With single and co-cultures of the malignant cells and healthy stromal cells, the reciprocal effects on their cellular functions were analyzed. Using Fibroblast mediated eotaxin as a marker we could show that the bi-directional cross-talk is not entirely cell-cell contact dependent. Not only soluble factors, but also E*Vs* had a positive effect on migration and chemotaxis, showing concentration depending effects. E*Vs* released by malignant cells are internalized by fibroblasts and induce an inflammatory phenotype, which resembles the phenotype of cancer associated fibroblasts (CAFs). As a result of EV exposure, fibroblasts show selective changes in the secretome with enhanced expression of pro-inflammatory cytokines and hits related to NF B-Signaling. Further experiments indicate that in this context, NF B-Signaling is induced by TNF- transported via E*vs* Results are further supported by *in vivo* experiments using a HL Xenograft model.

P027

PROGNOSTIC IMPLICATIONS OF AN ACTIVE, INNATE OR ANERGIC IMMUNE RESPONSE IN THE HODGKIN LYMPHOMA TUMOR MICROENVIRONMENT

P. Hollander[1], K. Rostgaard[2], K.E. Smedby[3,4], D. Molin[1], A. Loskog[5], P. de Nully Brown[6], G. Enblad[1], R.-M. Amini[7], H. Hjalgrim[2], I. Glimelius[1,3]

[1]Experimental and clinical oncology, Department of Immunology, Genetics and Pathology; Uppsala University, Uppsala, Sweden; [2]Department of Epidemiology Research; Statens Serum Institut, Copenhagen, Denmark; [3]Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [4]Hematology Center, Karolinska University Hospital, Stockholm, Sweden; [5]Clinical Immunology, Department of Immunology, Genetics and Pathology; Uppsala University, Uppsala, Sweden; [6]Department of Haematology, Rigshospitalet, Copenhagen, Denmark; [7]Clinical and Experimental Pathology, Department of Immunology, Genetics and Pathology; Uppsala University, Uppsala, Sweden

The classical Hodgkin lymphoma (cHL) tumor microenvironment includes a variable inflammatory response consisting of eosinophils, mast cells, macrophages, regulatory T lymphocytes (Treg) and active lymphocytes. We counted these inflammatory cells in tumor tissue from 459 patients with cHL from Sweden and Denmark, with complete clinical data available for 409 patients (Figure 1). Depending on the predominant cell types and their immunologic function we categorized the immune profile into an active, anergic or innate immune response with the aim to investigate if a specific tumor immune profile can predict survival. Time to progression (TTP) (primary progression, relapse or cHL death) and overall survival (OS) were analyzed using Cox proportional hazards regression. During follow-up (median 12.9 years) 49 patients had disease progression and 78 patients died. A high proportion of Treg (an anergic immune response) conferred shorter TTP when adjusted for age (hazard ratio (HR)=2.25; 95% confidence interval (CI) 1.15-4.41), especially in advanced stages (HR=2.83; 95%CI 1.25-6.40). In addition, a low proportion of Treg combined with a high proportion of macrophages conferred superior TTP when adjusted for age, stage, albumin and bulky tumor (HR=0.23; 95%CI 0.07-0.77). This is the first study to show that a tumor microenvironment characterized by an anergic immune response corresponds to a shorter TTP in cHL, indicating a reduced ability of an anergic immune system to attack the tumor cells. The programmed death receptor 1 (PD-1) is expressed by Treg, and these results warrant further investigation to determine if Treg is a predictor of response to PD-1 blocking drugs.

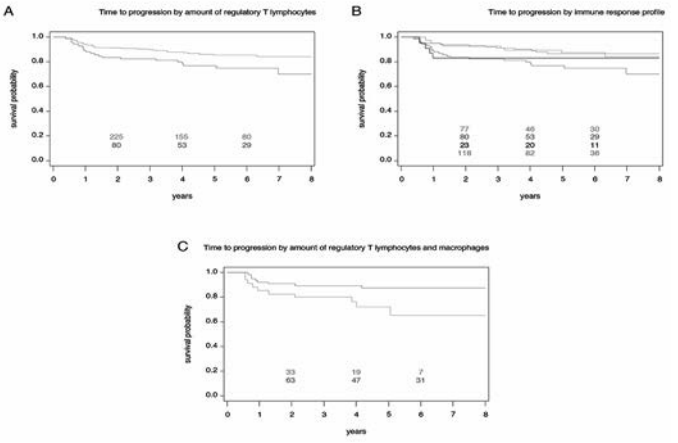


Figure 1. Univariate analysis for Time to Progression. (A) Kaplan-Meier estimates according to upper quartile Treg (Blue) and below upper quartile Treg (Red). (B) Kaplan-Meier estimates according to active (Red), anergic (Blue), innate (Black), and mixed immune responses (Green). (C) Kaplan-Meier estimates according to below upper quartile Treg and upper quartile macrophages combined (Blue), and upper quartile Treg and below upper quartile macrophages combined (Red).

P028

STUDYING THE ROLE OF ONCOGENIC miR-24-3^p IN HODGKIN LYMPHOMA

Y. Yuan, J. Kluiver, J. Koerts, D. de Jong, B. Rutgers, A. Diepstra, L. Visser, A. van den Berg

Department of Pathology & Medical Biology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands

Introduction. Micro (mi)RNAs negatively regulate gene expression at the transcriptional level by binding to complementary regions in the 3'-UTR. They play important roles in biological processes such as proliferation, metabolism, differentiation and apoptosis. Aberrant expression of miRNAs contributes to several diseases including cancer. Although several miRNAs have been implicated in the pathogenesis of Hodgkin lymphoma (HL), the function of most of the aberrantly expressed miRNAs is unknown. Therefore, the aim of this study is to investigate the role of miRNAs and the underlying mechanism in HL. *Results.* Small RNA-seq revealed 84 significantly differentially expressed miRNAs in HL cell lines as compared to GC-B cells, including 55 up- and 29 downregulated miRNAs. QRT-PCR validation confirmed the differential expression pattern as observed with small RNA sequencing for 15 out of 19 selected miRNAs. Among the upregulated miRNAs, miR-23a, miR-24 and miR-27a were transcribed from one primary miRNA transcript. Loss-of-function analysis for these 3 miRNAs and their family members resulted in decreased growth upon miR-24 inhibition in L428, L1236 and KMH2 and upon inhibition of miR-27a/b in L1236. No effect on cell growth was observed upon inhibition of miR-23a/b. Apoptosis analysis upon miR-24 inhibition revealed increased percentage of apoptosis cells, indicating that the decreased cell growth upon miR-24 inhibition was at least in part caused by an increase in apoptosis. To identify the target genes of these miRNAs we performed argonaute 2 (AGO2)-IP in four HL cell lines. This revealed 1,142 consistently AGO2-enriched genes. Gene set enrichment analysis revealed significant enrichment of the miR-23a/b, miR-24 and miR-27a/b miRNA target gene sets in the IP fraction. Furthermore, 51 out of 1,142 genes were predicated targets of miR-24 based on Targetscan, including 4 out of 5 proven miR-24 targets. Functional annotation analysis revealed a function related to cell growth, cell death and/or apoptosis for 15 out of the 52 genes. Western blotting for 2 of these genes, *i.e.* CDKN1B and MYC, showed downregulation at the protein level upon miR-24 inhibition.

Conclusions. A total of 84 miRNAs were significant differently expressed in HL cell lines compared to GC-B cells. MiR-24 has an oncogenic role in HL by inhibiting apoptosis.

P029

CHARACTERIZATION OF HODGKIN LYMPHOMA CLONOGENIC CELLS USING A NEW L428 *IN VIVO* XENOGRAFT MODEL IN IMMUNODEFICIENT NOD/SCID-GAMMAC-/- MICE AND PERIPHERAL LYMPHOCYTES STUDY IN HODGKIN LYMPHOMA PATIENTS

C. Cuceu[1], M. Al Jawhari[1], L. Morat[1], M. Frenzel[1], D. Lewandowski[2], S. Junker[2], F. Pflumio[3], J. Bourhis[4], T. Girinsky[5], L. Sabatier[1], P. Carde[6], R. M'kacher[1-7]

[1]Laboratoire de Radiobiologie et d'Oncologie, IRCM/DSV/CEA Fontenay aux Roses, France; [2]CEA/DSV/iRCM/LRTS, Fontenay-aux-Roses, France; [3]CEA/DSV/iRCM/,LSHL, Fontenay-aux-Roses, France; [4]INSERM 1030, Institut Gustave Roussy Villejuif, France; [5]Department of radiation oncology, Institut Gustave Roussy, Villejuif France; [6]Department of Hematology, Intitut Gustave Roussy, Villejuif France; [7]Cell Environment Oncology section Paris France

The characterization of the cells at the origin of Hodgkin and Reed Sternberg cells in Hodgkin lymphoma (HL) is hampered mostly because of the poor growth of HL cells *in vitro* and *in vivo*. Investigation of cell markers and signaling pathways specific to HL clonogenic cells may lead to progress in therapy and improve the prognosis of patients with HL. Using a newly developed murine *in vivo* L428 xenograft model and circulating lymphocytes of HL patients before treatment, we attempted to determine the immunophenotype and cytogenetic profile of the clonogenic cells. *Materials and Methods.* L428 HL cell line was used to establish an *in vivo* xenograft model in immunodeficient NOD/SCID-gammac-/- mice. *In vitro* and *in vivo* clonogenic cells derived from L428 cell line and circulating lymphocytes of 50 HL patients were characterized using immunofluorescence, immunochemistry and cytogenetic. Chromosomal instability was also investigated. Telomere maintenance mechanisms (telomerase activity (TA) and Alternative Lengthening Telomere (ALT)) were explored. *Results.* We confirmed previous data that L428 cell line contained small (<2%) subpopulations that lacked CD30 and CD15 expression and had greater clonogenic potential *in vitro* than the corresponding CD30+ and CD15+ cells. These cells were also clonogenic *in vivo* in NOD/SCID gamma -/- mice. Immunophenotype characterization of the first cells harvested from the mice demonstrated a CD30, CD15 and CD14 negative profile. Over time, the cells acquired CD14 followed by CD15 and finally CD30 surface markers. Cytogenetic analysis confirmed the diploid origin of the cells that grow in the mice. Cell sorting of negative cells in HL cell lines was performed to validate this hypothesis and demonstrate their clonogenic potential to recover the parental cell line. These cells were characterized by a higher telomere instability associated to the presence of higher frequency of dicentric chromosome. A high TA was detected in these cells as well as in the circulating lymphocytes in 10 out of 50 HL patients. *Conclusions.* We better characterized the origin of the cells which grow in the L428 xenograft model, and their different steps of transformation from "clonogenic cells" to monocytes/macrophages and finally to Hodgkin and HRS cells due to the unique microenvironment of HL. The assessment of TA could be used as a biomarker of the prevalence of clonogenic cells in circulating lymphocytes.

P030

THE LYMPHOID CELL SPECIFIC TRANSCRIPTION FACTOR ELF-1 IS TRANSCRIPTIONALLY DOWNREGULATED AND RECURRENTLY DELETED IN CLASSICAL HODGKIN LYMPHOMA

M. Giefing[1,2], N. Zemke[1], M. Bodnar[2,3], E. Domanowska[3], J. Janiszewska[1], J. Paczkowska[1], A. Ustaszewski[1], J.I. Martin-Subero[4], O. Ammerpohl[5], W. Klapper[6], A. Marszalek[3,7], R. Siebert[5,8]

[1]Institute of Human Genetics, Polish Academy of Sciences, Department of Cancer Genetics, Poznan, Poland; [2]Department of Otolaryngology and Laryngological Oncology, Poznan University of Medical Sciences, Poznan, Poland; [3]Department of Clinical Pathomorphology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Bydgoszcz, Poland; [4]Institut d'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), Department of Anatomic Pathology, Pharmacology and Microbiology, University of Barcelona, Barcelona, Spain; [5]Institute of Human Genetics, Christian-Albrechts-University Kiel, Kiel, Germany; [6]Department of Pathology, Hematopathology Section and Lymph Node Registry, University Hospital Schleswig-Holstein, Campus Kiel/Christian-Albrechts-University Kiel; [7]Chair of Oncologic Pathology and Prophylaxis Poznan University of Medical Sciences & Greater Poland Cancer Center Poznan, Poland; [8]Institute of Human Genetics, University of Ulm, Ulm, Germany

ELF-1 and ELF-2 belong to the ETS-family of transcription activators or repressors implicated in processes recurrently deregulated in human neoplasms. Recently, we have shown that genes hypermethylated in cHL are enriched for binding sites of ETS-family members ETS-1 (1.28 fold), ELF-1 (1.07 fold) and ELF-2 (1.91 fold). We hypothesized that hypermethylation of genes in cHL might be secondary towards genomic alterations of these B-cell related transcription factors. In line, we have recently reported recurrent alterations and significant downregulation of ETS-1 expression in cHL. Encouraged by this finding, here we analyzed the two other ETS family members in cHL. We show significant downregulation of ELF-1 (8.82 fold, p<0.0001, tag 40067_at) and 1.36 fold of ELF-2 (tag 507_s_at) in cHL cell lines (n=4) compared to GCB pools (n=20) (U95 microarray). This was further validated for ELF-1 in primary biopsies where using immunohistochemistry (AB99401) we observed loss or downregulation of the protein in HRS cells in 26/35 (74%) cases but not in no-tumor bystander cells. In case of ELF-2 no reduction of protein abundance was observed. To identify the underlying mechanism we sequenced the ELF-1 coding region in 7 cHL cell lines but no mutations were identified. In contrast, we analyzed copy number (CN) alterations of the ELF-1 locus in primary biopsies using combined immunophenotyping and *in situ* hybridization (FICTION) and identified deletions in 5/11 (45%) analyzed cases. Similarly, deletions or LOH were found in 4/7 (57%) cHL cell lines (Affymetrix SNP 6.0 array). Also epigenetic mechanism may contribute to ELF-1 downregulation as using next-generation miRnome sequencing we observed 3.26 fold overexpression (p=0.0018) of the hsa-miR-330-3p in cHL cell lines (n=7) compared to non-Hodgkin lymphomas (n=10). Hsa-miR-330-3p shows significant affinity (p=0.0013) towards the 3'UTR region of ELF-1 basing on in silico analysis (miRWalk). In conclusion, we show recurrent loss of ELF-1 expression in HRS cells that at least in part is attributable to the genomic deletions and overexpressed hsa-miR-330-3p. Moreover, our data support the concept, that downregulation of the ELF-1 transcription factor may lead to consequent hypermethylation and silencing of its target genes contributing to the loss of B-cell phenotype of HRS cells.

P031

MUTATIONS IN CD58 AND MYB IN HODGKIN LYMPHOMA

F.R. Abdul Razak, A. Diepstra, D. Jong, J. Koerts, B. Rutgers, J. Kluiver, L. Visser, A. van den Berg

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

Hodgkin lymphoma (HL) is characterized by constitutive activation of several signaling pathways and expression of a distinct set of transcription factors. This characteristic phenotype is partly caused by gene mutations as determined by targeted and whole genome sequencing approaches on cell lines and microdissected HRS cells. Here we studied CD58 and MYB, 2 genes we previously identified by whole exome sequencing (WES) in HL cell lines. CD58 gene mutations observed in 3 HL cell lines were confirmed by Sanger sequencing at the DNA and RNA level. CD58 protein expression as determined by flow, western blot and IHC was absent in all 3 HL cell lines with mutations and present in 4 HL cell lines with wild type CD58. In primary tissue samples, loss of CD58 expression was observed in 11% of the patients. Lack of CD58 was specifically observed in patients who developed a relapse. This suggests that loss of CD58 is a potential

immune escape mechanism of HRS tumor cells, especially in clinically aggressive disease. Frame shift mutations resulting in a truncated MYB protein were found in L428 and SUPHD1 cells. The mutation in L428 causes complete loss of most of the C-terminal domain whereas the mutation in SUPHD1 results in a MYB protein with a partial loss of the C-terminal domain. We confirmed the mutations at the DNA and RNA level and confirmed presence of a truncated protein by Western blot with C-terminal and N-terminal domain specific antibodies. RT-PCR with primers specific for each of the alternatively spliced exons, indicated that these were not included in the MYB transcript in any of the HL cell lines. In tissue samples, staining of MYB in HL cases revealed no staining with both antibodies in the vast majority of the cases, indicating complete loss of the MYB protein. Inhibition of MYB by shRNA constructs induced negative effects on cell growth in HL cell lines with wild type MYB (L540 & KMH2) and no or limited effects in HL cell lines with truncated MYB (L428 & SUPHD1). Microarray analyses of L540 & KMH2 cells treated with non-targeting and MYB shRNA constructs revealed 63 consistently MYB induced and repressed genes. In conclusion, we show that loss of CD58 expression is common in HL cell lines and restricted to the HRS cells of tissue samples of relapsed HL. For MYB, strong oncogenic effects were observed especially for the HL cell lines with wild type MYB.

P032

RE-FUSION OF SMALL MONONUCLEATED HODGKIN CELLS LEADS TO GIANT MULTINUCLEATED REED-STERNBERG CELLS IN HODGKIN LYMPHOMA

B. Rengstl[1], S. Newrzela[1], T. Heinrich[1], C. Weiser[1], F.B. Thalheimer[2,3], F. Schmid[1], K. Warner[4], S. Hartmann[1], T. Schroeder[5], R. Küppers[6], M.A. Rieger[2,3,7,8,*], M.-L. Hansmann[1,*]

[1]Dr. Senckenberg Institute of Pathology, Goethe-University of Frankfurt, Medical School, Frankfurt am Main, Germany; [2]LOEWE Center for Cell and Gene Therapy Frankfurt, Department of Hematology/Oncology, Goethe-University of Frankfurt, Medical School, Frankfurt am Main, Germany; [3]Georg-Speyer-Haus, Institute for Biomedical Research, Frankfurt am Main, Germany; [4]Department I of Internal Medicine, University of Cologne, Medical School, Cologne, Germany; [5]Stem Cell Dynamics Unit, Helmholtz Zentrum Munich, Neuherberg, Germany; [6]Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, Medical School, Essen, Germany; [7]German Cancer Consortium (DKTK), Heidelberg, Germany; [8]German Cancer Research Center (DKFZ), Heidelberg, Germany

**Shared last authorship*

The multinucleated Reed-Sternberg (RS) cells are pathognomonic for classical Hodgkin lymphoma (HL) and their presence is essential for diagnosis. However, the development of these giant tumor cells is controversially discussed. It was postulated that RS cells arise from mononucleated Hodgkin cells via endomitosis. Conversely, continuous single cell tracking of HL cell lines by long-term time-lapse microscopy showed that cell fusion is the main route of RS cell formation. In contrast to growth-induced formation of giant Hodgkin cells, fusion of small mononuclear cells followed by size increase gives rise to giant RS cells. Importantly, we nearly exclusively observed fusion of cells originating from the same ancestor, termed re-fusion. In the majority of cases, re-fusion of daughter cells was preceded by an incomplete cytokinesis, visualized by a microtubule bond between the cells. We confirm at the level of individual tracked cells that giant Hodgkin and RS cells have little proliferative capacity, further specifying small mononuclear Hodgkin cells as the proliferative compartment of the HL tumor clone. In addition, sister cells showed a shared propensity for re-fusion, which provides evidence of early RS cell fate commitment. Thus, RS cell generation is neither due to cell fusion of unrelated Hodgkin cells nor to endomitosis, but is mediated by re-fusion of daughter cells that underwent mitosis. This surprising finding indicates the existence of a novel mechanism for the generation of multinuclear RS cells, which might have implications beyond HL, as RS-like cells are frequently observed in several other lymphoproliferative diseases.

P033

MOLECULAR CHARACTERIZATION OF BRUTON'S TYROSINE KINASE INHIBITOR IN HODGKIN'S LYMPHOMA: CELLULAR AND ANIMAL MODELS

I. Muqbil[1], A. Aboukameel[1,2], A.S. Azmi[1], R.M. Mohammad[1], R. Ramchandren[1]

[1]Department of Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA; [2]Janssen Medical Affairs Oncology, Janssen Services, LLC

Abstract. Classical Hodgkin Lymphoma (cHL) is a malignancy of mature (post germinal center) B-lymphocytes that afflicts almost 20,000 individuals annually in North America and Europe alone. While the majority of patients diagnosed with HL are cured with multi-agent chemotherapy, 15% of patients are refractory to conventional chemotherapy and almost half of patients with high-risk disease relapse. Only 2 agents have been approved in the last 30 years for relapsed HL and novel therapies are needed. Bruton's Tyrosine Kinase (BTK) is a member of the TEC family and plays a central role in B-cell signaling, activation, proliferation and differentiation. Several studies have shown that BTK is upregulated in a proportion of Reed-Sternberg cells and has been associated with PI3K, mTOR, FAS and NF- B signaling. Furthermore, pathways upregulated in cHL such as CD40 ligand binding, elevated chemokines such as IL-6 and activation of toll like receptor (TLR) pathways have been associated with BTK upregulation. Thus, BTK inhibition may have therapeutic potential in cHL. *Methods.* The BTK inhibitor Ibrutinib at 0-15 micro molar doses was incubated for 72 hrs. with a panel of HL cell lines (KM-H2, L1236, L-428). Cell viability was evaluated using trypan blue. Apoptosis was analyzed using annexin V FITC and histone DNA ELISA. Protein expression was analyzed using western blotting with RNA post ibrutinib treatment subjected to RT PCR. *Results.* Ibrutinib suppressed viability of these HL cell lines in a dose dependent manner (IC50s ~5-7.5 μM in KM-H2, L1236 and L-428). The drug induced statistically significant apoptosis in the responsive cell lines in a dose dependent manner (>50% apoptosis at IC50 doses). Molecular analysis using western blotting and RT-PCR revealed significant induction of apoptotic markers and down-regulation of pro-survival markers. Further characterization of the effect of Ibrutinib on PI3K, mTOR, FAS and NF-kB signaling is ongoing. Ibrutinib is now being evaluated in ICR SCID mice with sub-cutaneous xenografts of KM-H2 and L1236. A pre-clinical efficacy trial using maximum tolerated dose (MTD) given by gavage is ongoing. *Conclusions*. These are the first studies showing *in vitro* and *ex vivo* effects of BTK inhibitors in HL and may provide support for further clinical investigation.

P034

FUNCTIONAL ANALYSIS TO ELUCIDATE THE SUSCEPTIBILITY MECHANISMS OF SNPs AT THE REL, GATA3 AND TCF3 LOCI IN CLASSICAL HODGKIN LYMPHOMA

R. Veenstra, J. Kluiver, D. de Jong, J. Koerts, L. Visser, A. Diepstra, A. van den Berg

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

Introduction. Genome Wide Association Studies (GWAS) revealed significant associations for SNPs mapping at the REL, GATA3 and TCF3 loci with cHL susceptibility. In this study, we aim to elucidate the susceptibility mechanism of these associations by establishing possible expression quantitative trait loci (eQTL) effects. *Methods*. EQTL analysis was performed in EBV transformed lymphoblastoid cell lines (LCLs) generated from 96 controls and 70 former cHL patients as well as in three previously published large gene expression studies of HRS cells and total HL tissue samples. *Results*. An eQTL effect for REL was found using cHL total tissue array data with increased REL expression levels for individuals carrying the homozygous risk allele. No significant effects were observed for the HRS cell data and for the LCLs. For GATA3 a significant association was found

in the patient derived LCLs with lower GATA3 levels in LCLs of homozygous risk allele carriers, while no effect was observed for the control LCLs, or the HRS cell and the cHL total tissue array data. Only In the control LCLs lower TCF3 expression levels were found for individuals homozygous for the risk allele. To identify the downstream targets of these three transcription factors we performed gene expression arrays of cHL cell lines infected with shRNA constructs. We identified 1805, 1052, 1602 differentially expressed genes for REL, GATA3 and TCF3, respectively. eQTL analysis of the array data focusing only on these downstream targets is ongoing. *Conclusions*. For REL, GATA3 and TCF3 we observed an eQTL effect in at least one of the studied groups. For REL and TCF3 the eQTL pattern is consistent with the proposed susceptibility effects of these genes, *i.e.* higher REL levels stimulating cell growth and lower TCF3 levels supporting the loss-of-B-cell phenotype for the risk alleles. Surprisingly, for the T-helper 2 specific transcription factor GATA3 the risk allele is associated with decreased levels in B-cells, but apparently not in T-cells. Our data support a functional rol for the risk and protective SNP alleles in cHL susceptibility.

P035

IGH-MEDIATED TRANSLOCATIONS, RECURRENT IN CLASSIC HODGKIN LYMPHOMA, FREQUENTLY CORRELATE WITH AN AGGRESSIVE BEHAVIOR

I. Wlodarska[1], D. Dierickx[2], U. Pluys[1], K. Doms[1], C. Graux[3], A. Van Hoof[4], P. Vandenberghe[1], L. Michaux[1], T. Tousseyn[5]

[1]Center for Human Genetics, KU Leuven, Leuven, Belgium; [2]Department of Hematology, UZ Leuven, Leuven, Belgium; [3]Department of Hematology, CHU UCL Namur, Belgium; [4]Department of Hematology, AZ Sint-Jan AV, Brugge, Belgium; [5]Department of Pathology, UZ Leuven, Leuven, Belgium

Cytogenetic features of classic Hodgkin lymphoma (cHL) remain largely unknown. Interphase FISH (iFISH) studies, however, suggest that IGH-mediated t(14q32) are recurrent in cHL (PMID: 17079453, 18940474). Recently, we have identified t(14;18)(q32;q21)/IGH-BCL2 and inv(14)(q11q32)/IGH-CEPBE in two patients with nodular sclerosis HL (NSHL) analyzed at time of relapse. To identify additional cHL cases with t(14q32/IGH) and check whether these rearrangements correlate with clinical outcome, we screened by iFISH: (i) 46 relapsed cHL, (ii) 40 cHL with a long-term remission, and (iii) 60 prospective cases. Altogether, IGH rearrangements were detected in 28 patients, including 17 representing the former group (35.4%), 4 cases representing the second group (10%) and 7 prospective cases (11.6%). LSI IGH FISH pattern suggested a reciprocal t(14q32/IGH) in 20 cases, nonreciprocal t(14q32/IGH) in 4 cases, inv(14q32/IGH) or ins(14q32/IGH) in 3 cases and interstitial del(14q32/IGH) in one case. Twenty six cases were further analyzed by iFISH with break-apart (BA) assays for BCL2, BCL3, BCL6 and MYC. In 3 cases with likely inv(14)/ins(14), CEPBE BA was applied. Altogether, we have identified the IGH-BCL2 rearrangement in two cases, including the index case with t(14;18), and the IGH-CEPBE rearrangement in the case with inv(14). All the remaining cases showed a non-rearranged status of the examined loci. The majority of patients (18/28) with t(14q32/IGH) were diagnosed with NSHL. There were 18 male and 10 female patients in age ranging from 18 to 91 years (mean 50). Patients presented with both early (10/26) and advanced (16/26) stage (two not staged). All were treated with chemotherapy with or without radiotherapy, except for two patients who were subjected to a palliative treatment. After induction therapy, complete and partial remission was achieved in 17 and 5 patients, respectively. Thirteen patients are alive (11 without disease and 2 with disease); 13 patients died, including 11 whose death was related with a disease, and two are lost for follow up. In summary, we confirmed that chromosomal aberrations involving 14q32/IGH occur recurrently in cHL. These rearrangements rarely target BCL2 and CEPBE, and do not affect BCL3, BCL6 and MYC. Interestingly, 17 out of 21 (81%) patients with t(14q32/IGH) showed an aggressive behavior. Our study allows a new insight into the pathogenesis of cHL and might help in further stratification of cHL patients.

P036

TIGHTLY REGULATED FOXO3 EXPRESSION IS CRITICAL FOR THE MAINTENANCE OF cHL

C.D. Weitzer[1], L. Xie[2], H. Guan[3], F. Herrmann[1], S. Pick[1], T. Wirth[1], A. Ushmorov[1]

[1]Institute of Physiological Chemistry, University of Ulm, Ulm, Germany; [2]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, China; [3]Department of Orthopaedic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

FOXO (forkhead box O) transcription factors regulate genes involved in cell cycle arrest, apoptosis, or oxidative stress response. Recently, we have shown that FOXO1 is specifically repressed in classical Hodgkin lymphoma (cHL) and thus acts as a tumor suppressor in this tumor entity. In contrast, FOXO3 was reported to be markedly expressed in the malignant Hodgkin and Reed-Sternberg (HRS) cells of cHL, but not in other B-cell lymphoma subtypes. We confirmed a high FOXO3/FOXO1 ratio in cHL by analysing publically available gene expression profiling (GEP) data and found that this ratio is similiar to those of plasma cells (PC) and multiple myeloma (MM). Of note, cHL FOXO3 expression was higher than in non-HL, but still less than in terminally differentiated MM cell lines. These intermediate FOXO3 levels might reflect the "abortive PC differentiation" phenotype of cHL. Moreover, analysis of GEP data of microdissected HRS cells revealed a positive correlation between FOXO3 and PRDM1 expression, the master regulator of PC differentiation and a tumor suppressor in cHL. This is similar to our previously published findings showing that FOXO1 regulates PRDM1, the active isoform of PRDM1. Using ChIP, we next proved that FOXO3, too, directly binds to the PRDM1 promoter in cHL. To further investigate this interaction, we overexpressed a constitutively active variant of FOXO3 (FOXO3(A3)ER) in cHL cell lines. FOXO3 activation increased PRDM1 expression levels and inhibited proliferation of cHL cell lines. So far, frequent genomic deletions are known to restrict FOXO3 levels in cHL. Aiming to identify additional factors involved in the tight regulation of FOXO3 in cHL, we found that miR-155 negatively influences FOXO3 expression. Paradoxically, knockdown of FOXO3 with the help of a specific shRNA also showed an antitumor effect in two of three cHL cell lines, whereas FOXO1 downregulation was not toxic. Our data suggest that intermediate levels of FOXO3 contribute to abortive PC differentiation of cHL and that tightly regulated FOXO3 expression might be critical for the oncogenic program of cHL.

P037

IN VITRO AND *IN VIVO* PRECLINICAL ACTIVITY OF EDO-S101 IN HODGKIN LYMPHOMA

M. Al Jawhari[1], C. Cuceu[1], M. Frenzel[1], L. Stimmer[2], S. Junker[3], J. Bosq[4], P. Carde[5], T. Mehrling[6], L. Sabatier[1], F. Pflumio[7], R. M'kacher[1,8]

[1]Radiobiology and Oncology Laboratory, CEA, iRCM, Fontenay aux Roses, France; [2]Platform for Experimental Pathology PathEX / CRC MIRCen / CEA-INSERM Fontenay aux Roses, France; [3]Institute of Human Genetics, University of Aarhus, Aarhus, Denmark; [4]Departement of Anapathology, Institut Gustave Roussy, Vilejuif, France; [5]Department of Medicine; Institut Gustave Roussy; Villejuif, France; [6]Mundipharma-EDO GmbH, Basel, Switzerland; [7]Laboratoire des Cellules Souches Hématopoïétiques et Leucémiques, UMR967 INSERM, Universités Paris 7 et Paris 11, IRCM/CEA, Fontenay-aux-Roses, France; [8]Cell Environment, Oncology Section, Paris, France

Background. EDO-S101 is an alkylating histone-deacetylase inhibitor (HDACi) fusion molecule that combines the strong DNA damaging effect of Bendamustine, with a fully functional pan-HDAC inhibitor, vorinostat. In this work, we investigated the preclinical rationale for the use of EDO-S101 in Hodgkin lymphoma (HL). *Materials and Methods. In vitro*, a panel of 8 HL cell lines was used to study the cytotoxicity of EDO-S101 alone and combined with radiation therapy, and to investigate its cellular and molecular effects. *In vivo*, we investigated in immunodeficient NOD/SCID-gammac-/- mice xenografted with the

L428 the antitumor effect of EDO-S101 alone . This evaluation, based on organ infiltration and survival, was performed following one single (60mg/kg or 80mg/kg) dosing or a repeat- dose (60mg/kg) of EDO-S101. *Results. In vitro*, the IC50 of EDO-S101 ranged between 1.6 to 6.3 M in 8 Hl cell lines after a 48 h-exposure. All HL cell lines showed a high sensitivity to EDO-S101; a clonogenic survival assay confirmed these observations. Multiple mechanisms of action of EDO-S101 were identified. In one group of HL cell lines (L428-L428-s, L540, SUP-HD, L591 and KMH2), activation of apoptosis was independent of the P53 status. The combination of EDO-S101 with irradiation demonstrated a dramatical enhancement of apoptotic cell death via G2 arrest. In a second group (L1236 and HDLM2), with the higher sensitivity to EDO-S101, resistance to apoptosis was associated with a higher frequency of chromatid aberrations involved in mitotic cell death. The effect of radiation was marginal in this group. *In vivo*, in mice engrafted with the L428 cells, treatment with EDO-S101 reduced drastically L428 cells infiltration, and prolonged survival of EDO-S101 treated mice in comparison with those untreated. Histological evaluation of the infiltration of tumoral cells after EDO-S101 treatment showed a significant reduction of tumor cell infiltration, more pronounced after a single dose of 80 mg/kg EDO-S101 than after two administrations of 60mg/kg. We observed a high liver weight heterogeneity in untreated mice, contrasting with homogeneous weight in treated mice. The absence of necrotic cells and cell degeneration in treated mice could be correlated to the anti-tumoral effect of EDO-S101 confirming the efficacy of EDO-S101. *Conclusions.* Our results show the antitumoral activity of EDO-S101 in pre-clinical models of HL, both *in vitro* and *in vivo*.

P038

HODGKIN REED-STERNBERG CELLS IN CLASSICAL HODGKIN LYMPHOMA ARE SURROUNDED BY T REGULATORY CELLS WHILE LYMPHOCYTE PREDOMINANT CELLS OF NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA ARE SURROUNDED BY T FOLLICULAR HELPER CELLS

L. Visser, A. Sattarzadeh, R. Wu, B. Rutgers, A. Diepstra, A. van den Berg

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

While it is clear that there is an important role for the microenvironment in Hodgkin lymphoma (HL), the composition and functionality is still a matter of discussion. Both a Th2 and a Th1 phenotype has been described in classical HL (cHL), irrespective of the Epstein Barr virus (EBV) status of the tumor cells. A systematic comparison between cHL and nodular lymphocyte predominant HL (NLPHL) has not been performed before and studies on the composition of the cells in- *versus* outside of the tumor area are missing. We compared the composition of the microenvironment of 14 cHL (7 EBV+ and 7 EBV-) and 10 NLPHL suspensions by flowcytometry. CD26 expression was used to identify cells in- (CD26-) and outside (CD26+) the tumor cell area. *Results.* In EBV+ cHL there were more CD56+CD16+ NK cells, and more CD69+, Granzyme B+ and TIA-1+ CD8+ cells than in EBV- cHL. We saw no differences between EBV+ and EBV- cHL when looking at the location of the cells. Compared to cHL, NLPHL contained more PD-1+ CD4+ cells and PD-1+CD57+CD4+ cells, while cHL showed more CCR7+CD45RA+CD4+, FoxP3+CD4+, CD25+CD4+, CXCR5+ICOS+CD4+, CXCR3+CD8+ and CD56+ cells. In cHL, we found more CD69+CD4+ and FoxP3+CD4+ cells inside, and more CD25+CD8+ cells outside the tumor cell area. In NLPHL, the distribution of CD69+CD4+ cells and CD25+CD8+ cells was similar to cHL. In addition, we found more CD69+CD8+, and more PD1+CD4+ cells inside, and more FoxP3+CD25+CD4+ cells outside the tumor cell area. Both HL subtypes are characterized by high numbers of CD69+CD4+ cells inside the tumor cell area, and a shift of CD25+CD8+ cells from in- to outside the tumor cell area. *Conclusions.* PD-1+CD4+ T follicular helper cells normally provide help to germinal center B cells and the increase in the tumor cell area of NLPHL indicates a similar function for LP cells. In cHL, the increase of FoxP3+ T regulatory cells might provide an immune suppressive environment for the HRS cells. Both types of HL depend on different cells in the direct tumor cell environment, fitting the different nature of the tumor cells.

P039

THE INCIDENCE OF BLEOMYCIN INDUCED LUNG TOXICITY IS INCREASED IN HODGKIN LYMPHOMA PATIENTS EXPOSED FOR GRANULOCYTE-COLONY STIMULATING GROWTH FACTOR

M.D. Andersen*, P. Kamper*, A. d'Amore, M. Clausen, H. Bentzen, F. d'Amore

Department of Hematology, Aarhus University Hospital, Aarhus C, Denmark

**Shared first authorship*

Background. In Hodgkin lymphoma (HL) the risk of developing bleomycin pulmonary toxicity (BPT) is well described. A number of factors that could potentially increase the risk of this condition have been suggested *e.g.* increasing age, bleomycin dose, smoking history. The use of granulocyte-colony stimulating factor (G-CSF) has also been proposed as a potential risk factor for BPT. In the present study, we have investigated the incidence of BPT in the face of possible risk factors in a cohort of HL patients treated at our institution between 1990 and 2014. *Methods.* Information on clinico-pathological parameters including the occurrence of BPT, the use of filgrastim/pegfilgrastim and smoke habits was obtained from clinical records. BPT was defined as pulmonary symptoms occurring during the course of chemotherapy, presence of infiltrates on chest X-ray or CT-scan and absence of infection. Patient characteristics were correlated to the presence of BPT and use of G-CSF using the chi2-test. Overall- and progression-free survival (OS and PFS), were analyzed by the Kaplan-Meier method. *Results.* 413 patients with a median age of 38.5 yrs (range: 16-86 yrs) were analyzed. The M:F ratio was 1,3. A total of 155 patients (38%) had disseminated disease. B-symptoms and bulky lesions were present in 48% and 31% of the patients, respectively. A history of smoking was reported in 47% of all patients. A total of 36 patients (9%) were diagnosed with BPT. The incidence of BPT was found to be higher among patents with high stage (p<0,001) and among those presenting with B-symptoms (p=0.008), *i.e.* the subsets that were likely to have received the largest amounts of bleomycin. A trend was found towards a higher incidence with increasing age (p=0.06). No correlation was found between BPT and a smoking history (p=0,37). Patients presenting with BPT were more likely to have been exposed to the use of G-CSF (p=0,03). Interestingly, the highest number of BPT events was observed among the patients exposed to the PEGylated forms of G-CSF (p=0,02). When stratifying the analysis according to age, the above correlations remained significant in the age group above 45 years, but did not seem to impact the younger patients. *Conclusions.* In the present study, the occurrence of BPT was correlated to the presence of disseminated disease and B-symptoms at the time of diagnosis. We also found a higher incidence of BPT among the patients that were exposed to G-CSF during the course of chemotherapy.

P040

CORRELATION BETWEEN PRE-TREATMENT LEVEL OF SOLUBLE PD-L1 AND OUTCOME IN CLASSICAL HODGKIN LYMPHOMA INCLUDED IN A PROSPECTIVE STUDY OF THE LYMPHOMA STUDY ASSOCIATION

H. Ghesquières, Y. Drouet, I. Azzaoui, D. Rossille, C. Rossi, M. Roussel, G. Salles, A. Traverse-Glehen, O. Casasnovas, T. Fest

Department of Hematology and Pathology, Centre Hospitalier Lyon Sud, Pierre-Benite, France; Unite de Prevention et d'Epidemiologie Genetique - UMR UCBL CNRS 5558, Centre Leon Berard, Lyon, France; INSERM U917, Hematology Laboratory, Universite de Rennes 1, Hopital Pontchaillou, Rennes, France; Department of Hematology, CHU Dijon, Dijon, France

Introduction. Classical Hodgkin Lymphoma (CHL) is characterized by PD-L1/L2 deregulation with the effectiveness of PD-1 blockage

treatment. Pre-treatment level of soluble PD-L1 (sPD-L1) was more elevated in diffuse large B-cell lymphoma (DLBCL) patients than in controls and was associated with overall survival. We evaluated pre-treatment sPD-L1 level of 126 CHL patients included in a prospective study of the Lymphoma Study Association (LYSA) and 37 controls. *Methods.* The cohort consisted in 126 CHL patients enrolled between 1998 and 2002 in a prospective study of the LYSA assessing the prognostic values of plasma cytokines and soluble receptors. A peripheral blood sample for plasma was collected from all patients at diagnosis before any treatment. The protein expression of sPD-L1 was evaluated in duplicate using an ELISA kit. A Zero-Inflated Binomial-Negative regression model was used to compare sPD-L1 levels in CHL patients and controls. Correlation between log-transformed sPD-L1 level and clinical characteristics, EBV status and cytokine levels measured before any treatment (IL-10, TNF, TNF-R1, TNF-R2, IL-6, IL-1R, sCD30), response to initial treatment and progression-free survival (PFS) were investigated. *Results.* the median age of the 126 CHL patients was 33 years (range, 15-93), 68% had an Ann Arbor stage I-II and 71% had an IPS score of 0-2. Nodular sclerosis was the main histologic subtype (83%). The EBV status was positive in 18 (27%) patients. 67% patients were treated with ABVD, 14% of patients progressed or relapsed and 11% died. sPD-L1 mean level in CHL patients was 3.56 times more elevated in cases than in controls (95% CI: 2.66-4.76, p= 8.2e-13; estimated means for cases and controls: 869 *vs* 3093 pg/ml; medians: 549 *vs* 1954 pg/ml). No statistically significant correlation/association was found between sPD-L1 level and age, Ann Arbor stage, ECOG-PS, IPS, lymphocyte count, EBV status, the different evaluated cytokines, response to treatment and PFS. *Conclusions.* CHL patients have a PD-L1 level in plasma which is higher than controls and DLBCL patients. Further studies are needed to decipher the prognostic role of sPD-L1 level in larger cohort including patients with more advanced stages and treated with immune checkpoint inhibitors.

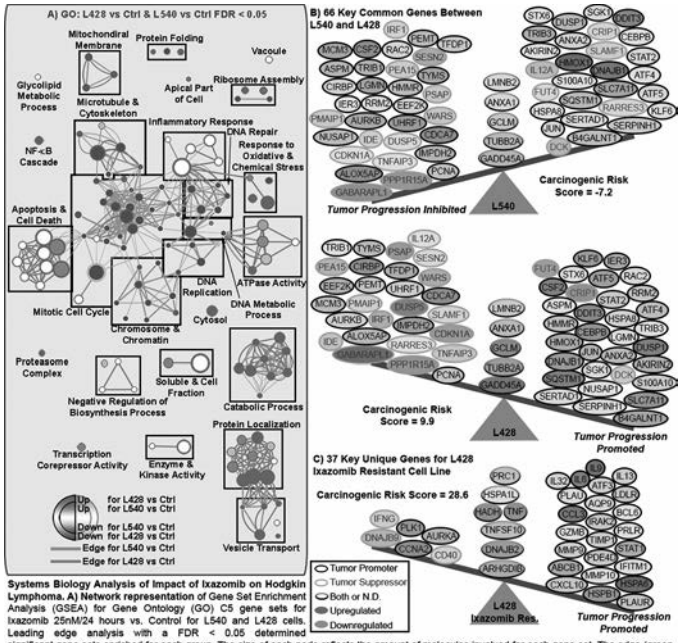
P041

PROTEASOME INHIBITOR THERAPY IN HODGKIN LYMPHOMA: LEVERAGING SYSTEMS BIOLOGY ANALYSES FOR CELL-SPECIFIC TRANSCRIPTOME ALTERATIONS AND OPTIMUM COMBINATORIAL THERAPY

F.C. Passero Jr., A. Beheshti, R. Dashnamoorthy, A.M. Evens

Division of Hematology Oncology and Molecular Oncology Research Institute, Tufts Medical Center, Boston, Massachusetts, USA

Introduction. NF- B has been shown to be critical for HL cell survival. Ixazomib is a new oral PI with favorable pharmacodynamic and pharmacokinetics; we recently reported activity of ixazomib in HL cells and *in vivo* SCID xenografts (Ravi *et al.* Cancer Research. 2016). SBA favored tumor inhibition via downregulation of MYC and CHK1 with CHK1 involved in Myc alteration through chromatin modification & histone H3 acetylation. Continued dissection of cell-specific transcriptome changes with PIT is needed and potential combination therapy with ixazomib should be explored. *Methods.* We examined ixazomib-induced transcriptome changes in L540 & L428 cells that were ixazomib sensitive and also with generated resistance. Key genes were derived from overlapping Ingenuity Pathway Analysis (IPA) and Gene Set Enrichment Analysis (GSEA). SBA were used to identify genes related to treatment response; and based upon the aforementioned results, we studied the HDAC inhibitor (HDACi), belinostat, combined with ixazomib. *Results.* On GSEA (Figure 1A), ixazomib induced downregulation of mitotic cell cycle in L540 cells, while L428 cells had noted upregulation. Chromatin architecture was downregulated in L540, while L428 had no change. Catabolic activity and vesicular function linked to protein localization and transport were upregulated in L540 & L428 cells. Furthermore, analysis of "key genes" predicted greater 'tumor promotion' in ixazomib-resistant L428 *vs* ixazomib-sensitive L428 and L540 cells (Figure 1B and 1C). Among 66 common key genes in L540 & L428, the most connectivity was seen between CDKN1A (p21), JUN, GADD45A, ATF4, HSPA8, SQSTM1 (p62), CSF2, CEBPB and its inhibitory binding partners DDIT3 and TRIB3 (associated with cell cycle, apoptosis, response to oxidative stress & autophagy). For combination studies, ixazomib+belinostat was highly synergistic with combination index <0.5. On Western blot, ixazomib+belinostat resulted in increased p21, cleaved caspases, decreased autophagy (ie, proteins p62 and cathepsin) and also decreased Myc, which had previously been implicated with ixazomib. *Conclusions.* Ixazomib alone has prominent *in vitro* and *in vivo* activity in HL, and via SBA, we identified rational synergistic therapy with HDACi. In addition, we identified HL cell-specific transcriptome changes affecting varied and distinct pathways involving cell cycle, autophagy and apoptosis. Continued understanding of cell and drug-specific omic alterations are warranted.



Systems Biology Analysis of Impact of Ixazomib on Hodgkin Lymphoma. A) Network representation of Gene Set Enrichment Analysis (GSEA) for Gene Ontology (GO) C5 gene sets for Ixazomib 25nM/24 hours vs. Control for L540 and L428 cells. Leading edge analysis with a FDR < 0.05 determined significant gene sets enriched for each group. The size of each node reflects the amount of molecules involved for each gene set. The edge (green or blue lines) represents the number of genes associated with the overlap of two gene sets (or nodes) that the edge connects. Clusters were named according to common function in each grouping. Upregulated gene sets were denoted with red color and downregulated gene sets were denoted by blue color. **B) The 66 common key genes between L428 and L540 cell lines treated with ixazomib vs controls. C) 37 unique key genes for the L428** ixazomib resistant cell line treated with ixazomib vs control. The schematics for B) and C) illustrate the balance between the "tumor promoters" (outlined in black) and "tumor suppressors" (outlined in blue) with the Log_2 fold-change to the gene expression with different shades of green and red indicating the amount of downregulation and upregulation compared to the controls. The Carcinogenic Risk Score was calculated by the subtracting the total fold-change values for the tumor promoters from the tumor suppressors. The greater the value, the higher prediction for cancer risk with a positive value indicating tumor progression being promoted and a negative value indicating the inhibition of tumor progression.

Figure 1.

P042

TELOMERE MAINTENANCE MECHANISMS AND TUMOR MICROENVIRONMENT ARE KEY FACTORS IN THE OUTCOME OF CLASSIC HODGKIN LYMPHOMA

R. M'kacher[1,2], C. Cuceu[1], L. Morat[1], M. Al Jawhari[1], M. Frenzel[1], G. Shim[1], A. Lenain[1], M. Ricoul[1], W. Hempel[1], E. Guilotto[3], S. Junker[4], T. Girinsky[5], C. Badie[7], B. Colicchio[8], A. Dieterlen[8], E. Jeandidier[9], O. Moralès[10], S. Renaud[10], Z. Van de Wyngaert[11], P. Carde[6], N. Delhem[10], L. Sabatier[1]

[1]Laboratoire de Radiobiologie et d'Oncologie, IRCM/DSV/CEA Fontenay aux Roses, France; [2]Cell Environment Oncology Section Paris France; [3]Laboratory of Cellular and Molecular Biology, University of Pavia, Italy; [4]Institute of Human Genetics University of Aarhus Hospital, Denmark; [5]Departement of Radiation Therapy, Gustave Roussy Institut, Villejuif, France; [6]Departement of Medicine, Gustave Roussy Institut, Villejuif, France; [7]Biological Effects Department, Centre for Radiation, Chemical and Environmental Hazards, Public Health England, Didcot, UK; [8]Laboratoire MIPS - Groupe TIIM3D Université de Haute-Alsace, Mulhouse, France; [9]Cytogenetic Service, Centre Hospitalier de Mulhouse, Mulhouse, France; [10]Université Lille, CNRS, Institut Pasteur de Lille, Siric OncoLille,UMR 8161 - M3T – Mechanisms of Tumorigenesis and Target Therapies, Lille, France; [11]Hematology department, CHRU de Lille, Lille, France

Background. About 15-20% of patients with advanced stage

Hodgkin lymphoma (HL) still die following relapse or progressive disease and a similar proportion of patients are over-treated, leading to treatment-related late sequelae, including solid tumors and organ dysfunction. We analyzed telomere maintenance mechanisms (TMMs) of HL cell lines as well as the samples from HL patients treated with standard therapy and compared the TMMs with favorable and unfavorable clinical outcome. *Materials and Methods.* Frozen lymph node samples obtained from 38 HL patients during diagnostic lymph node biopsy and from 24 patients with lymphadenitis were entered in this study. All HL patients were stage I (84.2%) and II (15.8%) with mean age of 36.7 years and 94.7% were nodular sclerosis. Seven HL cell lines were used as a positive control. Telomerase activity (TA) and alternative lengthening telomere (ALT) profile were assessed as well as Epstein Barr Virus (EBV) status and protein expression levels. The TMMs were correlated to clinical outcomes of patients (10.3 years) as well as to radiation sensitivity of HL cell lines. *Results.* The major finding of this study is the presence of both TA and ALT mechanisms in selected lymph nodes of HL patients. This TMMs heterogeneity was confirmed in HL cell lines. Hodgkin and Reed Sternberg (HRS) cells demonstrated an ALT profile, while the small cells exhibited a higher telomerase activity. We identified in the same tumor lymph node HRS cells containing ALT-associated PML bodies, a hallmark of ALT, and separate small cells expressing telomerase. Similarly, in HL cell lines, a high level of TA was detected in L428 and SUP-HD1. L1236 cell line demonstrated a lower TA and presented an ALT profile. The latent membrane protein (LMP1) staining revealed the presence of EBV genome in HRS cells in 13 lymph nodes (34.2%). A higher expression of TRF2/PML (ALT profile) and CD68 in EBV positive patients was correlated with Overall Survival (p=0.02), Freedom From Progression (p=0.02) and Event Free Survival (p=0.003). ALT HL cell lines demonstrated a lower radiation sensitivity as compared to TA HL cell lines. *Conclusions.* The presence of both TMMs (TA and ALT) in HL lymph nodes and HL cell lines is a singular oncology phenomenon. TMMs, related to tumor microenvironment in HL lymph nodes, are associated with treatment response and survival of HL patients.

advanced disease had also significantly lower numbers, compared to controls, of CD3+ (median 0.78 *vs* 1.36x10^9/L, p=0.04), CD4+ (median 0.3 *vs* 0.5x10^9/L, p=0.04), Tregs (median 0.008 *vs* 0.017x10^9/L, p=0.004), Th2 (median 0.18 *vs* 0.28x10^9/L, p<0.05) and Th17 cells (median 0.03 *vs* 0.08x10^9/L, p=0.006), while no difference was observed for Th1. HL pts had lower numbers of naive CD8+ cells irrespective of disease stage, while central memory CD4+ cells were lower in advanced disease. No difference was observed with regard either to the numbers of proliferating (Ki67+) or PD-1- and CTLA-4-expressing CD4+ and CD8+ cells. On the other hand, CD69+CD4+ cells were significantly higher in pts with limited disease compared to controls (median 0.04 *vs* 0.01x10^9/L, p=0.04) (Figure 1). *Conclusions.* These observations suggest that the immune microenvironment in HL plays a role that is far from being only local. Further studies are ongoing in larger cohorts of pts.

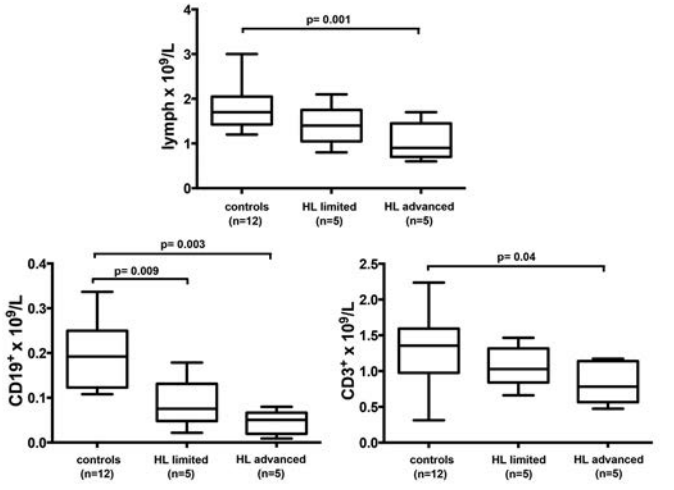


Figure 1.

P043

PHENOTYPIC CHARACTERIZATION OF CIRCULATING LYMPHOCYTES IN HODGKIN'S LYMPHOMA WITH FOCUS ON T CELLS

M. Palma[1,2], K. Heimersson[2], B. Näsman-Glaser[2], L. Hansson[1,2]

[1]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [2]Department of Oncology & Pathology, Karolinska Institutet, Stockholm, Sweden

Background. The malignant cells in HL comprise only a small fraction of the total tumor population but orchestrate an inflammatory microenvironment of reactive cells that sustains tumor cell survival and growth. HL patients (pts) have high systemic levels of inflammatory cytokines and chemokines and low lymphocyte count (<0.6x10^9/L) is a well-established prognostic factor in advanced disease. The aim of this pilot study was to characterize the phenotype of circulating lymphocytes in HL pts. *Materials and Methods.* Peripheral blood samples were obtained from 10 HL pts and 12 sex- and age-matched healthy controls. Nine pts had classical HL and 1 had nodular lymphocyte predominance (NLP) HL. Five pts had limited (stage I-IIA) and 5 had advanced (IIB-IV) disease. Pts with ongoing acute EBV infection were excluded. All pts had negative serology for HIV. Absolute numbers of CD19+, CD3+, CD4+, CD8+, NK and NKT cells, functional T helper subpopulations (Th1/Th2/Th17), CD4+ and CD8+ memory cell subsets and expression of CTLA-4, PD-1, CD69 and Ki-67 on CD4+ and CD8+ T cells were assessed by flow-cytometry. *Results.* HL pts with advanced disease had lower lymphocyte counts compared to controls (median 0.9 *vs* 1.7x10^9/L, p=0.01) while no difference was observed for pts with limited disease. Compared to controls, HL pts had lower CD19+ cell numbers irrespective of disease stage (0.075 *vs* 0.05x10^9/L in pts with limited and advanced disease *vs* 0.19x10^9/L in controls, p=0.009 and p=0.0003, respectively). Pts with

P044

SIP-F1: A NEW GRAY ZONE LYMPHOMA CELL LINE?

B. Rengstl[1], S. Hartmann[1], S. Eberth[2], C. Döring[1], C. Pommerenke[2], P.S.A. Becker[3], C. Weiser[1], K. Warner[1], C. Doering[1], C. Seidl[3], R. Küppers[4], H. Abken[5], R.A. MacLeod[2], H.G. Drexler[2], M.-L. Hansmann[1,*], S. Newrzela[1,*]

[1]Dr. Senckenberg Institute of Pathology, Goethe-University of Frankfurt, Medical School, Theodor-Stern-Kai 7, Frankfurt am Main, Germany; [2]Leibniz Institute DSMZ, German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany; [3]Institute for Transfusion Medicine and Immunohematology, Red Cross Blood Donor Service, Baden-Württemberg-Hessen, Frankfurt, Germany; [4]Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, Medical School, Essen, Germany; [5]Center for Molecular Medicine Cologne, University of Cologne, and Department I of Internal Medicine, University Hospital Cologne, Cologne, Germany

**Shared last authorship*

Lymphoid cancers are mainly classified according to their clinical presentation, morphology, immunology and molecular genetic features. Diagnosis of Hodgkin lymphoma (HL) is mainly based on pathognomonic Hodgkin and Reed-Sternberg cells (HRS). However, in the group of non-Hodgkin lymphomas (NHL), diffuse large B-cell lymphoma (DLBCL) can resemble typical features of HL. In some cases, a diagnostic pitfall exists at the interface of HL and DLBCL, so that, morphological overlaps and missing clear-cut diagnostic criteria complicate classification of these so-called gray zone lymphomas (GZL). In a recent study, we analyzed a newly established GZL cell line (SIP-F1) derived from a lymph node biopsy of a male 20-year-old

lymphoma patient. Histological sections of the primary GZL were characterized by striking pleomorphism of in part multinuclear blast infiltrates and areas of necrosis. Immunohistochemistry revealed tumor cell positivity for the markers CD15, CD20 and CD30. SIP-F1 presented clonal Ig gene rearrangement and flow cytometry analysis showed expression of B-cell markers as well as 50-60% positivity for HL marker CD30. In addition, we observed tumor growth of SIP-F1 in a xenograft mouse model, morphologically resembling the primary tumor with lacunar HRS-like cells growing in sheets. For closer characterization, we performed gene expression profiling (GEP) and compared SIP-F1 to several B-cell lymphoma cell lines. The GEP of SIP-F1 did not cluster with any of the compared entities. Interestingly, but yet quite surprisingly, cytogenetic analysis revealed a normal karyotype. As SIP-F1 is positive for EBV, the cell line probably displays more a transformed B-cell clone than a GZL cell line. The patient, SIP-F1 is derived from, showed fast tumor rejection after initialization of chemotherapy. We were able to receive T cells for a co-culture study and could show that his immune system regained anti-tumor strength. In conclusion, considering the paucity in prospective differentiation of GZL cases, their distinct clinical behavior and treatment, we think that SIP-F1 could be a helpful tool to study morphological and molecular features of GZL and to better understand the biology of these unusual cases, although we are still tackling the question, what is the real tumor cell clone.

P045

CD4 LYMPHOPENIA AS A PROGNOSIS FACTOR IN PREVIOUSLY UNTREATED HODGKIN LYMPHOMA

T. Bogatyreva, G. Neprina, I. Zamulaeva, A. Terekhova, S. Smirnova, N. Orlova, M. Daniliva, V. Pavlov

A.F. Tsyb Medical Radiological Research Centre - Branch of the National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation

Peripheral lymphopenia (PL) is included in IPS for advanced Hodgkin lymphoma (HL). Prognostic value of PL in stages I-II of HL as well as lymphocyte subsets responsible for PL have to be clarified. To evaluate the influence of baseline lymphocyte count on the treatment efficacy in HL total of 838 patients were included in the study. Flow cytometry was done in 83 patients, 47 (57%) had PL defined as lymphocyte count less than 1000/mm3. CD4 counts were available in additional 72 patients. Progression-free survival (PFS) and overall survival (OS) were analysed with reference to lymphocyte count at diagnosis and CD4 content. Results PL was found in 116/838 (14%) HL patients: 1,4% in early favorable (Gr.1), 7,5% in early unfavorable (Gr.2) and 18,6% in advanced HL(Gr.3). Flow cytometry data of 47 patients with PL revealed low T-cell counts in 41(87%) of cases, mixed T- and B-cell lymphopenia in 25/41 (61%) cases, B-cell lymphopenia in 6/47 (13%) of cases. Deep CD4 lymphopenia (less than 200/mm3) was observed in 24(16%) out of 155 patients; it was associated with age ≥45 (p=0.017), lymphoid depletion (p=0.13), advanced stage (p=0.061) and IPS score ≥4 (p=0.000). At a median follow up of 60 months, PFS rate and OS were significantly impaired in 58 patients with low CD4 count (less than 400/mm3). In Gr.1 progression occurred in one of the two patients who had both PL and CD4 lymphopenia; OS was 100%. In Gr.2, six patients with low CD4 counts at diagnosis had PFS 50% *vs* 95% in the rest, p=0.007; OS was 30% *vs* 100%, p=0.001. In 115 patients from Gr.3 those with low CD4 count (n=49) had PFS 72% *vs* 89%, p=0.037; OS was 75% *vs* 95%, p=0.003. Subset analysis in 91 patients with stages III-IV and IPS 0-3 supported negative impact of CD4 lymphopenia (PFS 79% *vs* 90%, p=0.266; OS 84% *vs* 97%, p=0.018). Conclusion The study shows that absolute lymphopenia is an independent adverse factor for stages I-II and for advanced HL patients with IPS 0-3. These results may justify alternative therapeutic strategies, including early antiCD30 therapy to account for CD4 lymphopenia at diagnosis.

P046

CAN PLASMA CHEMOKINES AND SOLUBLE RECEPTOR MONITORING PREDICT OUTCOME IN CLASSICAL HODGKIN'S LYMPHOMA PATIENTS?

A. Stamatoullas[1], A. Perdrix[2], E. Lemasle[1], C. Thill[3], V. Camus[1], L. Veresezan[2], J.M. Picquenot[2], A.L. Menard[1], P. Lenain[1], N. Contentin[1], H. Lanic[1], S. Lepretre[1], O. Brehar[1], N. Cardinael[1], M.L. Fontura[1], C. Fronville[1], F. Jardin[1], C. Bastard[2], H. Tilly[1]

[1]INSERM U918, Hematology Department; [2]Biopathology Department, Centre Henri Becquerel, Rouen, France; [3]Centre de traitement des Données du Cancéropole Nord Ouest (CTD-CNO), Centre François Baclesse, Caen, France

The usual prognostic scores used in cHL fail to identify some patients with worst outcome either in early or advanced stage HL. Pre-treatment cytokines, soluble receptor, cytokine signature (Casasnovas JCO 2007) and TARC profile have been described as biological markers correlated to tumour burden, to response and outcome. To evaluate the impact of TARC, IL6, IL1-RA, sCD30 and TNF-R1 levels on response and outcome, we collected plasma from 50 newly diagnosed cHL patients at baseline, during therapy and at the end of chemotherapy. We also analysed the correlation of usual prognostic factors with cytokines and soluble receptor level. Between April 2010 and November 2013, 50 cHL patients were enrolled (26 M/ 24F), median age was 31 years (18,5-63). Main clinical characteristics were as follow: stage I-II in 24 patients (according to EORTC classification: favourable: 7 and unfavourable: 17) and stage III-IV in 26 patients (IPS 1-2: in 15 patients). Thirty five patient were treated with ABVD and 15 patients with eBEACCOP. Radiotherapy was added in 24 patients. Mean TARC level was 281 pg/ml (27-83098), mean IL6 level was 2.9 pg/ml (0,6-175), mean IL1-RA was 252 pg/ml (0,9-6609), mean sCD30 level was 33 U/ml (8,8-1007), and mean TNR-F1 level was 2129,5 ng/ml (314-8463). Baseline cytokines level or cytokines signature did not correlate significantly with any clinical or biological factors nor with FDG-PET response. Ten patients disclosed relapse or progressive disease (R/R), only two patients died. With a median follow-up of 48 months, the event free survival (EFS) and overall survival (OS) at 3 years are 82% (95% CI 68-90) and 96% (95% CI 85-99) respectively. None of the classical prognostic factors as early response evaluated with FDG-PET were correlated with PFS. Neither baseline cytokines levels nor cytokine signature or early reduction of IL1-RA, sCD30, TNR-F1 level impacted significantly the outcome, but a trend was noted with early reduction of TARC and IL6. The decrease of TARC and IL6 seems to predict response to therapy and EFS. Unfortunately we failed to demonstrate any correlation between baseline cytokines or cytokine signature with biological or clinical characteristics, and outcome in this population. Surprisingly none of the usual prognostic factors predict outcome. These results could be perhaps explained by the small number of patients and should be confirmed in a larger prospective study.

P047

EXPRESSION AND PROGNOSTIC IMPACT OF INDOLEAMINE 2,3-DIOXYGENASE IN HODGKIN'S LYMPHOMA

I. Kryachok[1], O. Novosad[1], T. Skrypets[1], K. Ulianchenko[1], I. Tytorenko[1], N. Khranovska[2], O. Skachkova[2], N. Svergun[2], O. Gorbach[2]

[1]Oncohematology; [2]Experimental Oncology, National Cancer Institute, Kiev, Ukraine

Background. Indoleamine 2,3-dioxygenase (IDO) catalyzes the rate-limiting step in the metabolism of tryptophan along the kynurenine pathway. IDO is a key factor maintaining immune tolerance and expression correlates with poor clinical outcome in different types of cancer and hematological malignancies. Nowadays, not enough attempts have been made to evaluate IDO expression and its prognostic score value. We assessed the impact of the IDO expression on clinical outcome in patients with Hodgkin lymphoma (HL). *Methods.* The case group included 23 patients (5 male and 18 female) with HL (median age: 19-60 years, range: 39.5). With early stage were diagnosed 52.2% and 47.8% with

advanced. Only 26% cases had B-symptoms. ABVD or BEACOPP (14/esc) were administered as a first-line therapy. In 65.2% and 34.8% cases, achievement remission and progression disease after treatment, respectively. The relative mRNA expression levels of IDO were measured in pre-treatment tumor tissue specimens from HL patients using real-time qPCR analysis. *Results.* The mRNA expression of IDO was found in 15 cases (65.2%) and further this group was considered as IDO-positive. The presence of IDO expression was significantly associated with advanced stage of disease and B-symptoms ($p<0.05$). The relapse was more frequently found in cases with IDO+ compared IDO- HL (30.47% *versus* 4.3%, $p<0.05$). 13% patients with IDO+ expression died and had an early relapse or refractory disease. ROC analysis revealed that IDO+ expression in the tumor is an important marker which is associated with reduced progression-free (PFS) and overall survival (OS) in HL patients (Se=87.5%; Sp=78%; AUC=0.85). 5-year PFS for patients with IDO+ expression was 44% *versus* 89% of IDO- expression ($p=0.0003$). Two-sample comparison between the IDO+ *versus* IDO- expression was done by the Cox F-test. The difference was significant for PFS and OS ($p=0.03$) (Figure 1). *Conclusions.* The obtained results suggest that the IDO-positive expression can predict clinical outcome in patients with HL and seems to be promising for the future studies.

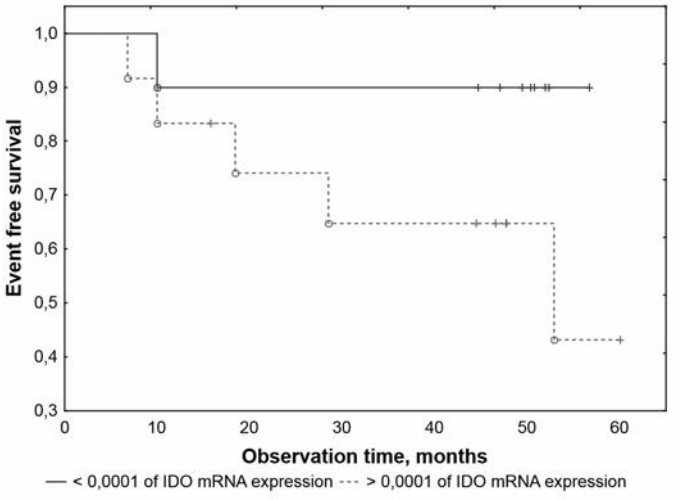


Figure 1.

P048

REED-STERNBERG CELLS ON BONE MARROW CYTOLOGY: THE VERY EARLY FEATURE ON HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ASSOCIATED TO HODGKIN LYMPHOMA

L. Niero-Melo[1], L.A. Lustri[1], B.F. Polegatto[2], C. Del Castanhel[1], L.O. Cantadori[1], C.C. Oliveira[3], R.D. Gaiolla[1]

[1]Hematology, Department of Internal Medicine, Botucatu School of Medicine, Sao Paulo State University - UNESP, Sao Paulo, Brasil; [2]Department of Internal Medicine, Botucatu School of Medicine, Sao Paulo State University - UNESP, Sao Paulo, Brasil; [3]Department of Pathology, Botucatu School of Medicine, Sao Paulo State University - UNESP, Sao Paulo, Brasil

Introduction. Hemophagocytic lymphohistiocytosis (HLH) is a hyper-inflammatory disorder resulting from primary or acquired immune dysfunction. In adults, HLH is most frequently associated to infections, autoimmune diseases, and lymphomas, although Hodgkin lymphoma (HL) has been less frequently described. This immune activation leads to a variety of clinical and laboratory features, including pancytopenia, which makes bone marrow examination an important tool in order to identify possible trigger factors for HLH. *Case Report.* A 53 year-old white female, was referred to the Hospital das Clínicas de Botucatu – UNESP (São Paulo, Brazil) with a 4-day history of mental confusion. She had no palpable lymphadenomegaly, hepatosplenomegaly or abdominal mass. Complete blood count showed markedly pancytopenia. Lactate dehydrogenase was normal and serum ferritin was 9.621 mg/dl. Bone marrow (BM) cytology evaluation showed markedly hemophagocytosis and some large cells were identified as "Owl Eye Cell" and "Mononuclear Hodgkin's Cells". The bone marrow clot evaluation showed frequent epithelioid granulomas, without necrosis, and bi-nucleated and mononuclear cells with large nuclei and evident nucleoli, featuring classic Reed-Sternberg cells and Hodgkin's cells. Immunohistochemistry confirmed the diagnosis of bone marrow infiltration by HL with granulomatous reaction. The Ziehl-Neelsen and Grocott-Gomori stains were negative (Figure 1). *Discussion.* BM cytological evaluation is immediately required in cases of pancytopenia for diagnostic purpose, regardless the level of blood counts. Especially in HLH, it is part of a systematic front-line clinical investigation for possible immune triggers. Epithelioid granulomas in BM or lymph nodes of patients with a nonspecific clinical presentation is a diagnostic challenge as it can be associated with a variety of autoimmune, inflammatory and neoplastic conditions. HL can present with granulomas in about 14% of cases, although it is unusually seen in BM biopsy. In this context, a careful morphological analysis with immunohistochemistry study is highly recommended considering that the absence of a typical HL presentation can sometimes postpone diagnosis and compromise disease outcome. *Conclusions.* This case highlights the importance of prompt investigation of pancytopenia in the context of HLH, with an early diagnosis of HL being made by BM cytology in a patient with no other symptoms that could suggest lymphoma.

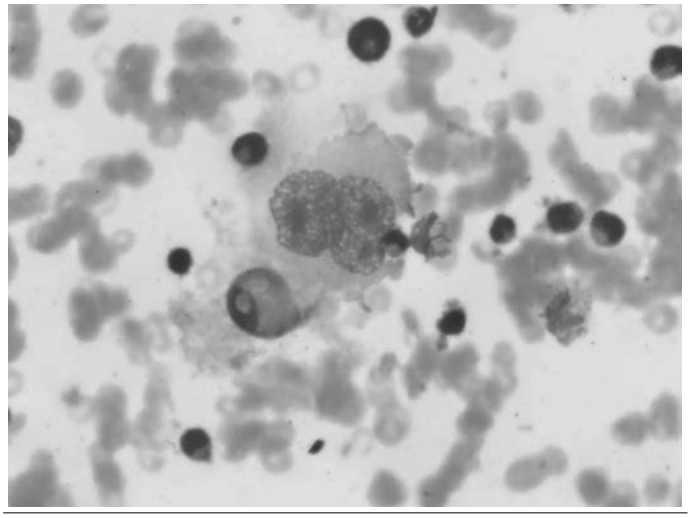


Figure 1.

P048B

A NOVEL PTPN1 SPLICE VARIANT REGULATES JAK/STAT ACTIVITY IN CLASSICAL HODGKIN'S LYMPHOMA CELLS

M. Zahn*, R. Marienfeld*, I. Melzner, J. Heinrich, A. Rehm, T.F. Barth, K. Dorsch, S. Brüderlein, P. Möller

Institute of Pathology, Ulm University, Ulm, Germany

**Equal contribution*

Background. Chronic activation of the Janus kinase (JAK)/ Signal Transducer and Activator of Transcription (STAT) signaling pathways is a hallmark of a variety of B cell lymphomas including the classical Hodgkin's lymphoma (cHL). Constitutive JAK/STAT signaling is crucial for survival and proliferation of Hodgkin/Reed-Sternberg (HRS) cells, the malignant cells of cHL. Although the exact molecular basis of this constitutive JAK/STAT signaling in cHL has not been understood completely, accumulating reports highlight the role of an inactivation or reduced expression of negative JAK/STAT regulators like Silencer of Cell signaling 1 (SOCS1) or Protein-Tyrosine Phosphatase 1B (PTP1B)

in this process. Given the essential role of PTP1B and SOCS1 for the constitutive JAK-STAT signaling in cHL, the identification and characterization of the regulatory mechanisms controlling the activity of these negative JAK/STAT regulators is crucial for the understanding of their role for the pathogenesis of cHL. Here, we report the expression of different truncated PTP1B mRNA variants identified in cHL cell lines and primary cHL tumor samples lacking either one or several exon sequences. We describe the expression of a shorter PTP1B isoform in cHL as a novel negative control mechanism for PTP1B involved in the dis-regulation of the JAK-STAT pathway. *Methods.* PTP1B mRNA of cHL cases and cell lines was isolated and sequenced by Sanger sequencing. PTP1B protein expression was determined by western blot and immunohistochemistry analyses. Expression analysis of PTP1B mRNA variants was done by qPCR. To determine the role of PTP1BΔ6 for JAK/STAT signaling, stably transfected L428 cell clones either expressing $PTP1B_{WT}$, $PTP1B_{C215S}$, or PTP1BΔ6 were generated. Functional analysis of the novel PTP1BΔ6 variant was achieved by western blot analysis using phospho-STAT antibodies, luciferase reporter analysis and EMSA. The impact of the PTP1B variants on cell proliferation was examined by MTS assays. *Results.* In order to determine the molecular basis of the reduced or absent PTP1B expression in selected cHL cases, we isolated and sequenced the PTP1B mRNA. In contrast to the previously published study highlighting inactivating point mutations in the PTP1B gene of PMBL and cHL cases, we obtained a set of PTP1B variants which lack different exon sequences. One of these novel PTP1B variants, lacking exon 6 (PTP1BΔ6), was found to be expressed at low levels in cHL cell lines. However, serum stimulation of cHL augmented the expression of PTP1BΔ6 significantly. Functional characterization of PTP1BΔ6 revealed a positive impact on IFN and IL-4 induced JAK/STAT activity in HEK293 or HEK293-STAT6 cells, and on the basal STAT activity in stably transfected L-428 and U-HO1 cHL cell lines. Furthermore, PTP1BΔ6 expression increased the proliferation of L-428 and U-HO1 cells and the reduced cytotoxic effect of the chemotherapeutical agents gemcitabine and etoposide distinctively. *Conclusions.* Collectively, these data suggest that the activity of PTP1B in cHL is regulated by different molecular mechanisms including the expression of shorter PTP1B variants like the novel PTP1BΔ6 variant which acts as a positive regulator of JAK/STAT signaling in cHL.

Early Stages

T010

LONG-TERM FOLLOW-UP OF CONTEMPORARY TREATMENT IN EARLY-STAGE FAVORABLE HODGKIN LYMPHOMA: UPDATED ANALYSES OF THE GERMAN HODGKIN STUDY GROUP HD7 AND HD10 TRIAL

S. Sasse*, P.J. Bröckelmann*, H. Görgen, A. Plütschow, H. Mueller, S. Kreissl, C. Bürkle, S. Borchmann, M. Fuchs, P. Borchmann, A. Engert

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

**Contributed equally*

Background. Combined modality treatment (CMT) is considered as standard of care in patients with early-stage favorable HL. During the years, a gradual toxicity reduction through balancing extent and intensity of radiotherapy (RT) and chemotherapy was achieved. Long-term follow-up (FU) of the pivotal trials is needed, to ensure the applied therapies are safe and beneficial for our patients. *Methods.* We analyzed updated FU data of 1817 patients who were treated for early-stage favorable HL in previously published GHSG trials between 1993 and 2003. In the HD7 trial patients were randomized to either 40Gy extended-field (EF)-RT only or CMT with 2xABVD, and in HD10 to either 4x or 2xABVD and 30 or 20Gy involved-field (IF)-RT respectively. Progression-free (PFS) and overall survival (OS) were analyzed according to the Kaplan-Meier method. Cumulative incidences of secondary neoplasias (SN) were compared using Pepe & Mori's test. The level of significance was set to 0.05. *Results.* The median FU was 120 and 98 months for patients in HD7 (n=627) and HD10 (n=1190), respectively. New FU data beyond the last evaluation were available for <50% of patients and last information was obtained from population registries in 18-30%. In HD7, CMT was superior to EF-RT with 15-year PFS estimates of 72.8% *vs* 52.2% and a hazard ratio (HR) of 0.45 (95% confidence interval CI: 0.33-0.61). No significant differences were observed regarding OS or SN. In HD10, non-inferiority of 2xABVD+20Gy IF-RT to more intensive treatment was confirmed with HRs of 1.0 (CI:0.6-1.5) and 0.9 (CI:0.5-1.6) and 10-year estimates of 87.2% and 94.1% for PFS and OS, respectively. No significant differences in SN were observed.

Summary: Long-term FU data of HD7 and HD10 confirm the current treatment-standard in early-stage favorable HL consisting of 2xABVD+20Gy IF-RT. In order to assess the risk of secondary neoplasia and long-term organ toxicity a prolonged follow-up period is required.

T011

PROTON RADIOTHERAPY FOR MEDIASTINAL HODGKIN LYMPHOMA: SINGLE INSTITUTION EXPERIENCE

K. Dědečková[1], H. Móciková[2], J. Marková[2], Ľ. Gahérová[2], I. Kantorova[3], B. Ondrova[1], V. Vondracek[1], P. Vitek[1], J. Kubes[1]

[1]Proton Therapy Department, Proton Therapy Center Czech, Prague, Czech Republic; [2]Department for Internal Medicine and Hematology, Faculty Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles Univesity in Prague, Czech Republic, [3]Nuclear Medicine Department, Proton Therapy Center Czech, Prague, Czech Republic

Introduction. Conventional radiotherapy (RT) based on photons has achieved its physical limits. Proton beam offers promising dosimetric benefits compared to photons, due to its potential to decrease unintended healthy tissue irradiation. Mediastinal proton RT can be safely provided with the awareness of targeting to a moving structure. The technological progress in proton RT allows solving this issue. It can be reasonably managed via pencil beam scanning technique with repainting and/or the use of deep inspiration breath hold method. We present our preliminary clinical experience with this technique. *Methods.* Between May 2013 and June 2016, 39 patients (pts) with Hodgkin lymphoma (HL) underwent

mediastinal proton RT. Pencil beam scanning technique was used in all pts. Overall 33 of 39 pts were evaluable for acute toxicity and early response. Proton RT was indicated in the first-line treatment in 30 pts, 3 pts were re-irradiated after previous photon RT. Median age at the time of RT was 32 years (range, 13-59 years). RT volume definition: involved field 9 pts, residual disease 10 pts, involved site 14 pts. RT to PET negative disease was indicated in 23 pts as a part of combined modality of treatment after chemotherapy. RT to PET positive disease after chemotherapy was performed in 10 pts. Median total dose was 30 GyE (range, 19.8-40 GyE). Overall 17 pts underwent RT in deep inspiration breath hold, the rest of pts received RT in free breathing after 4D control of mediastinal structures movement. *Results.* Of evaluable pts, 31 are in complete remission. Two pts with multiple sites of progression achieved a local control of disease. Acute and subacute RT toxicity was mild (pharyngeal mucositis gr. 2 in 3 pts, leukopenia gr.3 in 1 pt, leukopenia gr 2 in 1 pt, radiodermatitis gr.2 in 1 pt). No case of radiation pneumonitis or Lhermitte sign was observed. No pt required growth factor application or hemosubstitution during RT. *Conclusions.* Proton RT offers promising and safe option for most pts indicated for mediastinal RT. Proton irradiation has low acute toxicity profile and a potential to decrease the risk of significant late toxicity. Proton RT should be considered in all HL patients indicated for mediastinal RT or re-irradiation.

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T012

RESULTS OF US INTERGROUP TRIAL OF RESPONSE-ADAPTED CHEMOTHERAPY OR CHEMOTHERAPY/RADIATION THERAPY BASED ON PET FOR NON-BULKY STAGE I AND II HODGKIN LYMPHOMA (CALGB/ALLIANCE 50604)

D. Straus[1], B. Pitcher[2,*], L. Kostakoglu[3,*], J.C. Grecula[4,*], E.D. Hsi[5], H. Schöder[6,*], S.-H. Jung[2,*], L. Popplewell[7], J.E. Chang[8], C. Moskowitz[6], N. Wagner-Johnson[9,*], J. Leonard[10], J.W. Friedberg[11], B.S. Kahl[12], B.D. Cheson[13], N.L. Bartlett[14]

[1]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Alliance Statistics and Data Center, Duke University, Durham, NC, USA; [3]Mount Sinai Medical Center, New York, NY, USA; [4]Ohio State Univeristy, Columbus, OH, USA; [5]Cleveland Clinic, Cleveland, OH, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]City of Hope, Duarte, CA, USA; [8]University of Wisconsin, Madison, WI, USA; [9]Washington University, Saint Louis, MO, USA; [10]Weill Cornell Medical College, New York, NY, USA; [11]University of Rochester, Rochester, NY, USA; [12]Washington University, Saint Louis, MO, USA; [13]Lombardi Comprehensive Cancer Center, Georgetown University Hospital, Washington, DC, USA; [14]Siteman Cancer Center, Washington University School of Medicine, Saint Louis, MO, USA

**For Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group, and Southwest Oncology Group*

Interim positron-emission tomography (PET) following 1-3 cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) in newly-diagnosed, non-bulky stage I and II HL patients (pts) is a useful biomarker that predicts relapse rates of ≤10% for PET- pts. Relapse rates are higher in pts who are PET+. Interim PET thus provides an opportunity to minimize treatment for the majority of pts who are interim PET - and only intensify treatment for those who are PET+. This strategy could reduce short and long term treatment toxicity for the majority of pts. To test this hypothesis, the US Intergroup conducted a phase II clinical trial, CALGB/Alliance 50604, for newly-diagnosed non-bulky stage I and II HL pts. Between 5/15/10 and 5/4/12, 164 previously untreated pts with non-bulky stages I/II HL were enrolled. Pts received 2 cycles of ABVD followed by PET. Deauville scores 1-3 were negative (≤liver uptake), while scores of 4-5 were positive, based on central review. PET- pts received 2 more cycles of ABVD, and PET+ pts received 2 cycles of escalated BEACOPP+3060 cGy involved-field radiation therapy (IF RT). Median age was 31 years (18-58). There were 88 males and 76 females. Pt. stages were IA (16), IB (4), IIA (90), IIB (35), IIAE (4), and IIBE (3). All pts were PET+ prior to treatment. 144/164 patients had cycle 2 PET and adequate follow-up for assessment: 131 (91%) were PET- and 13 (9%) PET+. Of 20 not analyzed, 13 were excluded (6 never treated and 2 treated with <2 cycles) and 7 had insufficient follow up. At a median follow-up time of 2 years, 8/131 (6%) PET- pts relapsed or progressed with an estimated 3-year progression-free-survival (PFS) of 92%. 4/13 (31%) PET+ pts. failed (3 relapsed, 1 suicide) with an estimated 3-year PFS of 66%. By Cox model, observed hazard ratio comparing PET- and PET+ PFS for pts is 6.04 (1.82, 20.08). There was 1 death (suicide). These early results demonstrate that the 91% of pts PET- after 2 cycles of ABVD had an excellent PFS with total of 4 ABVD cycles (Figure 1). Updated results will be presented.

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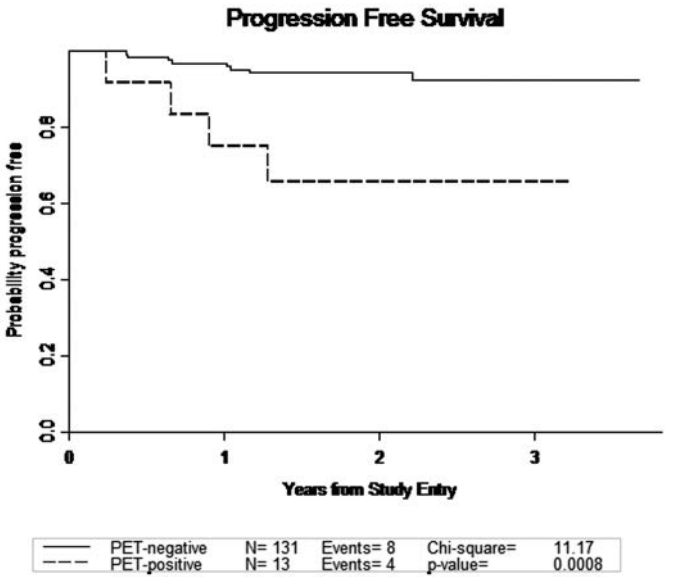


Figure 1. Kaplan Meier Plot of PFS for PET-negative and PET-positive patients.

P049

LONG-TERM FOLLOW-UP OF CONTEMPORARY TREATMENT IN EARLY-STAGE UNFAVORABLE HODGKIN LYMPHOMA: UPDATED ANALYSES OF THE GERMAN HODGKIN STUDY GROUP HD8 AND HD11 TRIAL

S. Sasse*, P.J. Bröckelmann*, H. Görgen, A. Plütschow, H. Mueller, S. Kreissl, C. Bürkle, S. Borchmann, M. Fuchs, P. Borchmann, A. Engert

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

**Contributed equally*

Background. Combined modality treatment (CMT) is currently considered standard of care in patients with early-stage unfavorable HL. By gradually increasing chemotherapy intensity an improvement of treatment efficacy and by reducing radiotherapy intensity a reduction of toxicity were attained. Long-term follow-up (FU) is needed to ensure the safety and efficacy of the applied therapies. *Methods.* We analyzed updated FU data of 2459 patients with early-stage unfavorable HL treated in the HD8 and HD 11 trial. In HD8 patients were randomized to either 30Gy IF- or extended-field (EF)-RT after 2xCOPP/ABVD and in HD11 patients received 20 or 30Gy IF-RT after 4xABVD or 4xBEACOPPbaseline. Progression-free (PFS) and overall survival (OS) were analyzed according to the Kaplan-Meier method. Cumulative incidences of secondary neoplasias (SN) were calculated and compared between groups

using Pepe & Mori's test. *Results.* The median FU was 153 and 106 months for patients in HD8 (n=1064) and HD11 (n=1395), respectively. New FU data were available for less than 50% of patients and last information was obtained from population registries in 23-27%. In HD8, non-inferiority of IF- compared to EF-RT was confirmed with HRs of 0.98 (95% confidence interval CI: 0.76-1.25) and 0.88 (CI:0.66-1.16) for PFS and OS, respectively. We observed a non-significant trend towards more SN (15-year cumulative incidence 17.1% *versus* 14.2%, respectively, p=0.3) and deaths from SN after EF-RT *versus* IF-RT. In HD11, no difference in PFS was found with BEACOPPbaseline compared to ABVD when followed by 30Gy IF-RT (HR: 1.1 (CI: 0.7-1.5)). In contrast, there was a significant difference in 10-year PFS rates estimated at 77.6% *versus* 83.3% in ABVD-treated patients who had received 20Gy instead of 30Gy IF-RT with a HR of 1.5 (CI: 1.0-2.1). After BEACOPPbas, 20Gy were non-inferior to 30Gy IF-RT with a HR of 1.0 (CI: 0.7-1.5) for PFS. No differences in terms of OS or SN were observed. *Summary.* Moderate intensification of chemotherapy does not improve the outcome but might facilitate the reduction of IF-RT-dose. Continued FU is necessary to assess long-term toxicity of the applied treatment strategies. 10-year PFS and OS estimates in early-stage unfavorable HL treated with 4xABVD+30Gy IF-RT leave room for improvement.

P050

FINAL RESULTS OF A QUALITY ASSURANCE PROGRAM WITHIN THE GERMAN HODGKIN STUDY GROUP HD13/14 TRIAL – A REPORT FROM THE RADIOTHERAPY REFERENCE PANEL INTEGRATING MODERN GUIDELINES

H.T. Eich[1], J. Kriz[1], R. Engenhart-Cabillic[2], U. Haverkamp[1], K. Herfarth[3], P. Lukas[4], H. Schmidberger[5], S. Staar[6], A. Plütschow[7], M. Fuchs[7], A. Engert[7], C. Baues[8]

[1]Department of Radiation Oncology, University Muenster, Germany; [2]Department of Radiation Oncology, University Marburg, Germany; [3]Department of Radiation Oncology, University Heidelberg, Germany; [4]Department of Radiation Oncology, University Innsbruck, Germany; [5]Department of Radiation Oncology, University Mainz, Germany; [6]Department of Radiation Oncology, Bremen Mitte, Germany; [7]Department of Internal Medicine, University Cologne, Germany; [8]Department of Radiation Oncology, University Cologne, Germany

Introduction. Since the foundation of the German Hodgkin Study Group (GHSG) in 1978 a central radiotherapy (RT) reference centre was established to evaluate and to improve the quality of treatment. During the study generations the quality assurance programs (QA) were continuously adapted and refined. The purpose of this analysis is to show the results of the work within the fifth study generation (HD13/14) and to demonstrate the establishment of a QA including modern RT-techniques *e.g.* intensity modulated RT (IMRT), image guided RT (IGRT) and involved node RT (IN-RT). *Methods.* With the fourth study generation (HD10-12) a central prospective review of all diagnostic imaging to create an individual treatment plan for every study patient was established in early stages and the quality of involved field RT was evaluated by an expert panel of radiation oncologists retrospectively. In the era of modern conformal RT this QA-program had to be adapted fundamentally and within several meetings a new process of evaluation has been developed. The findings were compared to the results of the QA within the fifth study generation (HD13-15). *Results.* The expert panel analyzed the RT-parameters of 1037 (28%) patients (HD13 n=465, HD14 n=572). In 85% simulation films and in 87% verification films were available. RT was assessed as unacceptable in 46% (HD13= 38%, HD14=52%), acceptable in 9% (HD13= 9%, HD14= 9%) and according to the protocol in 45% (HD13= 52%, HD14= 38%). These findings were compared to a data set of eleven patients treated within the sixth study generation (HD16-18) which was reviewed using the "new" revised QA-program including criteria for conformal techniques. *Conclusions.* The value for QA of RT within the GHSG trials is well known. To develop a QA-program of modern RT the expert panel defined criteria for analyzing current RT-procedures. With this schedule the QA of the GHSG serves as a model for other study groups.

P051

CLINICAL OUTCOME OF PATIENTS WITH EARLY STAGE FAVORABLE HODGKIN LYMPHOMA TREATED WITH ABVDX2 CYCLES FOLLOWED BY PET/CT RESTAGING AND 20 GY OF INVOLVED-SITE RADIOTHERAPY

S.C. Kamran[1], H.A. Jacene[2], Y.-H. Chen[3], P.M. Mauch[4], A.K. Ng[4]

[1]Harvard Radiation Oncology Program; [2]Department of Radiology; [3]Department of Biostatistics and Computational Biology; [4]Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA, USA

The publication of the GHSG HD10 trial changed the treatment paradigm for early-stage, favorable Hodgkin lymphoma (HL). Two cycles of ABVD followed by 20 Gy of involved-field radiotherapy (IFRT) has become a widely accepted treatment strategy for these patients. However, PET/CT is now increasingly used for response assessment after chemotherapy, and IFRT has largely been replaced by involved-site radiotherapy (ISRT). In this study, we describe our experience of 2 cycles of ABVD followed by PET/CT assessment, and ISRT to 20 Gy for patients with early-stage, favorable HL. With IRB approval, records of 20 patients (11 females, 9 males) with early-stage, favorable HL per the GHSG criteria, treated between 2008-2015, were reviewed. All patients underwent PET/CT for initial staging and for restaging after 2 cycles of ABVD. This was followed by ISRT to 20 Gy in 10 fractions, using 3-dimensional conformal technique. PET-response after 2 cycles of ABVD was independently assessed by a nuclear medicine physician with Deauville score assignment. Actuarial rates of relapse-free survival (RFS) and overall survival (OS) were calculated. RFS was defined as the time from start of chemotherapy to relapse or death, whichever occurred first. The median age at diagnosis was 33 years (range 20-82). All but 2 patients were without B symptoms, and 50% had 1 site of disease. Median ESR was 10 (range 1-16). Median maximal tumor dimension was 38 mm (range 12-80 mm). After 2 cycles of ABVD, 95% of patients had a Deauville score of 1-2, and 1 patient had a score of 3. Median follow-up is 46.9 months. As of this analysis, all patients are alive without disease. One patient had an out-of-field relapse, but was salvaged with chemotherapy followed by autologous stem cell transplant. This patient had 80 mm disease at time of diagnosis and a Deauville 2 score after chemotherapy. The 4-year RFS rate is 90.9% (95% CI: [50.8, 98.7]). Figure 1 shows RFS in this 20-patient cohort. Our results showed that with careful patient selection based on initial disease characteristics and PET-response to chemotherapy, the use of a more restricted radiotherapy treatment volume of ISRT to 20 Gy following ABVDx2 is associated with an excellent outcome with no local recurrences or marginal misses.

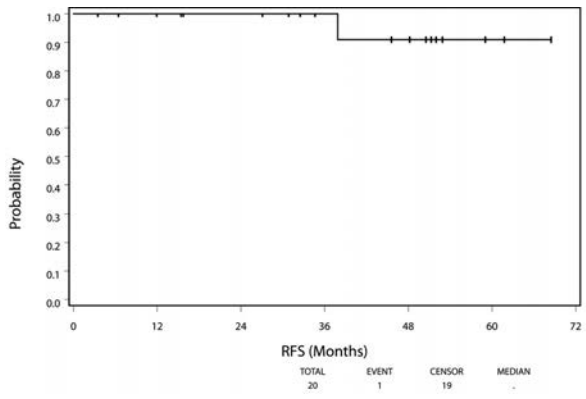


Figure 1.

P052

OPTIMIZED "BUTTERFLY" VMAT REDUCES MEAN DOSE TO CORONARY ARTERIES FOR EARLY STAGE HL PATIENTS UNDERGOING MEDIASTINAL RADIOTHERAPY

A.R. Filippi, M. Levis, A. Girardi, C. Fiandra, C. Piva, I. Donegani, R. Ragona, U. Ricardi

Department of Oncology, Radiation Oncology, University of Torino, Italy

Background and Objectives. A linear correlation was shown between the occurrence of coronary artery disease (CAD) and radiation dose received by coronary arteries for Hodgkin's lymphoma (HL) patients, derived by mean heart dose/long-term follow-up datasets. The purpose of this study was to delineate coronary arteries and optimize radiation planning on these substructures by using an optimized multi-arcs volumetric arc therapy (VMAT) solution, then to compare it to standard 3D-CRT with the aim of showing a potential dosimetric benefit for VMAT. *Materials and Methods.* We compared the plans of 14 HL patients (3 males and 11 females) with stage I-IIA mediastinal disease without axillary involvement, treated with involved site radiotherapy (ISRT); 11 had a bulky presentation at diagnosis. In every patient, a deformable fusion was performed with a dedicated software between the planning CT and the pre-ISRT contrast enhanced CT scan. The following structures were delineated: whole heart; left main, left descending, circumflex and right coronary arteries; aortic, pulmonary, mitral and tricuspid valves; right and left atria; right ventricle, left ventricle and interventricular septum; left ventricular apex, mid cavity, base and lateral wall. Two experienced radiation oncologists contoured target volumes (CTV), and heart substructures, after a validation session with a cardiologist and a heart radiologist. The VMAT approach consisted of multi non-coplanar arcs (the so-called "butterfly" VMAT or B-VMAT) and was compared with 3D-CRT. Mean and max dose received by the coronary arteries were compared by Student's T test. *Results.* Maximum doses to coronary arteries resulted similar; conversely, lower mean doses were delivered by using B-VMAT, reaching a significant difference for the left main trunk (p=0.002), the circumflex coronary artery (p=0.014) and the right coronary artery (p=0.002). Most significant findings are illustrated in the Figure 1. *Discussion.* This study suggests that an optimized intensity modulated RT solution (B-VMAT) is able to reduce the dose to coronary arteries for HL patients with mediastinal disease. As the dose-response relationship is linear, this reduction should translate in lower incidence of CAD.

Structure	VMAT	3D-CRT	p value
	Mean dose (Gy) ± SD	Mean dose (Gy) ± SD	
Heart	5.7 ± 3.4	7.2 ± 4.8	**0.032**
Left main coronary trunk	17.2 ± 8.8	25.9 ± 5.2	**0.002**
Left interventricular coronary	17.0 ± 10.7	17.9 ± 9.1	0.42
Circumflex coronary artery	13.1 ± 9.3	18.1 ± 10.6	**0.014**
Right coronary artery	12.8 ± 9.0	15.6 ± 10.2	**0.002**

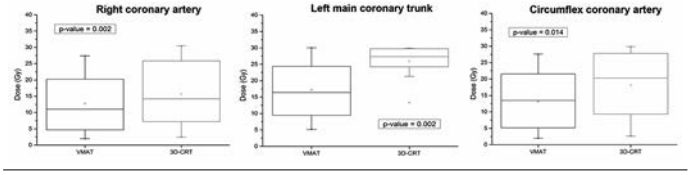


Figure 1.

P053

BIOLOGICAL EVALUATION IN THE TREATMENT PLANNING. IS THERE A USE FOR PATIENTS WITH HODGKIN'S LYMPHOMA?

J. Kriz, U. Haverkamp, N. Pepper, K. Elsayad, K. Kröger, G. Reinartz, M. Glashörster, C. Kittel, H.T. Eich

Department of Radiation Oncology, University of Muenstere, Germany

Introduction. The aim of the present analysis is to evaluate the value of a biological treatment planning for patients with Hodgkin's Lymphoma (HL). Because patients with HL have become longtime survivors the main goal of ongoing studies is to minimize treatment related late toxicity. Especially for patients with mediastinal involvement the use of IMRT should be considered carefully with regard to pulmonary toxicity. *Methods.* We included 27 patients with mediastinal involvement of HL. All patients received chemotherapy followed by 30.6 Gy Involved-Field RT. 20 patients were treated with APPA, 5 patients with a 5-field IMRT (5F-IMRT) and 3 patients with a 7-field IMRT (7F-IMRT). To compare the different techniques we calculated 3 treatment plans for every patient. We evaluated Dmean, V5, V10, V15, V20 and V30 of the lung, Dmax of the spinal cord and V50 of the body. To determine the probability of pneumonitis we used a biological evaluation of Eclipse© by Varian and compared them to values we calculated using the parameters of Quantec. We analyzed the follow-up CTs of all patients to test whether they had a radiogenic pneumonitis. *Results.* A total of 81 plans were calculated. The 7F-IMRT achieves the highest values with respect to Dmean, V5, V10, V15 and V20 of the lung. Regarding V30 APPA is inferior (14.9 Gy APPA *vs* 2.9 Gy 7F-IMRT median). With respect to Dmax of the spinal cord the 7F-IMRT is superior to 5F-IMRT and APPA (32.1 Gy APPA, 24.9 Gy 5F-IMRT and 19.9 Gy 7F-IMRT median). The 7F-IMRT achieves the highest NTCP-values: Left lung: (range 0.0-2.1%); 5F-IMRT (range 0.0-4.0%) and 7F-IMRT (range 0.0 – 5.1%). Right lung: APPA (range 0.0-2.1%); 5F-IMRT (range 0.0-2.9%) and 7F-IMRT (range 0.0-8.0%). The values calculated by using the Quantec-parameters were as follows: Left lung: APPA (range 1.4-12.2%); 5F-IMRT (range 1.6-15%) and 7F-IMRT (range 1.7 – 16.4%). Right lung: APPA (range 2.3-12.6%); 5F-IMRT (range 2.4-13.9%) and 7F-IMRT (range 2.3-18.2%). No patient had radiologic signs of pneumonitis by reviewing the follow up CTs. *Conclusions.* APPA is superior to IMRT with respect to the mean lung doses. This finding is underlined by the NTCP-values. If the local doses (*e.g.* V30) in the field of the PTV are observed, IMRT is superior. The calculated values show an increased risk by using the 7F-IMRT. The biological evaluation achieves remarkable results in both cases, that are usefull in the judgement of treatment plans.

P054

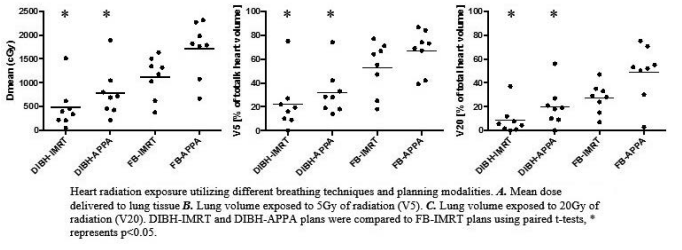
THE EFFECT OF DEEP INSPIRATION BREATH HOLD INTENSITY-MODULATED RADIATION THERAPY ON SPARING HEALTHY TISSUES IN THE TREATMENT OF LYMPHOMA INVOLVING THE MEDIASTINUM

B. Eastman, J. Uhl, V. Mosienko, J. Murphy, P. Sanghvi

University of California, San Diego, USA

Survivors of Hodgkin's lymphoma (HL) have an increased risk of developing secondary malignancies and cardiovascular disease. This risk is directly correlated to the amount of radiation exposure and is significant even with the use of modern radiation therapy modalities. Deep inspiration breath hold (DIBH) techniques have been shown to lead to the delivery of lower amounts of radiation to organs at risk (OARs) during the treatment of breast cancer and Hodgkin's lymphoma. In this study, we evaluated the ability to DIBH techniques to decrease the amount of radiation exposure of OAR in 16 consecutive HL lymphoma patients with mediastinal involvement. Majority of patients had Stage II bulky disease. For each patient four different plans were calculated – two utilizing deep inspiration breath hold technique and two with free breathing with IMRT and APPA plans created for both breathing modalities. DIBH plans delivered significantly decreased mean doses to the heart with Dmean of 474.5cGy (DIBH-IMRT) and 779.0cGy (DIBH-APPA), compared to the free breathing plans with 1125.6cGy (FB-IMRT) and 1709.3cGy (FB-APPA). In addition, specific cardiac substructures such as the coronary arteries and the aortic valve also received reduced mean doses of radiation. The coronary arteries in DIBH-IMRT plans received on average Dmean of 888cGy, DIBH-APPA plans -1528Gy, FB-IMRT 1921cGy and DIBH-APPA – 2529cGy. Similar trend is present within the average dose delivered to the aortic valve with average Dmean for DIBH-IMRT plans of only 894cGy, compared to average Dmean of 1694cGy for DIBH-APPA plans, 2718cGy for FB-IMRT plans, and 2874cGy for FB-APPA plans. Mean dose of lung exposure for DIBH-IMRT plans is also significantly lower than FB-IMRT plans (p=0.003). The volume of lung tissue receiving low dose radiation is significantly decreased in the DIBH-IMRT plan compered to the FB-IMRT plan, however the volume receiving 2000cGy is comparable between the DIBH and FB plans. These findings are con-

sistent with previous reports and suggest that utilizing DIBH could greatly decrease the radiation exposure of OAR and decrease the long-term complications young cancer survivors face.



Heart radiation exposure utilizing different breathing techniques and planning modalities. ***A.*** Mean dose delivered to lung tissue ***B.*** Lung volume exposed to 5Gy of radiation (V5). ***C.*** Lung volume exposed to 20Gy of radiation (V20). DIBH-IMRT and DIBH-APPA plans were compared to FB-IMRT plans using paired t-tests, * represents p<0.05.

Figure 1.

P055

MULTICENTRIC ITALIAN EXPERIENCE IN TREATMENT OF NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA IN THE RITUXIMAB ERA

M. Gotti[1], F. Merli[2], A. Re[3], C. Rusconi[4], A. Pulsoni[5], L. Rigacci[6], M. Merli[7], M. Liberati[8], V. Ferretti[1], V. Zoboli[1], A. Fama[2], D. Dalceggio[3], E. Meli[4], G. Annechini[5], B. Puccini[6], A. Ferrario[7], V. Appolloni[8], R. Sciarra[1], M. Frigeni[1], L. Arcaini[1], M. Bonfichi[1]

[1]Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]Hematology Unit, Arcispedale S Maria Nuova-IRCCS of Reggio Emilia, Italy; [3]Department of Hematology, Spedali Civili, Brescia, Italy; [4]Department of Haematology, Niguarda Ca' Granda Hospital, Milan, Italy; [5]Department of Cellular Biotechnologies and Hematology, "La Sapienza" University, Roma, Italy; [6]Department of Haematology, "Careggi" Hospital, Firenze, Italy; [7]Division of Hematology, University Hospital Ospedale di Circolo & Fondazione Macchi, Varese, Italy; [8]Onco-Hematology Departmant, S. Maria Hospital, Terni, Italy

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is characterized by the expression of B-cell associated antigen CD20. Due to this characteristic it has been proposed the use of the anti-CD20 antibody but at now, there is no consensus on which chemotherapy regimen should be used. In patients with stage IA two prospective studies evaluated the role of the anti-CD20 antibody in monotherapy (GHSG and Stanford); both of them concluded that rituximab cannot be recommended as a first-line therapy and ESMO guidelines recommend radiotherapy for this subset of patients. In other stages chemotherapy is generally recommended, but there is no consensus on whether classical HL-directed regimens, such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), or B-cell lymphoma-directed regimens, such as R-CHOP (rituximab, cychlophosphamide, doxorubicin, vincristine, prednisone) should be used. In order to plan clinical trials and to test our potential accrual we performed a retrospective analysis of patients treated between 2000 and 2016 in 8 Italian hematologic centers. We identified 113 pts affected by NLPHL (41 stage I without symptoms, 40 stage II, 21 stage III, 11 stage IV). 11 patients had extranodal disease (pancreas, intestine, skin, lung, liver, bone marrow, muscle), 14 had spleen involvement and 9 had B symptoms. Median age at diagnosis was 43, male:female ratio was 2.9. Median follow-up is 62 months (range 1-199 months). 5yr-OS and 3yr-EFS were respectively 95.5% and 85.9%.13 patients had relapse of NLPHL, 5 patients had transformation to DLBCL at a median of 14 months, 4 patients died (1 from acute myelogenous leukemia, 1 from progression of disease, 1 from stomach cancer and 1 for interstitial pneumonia during ABVD). Treatments for non-stage I pts were as follows: 29 ABVD ± IFRT (II 19, III 6, IV 4), 13 R-ABVD (II 5, III 5, IV 3), 24 R-CHOP ± IFRT (II 10, III 10, IV 4) and 6 other (2 observation, 2 IFRT, 1 Rituximab, 1 CHOP like).3-years event-free survival are as follows: 78.5% (58-90) for ABVD±RT, 100% for R-ABVD and 74% for R-CHOP (48-88). No statistically significant difference was observed in terms of EFS neither for therapy regimen (p 0.512), nor for stage and spleen involvement (p 0.33). Our data do not show any difference among classical HL-directed regimens, B-cell lymphoma-directed regimens or composite approach. A prospective randomized large cohort evaluation should be taken into account.

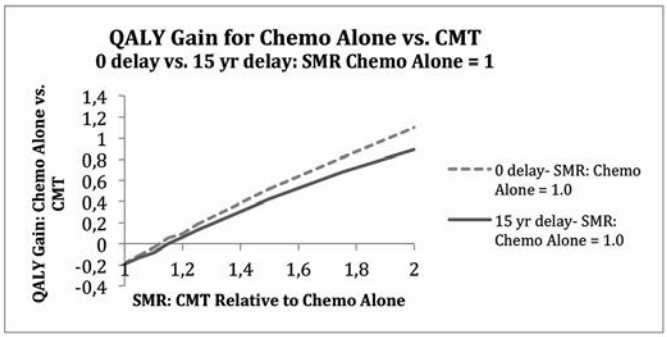
P056

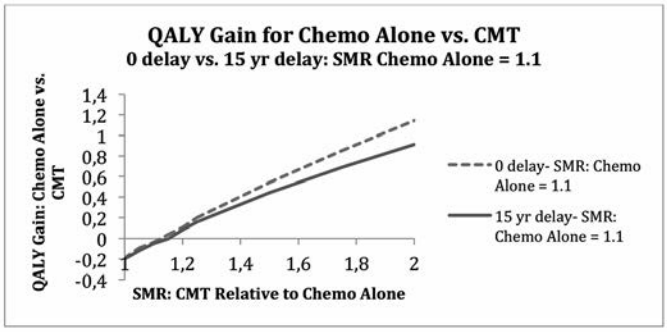
CONSTRUCTION OF A DECISION MODEL TO AID TREATMENT CHOICES FOR EARLY STAGE HODGKIN LYMPHOMA: BRINGING SURVIVORSHIP FORWARD

M.J. Kelly[1,2] S.K. Parsons[2,3,4], J.T. Cohen[3,5], S.M. Castellino[6], K. Kelly[7], F. Keller[6], T.J. Henzer[3], A. Kumar[4], P. Johnson[8], R.M. Meyer[9], L.M. Morton[10], J. Radford[11], J. Raemaekers[12], D.C. Hodgson[13], A.M. Evens[4]

[1]Division of Pediatric Hematology/Oncology, The Floating Hospital for Children at Tufts Medical Center MC, Boston, Massachusetts, USA; [2]Department of Pediatrics, Tufts University School of Medicine, Boston, Massachusetts, USA; [3]Institute for Clinical Research and Health Policy Studies, Tufts MC, Boston, Massachusetts, USA; [4]Division of Hematology/Oncology, Tufts MC, Boston, Massachusetts, USA; [5]Center for the Evaluation of Value and Risk in Health, Tufts MC, Boston, Massachusetts, USA; [6]Aflca Cancer Center and Blood Disorders Center, Children's Hospital of Atlanta, Emory University School of Medicine, Atlanta, USA; [7]Division of Pediatric Hematology/Oncology, Roswell Park Cancer Institute, Buffalo, New York, USA; [8]Cancer Research UK Centre, Southampton, United Kingdom; [9]Departments of Oncology, Medicine and Community Health and Epidemiology, NCIC Clinical Trials Group, Queen's University, Kingston, Canada; [10]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA; [11]Institute of Cancer Sciences, University of Manchester, United Kingdom; [12]Department of Hematology, Radboud University Medical Center, Nijmegen, the Netherlands; [13]Radiation Medicine Programme, University of Toronto, Princess Margaret Cancer Centre, Toronto, Ontario, Canada

Introduction. Decision-making for the treatment of ES HL patients continues to involve consideration of the tradeoff between shorter-term progression-free survival (PFS) and the impact of late effects (LE) on overall survival (OS). To evaluate the complex decision process arising from these factors, there is a desire to obtain integrated data that assimilates short-term outcomes, LE, and quality adjusted life expectancy (QALE) to help aid treatment choices. *Methods.* We analyzed PFS and OS from 4 large, modern randomized trials comparing chemotherapy alone with combined modality therapy (CMT) for ES HL (Meyer NEJM 2012; Wolden JCO 2012; Raemaekers JCO 2014; Radford NEJM 2015). We constructed a detailed Markov model comparing QALE after initial therapy for ES HL using chemotherapy alone *vs* CMT. The model incorporated: 3-year PFS from PET- patients; quality of life associated with relapse and cure; cure rates after relapse; 15-year latency period before onset of increased mortality from LE; and "discounting" of future life years. We also performed sensitivity analyses to determine the amount that CMT (with contemporary radiotherapy) must increase LE-associated mortality for that impact to outweigh its early PFS advantage. *Results.* All 4 trials demonstrated that short-term PFS was superior with CMT, including PET response-adapted paradigms, however OS was at least equivalent in each study. Collectively, the analyses showed that if CMT-associated LE increased deaths >15-20% (relative) compared with chemotherapy alone, then treatment with the latter was associated with overall improved QALE. This finding was consistent across a range of patient ages and among varied estimates for SMR after cure for those treated with chemotherapy alone (see Figure 1). Furthermore, sensitivity analyses demonstrated that these findings were most sensitive to assumptions regarding the impact of CMT on mortality after cure, and insensitive to moderate changes in the assumed short-term impact of CMT on PFS. *Conclusions.* We identified the "break-even point" whereby chemotherapy alone was associated with superior QALE *vs* CMT (ie, 15-20% relative increased death from LE). This model provides the base analytic framework to aid the complex decision of treating ES HL. Future model iterations may incorporate patient & tumor characteristics, patient preferences, and cost-effectiveness of varied therapeutics in order to help guide individualized decisions for providers and patients with HL.





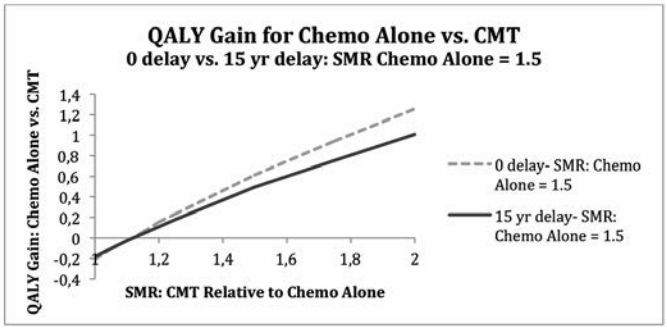


Figure 1. Quality-adjusted life expectancy (QALE) examining varied SMR values and delayed effect. The Y-axis of the figure shows the gain in QALE when treating with a strategy of chemotherapy alone compared with combined modality therapy (CMT). Negative values indicate that CMT is associated with superior QALE, while positive values indicate that chemotherapy alone is associated with superior QALE. The X-axis plots the relative standardized mortality ratio (SMR) after cure when treating with CMT compared with chemotherapy alone. For example, a relative of SMR of 1.2 means that treatment with CMT is associated with a 20% higher risk of death from late effects than treatment with chemotherapy alone. We performed the analysis three times, each time choosing a different SMR for those treated with chemotherapy alone (1.0, 1.1, and 1.5) and adjusting the relative CMT for those treated with CMT. Additionally, we performed the analysis two different ways: 1) assuming that the SMR after cure is incorporated into the model immediately after subjects enter the cured state – depicted as dashed lines (representing the immediate onset of an increased susceptibility to deaths from late effects); and 2) holding the SMR at 1.0 for 15 years after subjects enter the cured state and then incorporating the SMR after 15 years (to represent the latency period of approximately 15 years until there is an observed increase in deaths from late effects). We assumed a base case age of the subjects to be 25 years old. Altogether, the figure illustrates that the "break-even point" (*i.e.*, where the curves cross the horizontal axis) are nearly the same under the aforementioned set of assumptions and that it holds true in all three scenarios (*i.e.*, for chemotherapy alone with SMRs of 1.0, 1.1, and 1.5). Thus, if there is expected to a be a 15-20% or greater increase in deaths from late effects after treatment with CMT, then treatment with chemotherapy alone is associated with superior QALE.

P057

DOSES TO ORGANS AT RISK AT DIFFERENT MODES OF 3D-CONFORMAL RADIOTHERAPY FOR MEDIASTINAL STAGE II HODGKIN LYMPHOMA

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

FSBI "Russian Research Center for Radiology and Surgical Technologies" of the Ministry of Health care, St. Petersburg, Russian Federation

Purpose. In this study we evaluated the doses for organs at risk (lungs, heart, spinal cord) and CTV-PTV volume at 3D-conformal radiotherapy (3DCRT, ISRT) and intensity-modulated radiotherapy (IMRT) for mediastinal stage II HL (30-36Gy). *Patients and Methods.* From March 2014 to March 2015 63 patients with mediastinal stage II HL had chemotherapy 3-4 cycles ABVD than there was 3DCRT: 52 patients – involved site radiation therapy (ISRT) and 11 patients – IMRT. We compared CTV-PTV volumes and the doses to organs at risk in these groups. *Results.* CTV volume was not distinguished (401±15,0 cm3 and 385±61,5 cm3). PTV was significantly more at ISRT than IMRT-groupe (1270±84,0 cm3 and 604±89,0 cm3, p<0,01). Besides, at IMRT-groupe were less compared with ISRT-groupe V20 left lung (24,0±3,8% and 33,5±1,4%, p<0,05), right lung (28,0±1,3% and 16,6±2,4%, p<0,05), V30 heart (50,0±4,4% and 8,1±2,2%, p<0,01), mean heart dose (29,4±3,8 Gy and 7,0±1,5 Gy, p<0,001). Mean dose for spinal cord was similar in these groups. *Conclusions*. IMRT compared to 3DCRT (ISRT) substantially reduces V20 lungs, V30 heart and mean dose for heart without compromising the dose to the target in patients with mediastinal stage II HL.

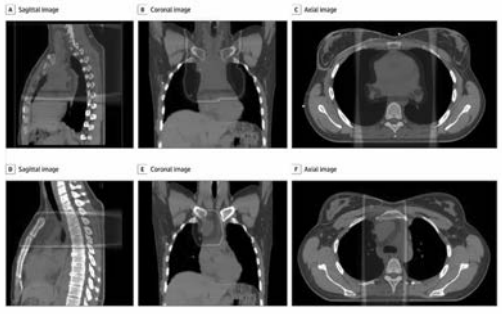
P058

RESIDUAL SITE RADIATION THERAPY: AN OPPORTUNITY TO INCREASE SAFETY OF COMBINED MODALITY THERAPY FOR EARLY STAGE HODGKIN LYMPHOMA

D. Straus, O. Cahlon

Memorial Sloan Kettering Cancer Center New York, NY, USA

In randomized controlled trials, the addition of RT to chemotherapy increases the progression-free survival but not overall survival in early stage HL. Extended field (EF) and involved field (IF) RT are both associated with late morbidity and mortality, particularly due to second malignancies and cardiovascular events. There do not appear to be safe doses of RT that will remain therapeutic, Doses as low as 20 Gy in CMT do not seem to reduce the risk of second cancers below that seen with traditionally therapeutic doses of 35-45 Gy. The risk of coronary heart disease is increased by 7.4% per Gy in median heart dose. Likewise the reduction of radiation therapy portals from EF to IF RT has not reduced the risk of second cancers. The latest iteration of IF RT is involved site RT (IS RT) (Figure 1).



Involved Site RT (IS RT) vs Residual Site RT (RS RT) (30 Gy)
20 year old woman with stage IIAX cHL

IS RT: mean heart dose 9.5 Gy; mean left breast dose 6.2 Gy; lung V20 27%
RS RT: mean heart dose 0.2 Gy; mean left breast dose 0.1 Gy, lung V20 4%
JAMA Oncol 2:69-70,2016

Figure 1.

However, despite the early observation that initially bulky nodal sites are at higher risk for recurrence than non-bulky sites following adequate chemotherapy, all initial nodal sites are still treated regardless of whether or not they resolve with chemotherapy despite their initial size. Involved site RT still results in large fields encompassing the pre-chemotherapy extent of disease, and as a result, in substantial off-target radiation exposure to adjacent organs. There is no data indicating that lowering the RT dose further in CMT will remain therapeutic.

Given the paradigm of treating all initial nodal sites of involvement, it will also be difficult to further substantially reduce off-target radiation exposure, even with new techniques such as three-dimensional conformal RT, intensity modulated RT, deep inspiratory breath hold, or even proton beam RT. Because of these considerations, we propose a change in the paradigm of treating all initial nodal sites of involvement when administering adjuvant RT following adequate chemotherapy. It is unclear whether initial nodal sites that have completely resolved with chemotherapy are at increased risk for recurrence. Rather, we propose clinical trials to test the concept of only treating the PET-negative residual remaining masses on CT imaging following chemotherapy (residual site RT – RS RT). A step in this direction was taken with the HD15 trial.

Advanced Stages

T001

BEACOPP-ESCALATED FOLLOWED BY RADIOTHERAPY OF INITIAL BULK OR RESIDUAL DISEASE IN ADVANCED-STAGE HODGKIN LYMPHOMA: LONG-TERM FOLLOW-UP OF THE GHSG HD9 AND HD12 TRIALS

B. von Tresckow*, S. Kreissl*, H. Haverkamp, S. Sasse, V. Diehl, A. Engert, P. Borchmann

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

**Both first authors contributed equally*

Introduction. The HD9 trial had established 8xBEACOPPescalated followed by radiotherapy (RX) of initial bulk or residual tumors as standard of care for advanced Hodgkin Lymphoma (HL) at that time. The successor study of HD9, HD12, evaluated a reduction of chemotherapy and RX. Since the long-term safety and efficacy of BEACOPPescalated and RX has been debated, we report the HD9 and HD12 long-term follow-up. *Patients and Methods.* All patients had advanced HL. 1,282 HD9-patients were randomized between 8xCOPP/ABVD, 8xBEACOPPbaseline, and 8xBEACOPPescalated. 1,670 HD12-patients were randomized between 8xBEACOPPescalated, and 4xBEACOPPescalated followed by 4xBEACOPPbaseline ("4+ 4"), both with or without RX to initial bulk and residual disease. *Results.* In HD9-patients treated with COPP/ABVD, BEACOPPbaseline, and BEACOPPescalated, the 15-year progression-free survival (PFS) was 57%, 66.8%, and 74% with overall survival (OS) rates of 72.3%, 74.5%, and 80.9%, respectively. BEACOPPescalated remains significantly better than COPP/ABVD in terms of PFS (P<0.0001) and OS (P=0.02). A total of 123 second malignancies corresponding to 15-year cumulative secondary malignancy incidences of 7.2%, 13%, and 11.4% were reported for COPP/ABVD, BEACOPPbaseline, and BEACOPPescalated, respectively, without a difference between COPP/ABVD and BEACOPPescalated (p=0.5). Standardized incidence ratios (SIR) with 95%-CI were 2.0[1.2-3.2], 2.6[1.9-3.4] and 2.6[1.9-3.4]. The 10-year PFS and OS rates in the two HD12 chemotherapy groups were not significantly different with 82.6% and 87.3% in the BEACOPPescalated group and 80.6% and 86.8% in the 4+4 group, respectively. However, omitting RX resulted in an significantly inferior 10-year PFS of 83.5% in no RX patients with initial bulk/residual disease compared to RX (88.6%, difference -5.1%; 95%-CI,-9.9% to -0.4%, hazard ratio [HR] 1.47; Figure 1) and a trend towards inferior OS in no RX patients (RX 93%; no RX 90.2%; difference -2.7%; 95%-CI,-6.5% to 1%).

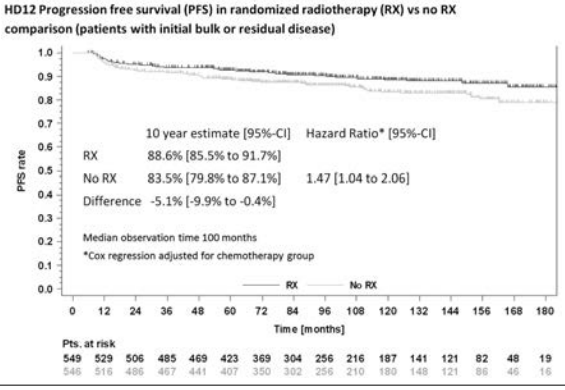


Figure 1.

Patients with residual lesions without RX had an inferior OS as compared to patients with RX (as treated comparison: RX 94.4%; no RX 88.4%; difference -6%; 95%-CI,-11.4% to -0.5%). *Conclusions.* The superiority of BEACOPPescalated to COPP/ABVD is confirmed by this HD9 long-term analysis. The HD12 long-term analysis shows an inferior PFS and trend towards inferior OS in patients in the no RX groups, particularly in patients with residual lesions.

T002

OVERALL SURVIVAL IMPACT OF BEACOPP *VERSUS* ABVD IN ADVANCED HODGKIN LYMPHOMA: A POOLED ANALYSIS OF 4 RANDOMIZED TRIALS

M. André[1], C. Fortpied[2], S. Viviani[3], M. Bellei[4], P. Carde[5], M. Hutchings[6], A. Gianni[7], P. Brice[8], O. Casasnovas[9], P. Gobbi[10], P.L. Zinzani[11], J. Dupuis[12], E. Iannitto[13], A. Rambaldi[14], J. Brière[15], A. Perrot[16], M. Heczko[17], P. Valagussa[18], J. Douxfils[19], C. Joubert[20], M. Federico[21], N. Mounier[22]

[1]Université Catholique de Louvain, CHU UCL Namur, Hematology, Yvoir, Belgium; [2]European Organization for Research and Treatment of Cancer, Brussels, Belgium; [3]Department of Hematology and Pediatric Onco-Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [4]Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy; [5]Gustave-Roussy Cancer Campus, Villejuif, France; [6]Department of Hematology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [7]Scientific Direction, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [8]Hematooncology, Hôpital Saint-Louis APHP Paris7, France; [9]Department of Hematology, CHU le Bocage, and INSERM, LNC URM866, Dijon, France; [10]Clinica Medica I, Fondazione IRCCS Policlinico S. Matteo, Dipartimento di Medicina Interna e Terapia Medica, Università di Pavia, Pavia, Italy; [11]Institute of Hematology L. e A. Seràgnoli, Sant'Orsola-Malpighi University Hospital, Bologna, Italy; [12]Hematology Department, Hôpital Henri Mondor, Créteil, France; [13]UOC Ematologia, AOU Policlinico P. Giaccone, Palermo, Italy; [14]Hematology and Bone Marrow Transplant Unit of Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; [15]Department Pathology, Hôpital Saint-Louis, Assistance Publique des Hôpitaux de Paris, France; [16]Service d'Hématologie, CHU de Nancy, Université de Lorraine, Vandoeuvre lez Nancy, France; [17]Department of Hematology, Besançon Hospital, France; [18]Fondazione Michelangelo, Milano, Italy; [19]Department of Pharmacy, NTHC, NARILIS, University of Namur, Namur, Belgium; [20]Biostatistics, LYSARC, CH Lyon-Sud, Pierre Bénite, France; [21]Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy; [22]Department of Onco-Hematology, Archet Hospital, Nice, France

Introduction. In 4 individual randomized trials comparing ABVD and BEACOPP in advanced HL, BEACOPP significantly improved disease control but not OS. We explored the potential OS benefit of BEACOPP in a pooled analysis of these 4 trials. *Methods.* The primary objective was to assess the impact of BEACOPP on OS by one-stage individual patient data meta-analysis stratified for trial. Secondary endpoints were PFS, early toxicities, second malignancies and use of hematopoietic stem cell transplantation (HSCT). *Results.* Four trials representing a total of 1227 patients (622 ABVD and 605 BEACOPP) were included (IIL Viviani 2011, LYSA H34 Mounier 2014, EORTC 20012 Carde 2016, HD2000 Merli 2016). Patients characteristics: median age: 32 yrs, male 64%, nodular sclerosis 78%, stage II-III-IV: 13-32-55%, B symptoms: 77%, Bulky disease: 38%, IPS>3: 66%. With a median fup of 4.9 yrs, the 5-yrs OS is 86.59% for ABVD (95%CI=83.0-89.3) *vs* 90.8% for BEACOPP (95%CI=88.0-93.0). The data indicated that the HR is not constant over time (P<0.05) preventing the use of a simple Cox model. Per analysis plan, two time periods (< and ≥18m) were defined from the observed survival and hazard curves. In the first 18 months (N=1227, 54 events), no difference was detected (HR:0.75, 95%CI=0.41-1.23). After 18 months (N=1083, 68 events), the risk of death appeared higher in patients in ABVD arm than in BEACOPP arm (HRABVD *vs* BEACOPP=2.52, 95%CI=1.48-4.28, p<0.001). Further adjustment for IPS showed that both treatment (p<0.001) and IPS group (p=0.0326) effects are significant. The 5-yr PFS was 72.0% for ABVD (95%CI=67.3-76.1) *vs* 82.9% for BEACOPP (95%CI=78.7-86.4) (p<0.001). Grade 3-4 toxicities (ABVD *vs* BEACOPP): anemia: 4.3% *vs* 24.2%; leukopenia: 23.2% *vs* 76.8%; thrombocytopenia: 1.7% *vs* 26.4%; infection: 7.9% *vs* 34.2%. After ABVD, 17 second malignancies (0 AML) (2.7%) were reported and 21(7 AML)(3.6%) after BEACOPP. After ABVD, 86 patients (13.8%) received HSCT *vs* 39 (6.4%) after BEACOPP. *Conclusions.* This pooled analysis of 4 studies with increased power, indicated a non-constant treatment effect over time. A statistically significant OS benefit of BEACOPP was observed from 18 months after randomization. Frontline use of BEACOPP increased PFS, early hematological toxicity, secondary leukemia incidence but halved the need of HSCT. Further follow-up is needed to explore the impact of BEACOPP on fertility, second malignancies and long term survival.

T003

LONG-TERM FOLLOW-UP OF SWOG S0816: RESPONSE-ADAPTED THERAPY OF ADVANCED STAGE HODGKIN LYMPHOMA USING EARLY INTERIM FDG-PET IMAGING

J.W. Friedberg, H. Li, H. Schöder, D. Straus, C. Moskowitz, M. LeBlanc, L.M. Rimsza, N.L. Bartlett, A.M. Evens, E.S. Mittra, A. LaCasce, J. Sweetenham, P.M. Barr, M.A. Fanale, M.V. Knopp, A. Noy, E.D. Hsi, J.R. Cook, M.J. Lechowicz, R.D. Gascoyne, J. Leonard, B.S. Kahl, B.D. Cheson, R.I. Fisher, O.W. Press

United States National Clinical Trials Network: SWOG, Alliance, ECOG-Acrin and AIDS Malignancy Consortium

S0816 was the first US intergroup clinical trial using early interim FDG–PET imaging to determine the utility of response-adapted therapy for adults with stage III–IV classical Hodgkin Lymphoma. After 2 initial cycles of ABVD, PET2-negative patients (Deauville 1-3) received an additional 4 cycles of ABVD, while PET2+ patients (Deauville score 4-5) switched to eBEACOPP for 6 cycles. Among 336 eligible and evaluable patients, the median age was 32 (18-60), with 52% stage III, 48% stage IV, and 49% IPS 0-2, 51% IPS 3-7. Central review of the interim PET2 scan was performed in 331 evaluable patients, with 271 (82%) PET2-negative and 60 (18%) PET2+. Of 60 eligible PET2+ patients, 49 switched to eBEACOPP as planned and 11 declined. The median follow-up of patients last known alive now exceeds 45 months (range 2.1-76 months). Eighty-two patients have either progressed or died, for an estimated 2-year progression-free survival of 79% (95%CI: 73.8%-82.7%). There were 61 failures in the PET2-negative group (2-year PFS 82%) and 20 failures in the PET2+ group (2-year PFS 64%), see Figure 1. In the entire trial, only 19 patients died, for estimated 2-year overall survival of 98%. Long-term or late (post therapy) grade 3 adverse events on ABVD arm were uncommon including 1 case each of neuropathy, heart failure, DVT, diarrhea and prolonged neutropenia. There was one case of late grade 3 osteonecrosis on the eBEACOPP arm. Six patients (1.4%) have developed secondary malignancies, including 3 cases (1%) on ABVD (non-Hodgkin lymphoma, renal cell carcinoma, and melanoma) and 3 cases (6%) on eBEACOPP (non-Hodgkin lymphoma, renal cell carcinoma and skin cancer). We conclude that response-adapted therapy based on interim PET imaging after two cycles of ABVD appears promising and durable with a high 2-year PFS for PET2+ patients (64%), and outstanding overall survival. However, surprisingly, with prolonged follow-up, the majority of failures have occurred in PET2-negative patients, indicating the limitations to a PET-adapted approach. To further improve ABVD using precision medicine, we need to further refine predictive markers of failure at the time of Hodgkin lymphoma diagnosis.

Support. National Cancer Institute (NCI), National Clinical Trials Network (NCTN) grants CA180888, CA180819, CA180821, CA180820, CA121947.

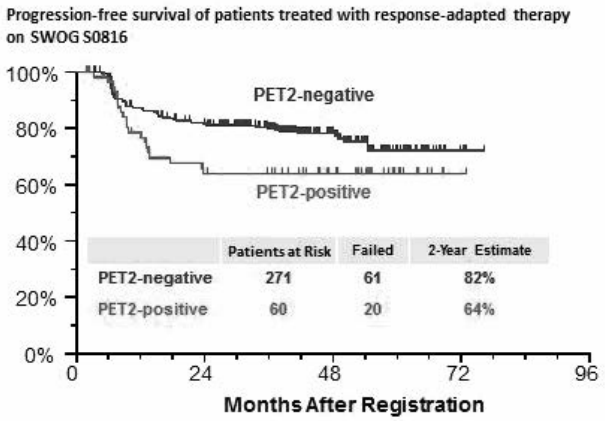


Figure 1.

P001

SEQUENTIAL BRENTUXIMAB VEDOTIN AND ADRIAMYCIN, VINBLASTINE, AND DACARBAZINE FOR OLDER PATIENTS WITH UNTREATED HODGKIN LYMPHOMA: FINDINGS FROM A PHASE II WINDOW STUDY

A.M. Evens[1], P.A. Hamlin[2], C. Nabhan[3], R. Advani[4], M. Fanale[5], A. Petrich[6], S. Smith[3], G. Bociek[7], J. Winter[6], L.I. Gordon[6]

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

Introduction. Outcomes for older patients (pts) with HL remain suboptimal. We initiated a multicenter study examining sequential brentuximab vedotin (BV) given before and after AVD chemotherapy (NCT01476410). *Methods.* Pts ages ≥60 years with stage II-IV, untreated HL were eligible. All pts received 2 "lead-in" cycles of single-agent BV 1.8 mg/kg (q 3 weeks), followed by 6 cycles of standard AVD chemotherapy. Responding pts then receieved consolidation therapy (Tx) with BVx4 cycles. Study design is Simon two-stage with plan of 48 total pts. The primary endpoint is complete remission (CR) rate after AVD (ie, prior to BV consolidation) using FDG-PET. If ≥12 CRs were observed among 20 evaluable pts, accrual continued to the 2nd stage. *Results.* 26 pts enrolled to the first study stage, of which 20 were evaluable for response. Characteristics for all pts included: median age 69 years (60-88); median ECOG PS of 1 (0-2); 92% stage III/IV disease; IPS 3-7 in 54%; and median CIRS co-morbidity score 5 (0-19). 6 pts were non-evaluable for response (n=3 withdrew consent/refused further therapy; n=2 toxicity; and n=1 death due to pancreatitis). Among 20 evaluable pts, overall response rate (ORR) to BV lead-in was 85% with 30% CR. After 3 AVD cycles, ORR and CR rates were 95% and 70%, respectively. The best ORR (including after BV consolidation therapy) was 95% with a CR rate of 90%. By intent-to-treat, best ORR and CR rates were 81% and 77%, respectively. Grade 3/4 AEs occurring in >1 pt were infection (15%), pancreatitis (4%), and peripheral neuropathy (PN) (4%); 31% of pts experienced grade 2 PN. Reasons for discontinuation of Tx included: 7/26 (27%) completed Tx; 7/26 (27%) on active Tx; 4/26 (15%) due to toxicity (grade 2: infusion reaction, hepatic, pneumonitis; and grade 3 wound infection); 3/26 (12%) refused additional Tx; 3/26 (12%) discontinued for PN (all grade 2 status-post cycles 6, 8,10); 1/26 (4%) due to lack of response; and 1 (4%) death (due to pancreatitis). At median follow-up of 22 months, 92% of all pts are alive, the progression-free survival is 85%, and notably, 95% of all evaluable pts are disease-free. *Conclusions.* Sequential integration of BV before and after standard AVD chemotherapy for newly diagnosed older HL pts is feasible and highly promising. The planned interim analysis confirmed the requisite CR rate needed for continuation to the 2nd stage of this multicenter phase II study. Updated results will be reported at the meeting.

P002

PRELIMINARY RESULTS OF A PHASE II STUDY OF BRENTUXIMAB VEDOTIN USING A RESPONSE ADAPTED DESIGN IN THE FIRST LINE TREATMENT OF PATIENTS WITH HODGKIN LYMPHOMA UNSUITABLE FOR CHEMOTHERAPY DUE TO AGE, FRAILTY OR CO-MORBIDITY (BREVITY)

A. Gibb[1], S. Pirrie[2], K. Linton[1,3], K. Paterson[2], A. Davies[4], G. Collins[5], T. Menne[6], P. McKay[7], P. Fields[8], F. Miall[9], E. Nagy[2], K. Wheatley[2], V. Warbey[10], S. Barrington[10], J. Radford[1,3]

[1]The Christie NHS Foundation Trust, Manchester, UK; [2]CRCTU, University of Birmingham, Birmingham, UK; Part of the Bloodwise Funded Trials Acceleration Programme; [3]University of Manchester, Manchester, UK; [4]Cancer Research UK Centre, Cancer Sciences Unit, Faculty of Medicine, University of Southampton, Southampton, UK; [5]Churchill Hospital, Oxford, UK; [6]Freeman Hospital, Newcastle, UK; [7]The Beatson West of Scotland Cancer Centre, Glasgow, UK; [8]Guys Hospital, London, UK; [9]Leicester Royal Infirmary, Leicester, UK; [10]PET imaging Centre at St Thomas' Hospital, Division of Imaging Sciences and Biomechanical Engineering, PET Imaging Centre, Kings College London, Kings Health Partners, UK

Introduction. Results of standard treatment for older patients (pts) with classical Hodgkin lymphoma (cHL) are sub-optimal and alternative approaches are required. Brentuximab vedotin (BV) is a CD30 targeted antibody-drug conjugate which in the pivotal* phase 2 trial in relapsed/refractory cHL produced an objective response rate of 75%, complete remission rate of 34% and manageable toxicity. BREVITY is a study of efficacy/tolerability of BV in older, frail or comorbid pts with previously untreated cHL. *Methods.* This was a phase II, Simon 2-stage, single arm study requiring 30 evaluable pts. Primary outcome was complete metabolic response rate (CMR, Deauville Score 1-3) by centrally reviewed PET-CT after 4 cycles of BV. Secondary outcomes included PFS, OS, toxicity and comorbidity assessment (CIRS-G). Inclusion criteria were previously untreated cHL stage 2 (with B symptoms and/or mediastinal bulk) or stages 3/4 with cardiac/respiratory compromise (at any age) or an ECOG score 1-3 and considered unfit for standard chemotherapy (in pts ≥60 yrs). BV dose was 1.8 mg/kg every 3 weeks, reduced to 1.2 mg/kg for toxicity. Pts in CMR/PMR after 4 doses BV continued to a total of 16 cycles if CT and/or PET-CT every 4 cycles confirmed ongoing response. PFS/OS data is not mature. *Results.* 38 pts were recruited Feb 2014-Oct 2015 at 12 UK centres; demographics are shown in Table 1.

Table 1.

Patient Characteristic	n=38 Median (Range)
Age	76 (59, 90)
CIRS-G Score	
No. categories endorsed	3 (0, 7)
Severity	1.5 (0, 3)
Total score	6 (0, 11)
	n (%)
Gender	
Male	22 (57.9)
Female	16 (42.1)
Stage	
Stage 2	7 (18.4)
Stage 3	13 (34.2)
Stage 4	18 (47.4)
B symptoms	27 (71.1)
Bulky Disease	5 (13.2)
Extranodal disease	22 (57.9)
ECOG Performance Status	
0	3 (7.9)
1	16 (42.1)
2	11 (28.9)
3	7 (18.4)
4	1 (2.6)

35 pts were treated and evaluable for toxicity, 31 are evaluable for response. Median follow-up for alive pts is 11.6(range 0.9, 21.4) months. A median of 4 cycles were given per pt (range 1, 16). 28(12%) cycles in 14 pts were modified due to toxicity and 11 pts stopped treatment due to adverse events (AEs). 695 AEs were reported of which 601(86%) were grade 1/2. 26(74%) pts had at least 1 AE ≥grade 3, most commonly infection, myelosuppression or neuropathy. CMR rate at PET4 was 25.8%(95% CI 13.7, 43.2) and combined CMR/PMR rate was 83.7(95%CI: 67.4, 92.9). To date 21(67.7%) pts have progressed. *Discussion.* In this study BV monotherapy produced a high objective response rate although the CMR rate after 4 cycles did not meet the pre-specified 40% level. Toxicity was greater than in the pivotal* study where pts were younger/fitter and led to treatment termination in some pts. Nevertheless BV is effective in this older comorbid population. A follow-on study incorporating BV at lower dose in combination with other agents and growth factor support aimed at improving the CMR rate is in development.

P003

CAUTION IN THE ELIMINATION OF RADIOTHERAPY FROM THE TREATMENT OF PATIENTS WITH STAGE III CLASSICAL HODGKIN LYMPHOMA: A SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS DATABASE ANALYSIS

J.E. Bates[1], S. Dhakal[2], A. Mazloom[3], C. Casulo[4], L.S. Constine[2]

[1]Department of Radiation Oncology, University of Florida, Gainesville, FL, USA; [2]Department of Radiation Oncology, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA; [3]Tacoma Valley Radiation Oncology Center, Tacoma, WA, USA; [4]Department of Medical Oncology, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA

Background. The role of radiotherapy (RT) in the primary management of advanced stage classic Hodgkin lymphoma (HL) remains controversial based on conflicting study *results.* While the definition for advanced stage is widely agreed upon as patients with stage III or IV disease, the difference in disease distribution and burden, as well as the difference in overall survival, between these stages may make RT more beneficial to patients with stage III disease. *Methods.* We queried the Surveillance, Epidemiology, and End Results (SEER) database, restricting our search to patients with stage III classical HL diagnosed from 2004 - 2012, to examine the difference in overall and cause-specific survival (OS and CSS) between patients who did or did not receive RT in combination with chemotherapy. *Results.* Patients treated with RT had improved OS and CSS relative to those treated without RT (5-year OS 91.6% with RT compared to 71.4% without RT, HR=0.34, p <0.001) and CSS (5-year OS 95.4% with RT compared to 84.7% without RT, HR=0.32, p <0.001). A benefit in OS and/or CSS was seen in both pediatric and adult patient subgroups, and patients with B symptoms and/or extranodal disease (Table 1).

Table 1. Multivariate Analysis of Treatment Outcomes in Patients with Stage III Classical Hodgkin Lymphoma (n=4,108).

	Overall Survival			Cause-Specific Survival		
Variable	HR	95% CI	p-value	HR	95% CI	p-value
Age Group						
Pediatric (0-19 yrs)	0.23	0.14 – 0.40	<0.001	0.23	0.11 – 0.49	<0.001
Adult (20 – 64 yrs)	–	–	–	–	–	–
Older Adult (>64 yrs)	4.85	4.17 – 5.65	<0.001	4.20	3.38 – 5.21	<0.001
B Symptoms (n = 3,787)						
Present	1.39	1.20 – 1.61	<0.001	1.61	1.30 – 2.00	<0.001
Absent	–	–	–	–	–	–
Radiation						
Yes	0.65	0.50 – 0.85	0.001	0.59	0.41 – 0.87	0.007
No	–	–	–	–	–	–

Conclusions. This large, hypothesis-generating, population-based study of the effect of radiotherapy in the treatment of stage III HL shows a benefit to radiotherapy across most subgroups. This supports a cautionary approach to omitting radiation therapy from treatment strategies for patients with advanced stage HL.

P004

GRAY ZONE LYMPHOMA WITH FEATURES INTERMEDIATE BETWEEN DIFFUSE LARGE B-CELL LYMPHOMA AND CLASSICAL HODGKIN LYMPHOMA: DIAGNOSTIC EXPERIENCES AND CHALLENGES FROM A MULTICENTER STUDY

M. Pilichowska[1], S. Pittaluga[2], J.A. Ferry[3], J. Hemminger[4], G. Gupta[1], A. Kritharis[5], R.D. Gascoyne[6], A.M. Evens[5], E.S. Jaffe[2]

[1]Department of Pathology, Tufts Medical Center, Boston, Massachusetts, USA; [2]Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA; [3]Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts, USA; [4]Department of Pathology, The Ohio State University, Wexner Medical Center, Columbus, Ohio, USA; [5]Division of Hematology/Oncology, Tufts Medical Center, Boston, Massachusetts, USA; [6]Centre for Lymphoid Cancer, British Columbia Cancer Agency, Vancouver, BC, Canada, USA

Background. GZL (B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL) was described in 2005 and included in the 2008 WHO classification. Most cases present with mediastinal disease and share features with cHL and primary mediastinal large B-cell lymphoma (PMBCL). Non-mediastinal lymphomas with similar pathologic features have also been reported. Because of rarity and diagnostic complexity, data on GZL are limited and further study of this entity is desired.

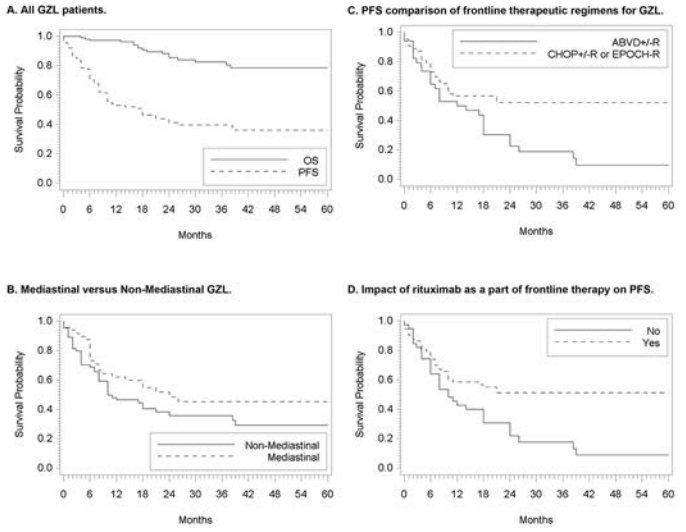


Figure 1. Outcomes in gray zone lymphoma (GZL). The 2-year (A) progression-free survival (PFS) and overall survival (OS) rates for 112 patients with GZL were 40% and 88%, respectively. (B) Outcome based on the presence of a mediastinal or non-mediastinal mass. Outcome (C) based on frontline therapeutic regimen: 2-year PFS for patients who received a standard frontline DLBCL regimen (*i.e.*, CHOP+/-R and DA-EPOCH-R) *versus* ABVD+/-R were 52% *versus* 23%, P=0.03. Kaplan-Meier survival curves (D) for patients who received rituximab as a part of frontline therapy *versus* not; 2-year PFS were 51% *versus* 22%, respectively, P=0.01.

Methods. Clinical data from cases originally diagnosed as GZL were collected from 19 academic centers across the US and Canada (Evens AM *et al.* Am J Hematol 90:778-83, 2015). To further characterize the diagnostic features and correlations, 73 cases (majority from the above series and n=4 subsequent cases) were submitted for central pathology review using criteria of the 2016 revised WHO classification. Initial diagnostic samples were evaluated with a panel comprising CD20, CD79a, PAX5, OCT2, BCL6, MUM1, CD30, CD15, CD3 and EBV by *in situ* hybridization (EBER). Beyond the tumor cell immunoprofile, diagnostic criteria included tumor cell density and morphology, necrosis, and the microenvironment. cHL nodular sclerosis grade 2 (cHL-NS2) were classified according to prior criteria (MacLennan K. *et al.* Cancer 64: 1686-93, 1989). 5 cases were rejected for insufficient material/technical issues; 68 cases were evaluated by 5 hematopathologists and consensus diagnosis was reached at multiheaded scope review. *Results.* Of 68 cases submitted with an original diagnosis of GZL, only 26 cases were confirmed as GZL on consensus review (14M/12F, median age 38 years, range 19-69). 11/26 biopsies were mediastinal in origin, and in an additional 4 cases, a mediastinal mass was present clinically; 11 had only peripheral lymphadenopathy (ie, non-mediastinal). 42 cases were reclassified as follows: NS cHL, n=27 (n=10 of which were cHL-NS2); DLBCL NOS, n=4; nodular lymphocyte predominant HL (NLPHL), n=3; EBV positive LBCL, n=3; PMBCL, n=2; lymphocyte-rich cHL, n=1; and B-cell lymphoproliferative disorder, n=1. Most cases of cHL diagnosed as GZL had strong CD20 expression. Furthermore, cHL-NS2 was frequently misdiagnosed as GZL typically due to confluent growth of lacu-

nar cells (Figure 1). *Conclusions.* Diagnosis of GZL remains a challenge. Rarity of the cases, and overlap with cHL-NS2, contribute to the difficulty. Further biologic and clinical analyses may contribute to improved understanding.

P005

HODGKIN LYMPHOMA IN SWEDEN SINCE 2000: BETTER SURVIVAL ONLY IN ELDERLY WOMEN - A SWEDISH LYMPHOMA REGISTRY STUDY

B.E. Wahlin[1], N. Övergaard[2], S. Peterson[3], E. Digkas[4], I. Glimelius[2], I. Lagerlöf[5], A.-S. Johansson[6], M. Palma[1], L. Hansson[1], J. Linderoth[7], C. Goldkuhl[8], D. Molin[2]

[1]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [2]Experimental and Clinical Oncology, Department of Immunology, Genetics and Pathology; Uppsala University, Uppsala, Sweden; [3]Regional Cancer Center South, Lund, Sweden; [4]Department of Oncology, Mälarsjukhuset Eskilstuna; [5]Department of Haematology, University Hospital of Linköping, Sweden; [6]Department of Oncology, Umeå University, Sweden; [7]Department of Oncology, Lund University, Lund, Sweden; [8]Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden

Two major areas of dispute in Hodgkin lymphoma are treatment of advanced stages and of elderly patients. For advanced stages the debate is whether BEACOPPesc/14 or ABVD is to be considered standard. ABVD is standard in many countries, especially for those with IPS 0-2. There is no golden standard for therapy in elderly patients. In Sweden CHOP has been the standard treatment in patients >70 years during the study period. Outcome is also inferior in elderly compared with younger patients. We have analysed data from all 2345 Hodgkin lymphoma patients (1257 men and 1088 women, median age 42, range 16-99) diagnosed from 2000 through 2014 in the Swedish Lymphoma Registry. Median follow-up was 6.7 years. Overall survival (OS) at 3 and 5 years were 83% and 79%, without any differences between calendar periods (2000-2004, 2005-2009, and 2010-2014). In the most recent calendar period (2010-2014), longer survival was observed among patients ≥61 years (P=0.027), but not among those <61 (P=0.49). This improvement was restricted to women with advanced stage disease (P=0.005). Stage IV disease was more common in the most recent calendar period (2010-2014) compared to the first (2000-2004), both in women (22% *vs* 15%, P=0.003) and in men (28% *vs* 21%; P=0.006), likely explained by the increasing use of PET-CT. In multivariate analysis, adjusted for all factors significant in univariate analysis, of patients ≥61 years, CHOP (compared with ABVD) was an independent adverse factor for OS (HR 1.7; 95% CI, 1.1-2.7; P=0.027). Patients <61 with advanced stages treated with BEACOPPesc/14 and ABVD showed identical OS in univariate and multivariate analysis (P=0.51). In conclusion, outcome was not improved over time except in elderly women. The implementation of FDG-PET/CT has resulted in a stage migration with an increased proportion of patients with stage IV disease. ABVD seems superior to CHOP for elderly who tolerate this regimen. BEACOPP and ABVD show equal OS in younger patients with advanced stage disease, supporting the use of PET/CT-adapted ABVD as initial therapy.

P006

ADVANCED HODGKIN LYMPHOMA IN THE EAST OF ENGLAND CANCER NETWORK: A 10 YEAR COMPARATIVE ANALYSIS OF OUTCOMES FOR ABVD AND ESCALATED BEACOPP TREATED PATIENTS AGED 16-59

A. Collins[1], A. Fowler[2], M. Karanth[3], C. Saha[4], J. Russel[5], V. Shyamsundar[1], S. Docherty[6], K. Maw[7], J. Padayatty[4], A. Hodson[5], J. Wimperis[6], S. Sadullah[7], N. Grigoropoulos[1], B. Uttenthal[1], G. Follows[1]

[1]Cambridge University Hospitals, Cambridge, UK; [2]Peterborough Hospital, Peterborough, UK; [3]West Suffolk Hospital, UK; [4]Kings Lynn Hospital, Kings Lynn, UK; [5]Ipswich Hosptial, Ipswich, UK; [6]Norfolk and Norwich University Hospital, Norwich, UK; [7]James Paget University Hospital, Norfolk, UK

The majority of young patients presenting with advanced stage Hodgkin lymphoma (HL) in the UK are managed with ABVD. However, following the 2009 HD9 trial publication, escalated BEACOPP (escB) was introduced as a treatment option in certain UK cancer centres. Here we present the data from advanced stage HL patients aged 16 to 59, who presented between 2004 and 2014 in the East of England Anglia Cancer Network with a referral population of 2.64 million. 250 cases were diagnosed, giving an incidence of 0.95 cases per 100,000 which is in-line with expected incidence of advanced HL in this age group. Six of the eight Anglia cancer centres introduced escalated BEACOPP for patents as determined by physician and patient choice. Over this 10 year period, 44 patients were managed with escB, 202 with ABVD, 3 with an alternative regimen and 1 patient died pre-treatment. The 5 year progression free survival (PFS) for all patients was 82% and 5 year overall survival (OS) was 92%. There was a clinician / patient preference for escB for worse prognosis patients as escB patients had a higher international prognostic score (IPS) than patients treated with ABVD (IPS3+: escB 75% *vs* ABVD 38%, p<0.0001). For the whole cohort, PFS was better for patients treated with escB compared with ABVD (5 year PFS 95% *vs* 80%; HR 4.3 (95%CI:1.97-9.7), p=0.0261)), but there was no OS difference (5 year OS 97% *vs* 92%; HR 2.6 (95%CI:0.69-10.4), p=0.312). However, patients with IPS 3+ had both a PFS and OS advantage when treated with escB compared with ABVD (5 year PFS 96% *vs* 74%; HR 9.24 (95%CI:3.43-24.89), p=0.012: 5 year OS 100% *vs* 84%; p=0.0325). The use of consolidation radiotherapy(RT) was equal between regimens with 11% of patients receiving RT with both escB and ABVD. 29 ABVD-treated and 3 escB-treated patients had at least one subsequent transplant procedure (including 6 allografts post ABVD and 3 allografts post escB, including one allograft for tAML/MDS). Of the 20 pre-menopausal women treated with escB, 11 of 14 aged <30 regained menstrual periods (5 pregnancies) but only 1 of 6 aged >30 regained menstrual periods which were not sustained beyond 3 years. Our data reflect clinical trials results which indicate a first remission PFS but not OS advantage for unselected young advanced stage HL patients treated with escB compared with ABVD. However, our data strongly suggest that patients with a poor IPS score derive a PFS and OS benefit from treatment with escB compared with ABVD.

P007

SUPERIORITY OF MODIFIED PROGRESSION FREE SURVIVAL TO EVALUATE CHEMOTHERAPY EFFECTIVENESS FOR ADVANCED STAGE HODGKIN LYMPHOMA

J.M. Connors, A.S. Gerrie, D.W. Scott, L.H. Sehn, D. Villa, K.J. Savage

From the BC Cancer Agency Centre for Lymphoid Cancer, Vancouver, British Columbia, Canada

Background. Assessment of the effectiveness of chemotherapy for advanced stage Hodgkin lymphoma may be obscured by the incorporation of radiotherapy in primary treatment when standard endpoints such as progression free survival (PFS) are used. Ineffective chemotherapy may be "rescued" by the addition of radiotherapy residual PET-positive masses. Use of a modified PFS endpoint (mPFS), in which addition of radiotherapy after the conclusion of chemotherapy is scored as an event, more accurately assesses chemotherapy effectiveness. *Methods.* We examined the records of 207 consecutive adult patients (age 16-82 y, median 36; males 55%) with advanced stage HL (IIIA, 23%; IIIB, 24%; IVA, 17%; IVB, 36%) treated between 2004 and 2015 with ABVD with or without involved field radiotherapy (IFRT). Standard PFS events were the first of relapse or progression (REL/PROG) despite primary treatment (ABVD +/- IFRT) or death from any cause; mPFS events were the first of radiotherapy given after ABVD if the post-ABVD PET was positive (PET-RT), relapse or progression after primary treatment (REL/PROG) or death from any cause. *Results.* We observed 56 PFS events (REL/PROG, 54; death 2) and 64 mPFS events (PET-RT, 17; REL/PROG 45; death 2). Thus, 8/64 (13%) of the relevant events (failure of the primary chemotherapy to cure the lymphoma) were unappreciated using the standard PFS endpoint. This resulted in an overestimate of the effectiveness of primary chemotherapy (2-y PFS 78%; 2-y mPFS 72%) and of the duration of survival free of death,

relapse or progression (time to 25% treatment failures using standard PFS=2.8 y; using mPFS=1.1 y) (Figure 1). These overestimates occur because the addition of radiotherapy to the primary chemotherapy "rescues" patients whose primary chemotherapy has failed (PET positive residual disease still present after completion of the primary chemotherapy) and creates the appearance of successful treatment. *Conclusions.* Use of the mPFS endpoint provides a superior assessment compared to standard PFS if the goal of a clinical trial testing treatment for advanced stage Hodgkin lymphoma is to identify the most effective chemotherapy regimen. This is particularly important in an era when post-chemotherapy evaluation with PET has become standard and major efforts are being made to determine the potential benefit of adding novel agents such as antibody-drug conjugates and checkpoint inhibitors to standard chemotherapy.

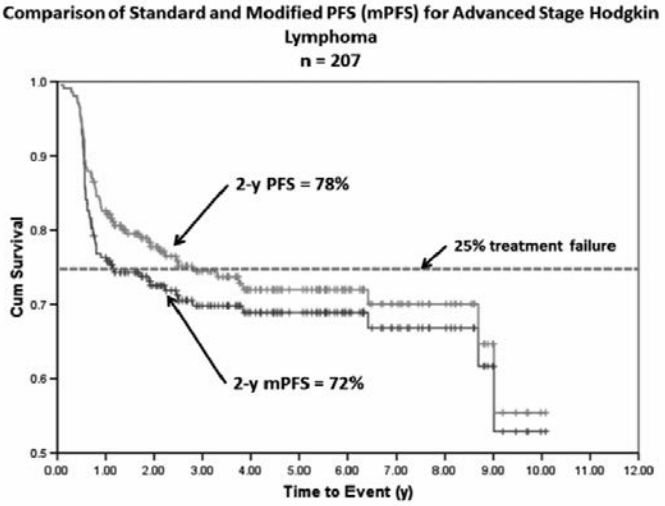


Figure 1.

P008

TREATMENT RESULTS FOR HODGKIN LYMPHOMA IN BRAZIL: FIRST REPORT FROM THE BRAZILIAN PROSPECTIVE HODGKIN'S LYMPHOMA REGISTRY

I. Biasoli[1], N. Castro[2], M. Delamain[3], T. Silveira[4], J. Farley[5], B. Pinto Simões[6], C. Solza[7], M. Praxedes[8], O. Baiocchi[9], R. Gaiolla[10], F. Franceschi[11], C. Bonamin[12], C. Boquimpani[13], N. Clementino[14], G. Perini[15], K. Pagnano[3], G. Steffenello[16], J. Tabacof[17], G. de Freitas Colli[2], A. Soares[7], C. de Souza[3], C.S. Chiattone[4], C. Milito[1], J.C. Morais[1], N. Spector[1]

[1]School of Medicine, Universidade Federal do Rio de Janeiro, Brasil; [2]Hospital de Cancer de Barretos, Brasil; [3]Hematology and Hemotherapy Center, University of Campinas, Brasil; [4]São Paulo Santa Casa Medical School, Brasil; [5]Liga Norte Rio Grandense Contra o Cancer, Brasil; [6]USP-Ribeirão Preto, Brasil; [7]Universidade do Estado do Rio de Janeiro, Barsil; [8]Universidade Federal Fluminense, Brasil; [9]Federal University of São Paulo, Brasil; [10]Universidade Estadual Paulista, Brasil; [11]Fundação Amaral Carvalho, Jaú, Brasil; [12]Universidade Federal do Paraná, Brasil; [13]HEMORIO, Rio de Janeiro, Brasil; [14]Universidade Federal de Minas Gerais, Brasil; [15]Hospital Albert Einstein, São Paulo, Brasil; [16]Universidade Federal de Santa Catarina, Brasil; [17]ESHO - Centro Paulistano de Oncologia, Brasil

Introduction. Data about Hodgkin Lymphoma (HL) in developing countries are scarce. In 2009, a prospective registry of HL was implemented in Brazil. *Methods.* Twenty institutions take part in the registry. Clinical, treatment and outcome data were prospectively collected in a web-based platform, and are reported here for the first time. *Results.* 756 HL patients (pts) with diagnosis until December 31, 2014 were identified. Twenty-one pts with nodular-predominant HL, 11 pts younger than 13 years-old and 38 pts with HIV were excluded, with 686 pts available for this analysis. Median age was 30 years-old (13-90); 67 (10%) pts were older than 60. Females comprised 346 pts (50%). Median time from onset of symptoms to diagnosis was 6 (0-60) months. Forty-four (7%) pts had limited disease, 180 (26%) had intermediate disease and 445 (65%) had advanced disease by GHSG criteria. Stage IVB was present in 26%, B symptoms in 69%, low albumin in 63% and a high-risk IPS score in 38%. Median time from diagnosis to beginning of treatment was 0.72 months (0-10.87 months). Median follow-up was 37 months (0.53-94) for all patients, and 40 months (4-94) for patients alive. ABVD was the first-line treatment in 93% of pts. Twenty-one patients died during treatment. After completed treatment, the complete remission (CR) rate was 73%, unconfirmed CR was 12%, partial remission was 4%, stable disease was 2% and progressive disease was 9%. Among those who received ABVD, the median number of cycles was 4 for limited and intermediate and 6 for advanced disease. Radiotherapy (RT) was used in 33% of advanced disease pts, 65% of intermediate disease pts, and 77% of limited disease pts. The median dose of RT was 36 Gy for localized disease, and 32 Gy for advanced disease. The median time from the end of chemotherapy to the beginning of RT was 1.7 months. The 3-year OS and 3-year PFS were 90% and 74%, respectively. The 3-y PFS in limited disease, intermediate disease and advanced disease were 95%, 88% and 66% ($p<0.0001$), respectively. The 3-year OS for limited disease, intermediate disease and advanced disease were 100%, 96% and 86% ($p=0.0001$), respectively. *Conclusions.* Advanced stage and poor risk patients predominated. Radiation doses used for localized disease appear higher than current recommendations. Outcomes for advanced disease appear to be 5-10% lower than in developed countries, in part due to very advanced disease at diagnosis, and to an excess of deaths during treatment.

P009

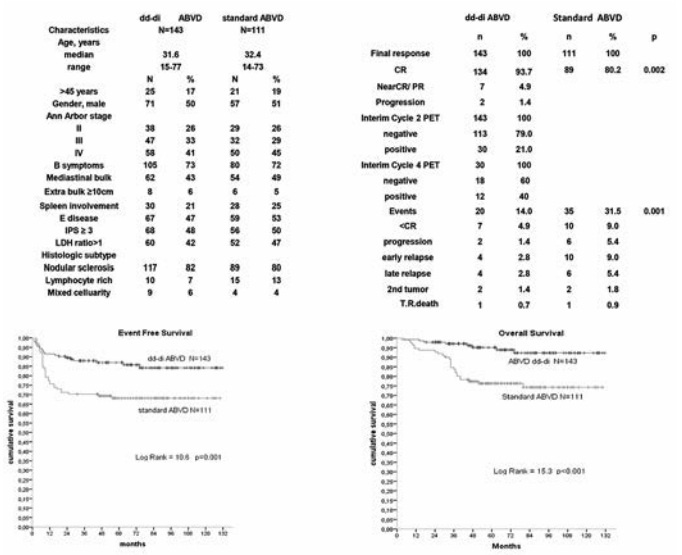
DOSE-DENSE/DOSE-INTENSE ABVD IN ADVANCED-STAGE HODGKIN'S LYMPHOMA: A LONG-TERM FOLLOW UP STUDY

F. Russo[1], L. Aloj[2], G. Svanera[3], P. Fimiani[4], S. Lastoria[2]

[1]V.A.L.E. Lymphoma Study Group, Naples, Italy; [2]Nuclear Medicine Unit, National Cancer Institute of Naples, Naples, Italy; [3]Onco-Hematology Unit Ospedale San Giuliano, Giugliano in Campania (NA), Italy; [4]Oncology Unit Clinica Stabia, Castellammare di Stabia (NA), Italy

One-hundred forty-three patients with advanced-stage HL were treated with a dose-dense three-weekly version of the ABVD regimen, which was also dose intensified, in the first 4 cycles, by escalating doxorubicin. Specifications are contained in the published article (Russo F BHJ 166,1,118, 2014). Twelve patients (8.4%) received radiotherapy (RT) on residual mediastinal or extramediastinal bulk disease. Results were compared with a historical series of 111 patients treated with standard ABVD+/-RT. The demographics and clinical characteristics are in Figure 1. Ninety-six percent of patients completed the planned 6 cycles (median time=16.8 weeks). Median actual dose intensities were 20.87 (23.11 cycles 1-4), 6.72, 3.89 and 248 mg/m^2/week for doxorubicin, bleomycin, vinblastine and dacarbazine, respectively. This corresponded to a 66.9% (85.0%, cycles 1-4) increase in dose intensity for doxorubicin, (total dose 380 mg/m^2) and of 32% for the other agents, over standard ABVD. Intensified ABVD confirmed to be highly tolerated with low rates of hospitalization during treatment, a low incidence of G3/ G4 events, low post-treatment cardiac and pulmonary toxicities and a very low rate of gonadic toxicity. Only two cases of second cancer were recorded. One-hundred-eleven out of 143 (79%) showed a PET normalization at the end of 2nd cycle. Comparison between intensified and standard ABVD showed complete remission (CR) rates 93.7% in intensified ABVD and 80.2% in standard ABVD, respectively ($p=0.002$). EFS and OS rates at 7 years were 85.7% *vs* 68.1% and 93.9% *vs* 76.3%. At univariate analysis the predictive factors of low CR rate were IPS≥3 ($p=0.032$), and PET2pos ($p<0.001$). At multivariate analysis PET2pos ($p<0.001$) was the only independent risk factor predictive of low CR rate. Seven-yr EFS was significantly better in patients with PET2neg (log rank 13.2, $p<0.001$) and in patients with IPS 0-2 (log rank 4.3, $p=0.032$). At Cox regression analysis PET2 was the only independent factor predictive of EFS. As on

09/2015, one-hundred-thirty-five out of 143 are alive with 131 free of disease (123 in 1stCR,8 in 2ndCR). Intensified ABVD seems to be adequately powered to exploit early disease chemo-sensitivity yielding high percentage of PET2neg, high rate of response and survival, without new severe or critical short and long-term toxicities. Selective use of low dose RT in residual PET+ tissue seems to rescue a subset of patients with bulky disease and suboptimal response.



Characteristics	dd-di ABVD N=143		standard ABVD N=111	
Age, years				
median	31.6		32.4	
range	15-77		14-73	
	N	%	N	%
>45 years	25	17	21	19
Gender, male	71	50	57	51
Ann Arbor stage				
II	38	26	29	26
III	47	33	32	29
IV	58	41	50	45
B symptoms	105	73	80	72
Mediastinal bulk	62	43	54	49
Extra bulk ≥10cm	8	6	6	5
Spleen involvement	30	21	28	25
E disease	67	47	59	53
IPS ≥ 3	68	48	56	50
LDH ratio>1	60	42	52	47
Histologic subtype				
Nodular sclerosis	117	82	89	80
Lymphocyte rich	10	7	15	13
Mixed celluarity	9	6	4	4

	dd-di ABVD		Standard ABVD		
	n	%	n	%	p
Final response	143	100	111	100	
CR	134	93.7	89	80.2	0.002
NearCR/ PR	7	4.9			
Progression	2	1.4			
Interim Cycle 2 PET	143	100			
negative	113	79.0			
positive	30	21.0			
Interim Cycle 4 PET	30	100			
negative	18	60			
positive	12	40			
Events	20	14.0	35	31.5	0.001
<CR	7	4.9	10	9.0	
progression	2	1.4	6	5.4	
early relapse	4	2.8	10	9.0	
late relapse	4	2.8	6	5.4	
2nd tumor	2	1.4	2	1.8	
T.R.death	1	0.7	1	0.9	

Figure 1.

were in the AU group. 30 started treatment with eBEACOPP and 4 with ABVD, one switched to eBEACOPP because of interim PET positivity; 10 received additional RT. One patient died during treatment, presumably due to pulmonary embolism; one relapsed. EFS at three years was 94% and OS 97%. The difference in EFS between EU and AF is statistically significant (p=0.023) (Figure 1). If eBEACOPP is used for front-line treatment only in patients with high-risk advanced stage disease, this results in paradoxical inversion of EFS between prognostic groups. eBEACOPP should be considered for all newly diagnosed HL patients younger than 60, except those in the lowest risk group.

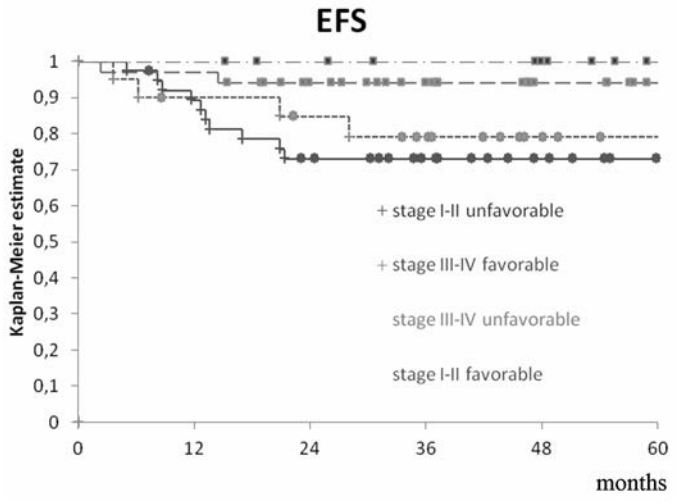


Figure 1.

P010

THE SWITCH FROM ABVD TO eBEACOPP AS FRONT-LINE THERAPY FOR HIGH-RISK STAGE III-IV CLASSICAL HODGKIN LYMPHOMA PATIENTS RESULTS IN AN INVERSION OF EVENT-FREE SURVIVAL OF PROGNOSTIC GROUPS

I. Aurer, S. Basic-Kinda, D. Dujmovic, I. Radman, B. Dreta, S. Dotlic, L. Galunic-Bilic, M. Dobrenic, M. Kralik, P. Roncevic

University Hospital Centre Zagreb and Medical School, University of Zagreb, Croatia

When ABVD is used as the chemotherapy backbone for newly diagnosed cHL, patients with favorable stage I-II (EF), unfavorable stage I-II (EU), favorable stage III-IV (Hasenclever index 0-2) (AF) and unfavorable stage III-IV (Hasenclever index ≥3) (AU) differ in EFS with the latter having the worst prognosis. GHLSG has reported that the introduction of eBEACOPP-based chemotherapy for EU and advanced stage groups annuls this difference. To our knowledge, no other group has reproduced these findings.

Since 2010, after the end of accrual into the EORTC 20012 trial, we recommend eBEACOPP as front-line therapy for AU. During 2014/5 this recommendation was extended to AF and EU patients. Here we analyze the outcome of different prognostic groups of newly diagnosed cHL patients below 60 years of age treated at our institution during the period of almost 5 years when eBEACOPP was used as initial treatment only for AU patients. There were 13 patients in the EF group, one was treated with ABVD only, one with radiotherapy (RT) only, and 11 with the combination of ABVD and RT. None relapsed or died. 38 patients were in the EU group. All started ABVD, two switched to eBEACOPP because of interim PET positivity; 33 received RT and five chemotherapy only. Two progressed immediately after RT, additional 8 relapsed, 2 died. EFS at three years was 72% and OS 97%. 20 patients were in the AF group. All received ABVD, three switched to eBEACOPP because of interim PET positivity; four received additional RT. Two patients died, one due to sepsis after switching to eBEACOPP and one, treated with ABVD, due to bleomycin-related pneumonitis; additional two relapsed. EFS at three years was 79% and OS 90%. 34 patients

P011

HALO STUDY: A PHASE 1/2 CLINICAL TRIAL OF BRENTUXIMAB-VEDOTIN AND BENDAMUSTIN IN ELDERLY PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED HODGKIN LYMPHOMA. PRELIMINARY DATA

S. Viviani[1], B. Fontanet[2], A. Rambaldi[3], A. Perrot[4], C. Patti[5], L. Gastaud[6], R. Sorasio[7], C. Debaigt[6], E. Chamorey[6], A. Gallamini[6], A. Thyss[6]

[1]Istituto Nazionale dei Tumori, Milano, Italy; [2]Institut Bergonié, Bordeaux, France; [3]Ospedale Papa Giovanni XXII, Bergamo, Italy; [4]CHU Nancy-Brabois, Vandoeuvre-lès-Nancy, France; [5]Ospedale Riuniti Villa Sofia e Cervello, Palermo, Italy; [6]Centre Antoine-Lacassagne, Nice, France [7]Ospedale Santa Croce, Cuneo, Italy

Treatment of elderly patients with HL remains a difficult challenge as results and tolerance of the standard treatment with ABVD remains very inferior to adults. Bendamustine (Be), andwith Brentuximab Vedotin (BV), are active drugs, which have demonstrated a good tolerance and an high level of response in relapsing/refractory HL. To assess the safety and the efficacy of the combination of this two drugs in elderly HL, we conduct a prospective multicentric open-label stydy of Brentuximab-Vedotin (BV): 1.2 mg/kg D1 and Bendamustin (Be) 90 mg/m^2/day, D1 and D2, every 3 weeks up to 6 cycles, for patients from 60 to 80 years of age, with advanced HL, stage 2B to 4,. Ten centers, 5 from Italy and 5 from France, participate to the study. A total of 60 patients are planned to be included. An evaluation by TEP-Scan will be performed after the 2nd cycle and treatment will be pursued until the 6th cycles for patients in CR according to Lugarno's criteria. A supplementary control by TEP-scan is planned after the 4th cycle for patients in PR after 2 cycles. . Patients with progressive disease at any time or not in CR after 4 cycles will receive salvage therapy according the choice of the local investigator. A final evaluation by PET-Scan is planned for all patients after the 6th cycle. A centralized review of all TEP-Scan is planned. . The patients will be followed up for 3 years. The study is divided in 2 phases: the phase 1 with 12 patients with the main objective to evaluate the tolerability and toxicity of Be-BV and

the phase 2 with 48 patients, with the primary objective to evaluate the efficacy in terms of response rate after treatment completion. The secondary objectives of the phase 2 are to evaluate the efficacy in terms of PFS, EFS and OS at 3 years, to evaluate the efficacy in terms of complete response rate after two cycles of Be-BV and to evaluate the feasibility of the treatment. Currently, we have enrolled 14 patients: 9 patients have performed the first TEP-Scan evaluation after 2 cycles: 7 were in complete response and 2 in partial responses according to local evaluation. The 2 patients in PR after 2 cycles were in CR at the evaluation by PET-Scan after 4 cycles. None unexpected toxicity has been observed and the trial remains open to inclusions. The precise design of the study and updated results will be presented for the symposium.

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P012

TRANSFORMATION OF NODULAR HODGKIN'S LYMPHOMA WITH LYMPHOCYTE PREDOMINANCE TO T-CELL-RICH LARGE B-CELL LYMPHOMA

T. Moiseeva, L.S. Al-Radi, E.I. Dorokhina, S.R. Goryacheva, O.V. Margolin, A.U. Magomedova, H.L. Julhakyan, S. Kravchenko

National Reserch Center for Hematology, Moscow, Russian Federation

Aim. To describe clinical features of transformation of nodular Hodgkin's lymphoma (HL) with lymphoid predominance (NLHLP) to T-cell-rich large B-cell lymphoma (TCRLBCL), to evaluate the effectiveness of therapy program BEACOPP-14 in this group of patients. *Materials and Methods.* During the period from 2010 to 2016 the transformation NLHLP to TCRLBCL was diagnosed in 15 patients. Male to female ratio 4: 1, median age 40 (23-68) years. NLHLP diagnosis was based on histological and immunohistochemical study of the biopsy of the tumor, the stage of disease - by standard for LH methods. *Results.* Of the 46 patients with NLPLH observed in National Reserch Center for Hematology, transformation NLHLP to TCRLBCL was diagnosed in 15 (33%) patients (13 untreated patients with a long history of lymphadenopathy, and 2 patients with relapsed Hodgkin's lymphoma after 3 years and 21 years). All patients had advanced stages of disease. All untreated patients had previous long-term asymptomatic lymphadenopathy. B - symptoms were noted in 11 (73%) cases. Extranodal involvement had 12 (80%) patients: liver damage - in 7 (47%), lung involves - in 5 (33%), spleen involves - in 10 (67%), bone marrow lesions was found in 9 (60%) patients and was proved by histological and immunohistochemical study. Follow-up of the 15 patients: 1 patient with transformation to TCRLBCL in relapse (in 21year after the end of LH treatment) was not treated (refusal of treatment, death), 1 patient received ABVD and achieved complete remission, the remaining 13 patients received BEACOPP-14, complete remission was achieved in 11 (85%), partial remission - in 2 (15%) patients. In one young patient with transformation NLHLP to TCRLBCL with aggressive clinical presentation of disease complete remission was consolidated by high-dose chemotherapy followed by autologous peripheral blood stem cells transplantation. *Conclusions.* The clinical features of transformation NLHLP to TCRLBCL are advanced stages of disease with presence of B-symptoms, frequent involvement of extranodal sites and bone marrow. Therapy by BEACOPP-14 program can lead to complete remission in 85% of patients.

P013

ABVD AS THE TREATMENT OPTION IN HODGKIN LYMPHOMA WITH LARGE MEDIASTINAL TUMOR

B. Andjelic[1,2], L.J. Jakovic[1], D. Antic[1,2], M. Todorovic[1,2], J. Bila[1,2], V. Djurasinovic[1], A. Sretenovic[1], V. Vukovic[1], J. Jelicic[1], M. Smiljanic[1], B. Mihaljevic[1,2]

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

Background. Large mediastinal tumor is considered as an unfavorable prognostic factor for Hodgkin's lymphoma (HL). Patients with advanced Ann Arbor clinical stages (CS III and IV) are considered as advanced disease. Nevertheless, some study groups are also stratifying patients with large mediastinal tumor as advanced disease. *Aim.* The aim of this study was to assess the outcome of ABVD treated HL patients with large mediastinal tumor, as well to identify risk factors for poor outcome. *Patients and Methods.* A study was performed on 173 HL patients with large mediastinal tumor (more than one-third of the maximum horizontal chest diameter on CXR) diagnosed between 1997 and 2011. The standard initial treatment was 6-8 cycles of ABVD +/- radiotherapy. Beside the patients with advanced CS, this study also included patients wirh CS II who were according to institutional guidelines treated the same as patients with advanced CS. *Results.* The median age was 29 (range 16-68). The median follow up was 94 months. Five-year event free survival (EFS) was 62% and 5-year overall survival (OS) was 76%. In univariate analysis, there was no difference in survival based on CS, both in OS (log rank; p=0.180) and EFS (log rank; p=0.126). Worse OS was found only in patients with IPS≥3 (5-year OS 62.5% *vs* 82.1%; log rank, p=0.011), while presence of age>45, male gender, ESR≥50 mm/h, B symptoms or EN disease didn't influence OS (log rank; p=0.499, p=0.145, p=0.631, p=0.111, p=0.900, respectively). Worse EFS was found in patients with IPS≥3 (5-year EFS 51.8% *vs* 67.6%) and males (5-year EFS 54.8% *vs* 66.7%) (log rank; p=0.037, p=0.016, respectively), while presence of age>45, ESR≥50 mm/h, B symptoms or EN disease didn't influence EFS (log rank; p=0.960, p=0.885, p=0.295, p=0.887, respectively). The multivariate Cox regression analysis identified IPS≥3 as the independent prognostic factor for OS (p=0.023; RR=1.982; 95% CI 1.100-3.570) and male gender for EFS (p=0.011; RR=1.852; 95% CI 1.153-2.974). *Conclusions.* The initial approach in patients with CS II and large mediastinal tumor shouldn't be different from advanced clinical stages. More effective approach seems to be required, especially in males and patients with high IPS.

P014

PERIPHERAL BLOOD EOSINOPHILIA IS A GOOD RISK FACTOR IN POOR PROGNOSIS GROUP: ADVANCED HODGKIN LYMPHOMA WITH LOW ALC/AMC

L.R. Jakovic[1,2], B. Mihaljevic[1,2], B. Andjelic[1,2,] A.D. Bogdanovic[1,2], M.D. Perunicic Jovanovic[3], V.Z. Bumbasirevic[4]

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

We studied the prognostic significance of the absolute neutrophil/lymphocyte ratio (ANC/ALC), the absolute lymphocyte/monocyte ratio (ALC/AMC), absolute eosinophil count (AEoC) and their contribution to prognostic value of the International Prognostic Score (IPS) in 361 advanced Hodgkin lymphoma (HL) patients. The receiver operating characteristic curve identified the best cut-off values as 4.3 for ANC/ALC and 2.0 for ALC/AMC. Univariate analysis showed that all analyzed factors were associated with lower OS: ANC/ALC>4.3 (OS5yrs with/without risk factor 72% *vs* 85%, respectively, p<0.01); ALC/AMC<2 (OS5yrs with/without risk factor 64% *vs* 86%, respectively, p<0.01); AEoC<0.5x10e6/L (OS5yrs with/without risk factor 76% *vs* 88%, respectively, p<0.01); IPS >2 (OS5yrs with/without risk factor 66% *vs* 86%, respectively, p<0.01). Apart from AEoC, these factors also had a significant impact on EFS - ANC/ALC>4.3 (EFS5yrs with/without risk factor 55% *vs* 72%, respectively, p<0.01); ALC/AMC <2 (EFS5yrs with/without risk factor 46% *vs* 73%, respectively, p<0.01); IPS >2 (EFS5yrs with/without risk factor 51% *vs* 71%, respectively, p<0.01). Overall survival multivariate analysis identified ALC/AMC<2, IPS>2 and AEoC<0.5x10e6/L as prognostic factors for poor OS (p<0.01; p<0.01; p<0.01 respectively). In a respective model for EFS, ALC/AMC<2 and IPS>2 were also significant (p<0.01; p<0.05, respectively). After evaluating ALC/AMC and IPS, we stratified patients into 3 progressively-worse-outcome groups (low-risk: 0; intermediate: 1 risk factor; high: 2

risk factors) both for OS (91%; 74%; 56%, p<0.01) and EFS (77%; 58%; 41%, p<0.01). Furthermore, we observed that patients with eosinophilia, AEoC>0.5x10e6/L had significantly better OS in group with ALC/AMC<2 (82% *vs* 58%, p<0.01), as well as in low IPS group (97% *vs* 84%, p<0.05), but not in group with high IPS (75% *vs* 64%, p>0.05). Our study encourages the combination of ALC/AMC with IPS, thus providing an improved risk prediction in advanced HL patients. Moreover, present peripheral blood eosinophilia separates patients with better prognosis in poor prognostic group.

P015

LOWER SOCIOECONOMIC STATUS IS ASSOCIATED WITH SHORTER SURVIVAL IN HL PATIENTS - AN ANALYSIS FROM THE BRAZILIAN HODGKIN LYMPHOMA REGISTRY

I. Biasoli[1], N. Castro[2], M. Delamain[3], T. Silveira[4], J. Farley[5], B. Pinto Simões[6], C. Solza[7], M. Praxedes[8], O. Baiocchi[9], R. Gaiolla[10], F. Franceschi[11], C. Bonamin[12], C. Boquimpani[13], N. Clementino[14], G. Perini[15], K. Pagnano[3], G. Steffenello[16], J. Tabacof[17], G. de Freitas Colli[2], A. Soares[7], C. de Souza[3], C.S. Chiattone[4], R. Raggio[18], C. Milito[1], J.C. Morais[1], N. Spector[1]

[1]School of Medicine, Universidade Federal do Rio de Janeiro, Brasil; [2]Hospital de Cancer de Barretos, Brasil; [3]Hematology and Hemotherapy Center, University of Campinas, Brasil; [4]São Paulo Santa Casa Medical School, Brasil; [5]Liga Norte Rio Grandense Contra o Cancer, Brasil; [6]USP-Ribeirão Preto, Brasil; [7]Universidade do Estado do Rio de Janeiro, Barsil; [8]Universidade Federal Fluminense, Brasil; [9]Federal University of São Paulo, Brasil; [10]Universidade Estadual Paulista, Brasil; [11]Fundação Amaral Carvalho, Jaú, Brasil; [12]Universidade Federal do Paraná, Brasil; [13]HEMORIO, Rio de Janeiro, Brasil; [14]Universidade Federal de Minas Gerais, Brasil; [15]Hospital Albert Einstein, São Paulo, Brasil; [16]Universidade Federal de Santa Catarina, Brasil; [17]ESHO - Centro Paulistano de Oncologia, Brasil

Introduction. Socioeconomic status (SES) is a well-known determinant of outcomes in cancer. We have previously reported that Hodgkin's lymphoma (HL) patients (pts) with a lower SES had inferior survival in a different cohort from Rio de Janeiro. *Methods.* SES stratification was done using an asset/education-based household index widely used in publicity and political polls in Brazil. *Results.* 624 classical HL pts with diagnosis until December 31 2014, ≥13 y-old and HIV-, treated with ABVD, were analysed. The median follow-up was 35.6 months for all pts, 67% (390/578) were classified as higher SES and 33% (188/578) as lower SES. The 3-y PFS in higher and lower SES were 78% and 64% (p<0.0001), respectively. The 3-year OS in higher and lower SES were 94% and 82% (p<0.0001), respectively. Lower SES pts were more likely to be ≥60 years (16% *vs* 8%, p=0.003), to have a poor performance status (20% *vs* 10%, p=0.001) and high risk IPS (44% *vs* 31%, p=0.004), to present with advanced disease (71% *vs* 58%, p=0.003) and to have histopathology other than nodular sclerosis (31% *vs* 19%, p=0.002). Also, time to diagnosis >4 months was more frequent in lower SES pts (69% *vs* 53%, p=0.0001). After adjustments for potential confounders (age, PS, advanced disease, IPS, histopathology and time to diagnosis), lower SES remained associated with poorer survival (HR=3.15 [1.8-5.2] for OS and HR=1.67 [1.2-2.31] for PFS). Twenty-one patients died during treatment, accounting for a death rate of 7.5% and 1.3% for lower and higher SES (p=0.0001). Infections and treatment toxicity accounted for 81% of deaths during treatment. No differences were found according to the distance and travel time from residence to hospital, or to availability of someone to transport pts to hospital in an emergency. Independent factors associated with death during treatment were: age ≥60 year, poor PS, advanced disease, lower SES and low educational level. Deaths after the conclusion of treatment occurred in 48 patients, mostly due to progressive disease. However, follow-up is still short for analysis of long-term outcomes. *Conclusions.* SES is an independent factor associated with shorter survival in Brazil. Along with age, advanced disease, and poor PS, SES and educational level allow the identification of vulnerable patients who might benefit from a program of intensive medical and social supervision, or from management modifications to reduce serious infections and drug toxicity during treatment.

P016

THE IMPACT OF OUTCOME OF INTERIM PET/CT ON ADVANCED HODGKIN LYMPHOMA TREATED WITH EACOPP-14

E. Medvedovskaya[1], A. Leontjeva[1], E. Demina[1], J. Ryabukhina[1], G. Tumyan[1], N. Kokosadze[1], O. Trofimova[1], V. Larionova[1], M. Dolgushin[1], A. Odzharova[1], O. Mukhortova[2], I. Aslanidis[2], D. Osmanov[1]

[1]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [2]A.N. Bakoulev Scientific Center for Cardiovascular Surgery, Moscow, Russia

Introduction. To assess the role of interim positron emission tomography/computed tomography (PET/CT) and compare its with PET\CT results after the end of treatment the patients (pts) with advanced stages classical Hodgkin lymphoma (cHL). *Methods.* 114 newly diagnosed cHL pts received 6 cycles EACOPP every 14 days (doxorubicin 50 mg\m^2, cyclophosphamide, etoposide, procarbazine, vincristine, prednisone). Consolidation radiotherapy was given to 78 (68%) pts. Interim PET/CT (iPET) imaging after 2 cycles was done in 54 (48%) pts. *Results.* With a median follow-up 35 months, 3-year progression-free survival (3-PFS) were 85%, overall survival - 92%. In 33 pts (61%) the iPET was negative - Deauville score 1-2 (DS 1-2). The residual uptake was higher than the mediastinal blood pool (MBP) uptake but below the liver uptake (DS 3) in 17 pts (31%) and 4 pts (8%) were PET-positive (DS 4-5). omplete metabolic response (CMR) after 2 cycles predicted higher 3-PFS compared PETpos (100% *vs* 75%; p=0,0035 - Figure 1).

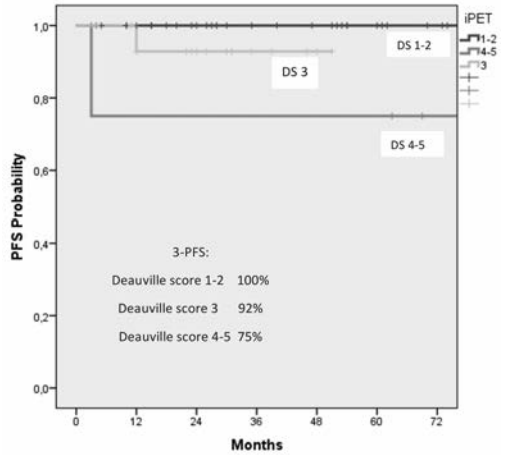

Figure 1. 3-PFS in patients with advanced stage cHL according results of iPET.

Patients with residual metabolic activity had equally good outcomes (100% *vs* 92%; p=0,1). Of the 60 pts who not done iPET, 24 (40%) were performed PET\CT after the end of 6 EACOPP-14. There is not difference of outcome between 19 pts with CMR after the end of chemotherapy and 36 pts with CR\uCR according chest\abdominal\pelvic CT with contrast of diagnostic quality (3-PFS 78% *vs* 91%; p<0,1). *Conclusions.* The intensive EACOPP-14 program showed good and early response for pts with advanced stage cHL. Predictive value of metabolic response after 2 cycles was higher than PET-negativity after the end of chemotherapy.

P017

ADVANCED HODGKIN LYMPHOMA - A RISK STRATIFICATION OF ABVD TREATED FEMALES IN GENERATIVE AGE

B. Andjelic[1,2], L.J. Jakovic[1], D. Antic[1,2], M. Todorovic[1,2], J. Bila[1,2], V. Djurasinovic[1], A. Sretenovic[1], V. Vukovic[1], J. Jelicic[1], M. Smiljanic[1], B. Mihaljevic[1,2]

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

Background. Recent trials demonstrated that treatment results of

BEACOPPesc are likely better than ABVD for advanced Hodgkin Lymphoma (HL). However, BEACOPPesc is associated with more toxic effects, with post treatment infertility as one of the major concerns. *Aim.* The aim of this study was to identify females in generative age with advanced HL who do not require more aggressive approach than ABVD. *Patients and Methods.* This study was performed on 147 females younger than 40 years with advanced HL, diagnosed between 1997 and 2011. The initial treatment was 6-8 cycles of ABVD +/- radiotherapy. Prognostic relevance of IPS, ESR≥50 mm/h, as well presence of B symptoms, bulky disease and extranodal disease (EN) were examined. *Results.* For the whole group 5-year overall survival (OS) was 81% and 5-year event free survival (EFS) was 66%. Based on examined parameters, in univariate analysis worse OS had patients with IPS≥3 (5-year OS 61.1% *vs* 87.3%; log rank, p=0.000) and EN (5-year OS 71.9% *vs* 83.5%; log rank, p=0.036). Worse EFS had patients with IPS≥3 (5-year EFS 41.7% *vs* 73.9%) and EN (5-year EFS 40.6% *vs* 73.0%) (log rank; p=0.000, p=0.000, respectively). The multivariate analysis identified IPS≥3 as the independent prognostic factor both for OS (p=0.002) and EFS (p=0.023), as well as EN for EFS (p=0.027). Subsequently, we analyzed the subgroup of 111 patients with low IPS. Thirty patients without bulky disease (27.0% of low IPS patients, 20.4% of the entire group) had better OS (5-year OS 100% *vs* 82.7%, log rank, p=0.028) and trend toward better EFS (5-year EFS 90% *vs* 67.9%, log rank; p=0.06), with only 2 deaths until the end of follow up. Based on IPS score (0, 1, 2), presence of ESR≥50 mm/h, B symptoms and EN there was no difference both in OS (log rank; p=0.166, p=0.359, p=0.459, p=0.865, respectively) and EFS (log rank; p=0.098, p=0.933, p=0.383, p=0.187, respectively). Moreover, bulky disease in this subgroup retained its prognostic significance in multivariate analysis for OS (p=0.044; RR=4.577; 95% CI 1.042-20.106). *Conclusions.* ABVD is very effective for females with advanced HL younger than 40 years with low IPS and without bulky disease.

P018

ADVANCED STAGE HODGKIN LYMPHOMA IN MOROCCAN ADULTS: CLINICO-PATHOLOGICAL FEATURES AND THERAPEUTIC OUTCOMES

W. Kaddouri, S. Anoun, N. Khoubila, S. Cherkaoui, M. Lamchahab, M. Quachouh, M. Rachid, A. Madani, A. Quessar

Hematology and Oncology Pediatric Unit, 20 August Hospital, Ibn Rochd UH, Hassan II Univerity, Casablanaca, Morocco

Introduction. Advanced stage Hodgkin lymphoma (ASHL) is still a major concern to face in both developed and developing countries. Five-year survival rate ranges between 51% and 94.6% in Western literature. However, few is known about the features of ASHL in developing countries. The purpose of this study is to describe the clinic-pathological features of ASHL in Morocco. *Methods.* Retrospective descriptive study of diagnosed ASHL carried over a period of 6.5 years from January 2007 to August 2013 in a single Moroccan University Hospital, including all patients with ASHL (stage III and IV of Ann Arbor) aged over 18. Patients with retroviral infections and secondary HL were excluded. The diagnosis was based on histological examination of biopsy and immunohistochemistry. Patients were classified according to the classification of Ann Arbor, and stratified according to the score of IPS. *Results.* Four hundred and seventy-eight patients were diagnosed with HL (all stages) during the period study, among them 200 patients ASHL account for 46.3. The age was ranged between 18 and 91 years old (yo) with a median age of 32 yo. Sex ratio H/F was 1.66. Seventy three percent of ASHL patients didn't have medical insurance and 47% were jobless. the median time to diagnosis was 6 months [1-52]. Lymphadenopathy was the most common presentation (61.5%). Eighty three patients (41,5%) were stage III, 117 patients (58,5%) were stage IV. Eighty two percent of the patients reported B symptoms. Nodular sclerosis was the predominant histological presentation of ASHL in adult (60.5%) followed by mixed cellularity (17.5%). Ninety nine percent of lymphoma's biopsies were CD30+, 82.5% were CD15+ and LMP-1 was positive in 33.6%. Bulky disease was present in 37% of the ASHL. IPS score was ranged between 0 and 6 with a median of 3, 42,5% patients had a score less than 2. Survival was rated in patients treated with 8 cycles of ABVD +/- Radiotherapy (150 patients fulfilled the inclusion criteria). Twenty-one percent of patients were treatment failure, 12% relapsed. The death rate was 20.6% of which 45% was by progression disease. The 5-years overall survival and event free survival of ASHL patients were 70,9% and 41,7% respectively. *Conclusions.* This current pattern for epidemiological features and outcomes of ASHL enables delineate key populations in order to explore risk factors for ASHL and strategies to improve treatment outcomes, especially intensification strategies.

P019

GENERAL POPULATION-DERIVED SPECIFIC SURVIVAL APPLIED TO HODGKIN LYMPHOMA

P. Gobbi[1], M. Bellei[2], L. Marcheselli[2], T. Chisesi[3], F. Merli[4], S. Galimberti[5], E. Iannitto[6], S. Luminari[2], M. Manni[2], C. Stelitano[7], P. Musto[8], V. Pavone[9], U. Vitolo[10], M. Federico[2]

[1]Clinica Medica I, Università di Pavia, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; [2]Dipartimento di Medicina Diagnostica, Clinica e di Sanità Pubblica, Università di Modena e Reggio Emilia, Modena, Italy; [3]SOLCA, Instituto Oncológico Nacional Dr. Juan Tanca Marengo, La Atarazana, Guayaquil, Ecuador; [4]Ematologia, AO Arcispedale S. Maria Nuova, IRCCS, Reggio Emilia, Italy; [5]UO Ematologia, Dipartimento di Medicina Interna e Sperimentale, Università di Pisa, Pisa, Italy; [6]UO Ematologia, AOU Policlinico Paolo Giaccone, Palermo, Italy; [7]UOC Ematologia, AO Bianchi Melacrino Morelli, Reggio Calabria, Italy; [8]IRCCS-CROB, Rionero in Vulture (Potenza), Italy; [9]Ematologia e Centro Trapianti Midollo Osseo, AO Cardinal Panico, Tricase (LE), Italy; [10]Divisione di Ematologia, AOU Città della Salute e della Scienza, Torino, Italy

Mortality of patients (pts) affected with cancer can be partially unrelated to tumor, while accurate clinical investigation must be focused mainly on that tumor related. Specific survival (SS) is obtained by subtracting expected mortality (EM) – inferred from national or regional mortality tables – to the observed one. The expected survival (ES) is that enjoyed in the absence of tumor. ES corresponds to the time still at patients' disposal in case of hypothetical full recovery and represents an absolute ceiling of maximal mean attainable SS for a given tumor in a given time. SS limits of variability clinically correspond to full recovery and death, and SS can be evaluated by the measure of how much, in a given time/site, a group of pts has approached the potentially attainable ES. On this full range of prognostic variability relies the comparability of SS, whatever time/site are involved. The number of years lost with respect to those expected represents a useful additional measure. ES and SS are subjected to the same conditioning factors, being contextualized into the evolving conditions of the health services, and depending on customs and behaviours. SS allowed comparison of the effectiveness of some chemotherapy regimens administered to pts with advanced-stage (IIB-IV) Hodgkin lymphoma (HL), whatever histologic subtype, age 16-65 years, of two randomized trials of the past decades. The IIL-HD9601 (1996-2000) enrolled 355 pts in three different arms: ABVD, Stanford-V and MOPPEBVCAD (MEC). The GISL-HD2000 (2000-2007) randomized 307 pts into three arms: ABVD (identical to IIL-HD9601), BEACOPP and COPPEBVCAD (CEC), a variant of MEC adopting cyclophosphamide instead of mechlorethamine at the dose considered with identical anti-lymphoma activity. CEC, ABVD and MEC showed the smallest ratio of expected/observed deaths. BEACOPP, ABVD and MEC allowed the relatively minimal loss of years of life per patient. The evaluation of the curves of ES confirmed the starting prognostic homogeneity of each arm of randomization (12-year ES from 0.965 [MEC] to 0.987 [BEACOPP]). The 12-year SS was 0.88, 0.81, 0.79, 0.79 for CEC, ABVD, BEACOPP, Stanford-V and MEC, respectively. The estimation of SS inferred from national or regional mortality tables allows a potentially unbiased comparison between treatments adopted in different time-spans, since it takes into account the social and health status along time. This method could be extended to other neoplasia.

P020

THE DIAGNOSTICS AND THERAPY OF HODGKIN LYMPHOMA IN PREGNANCY, THE EXPERIENCES OF ONE CENTER

Ľ. Gahérová, H. Móciková, J. Marková

Department of Internal Medicine of Hematology, University Hospital Královské Vinohrady, Prague, Czech Republic

Hodgkin lymphoma is one of the most frequently diagnosed malignancies in pregnancy. In the group of nine patients of one center with manifestation of Hodgkin lymphoma in pregnancy we demonstrate the management of diagnostic and therapeutic procedures. Seven patients were diagnosed in 20-30th week of pregnancy; one with progressive lymphadenopathy already before confirmation of pregnancy and one patient with the diagnosis in 7th week. Only in one case there was induced abortion, and in one case the corticotherapy was started in the third trimester, in the rest of patients (7) the therapy was started after the delivery. Although there are some publications about therapy with single vinblastin, respectively combination chemotherapy ABVD in the second half of pregnancy, our experiences are based on preferation of thorough observation in pregnancy and indication of specific chemotherapy after delivery.

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P021

DIFFICULTIES IN DISTINGUISHING SYNCYTIAL VARIANT OF NODULAR SCLEROSIS CLASSICAL HODGKIN'S LYMPHOMA FROM DIFFUSE LARGE B-CELL LYMPHOMA AND COMPLETE REMISSION AFTER INTENSIVE CHEMOTHERAPY

T. Okatani[1], H. Asaoku[1], M. Fujiwara[2], Y. Sato[3], M. Seto[4]

[1]Division of Hematology, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima, Japan; [2]Division of Pathology, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima, Japan; [3]Department of Pathology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; [4]Department of Pathology, Kurume University School of Medicine, Fukuoka, Japan

Case report. A 31-year-old woman presented at a primary care physician with a dry cough and a sore throat that had persisted for one month. A cold was diagnosed, but dyspnea gradually developed. A chest X-ray and computed tomography (CT) revealed a bulky mediastinal mass and several enlarged lymph nodes. Positron emission tomography/computed tomography (PET-CT) imaging showed increased 18-fluoro-deoxyglucose uptake in the bilateral supraclavicular, axillary, mediastinal, hilar, and paraaortic lymph nodes (maximum standardized uptake value [SUVmax], 13.4). A lymph node biopsy showed destruction of the basic structure, hyperplastic fibrous connective fibrous tissue and cohesive clusters and sheets of large malignant cells with a clear, vacuolated cytoplasm and sharply-defined borders. Flow cytometry could not determine the phenotype of the tumor cells. Immunostaining at our hospital showed that the tumor cells expressed CD15, CD30, and CD79a but not CD2, CD3, CD10, or CD20. We initially diagnosed clinical stage 3, CD20-negative diffuse large B-cell lymphoma (DLBCL) and started the patient on the original intensive treatment protocol for advanced, aggressive lymphoma (ML5 protocol). The patient partially responded to the first CHOP-like regimen (doxorubicin 40mg/m^2 day1,5,9, vindesine 3mg/body day1,5,9, cyclophosphamide 1000mg/m^2 day2,6,10, prednisolone 60mg/m^2 day1-10) and then an etoposide-based second regimen(etoposide 100mg/m^2 day1-3, 8-10, mitoxantrone 8mg/m^2 day1, 8, cyclephosphamide 400mg/m^2 day2, 9, prednisolone 60mg/m^2 day1-3, 8-10, procarbazine 100mg/m^2 day1-10) resulted in a complete response (CR) on PET-CT images. The Department of Pathology, Okayama University, Japan found that the tumor cells were CD79a-, Bob.1-, Oct.2-, indicating a syncytial variant of nodular sclerosis classical Hodgkin lymphoma (NSCHL). *Discussion.* A syncytial variant of NSCHL has been described in Cancer (1990), and this disease is statistically more advanced at diagnosis and often accompanied by huge mediastinal masses that require treatment after diagnosis. We applied the intensive chemotherapy used for DLBCL to our patient, but seven of eight other patients achieved CR after the administration of MOPP (mechlorethamine, vincristine, procarbazine, prednisolone) or ABV (doxorubicin, bleomycin, vinblastine) regimens. Therefore, awareness of this variant is needed at initial diagnosis to ensure appropriate treatment.

P022

SYSTEMIC HODGKIN'S DISEASE WITH OSSEOUS INVOLVEMENT

A. Banti, E. Papadakis, A. Kioumi

Hematology Department, Papageorgiou Hospital, Thessaloniki Greece

Hodgkin's Disease most commonly presents with progressive painless enlargement of peripheral lymph nodes. At diagnosis, osseous involvement is rare (<2%) and even in refractory or relapsing disease only 1/3 of the patients have any bony involvement. Systemic Hodgkin's Disease with skeletal involvement is considered to have worse prognosis. We present a 26-year-old female, who admitted to our orthopedic department with complaints of deformity and pain in the left shoulder. Upon examination, mild local tenderness was noted with no neurological findings. Patient also had involvement of adjacent axillary and supraclavian nodes. Regarding laboratory tests, mild anemia and leukocytosis along with increased ESR and CRP were noted. Left shoulder X-Ray showed osteolytic lesion of capita arm extended to the upper third of diaphyseal humeral. Magnetic resonance imaging (MRI) showed lesions of the capita arm and diaphyseal humeral (low T1/high T2) with surrounding soft tissue mass. CT scanning revealed left axillary/supraclavian and mediastinal lymphadenopathy. Lymph node and bone mass biopsies confirmed the diagnosis of Hodgkin' Disease (nodular sclerosis).The patient received 8 courses of ABVD with PET positivity after completion in left humerus (18FDG suv max : 3.8). Subsequently involved field radiotherapy (4000cGy) was given with no additional treatment benefit. The patient was then deferred to transplantation unit and underwent ASCT, resulting in long term complete remission (PET negative-4,5 years). Osseous involvement in systemic Hodgkin' Disease is rare but warrants intensive treatment in order to achieve sustained remission.

P023

BRENTUXIMAB VEDOTIN ALONE AND IN COMBINATION WITH DACARBAZINE OR BENDAMUSTINE IN PATIENTS AGED ≥60 YEARS WITH NEWLY DIAGNOSED HODGKIN LYMPHOMA: INTERIM RESULTS OF A PHASE 2 STUDY

J.W. Friedberg[1], A. Forero-Torres[2], V.J.M. Cline-Burkhardt[3], R.E. Bordoni[4], D. Patel-Donnelly[5], P.J. Flynn[6], R. Chen[7], A. Fong[8], C.A. Yasenchak[9]

[1]University of Rochester Medical Center, Rochester, NY, USA; [2]University of Alabama at Birmingham, Birmingham, AL, USA; [3]Texas Oncology-Round Rock Seton Williamson, Round Rock, TX, USA; [4]Georgia Cancer Specialists, Marietta, GA, USA; [5]Virginia Cancer Specialists, Fairfax, VA, USA; [6]Minnesota Oncology, Woodbury, MN, USA; [7]City of Hope National Medical Center, Duarte, CA, USA; [8]Seattle Genetics, Inc., Bothell, WA, USA; [9]Willamette Valley Cancer Institute and Research Center/US Oncology Research, Eugene, OR, USA

Background. Treatment-related mortality and inferior responses to chemotherapy lead to poorer outcomes for patients aged ≥60 years with newly diagnosed Hodgkin lymphoma (HL). This phase 2, frontline, open-label study is evaluating safety, efficacy, and durability of response to treatment with brentuximab vedotin (BV) as monotherapy and in combination with dacarbazine (DTIC) or bendamustine. The primary endpoint is objective response rate (ORR) (NCT01716806). *Methods.* Patients with classical HL who were ineligible for or declined initial conventional chemotherapy and had ECOG ≤3 were eligible. The study evaluated cohorts of 1.8 mg/kg BV (16 cycles), 1.8 mg/kg BV+375 mg/m^2 DTIC (12 cycles), and 1.8 mg/kg BV+90 or 70 mg/m^2

bendamustine (starting dose reduced to improve tolerability after 10 patients treated) (6 cycles). Patients with clinical benefit could subsequently continue BV treatment. Responses were assessed per the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). *Results.* Enrollment was completed sequentially (treated patients: n=27 BV; n=22 BV+DTIC; n=20 BV+bendamustine), all patients are off treatment, and 44 remain in long-term follow-up (n=16 BV; n=18 BV+DTIC; n=10 BV+bendamustine). Overall, median age was 76 years (range, 62–92). At baseline, 70% of patients had Stage III-IV HL, 13% presented with bulky disease, 41% had B symptoms, 25% had ECOG 2-3, and 72% were ineligible for frontline chemotherapy. Treatment was discontinued for adverse events (n=35; mostly peripheral neuropathy, n=24), progressive disease (PD; n=15), or other reasons (n=19). Although no specific safety signal was identified, the sponsor suspended treatment with bendamustine because the tolerability did not meet the study goal of defining a low toxicity regimen for this patient population (Table 1). Median number of treatment cycles, median observation time, ORR, complete remission (CR) rate, median progression-free survival (PFS), and overall survival (OS) are presented by cohort (Table 1). *Conclusions.* Both BV monotherapy and BV+DTIC appear tolerable and yield high response rates (ORR 92-100%) in this fragile patient population. Furthermore, the combination with DTIC appears to increase the durability of response without increasing toxicity; and therefore, may represent a reasonable frontline treatment option for elderly HL patients. Other treatment combinations are being considered.

Table 1.

	BV (N=27)[b]	BV+DTIC (N=22)	BV+Bendamustine (N=20)
Median cycles of treatment	8.0	BV, 12.5 DTIC, 12.0	BV, 5.0 bendmustine, 3.5
Median observation time, months (range)[a]	28.0 (4.6, 40.1)	19.6 (14.8, 23.4)	10.5 (2.9, 15.0)
Efficacy-evaluable patients, N	26	21	17
ORR, n (%)	24 (92)	21 (100)	17 (100)
CR rate, n (%)	19 (73)	13 (62)	15 (88)
Median PFS, months (range)	10.5 (2.6+, 40.1)	Not reached (4.2+, 23.2+)	Not reached (2.5+, 14.3+)
PFS rate at 18 months (95% Confidence Interval)	34% (16%,53%)	55% (27%,76%)	57% (28%,78%)
Median OS, months (range)	40.1 (4.6+, 40.1)	Not reached (14.8+, 23.4+)	Not reached (2.9, 15+)
OS rate at 18 months (95% Confidence Interval)	88% (66%,96%)	94% (65%,99%)	75% (46%,90%)
Treatment-related AE ≥ Grade 3, n (%)	13 (48)	9 (41)	16 (80)
Any SAE, n (%)	6 (22)	3 (14)	13 (65)
Death within 30-day safety period	0	0	2 (10)[c]

a Time from first dose to death or last contact
b Reported in part in Forero-Torres 2015
c Unrelated to study treatment

Immunotherapy (Basic Science)

T007

HODGKIN LYMPHOMA INFILTRATING T CELLS: CONSIDERING VARIOUS MEANS OF TUMOR EVASION

F. Wein[1], K. Stock[2], S. Hartmann[2], M.-L. Hansmann[2] R. Küppers[1]

[1]Institute of Cell Biology (Cancer Research), Medical Faculty, University of Duisburg-Essen, Essen, Germany; [2]Dr. Senckenberg Institute of Pathology, Goethe-University of Frankfurt, Medical School, Frankfurt am Main, Germany

The cellular microenvironment in classical Hodgkin lymphoma (cHL) is dominated by a mixed infiltrate of inflammatory cells with typically only one or a few percent of Hodgkin and Reed/Sternberg (HRS) tumor cells. HRS cells orchestrate this infiltrate by the secretion of a multitude of chemokines and direct cell–cell interactions. T cells are usually the largest population of cells in the HL tissue, encompassing T helper (Th) cells, regulatory T (Treg) cells and cytotoxic T cells. Helper and regulatory T cells presumably provide essential survival signals for the HRS cells, and the regulatory T cells also play an important role in rescuing HRS cells from cellular immune response. Here, we investigate the significance of the cHL-specific T cell infiltrate in regard to its role in tumor evasion. Comparing the global gene expression profiles of T cells isolated from cHL lymph nodes (LN) and reactive human tonsils revealed substantial phenotypical differences. Performing gene expression profiling, the T cell compartment in the cHL microenvironment featured an activated, highly proliferative and yet immunosuppressive phenotype. However, the nature of the regulative phenotype in both cHL CD4+ T cell subsets (Th: CD25- and CD127+; Tregs: CD25+ and CD127-) differs to the corresponding tonsillar Treg subset that comprises a purer population of natural FOXP3+ T cells. The ability of HRS cells to induce suppressive T cells was analyzed with an *in vitro* model system using human CD4+ peripheral blood (PB) T cells that were co-cultured with cHL cell lines. Co-cultured, naive T cells displayed an induced, CD25+ subpopulation and upregulated levels of FOXP3, CTLA4 and IRF4. Moreover, the exposure to HRS cells caused a dampened Th1 specific immune response. As for specific means of tumor evasion, the purinergic pathway seems an attractive co-factor. *In vitro* observations support a HRS dependent generation of environmental adenosine. Additionally, we observed an increase expression of the surface molecules BTLA and CD200R in cHL-infiltrating T cell subsets. Regarding their corresponding binding partners, typically expressed on tumor cells, most cHL cell lines were positive for HVEM and CD200. Taken together, we provide a novel perspective on the complex HRS - T cells interaction, verify its immunosuppressive nature and provide further insights into various means of tumor evasion in cHL.

T008

CCR5 BLOCKING BY MARAVIROC INHIBITED RECRUITMENT, PROLIFERATION AND PRO-TUMOR EFFECTS OF MESENCHYMAL STROMAL CELLS AND MONOCYTES IN 2D AND 3D MODELS OF HODGKIN LYMPHOMA MICROENVIRONMENT

N. Casagrande, C. Borghese, M. Celegato, D. Aldinucci

Department of Experimental Oncology 2, CRO Aviano National Cancer Institute, Aviano (PN) Italy

In classical Hodgkin Lymphoma (cHL), the tumor microenvironment (TME) is dominated by an extensive mixed cellular inflammatory infiltrate that plays a decisive role in the pathobiology of the disease. CCL5 and its main receptor CCR5, expressed by cHL cells and by bystander cells including stromal cells and macrophages, are increased in cHL lymph nodes respect to normal lymph nodes. Recently, CCL5 and CCR5 have been implicated in cancer progression. Our hypothesis is that CCL5 secreted by cHL cells could recruit Mesenchymal Stromal cells (MCS) and monocytes, which in turn educated by tumor cells may affect tumor progression. To demonstrate the involvement of CCL5 in

the cross-talk of cHL cells with the TME we used neutralizing anti-CCL5 antibody and the CCR5 antagonist Maraviroc. We found that CCL5 secreted by L-1236, L-428, KM-H2 and HDLM-2 cHL cell lines, recruited and increased the proliferation of MSCs from Bone Marrow and Adipose Tissue. In turn, tumor-educated MSCs (E-MSCs) secreted higher amounts of CCL5, which increased the proliferation, the clonogenic growth and the movement/spread of cHL cells. Both E-MSCs and cHL cells by secreting CCL5 were able to recruit monocytes purified from Peripheral blood, suggesting that monocytes may be recruited directly by tumor cells and indirectly by E-MSCs. Treatment of monocytes with L-1236-conditioned medium (CM) enhanced the surface expression of CCR5, the proliferation and induced the secretion of CCL5. In turn, tumor-educated monocytes, by secreting CCL5, increased the proliferation and the clonogenic growth of L-1236 and HDLM2 cells. Only CM from tumor-educated monocytes inhibited the proliferation of PHA activated peripheral blood mononuclear cells. Finally, using a new tridimensional (3D) approach (mixed organoids) to mimic the TME, we found that the cocultivation of L1236 and HDLM-2 cells with monocytes, MSCs and especially the combination cHL/monocytes/MSCs increased the survival/proliferation of tumor cells. Treatment with Maraviroc not only decreased cHL cell survival/proliferation due to the cocultivation with MSCs and monocytes, but also disrupted the 3D mixed organoids. Taken together our results suggest that CCL5 secreted by cHL cells, as well as by tumor-educated MSCs and monocytes, may build the protective TME and suggest a potential for Maraviroc as adjuvant therapy to block TME formation and tumor cell proliferation due to CCR5 ligands.

T009

DISTURBED ANTIGEN PRESENTATION IN CLASSICAL HODGKIN LYMPHOMA; IMPLICATIONS FOR IMMUNE CHECKPOINT INHIBITOR THERAPY?

M. Nijland[1], L. Visser[2], R. Veenstra[2], K. Kushekhar[2], G. van Imhoff[1], A. van den Berg[2], A. Diepstra[2]

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

Immune checkpoint inhibitors are being tested in clinical trials and show great promise in the treatment of classical Hodgkin lymphoma (cHL). The proposed mechanism of action of these inhibitors consists of reactivating T lymphocytes that have become unresponsive as a consequence of inhibitory mechanisms exerted by the tumor cells. These reactivated T cells are expected to kill tumor cells after recognizing tumor cell derived antigens that are presented by Human Leukocyte Antigens (HLA) at the tumor cell surface. Consequently, lack of tumor cell surface expression of HLA may be one of the explanations why immune checkpoint inhibitor therapy does not always result in a complete remission in cHL. We evaluated expression of HLA class I, HLA class II and HLA-DM in primary diagnostic tissue in a large population based cohort of cHL, by using immunohistochemistry. HLA class I cell surface expression was lacking in tumor cells in 229 out of 361 cases (63.3%), more often in EBV- cHL (83.2%) than in EBV+ cHL (27.4%). HLA class II cell surface expression was missing in 147 out of 361 cHL cases (40.8%; EBV- 46.8% and EBV+ 29.7%). In addition, we scored lack of cytoplasmic expression of the non-polymorphic HLA-DM. This molecule is essential in the intracellular assembly of HLA class II-antigenic peptide complexes. HLA-DM displaces the invariant chain peptide CLIP from the antigen binding groove of HLA class II molecules, to make this groove accessible for loading of antigens. We show that in the absence of HLA-DM, CLIP is not displaced and is aberrantly expressed on the cell surface of Hodgkin tumor cells in frozen sections (n=8). We found that in HLA class II cell surface expressing tumor cells, HLA-DM expression was lacking in 44 out of 89 cases of cHL (49.4%), indicating that no immunogenic peptides are being presented. Combined results for HLA class I, class II and DM show that only 12.4% of cHL cases show HLA expression that is compatible with normal antigen presentation. In conclusion, antigen presentation is often disturbed in cHL. It is expected that this will influence the success of immune checkpoint inhibitors. We therefore propose to take tumor cell HLA expression into account in the evaluation of (lack of) clinical response to these inhibitors.

P059

TUMOR INFILTRATING HLA-MATCHED CD4+ T CELLS RETARGETED AGAINST HODGKIN AND REED-STERNBERG CELLS

B. Rengstl[1], F. Schmid[1], C. Weiser[1], C. Döring[1], T. Heinrich[1], K. Warner[1,2], P.S.A. Becker[3], R. Wistinghausen[1], S. Kameh-Var[1], E. Werling[1], A. Billmeier[1], C. Seidl[3], S. Hartmann[1], H. Abken[2], R. Küppers[4], M.-L. Hansmann[1,*], S. Newrzela[1,*]

[1]Dr. Senckenberg Institute of Pathology, Goethe-University of Frankfurt, Medical School, Frankfurt am Main, Germany; [2]Center for Molecular Medicine Cologne, University of Cologne, and Department I of Internal Medicine, University Hospital Cologne, Cologne, Germany; [3]Institute for Transfusion Medicine and Immunohematology, Red Cross Blood Donor Service, Baden-Württemberg-Hessen, Frankfurt, Germany; [4]Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, Medical School, Essen, Germany

**Shared last authorship*

Hodgkin lymphoma (HL) presents with a unique histologic pattern. Pathognomonic Hodgkin and Reed-Sternberg (HRS) cells usually account for less than 1% of the tumor and are embedded in a reactive infiltrate mainly comprised of CD4+ T cells. HRS cells induce an immunosuppressive microenvironment and thereby escape anti-tumor immunity. To investigate the impact of interactions between HRS cells and T cells, we performed long-term co-culture studies that were further translated into a xenograft model. Surprisingly, we revealed a strong anti-tumor potential of allogeneic CD4+ T cells against HL cell lines. HRS and CD4+ T cells interact by adhesion complexes similar to immunological synapses. Tumor-cell killing was likely based on the recognition of allogeneic major histocompatibility complex class II (MHC-II) receptor, while CD4+ T cells from MHC-II compatible donors did not develop any anti-tumor potential in case of HL cell line L428. However, gene expression profiling of co-cultured HRS cells as well as tumor infiltration of matched CD4+ T cells indicated cellular interactions. Moreover, matched CD4+ T cells could be activated to kill CD30+ HRS cells when redirected with a CD30-specific chimeric antigen receptor. Our work gives novel insights into the crosstalk between HRS and CD4+ T cells, suggesting the latter as potent effector cells in the adoptive cell therapy of HL.

Minimal Residual Disease and Prediction

T013

PLASMA VESICLE-ASSOCIATED miRNAs AS THERAPY RESPONSE BIOMARKERS IN HODGKIN LYMPHOMA

D.M. Pegtel[1,*], E. Drees[1], M.A.J. van Eijndhoven[1], N.J. Groenewegen[1], S. van Niele[1], R. Prins[1], S.R. Baglio[1], J.M. Zijlstra[2], H. van der Voorn[3], S.F.W.M. Libregts[4], M.H. Wauben[4], R.X. de Menezes[5], J.R.T. van Weering[6], R. Nieuwland[7], A. Diepstra[8], A. van den Berg[8], D. de Jong[1]

[1]Department of Pathology, Exosomes Research Group, VU University Medical Center, Amsterdam, The Netherlands; [2]Department of Hematology, VUmc, Amsterdam, The Netherlands; [3]iZON Science, Oxford, UK; [4]Department of Biochemistry & Cell Biology, Utrecht University, Utrecht, The Netherlands; [5]Department of Epidemiology and Biostatistics, VUmc, Amsterdam, The Netherlands; [6]Department of Functional Genomics, Center for Neurogenomics and Cognative Research, Neuroscience Campus Amsterdam, VU University, Amsterdam, The Netherlands; [7]Department of Clinical Chemistry, Academic Medical Center Amsterdam, The Netherlands; [8]Department of Pathology & Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Cure rates for classical Hodgkin Lymphoma (CHL) patients are generally high. CHL patients that are cured remain at risk for long-term side effects from the aggressive radiation/chemotherapy regimens and relapses occur. Upcoming treatment strategies aim towards personalized therapy by early assessment of the effectiveness of active treatment by measuring vital tumor tissue with FDG-PET/CT imaging. Apart from radiation burden, imaging is costly and reported positive predictive values are suboptimal. Studies suggest that tumors actively secrete small extracellular vesicles (EVs) that encapsulate tumor-derived nucleic acids, including 22nt non-coding microRNAs (miRNAs). Here we identified with RNAseq, CHL-associated miRNAs in circulating E*Vs* as defined biosource, using size-exclusion chromatography (SEC) as isolation method. Apart from miR-21-5p and miR-155-5p oncomiRs already implicated in lymphomagenesis, we identified let7-a-5p, miR-24-3p and miR-127-3p as circulating CHL biomarkers. Notably, a high abundance of these miRNAs in circulation of CHL patients pre-therapy, correlated with a high concentration of 100nm EVs, as determined with tunable-resistive pulse sensing (TRPS). Using logistic regression modeling we determined that EV-associated miR-127-3p levels alone can distinguish primary and relapse CHL patients from healthy controls. Importantly, the calculated AUC for miR127-3p in vesicles outperform ROC calculations using unfractionated (total) plasma. Finally, in serial samples of individual CHL patients, during- and after treatment but also in long-term follow up, we measured robust and consistent decreases in EV-miRNA levels that corresponded with FDG-PET/CT outcome . Thus defined EV-miRNAs in circulation reflect the presence of vital tumor tissue. This liquid biopsy method may proof suitable for early respsonse and relapse monitoring, MRD detection and guiding therapy decisions. Upcoming studies in serial samples are ongoing to determine whether RNAseq-generated small RNA signatures are useful for diagnosis, prognosis and prediction in CHL.

T014

MID-TREATMENT TARC AND MID-TREATMENT FDG-PET PREDICT FOR PROGRESSION FREE SURVIVAL IN CLASSICAL HODGKIN LYMPHOMA

W.J. Plattel[1], A. van den Berg[2], L. Visser[2], A. Glaudemans[3], A. Diepstra[2], G. van Imhoff[1]

[1]Department of Hematology, University Medical Center Groningen, The Netherlands; [2]Department of Pathology and Medical Biology, University Medical Center Groningen, The Netherlands; [3]Department of Nucleair Medicine and Molecular Imaging, University Medical Center Groningen, The Netherlands

Background. Plasma or serum CC-chemokine ligand 17 (CCL17) / Thymus and Activation Regulated Chemokine (TARC) is a highly specific biomarker for classical Hodgkin lymphoma (cHL) disease activity. Serial TARC levels correlate with treatment response as early as after one cycle of chemotherapy. In the current study we compared predictive value of mid-treatment TARC with mid-treatment FDG-PET for modified progression free survival (mPFS) in primary cHL patients. *Patients and Methods.* Serial serum or plasma samples were prospectively obtained from 112 newly diagnosed (65 early stage and 57 advanced stage) cHL patients. Patients were mainly treated with ABVD or eBEACOPP based treatment regimens. TARC levels were quantified using ELISA. FDG-PET results were quantified and reassessed according to the Lugano classification including Deauville five point score. Events for mPFS were scored in case of death due to any cause, progression of cHL or start of second line treatment. Patients without elevated TARC at pre-treatment and patients with active atopic dermatitis were excluded for survival analysis on TARC. *Results*. Median follow-up was 45 months for the entire cohort. Out of 112 patients, 103 (92%) achieved a complete remission, 8 patients (7%) had a partial response and one patient (1%) had progressive disease. Of 92 patients with a mid-treatment FDG-PET scan 16 (17%) were positive (Deauville ≥4). Mid-treatment FDG-PET positive patients had significantly reduced mPFS compared to mid-treatment FDG-PET negative patients (56% *versus* 93% at 3 years, p<.001, Figure 1A). Pre-treatment TARC levels were elevated in 100/112 patients (89%) of which two patients had active atopic disease. Of 92 patients with a mid-treatment plasma or serum sample, TARC was elevated (>900 pg/ml) in 8 (9%). mPFS at 3-years was 25% for patients with high mid-treatment TARC and 92% for patients with low mid-treatment TARC levels (p<.001, Figure 1B). Elevated mid-treatment TARC levels were associated with mid-treatment Deauville score of 5. In multivariate analysis both mid-treatment FDG-PET and mid-treatment TARC independently predicted for mPFS. *Conclusions*. Elevated levels of TARC at mid-treatment are highly predictive for inferior mPFS. Both negative and positive predictive value of mid-treatment TARC are at least as good or even better than mid-treatment FDG-PET imaging. TARC might serve as a substitute for mid-treatment FDG-PET imaging in future response evaluation.

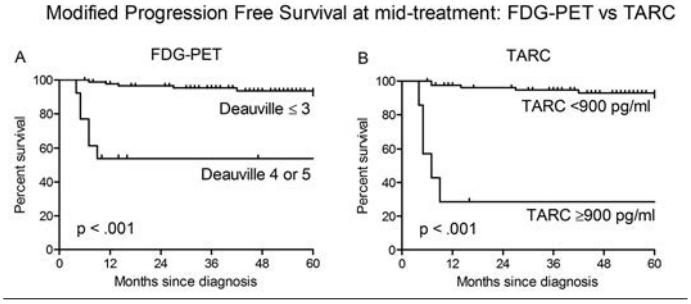

Figure 1.

T015

A COMPREHENSIVE ANALYSIS OF HODGKIN LYMPHOMA SEASONALITY ACROSS VARIOUS GEOGRAPHIC REGIONS

S. Borchmann, H. Müller, A. Engert

First Department for Internal Medicine, University Hospital of Cologne, Köln, Germany

Introduction. Seasonal variations in incidence and mortality after a Hodgkin lymphoma (HL) diagnosis have been previously described with partly conflicting *results.* The goal of this study is to comprehensively analyze seasonal variation in incidence and mortality risk of HL with a focus on geographic differences. *Methods.* HL cases diagnosed between 1973 and 2012 in the 18 Surveillance, Epidemiology, and End Results (SEER) registries were eligible (n=50,179). Cases with missing data for at least one of the analyzed variables (n=8,700) and from the two SEER registries "Alaska natives" (n=17) and "Rural Georgia" (n=57) were excluded, leaving 41,405 cases for the study. Seasonality of inci-

dence was analyzed using cosinor analysis. The risk of overall mortality within 3 years following a HL diagnosis in winter (Sep.-Feb.) *vs* summer (Mar.-Aug.) was analyzed by employing a Cox proportional-hazards model with correction for known risk factors. *Results.* HL shows a seasonal incidence pattern with a peak in March and a trough in September (p<0.001). In predefined subgroup analyses, cases of the mixed cellularity (p<0.001), nodular sclerosis (p<0.001) and lymphocyte depleted subtype (p=0.002) showed a seasonal incidence pattern. Seasonality was particularly pronounced in the age groups 20-29, 30-39 and 60-69, coinciding with age groups of increased HL incidence. Cases from lower (<38.05°N) latitudes showed a decreased seasonality of incidence (amplitude=0.055) compared to cases from higher (≥38.05°N) latitudes (amplitude=0.102) (p(diff.)=0.023). The risk of dying in winter *vs* summer is increased at higher latitudes (HR: 1.082[1.009;1.161], p=0.027), whereas no seasonal difference in mortality was observed for cases from lower latitudes (HR: 0.990[0.926;1.059], p=0.772). A multiplicative interaction term showed interaction between the latitude and a diagnosis in winter on mortality risk (HR(interaction): 1.119[1.009;1.241], p=0.033). *Conclusions.* HL exhibits a seasonal incidence and mortality pattern in this most comprehensive analysis performed to date. The seasonal effect on incidence is exacerbated at and the effect on mortality restricted to higher latitudes. As latitude is closely linked to seasonal variations in Vitamin D serum levels, a protective effect of Vitamin D in HL is a possible explanation. Evidence on the direct association between Vitamin D levels and the clinical course of HL should be collected to improve the understanding of Vitamin D in HL.

P060

EVALUATION OF SERUM TARC LEVELS IN PATIENTS AT RISK OF PROGRESSION FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANT FOR HODGKIN LYMPHOMA: RESULTS FROM THE AETHERA TRIAL

V. Bachanova[1], A. Carella[2], T. Masszi[3], J. Holowiecki[4], S. Viviani[5], D. Huebner[6], N. Hunder[7], E. Larsen[7], J. Odegard[7], M. Onsum[7], C. Moskowitz[8]

[1]University of Minnesota Medical Center, Minneapolis, MN, USA; [2]IRCCS Azienda Ospedaliera Universitaria San Martino-Ist, Genova, Italy; [3]Szent Istvan & Szent Laszlo Corporate Hospital Hematology & Stem Cell Dept., Budapest, Hungary; [4]Department of Bone Marrow Transplantation & Oncohematology, Maria Sklodowska-Curie Institute of Oncology, Gliwice, Poland; [5]Istituto Nazionale dei Tumori, Milano, Italy; [6]Millennium Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceuticals Limited; [7]Seattle Genetics, Inc., Bothell, WA, USA; [8]Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Background. In patients with Hodgkin lymphoma (HL), serum concentrations of thymus and activation-regulated chemokine (TARC) and other cytokines may have prognostic significance in both the front-line and salvage therapy settings. The potential utility of TARC to predict relapse or progression of HL following autologous hematopoietic cell transplant (AHCT) is unknown. AETHERA (NCT01100502) is a phase 3, randomized, placebo-controlled trial that demonstrated improved progression-free survival (PFS) in patients with high risk HL who received post-AHCT consolidation treatment with brentuximab vedotin (BV) (hazard ratio [HR]=0.57, P=0.001), and an acceptable safety profile. *Methods.* In this exploratory analysis, we measured baseline serum TARC levels in patients enrolled in AETHERA, and evaluated impact of TARC on outcomes after AHCT with or without BV consolidation therapy. Additional serum biomarkers under analysis include sCD30, sCD163, IL-6, sIL-2R, and sCD68. Descriptive statistics were used to characterize baseline TARC concentrations as a function of baseline clinical characteristics, and Kaplan-Meier analysis was used to assess PFS over 24 months of follow-up. *Results.* Among 329 patients enrolled, 312 (156 BV and 156 placebo) had available serum samples collected between days 28-45 post-AHCT. The median (range) baseline TARC concentration was 472 (18-18,092) pg/mL, and was similar among patients in the BV (481 [18-18,092] pg/mL) and placebo (446 [43-9,756] pg/mL) arms. Median TARC levels were higher among patients with (*vs* without) established risk factors for progression; these included B symptoms (537 *vs* 414 pg/mL), extranodal involvement (501 *vs* 450 pg/mL), FDG-avid PET status (543 *vs* 433 pg/mL), and incomplete response to salvage therapy (532 [stable disease] *vs* 474 [partial remission] *vs* 404 [complete remission] pg/mL, respectively). The median TARC level was also higher among patients with ≥2 risk factors *vs* those with 1 risk factor (487 *vs* 410 pg/mL). PFS at 12 months decreased progressively with increasing TARC among patients who received placebo, but not among those who received BV consolidation (Figure). PFS at 24 months was more similar across TARC levels within each treatment arm. *Conclusions.* Overall, these data suggest that serum TARC may help to identify HL patients at increased risk of disease progression following AHCT.

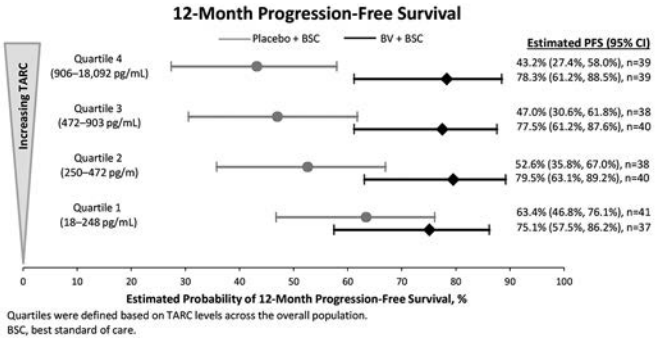

Figure 1.

P061

VALIDATION OF A CLINICAL/BIOLOGICAL PROGNOSTIC MODEL IN A LARGE COHORT OF ELDERLY PATIENTS WITH A CLASSICAL HODGKIN LYMPHOMA

V. Safar[1], M. Morelle[2], P. Brice[3], C. Rossi[4], J. Dupuis[5], A. Perrot[6], A. Stamatoullas[7], S. Garciaz[8], S. Carras[9], J. Lazarovici[10], H. Ghesquières[1]

[1]Hematology Department, Centre Hospitalier Universitaire de Lyon Sud, Pierre Bénite, France; [2]Biostatistics Department, Centre Léon Bérard, Lyon, France; [3]Hematology Department, Hôpital Saint-Louis, Paris, France; [4]Hematology Department, Hôpital Le Bocage, Dijon, France; [5]Lymphoid Malignancies Unit, Groupe Hospitalier Henri Mondor-Albert Chenevier, Créteil, France; [6]Hematology Department, Hôpital de Brabois, Nancy, France; [7]Hematology Department, Centre Becquerel, Rouen, France; [8]Hematology Department, Institut Paoli-Calmettes, Marseille, France; [9]Hematology Department, Centre Hospitalier Universitaire, Grenoble, France; [10]Hematology Department, Institut Gustave Roussy, Villejuif, France

Introduction. Our goal is to investigate the external validity of two previously developed prognostic models for overall survival (OS) and progression free survival (PFS) using a scoring system counting unfavorable risk factors (age, performans status, bone marrow involvement, gamma globulin level and fibrinogen level) in elderly patients with a classical Hodgkin lymphoma (cHL). *Methods.* The performance of the prediction models was evaluated on a retrospective cohort of patients ≥59 years with newly diagnosed cHL treated in eight hospitals in France. Model discrimination was evaluated by computing hazard ratio (HR) across risk groups. A comparison with the International Prognostic Score (IPS) was performed using ROC curves. *Results.* 288 patients were included (November 1990 –June 2015): median age at diagnosis was 70 years (range, 59-93), 55% were male, 53% presented with B symptoms, 25% had a PS>2, 61% had Ann Harbor stage III/IV, 26% had at least one comorbidity scored 3 or 4 on CIRS. Median follow up is 64 months (0-232). 25% of patients have progressed or relapsed and 103 patients died, 40% within the first year of treatment. OS and PFS at 36 months were 72.1% [95% CI: 66.2%; 77.1%] and 63.5% [57.5%; 68.9%], respectively. On 188 evaluable patients, HR for PFS were 8.2, 7.9, and 9.6 for the presence of 1, 2, and 3/4 factors respectively (reference=absence of factor). On 215 evaluable patients, HR for OS

were 1.3, 2.2 and 4.0 for the presence of 1, 2 and 3 factors respectively. Patients with 0, 1, 2 and 3 factors had a 3 years OS of 82.3, 77.3, 69.5 and 38.1% respectively (p=0.001). The areas under the curve were not significantly different (p=0.9754) for OS between our score and IPS. *Conclusions.* These results provide evidence of a satisfactory discrimination ability of the prediction model for OS, with a predictive power similar to IPS. A larger evaluable cohort is required to have a better prognostic model for PFS. This study is a first step in establishing the external validity of these models before use in clinical practice, together with geriatric assessment, in order to offer adequate treatment to patients.

P062

OUTCOMES AND PROGNOSTIC FACTORS IN HODGKIN LYMPHOMA – A SINGLE CENTER EXPERIENCE

A. Pinto, D. Mota, M. Santos, R. Guilherme, M. Gomes, L. Ribeiro

Clinical Hematology Department, Coimbra University Hospital Center, Coimbra, Portugal

Background. Identification of patients with Hodgkin lymphoma (HL) at risk of treatment failure remains an important unsolved question. Several prognostic models have been proposed to define risk-adapted therapeutic strategies, avoiding overtreatment and identifying in whom standard treatment is not sufficient. *Aims.* To test validated prognostic factors and identify other predictors of survival in a cohort of patients with classical HL (cHL) in a tertiary health institution. *Methods.* Retrospective analysis of patients with cHL treated between 1990 and 2015. Univariate analysis was performed and significant predictors at the level of 0.05 were used to adjust a multivariate Cox regression model. *Results.* We included 355 cHL patients, mainly males (55.2%) with a median age at diagnosis of 29 years (12-80). The most prevalent histological subtype was nodular sclerosis (78.3%). Ann Arbor stage III/IV was observed in 41.1% (n=146) patients, B symptoms in 54.6% (n=194) and bulky disease in 22.8% (n=81). According to GHSG criteria, 50.1% (n=178) had advanced disease of which 49.4% (n=88) had an IPS≥3. Among the 344 patients treated, ABVD was performed in 210 (59.2%); MOPP/ABVD in 78 (21.9%); MOPP/MOPP like in 30 (8.5%); BEACOPP in 25 (7.0%); other regimens in 17 patients (4.8%) and radiotherapy alone in 11 (3.1%). Overall response rate was 83.9% (77.2% of complete responses). With a median follow-up of 100.1 months (0.3-316.0), overall survival (OS) at 5, 10 and 20 years was 84.3%, 78.1% and 67.8% and progression free survival (PFS) was 71.6%, 67.3% and 57.9%, respectively. We analyze the prognostic significance of several factors accepted previously with regard to survival. On multivariate regression analysis only 3 factors were associated with impact on OS: age (HR 1.04; 95%CI 1.02-1.06, p<0.001); hemoglobin level (HR 0.78; 95%CI 0.66-0.93, p=0.005) and LDH>2xULN (HR 2.13; 95%CI 1.06-4.28, p=0.034). Four factors were predictors of PFS: age (HR 1.02; 95%CI 1.01-1.04, p<0.004); lymphocyte count (HR 0.60; 95%CI 0.39-0.92, p=0.02), LDH>2xULN (HR 2.55; 95%CI 1.31-4.97, p=0.006) and Ann Arbor stage III/VI (HR 2.40; 95%CI 1.18-4.86, p=0.015). *Conclusions.* This data provides evidence for age, hemoglobin and LDH as independent predictors of OS and age, lymphocyte count, LDH and Ann Arbor stage as predictors of PFS in patients with cHL. Further work in larger groups is warranted to create an accurate predictive model for adequate stratification of newly diagnosed patients.

P063

COMBINED PROGNOSTIC ROLE OF TARC PROTEIN AND PET/CT IN PATIENTS WITH HODGKIN LYMPHOMA

K. Husi[1], Á. Illés[1], Á. Jóna[1], B. Nagy[2], Z. Fejes[2], S. Barna[3], Z. Miltényi[1]

[1]Department of Hematology; [2]Department of Laboratory Medicine; [3]University of Debrecen, Faculty of Medicine; Scanomed Ltd, Debrecen, Hungary

Introduction. It is well known that long-term survival of Hodgkin lymphoma (HL) patients is very favourable, that is why we have to detect those high-risk patients in time who don't respond to first-line therapy on a desirable way. Nowadays interim and restaging PET/CT is widespread, but there are some biomarkers in addition, which may help us to choose the best way of therapy and to avoid undertreatment. *Patients and Methods.* We examined HL patients who were treated in our institute from September 2013 to March 2016. Our aim was to detect whether serum TARC (Thymus and Activation- Regulated Chemokine) protein alone or combined with PET/CT is appropriate for being a helpful biomarker in HL patients or not. *Results.* During this period we collected serum samples from 39 patients treated with Hodgkin lymphoma. We have got samples from 3 different times (before treatment, after 2 cycles of chemotherapy and after 6 cycles of chemotherapy) in the case of 20 patients. The mean age of the 20 patient (11 males and 9 females) was 42,4 years (18-75 years) at the time of the diagnosis. Three of them were in an early stage and 17 of them were in advanced stage. According to our results the activity of TARC protein measured before treatment is fit for indicating extranodal manifestations, the presence of bulky disease, and the extension of the disease, but neither it's activity after 2 cycles of chemotherapy, nor at the end of treatment indicated refractory disease nor alone, neither combined with interim PET/CT. *Conclusions.* Nevertheless, Hodgkin lymphoma is one of the best curable malignancies; there are no methods except PET/CT which may help us to identify high-risk patients in time. The exact role of biomarkers needs further investigations.

Pediatric Hodgkin Lymphoma

T016

WHOLE BODY FUNCTIONAL AND ANATOMICAL MRI: ACCURACY IN STAGING AND TREATMENT RESPONSE MONITORING IN CHILDHOOD AND ADOLESCENT HODGKIN'S LYMPHOMA COMPARED TO CONVENTIONAL MULTIMODALITY IMAGING (CRUK C23580/A12707)

S. Daw, S. Punwani, A. Latifoltojar, P.D. Humphries, L. Menezes, D. Neriman, A. Shankar, B. Popova, P. Smith, K.M. Condne, A. Lopes, S.A. Taylor

Cancer Research UK and UCL Cancer Trials Office, University College London, London, UK; Centre for Medical Imaging, University College London, London, UK; Institute of Nuclear Medicine, University College London, London, UK; University College London Hospital, London, UK

This is a single centre cohort trial to compare whole body MRI (WB-MRI) & conventional investigations for staging & treatment response monitoring in childhood Hodgkin's lymphoma. A total of 50 patients (32 male, median age 16, range 6-19) prospectively underwent WB-MRI in addition to conventional CT and PET CT at initial staging and during response assessment (n=37) after 2 chemotherapy cycles. WB-MRI included axial/coronal FS T2/T1 TSE, axial FS DWI (5 b values 0 to 800), & dynamic contrast enhanced T1 FLASH through the liver/spleen. The reference standard disease status at 30 sites (17 nodal, 13 extra nodal) & Ann Arbour stage was assigned by a multidisciplinary committee using PET CT and CT, based on EURONET trial criteria (nodal positivity >2cm and/or focal 18-FDG uptake above background). Treatment response (progression, none, partial inadequate (PRi), partial adequate (PRa) and complete) was defined using nodal volume change & FDG avidity. WB-MRI was read in consensus by 2 radiologists blinded to conventional imaging. Based on pilot data, nodal positivity was defined as >2cm &/or mean ADC <1.2 x10-3mm2 s-1. Nodes 1 to 2cm with ADC 1.2-1.8 were equivocal. Treatment response was assigned using nodal volume change and rise in ADC (cut off of 70% to differentiate between PRi & PRa). Agreement between WB-MRI and the reference was expressed as percentage concordance for all reported disease sites and kappa statistics. Equivocal sites were treated as disease positive. Results are uncorrected for discrepancies in nodal site description. A total of 44 (88%) patients were concordant for at least 80% of nodal sites, although only 12 (24%) achieved 100% concordance between WB-MRI and the reference standard. Equivalent results for extra nodal disease were 48 (96%) and 34 (68%) respectively. There was 72% agreement for stage (36/50), (kappa 0.56-moderate), with 10 (20%) patients under staged by WB-MRI and 4 (8%) over staged. There was 68% agreement for response classification (25/37) (kappa 0.34-fair) with response over estimated by WB-MRI in 4 (11%) & under estimated in 8 (22%). In conclusion, WB-MRI holds promise as an alternative to conventional staging modalities using ionising radiation, but levels of discordance suggest it is not ready to fully replace them. WB-MRI is attractive as a staging modality for paediatric lymphoma but disagreement with standard modalities suggests caution must be applied before introducing into staging algorithms.

T017

PHASE III STUDY OF RESPONSE ADAPTED THERAPY FOR THE TREATMENT OF CHILDREN WITH NEWLY DIAGNOSED VERY HIGH RISK HODGKIN LYMPHOMA (STAGES IIIB/IVB) (AHOD0831): A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

K. Kelly[1], P.D. Cole[2], L. Chen[3], K.B. Roberts[4], D.C. Hodgson[5], K. McCarten[6], S.Y. Cho[7], C.L. Schwartz[8]

[1]Roswell Park Cancer Institute; [2]Montefiore Medical Center; [3]Children's Oncology Group; [4]Yale Cancer Center; [5]Princess Margaret Cancer Centre; [6]Brown University; [7]University of Wisconsin Carbone Cancer Center; [8]UT MD Anderson Cancer Center

Purpose. AHOD0831 tested a response-based treatment approach for children with very high risk Hodgkin lymphoma (HL). Central review following 2 cycles by FDG-PET was used to assign consolidation chemotherapy and radiotherapy (RT). As many patients with relapsed HL can be successfully cured with retrieval therapy, 2ndEFS (freedom from 2nd relapse or malignancy) was used as a surrogate for long term HL-related cause of death. AHOD0831 tested whether this treatment would maintain 4yr 2ndEFS ≥95%. *Methods.* Patients ≤21 with stage IIIB/IVB HL were nonrandomly assigned to receive two 21-day cycles of ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide). Rapid Early Response (RER) was defined by FDG-PET without activity above background, irrespective of residual masses. RER received 2 additional cycles of ABVE-PC. Slow early responders (SER) received 2 cycles of ifosfamide/vinorelbine and 2 more ABVE-PC. Sites of initial bulky involvement (large mediastinal mass, nodal aggregate >6cm, splenic macronodules) and regions of SER received RT 21 Gy. 2nd events were defined as relapse/PD of HL or SMN, new SMN or death after a 1st event (relapse/PD, SMN, biopsy proven HL at end of chemotherapy). *Results.* The 165 eligible patients were: median age 15.8 yrs (5.2-21.4), 61% male, 43% stage IIIB. 50% were RER. Median follow-up was 42 mos. 1st events: 29 relapse/PD, 1 SMN, 1 fungal death. 4yr 1stEFS rates 80.2% (73%-85.6%). 4yr OS 95.9% (90%-98.4%). 12 SER were persistently PET+ at end of chemotherapy; 8 had clinical evidence of active HL: 3 biopsy-proven HL, 2 PD by clinical or radiographic criteria, and 3 relapsed. 20 patients were excluded from 2ndEFS analysis due to premature termination or deviation of protocol therapy. 2ndEFS at 4yrs is 89.8% (95% CI:80.8%-94.8%). 4yr 2ndEFS was 91.9% (76.3%-97.4%) for RER, 87.8% (75.8%-94.1%) for SER (n=68) and 89.6% (76.3%-95.7%) for stage IVB. *Conclusions.* Among pediatric patients with VHR HL, a response directed approach with limited chemotherapy and risk-directed RT achieved EFS and OS rates comparable with results of recent trials for this population (POG 9425: IIIB/IVB, n=88: 4yr EFS 81.7%; 4 yr OS 92.9%) despite reduction in RT volumes. The similar EFS/2ndEFS for RER and SER supports therapeutic tailoring based on response. Persistent PET at end of chemotherapy identifies a cohort at especially high risk for relapse/early PD. Novel approaches are needed for this group.

T018

OUTCOMES IN ADOLESCENTS AND YOUNG ADULTS WITH HODGKIN LYMPHOMA TREATED ON US COOPERATIVE GROUP PROTOCOLS: AN ADULT INTERGROUP (E2496) AND CHILDREN'S ONCOLOGY GROUP (COG AHOD0031) COMPARATIVE ANALYSIS

T.O. Henderson[1], S.K. Parsons[2], K. Wroblewski[3], L. Chen[4], F. Hong[5], S. Smith[6], J. McNeer[1], R. Advani[7], R.D. Gascoyne[8], L.S. Constine[9], S. Horning[10], N.L. Bartlett[11], B. Shah[12], J.M. Connors[8], J. Leonard[13], B.S. Kahl[11], K. Kelly[14], C.L. Schwartz[15], D. Friedman[16], L.I. Gordon[17], A.M. Evens[2]

[1]Department of Pediatrics, University of Chicago, Chicago, IL, USA; [2]Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA; [3]Department of Public Health Sciences, University of Chicago, Chicago, IL, USA; [4]Children's Oncology Group, Acadia, CA, USA; [5]Department of Biostatistics, Dana-Farber Cancer Institute, Boston, MA, USA; [6]Department of Medicine, University of Chicago, Chicago, IL, USA; [7]Stanford University, Palo Alto, CA, USA; [8]BC Cancer Agency, Vancouver, BC, USA; [9]Departments of Radiation Oncology and Pediatrics, University of Rochester, Rochester, NY, USA; [10]Genentech, San Francisco, CA, USA; [11]Washington University School of Medicine, St. Louis, MO, USA; [12]Moffitt Cancer Center, Tampa, FL, Madison, WI, USA; [13]Department of Medicine, Cornell Weill School of Medicine, New York, NY, USA; [14]Roswell Park Cancer Institute, Buffalo, NY, USA; [15]Division of Pediatrics, MD Anderson Cancer Center, Houston, TX, USA; [16]Department of Pediatrics, Vanderbilt University, Nashville, TN, USA; [17]Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Introduction. The optimal therapeutic approach for AYAs with HL remains unclear. We examined AYAs treated on 2 recent, randomized pediatric and adult North American HL studies. *Methods.* The characteristics, failure free survival (FFS) and overall survival (OS) of 114 AYA HL patients (pts) [17-21 years(yr)] treated on E2496 (ABVD *vs* Stanford

V [SV], Gordon JCO 2013) were compared with pts >21 years on E2496. The characteristics, FFS and OS of these ECOG AYAs were compared with 391 AYAs (17-21 yr) treated on COG AHOD0031 (ABVE-PC backbone, Friedman JCO 2014). Stratified log-rank tests and propensity score analysis were utilized to compare outcome differences. *Results.* In E2496, the 5-year FFS and OS rates for AYAs were 68% and 89%, respectively, with significant variations identified by pt age (Table). There was no FFS difference between ECOG AYAs treated with ABVD *vs* SV (P=0.66). FFS in AYAs were inferior to those ages 21 to 44 yr (P =0.005) but appeared more similar to patients aged 45-59 yr. There was no significant difference in sex, race, or histology in COG or E2496 AYAs. Due in part to trial design differences, a larger proportion of E2496 AYAs were stage III or IV *vs* COG AYAs (63% *vs* 29%, P<0.001) and had B symptoms (63% *vs* 27%, P<0.001); fewer E2496 pts had bulk disease (33% *vs* 77%, P<0.001). There was no significant difference in extralymphatic disease, anemia or low albumin. More COG AYAs received radiotherapy (76% *vs* 66%, P=0.03), though in smaller doses (21 Gy *vs* 36 Gy). The 5-year FFS and OS for COG AYAs were 80% and 97%, respectively. COG AYAs appeared to have superior FFS compared with E2496 AYAs (P=0.001). In multivariable analyses (controlled for stage, anemia, bulk), E2496 AYAs appeared to have worse FFS compared with COG AYAs in all strata except among those with stage I/II without anemia. Propensity score analysis matched on stage, anemia, and bulk disease confirmed inferior FFS for E2496 compared with COG AYAs (P=0.004). The AYA survival disparity across studies persisted after additional covariates were incorporated into the propensity score (ie, age, gender, B symptoms and hypoalbuminemia; P=0.026). *Conclusions.* AYA HL pts treated on E2496 had inferior outcomes compared with older pts (22-44 yr) on same study, and to similarly matched AYA pts treated on COG AHOD0031. This may reflect differing treatment regimens, risk profiles, biology, or other factors. Prospective examination of these issues in AYA HL pts is warranted.

Table 1. Survival outcomes within E2496 by age.

PFS	3-yr	5-yr	P
17-21	70%	68%	0.005
21-44	79%	76%	
45-59	68%	68%	
>=60	56%	48%	
OS			P
17-21	93%	89%	<.0001
21-44	96%	93%	
45-59	79%	76%	
>=60	70%	58%	

P064

FIRST INTERNATIONAL INTER-GROUP STUDY FOR CLASSICAL HODGKIN LYMPHOMA IN CHILDREN AND ADOLESCENTS: EuroNet-PHL-C1. REPORT OF THE LATEST INTERIM ANALYSIS

J. Landman-Parker[1], H. Wallace[2], D. Hasenclever[3], W. Balwierz[4], J. Karlen[5], A. Fossa[6], A. Fernandez-Teijero Alvarez[7], M. Cepelova[8], K. Dieckmann[9], T. Leblanc[10], S. Daw[11], A. Beishuizen[12], R. Kluge[13], D. Körholz[14], C. Mauz-Körholz[14,15] on behalf the EuroNet-Pediatric-Hodgkin-lymphoma (EuroNet-PHL) Group

[1]Hopital Armand Trousseau, HUEP APHP/UPMC,Paris, France; [2]Royal Hospital for Sick Children, Edinburgh, UK; [3]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Germany; [4]Department of Pediatrics, Jagellonian University, Krakow, Poland; [5]Karolinska University Hospital, Stockholm, Sweden; [6]6Radium hospitalet, University of Oslo, Norway; [7]Pediatric Hematology and Oncology, University of Sevilla, Spain; [8]Motol Hospital, Pediatric Oncology and Hematology, University of Prague, Czech Republic; [9]Department of Radiooncology, Medical University of Vienna, Austria; [10]Hopital Robert Debré,APHP, Paris, France; [11]Adolescent Oncology and Hematology Unit, UCLH London, UK; [12]Pediatric Heatology and Oncology, Erasmus University of Rotterdam, Netherlands; [13]Department of Nuclear Medicine, University of Leipzig, Germany; [14]Pediatric Hematology and Oncology, Justus-Liebig-University, Giessen, Germany; [15]Medical Faculty of the Martin-Luther-University, Halle, Germany

Dose-intensive chemotherapy regimens combined with radiotherapy have demonstrated high efficacy in classical Hodgkin Lymphoma (cHL) in children and adolescents with about 90% EFS after 10 years. Nevertheless these results are hampered by long-term adverse events like radiotherapy-induced malignancies or procarbazine-induced male infertility. The primary objectives of the EuroNet-PHL-C1 trial aimed at demonstrating a 90% 5-year EFS in patients who were PET-negative after the two OEPA (vincristine, etoposide, prednisone,doxorubicine) induction chemotherapy cycles and thus received no radiotherapy (RT). In addition, patients in intermediate and advanced stages have been randomized between COPP (cyclophosfamide, vincristine, prednisone, procarbazine) and COPDAC (cyclophosfamide, vincristine, prednisone, dacarbazine) consolidation chemotherapy to demonstrate whether procarbazine could be replaced by dacarbazine without impairing treatment *results.* From January 2007 to January 2013, 2111 patients at median age of 14.3 years were enrolled in 16 European countries. 716 patients were classified as early stages (IA/IB-IIA) (treatment group 1, TG-1), 490 as intermediate stage (IIAE-IIB-IIIA)(TG-2) and 905 as advanced stages (IIEB,IIIB,IVA/B) (TG-3). RT was assigned to 1114 pts (52%). In the randomized part of the trial 473 pts TG-2 and TG-3 pts received COPP and 468 pts COPDAC. At the latest interim analysis the 48 months OS/EFS are 98% and 88%, EFS- TG1, EFS-TG2 and EFS-TG3 are 87.5%, 91% and 86.6% respectively (p=0.08). The EFS in patients with or without RT is 88% and 87%. EFS did not differ between the COPP and the COPDAC arm in TG2 and TG3. In TG1 ESR >30 or bulky disease was associated with inferior EFS . *Conclusions.* in this trial RT could be avoided in about 50% of patients without impairing treatment results by using an early response PET-based strategy. Dacarbazine could safely replace procarbazine in the COPP consolidation cycle, rendering COPDAC as standard consolidation. EuroNet PHL-C2 will further focus on reducing RT indication by proposing a moderate increase of chemotherapy burden in a randomized fashion.

P065

JOINT PEDIATRIC HODGKIN AND NON-HODGKIN LYMPHOMA STUDY GROUP ON GREY ZONE LYMPHOMA IN CHILDREN AND ADOLESCENTS

B. Burkhardt[1,*], O. Makarova[1,*], D. Koerholz[2], M. Zimmermann[3], S. Mueller[1], F. Knoerr[2], I. Oschlies[4], W. Klapper[4], W. Woessmann[2], C. Mauz-Körholz[2]

[1]Pediatric Hematology and Oncology, University Children's Hospital, Münster, Germany; [2]Pediatric Hematology and Oncology, Justus Liebig University, Giessen, Germany; [3]Pediatric Hematology and Oncology, Medical School Hannover, Hannover, Germany; [4]Pathology, Hematopathology Section and Lymph Node Registry, Christian-Albrechts-University Kiel and University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany

Background. In the current version of the WHO classification of lymphoid tumors the term 'grey zone lymphoma' (GZL) was introduced for the first time. The cases of GZL with characteristics of Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL) are poorly characterized in children and adolescents and need further improvement of diagnostic and treatment approaches. *Patients and Methods.* We evaluated patient's characteristics, treatment and outcome of young GZL patients reported to the German Pediatric Hodgkin lymphoma study center and/or to the NHL-Berlin-Frankfurt-Muenster study center. *Results.* Between 2003 and 2015, 27 children and adolescents with GZL, comprised of 22 boys and 5 girls, with a median age of 15 years, were identified. The GZL was identified at the time of initial diagnosis in 19 patients, in six patients the diagnosis was established at the time of relapse by comparing initial and relapse samples, and in two patients by

a reference pathology panel which reviewed primary mediastinal B-cell lymphoma (PMLBL) cases. GZL between classical Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL) was diagnosed in eleven patients, GZL between cHL and PMLBL in three cases, GZL of lymphocyte predominant Hodgkin (LPHL) and T-cell rich B-cell lymphoma (TCBCL) in eleven and in two cases grey zone between LPHL and DLBCL. Fifteen patients received frontline treatment according to protocols for HL, ten patients had treatment for mature B-NHL and two had DA-R-EPOCH. Seventeen of the 27 patients relapsed. Among them, nine patients with cHL/DLBCL - four after HL treatment, four after B-NHL treatment and one after DA-R-EPOCH; both patients with cHL/PMLBL - one after HL and one after B-NHL treatment; and six with LPHL/TCRBCL - five after HL and one after B-NHL treatment. Five of the eleven patients with GZL between LPHL and TCRBCL stayed in remission after frontline treatment, compared to only three of fourteen patients with GZL between cHL and DLBCL or PMLBL. Both patients with GZL between LPHL and DLBCL stayed in remission after frontline treatment. *Conclusions.* The diagnosis of GZL requires expert reference pathology and centralized review of staging and response evaluation. Since the relapse incidence of GZL is higher than in each of both "pure" entities HL and NHL, implementation of optimized treatment strategies for GZL is urgently needed. Therefore, global cooperative initiatives have to be undertaken, since GZL is a rare entity.

P066

HODGKIN LYMPHOMA IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS- A COMPARATIVE STUDY OF CLINICAL PRESENTATION AND TREATMENT OUTCOME

A. Englund[1,*], I. Glimelius[2,3,*], K. Rostgaard[4], S. Eloranta[2], D. Molin[3], T. Kuusk[1], P. de Nully Brown[6], P. Kamper[7], K.E. Smedby[2], H. Hjalgrim[4], G. Ljungman[1], L. Lyngsie Hjalgrim[4,5]

[1]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden; [2]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [3]Experimental and Clinical Oncology, Department of Immunology Genetics and Pathology, Uppsala University, Sweden; [4]Statens Serum Institut, Department of Epidemiology Research, Copenhagen S, Denmark; [5]The Child and Youth Clinic, Department of Paediatric Haematology and Oncology, Rigshospitalet, Copenhagen, Denmark; [6]Department of Haematology, Rigshospitalet, Copenhagen, Denmark; [7]Department of Haematology, Aarhus University Hospital, Denmark

**Both first authors contributed equally*

Hodgkin lymphoma (HL) treatment protocols for adolescents and young adults traditionally vary by age, but the biological and clinical rationale for this remains uncertain. Our aim was to investigate clinical presentation and outcome in different age groups (0-9, 10-17, 18-24 years) and to compare prognosis among patients treated in pediatric or adult departments. *Patients and Methods.* 1345 classical HL (cHL) 0-24 years were diagnosed in Denmark 1990-2010 and Sweden 1992-2009. Disease characteristics and treatment outcome were available for 1083 cHL patients treated in pediatric (n=325) or adult departments (n=758). Outcome was estimated as event free survival (EFS) and overall survival (OS) and using Cox regression. Patients treated in adult departments were mainly treated with ABVD (doxorubicine, bleomycin, vinblastine, dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicine, cyclophosphamide, vincristine, procarbazine, prednisone) +/- radiotherapy (RT) and the majority of the pediatric patients with OPPA/OEPA (vincristine, etoposide *vs* procarbazine, prednisone, doxorubicine) and COPP/COPDAC (cyclophosphamide, vincristine, prednisone, procarbazine *vs* dacarbazine) +/- RT. *Results.* Children0-9yrs had male predominance and presented with lower stage disease and lower frequency of B-symptoms and extra nodal disease. Five-year EFS was lower among Danish paediatric patients (0-14 years) [0.81 (95% confidence interval (95%CI):0.72-0.88)] than among Danish adults [0.85 (0.81-0.88)], Swedish pediatric patients (0-17 years) [0.89 (0.85-0.93)] and adults [0.90 (0.86-0.92)] (Figure 1A). There was no difference in 5- or 10-year OS (Figure 1B). Danish pediatric patients received RT (32%) less frequently than Swedish pediatric patients (71%), p<0.002, while in adults the difference was not as pronounced (Denmark 67%, Sweden 56%). In analyses adjusted for sex, stage and country, EFS and OS did not vary among patients treated in pediatric compared to adult departments. *Conclusions.* Children 0-9yrs had a different clinical presentation in several aspects, whereas adolescents 10-17yrs and young adults 18-24yrs shared similar features. There was no difference in treatment outcome between pediatric and adult departments overall. Patients in Denmark treated in pediatric departments had lower EFS than patients in Swedish pediatric departments and Swedish and Danish adult departments. This correlated to a lower use of RT in primary treatment. OS was equal between the groups.

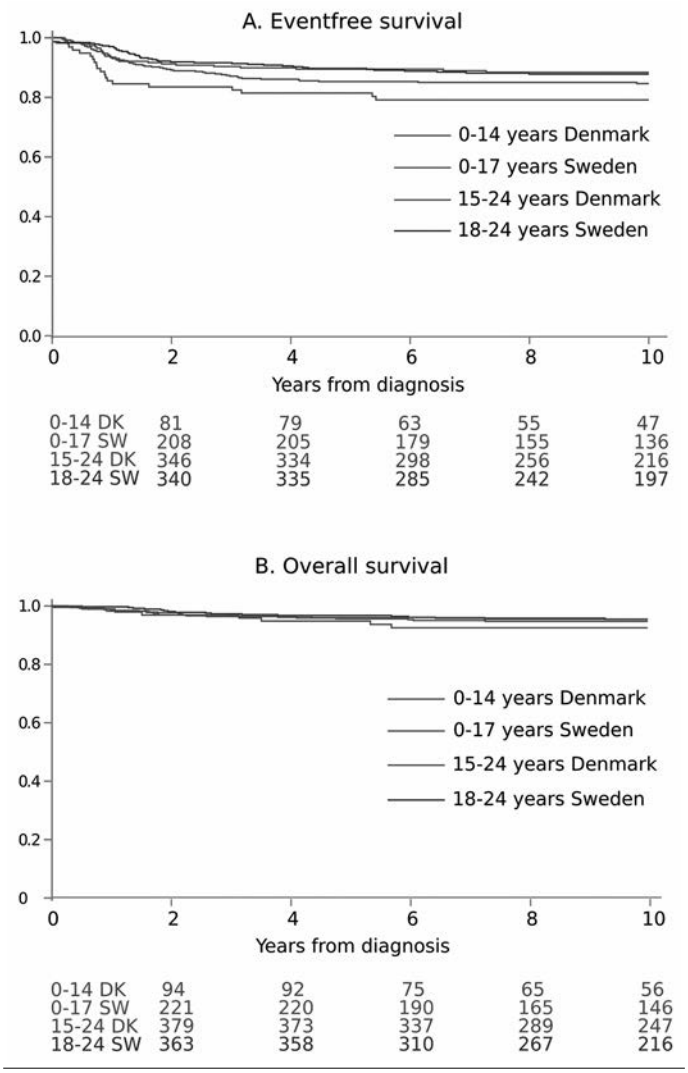

Figure 1.

P067

PHARMACOKINETICS, IMMUNOGENICITY AND SAFETY OF WEEKLY DOSING OF BRENTUXIMAB VEDOTIN IN PEDIATRIC PATIENTS WITH HODGKIN LYMPHOMA

J. Flerlage[1], M. Metzger[1], J.C. Panetta[2]

[1]Department of Oncology, St. Jude Children's Research Hospital and the University of Tennessee Health Sciences Center, Memphis, TN, USA; [2]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital and the University of Tennessee Health Sciences Center, Memphis, TN, USA

Background. To improve the success of treatment for Hodgkin Lymphoma (HL) the novel agent brentuximab vedotin (anti-CD30 agent) was developed as CD30 is highly expressed in both HL and anaplastic

large cell lymphoma. Based off the success of phase 1 and II trials it is now used as a frontline agent in a high-risk pediatric HL trial HLHR13. *Purpose.* The primary goal of this study was to evaluate the variability of pharmacokinetics for weekly dosing of 1.2 mg/kg of brentuximab vedotin, determine factors that may explain this variability, compare our drug exposure with published data for the recommended 1.8 mg/kg every 3 week dosing and evaluate toxicity with this novel agent in the pediatric population. *Methods.* Serum samples for brentuximab vedotin levels were collected at day 1 pre and post infusion, 48 hours and day 8 pre-infusion for 16 patients. A compartmental pharmacokinetic model was fit to the data using non-linear mixed effects modeling *methods.* Serum concentration of anti-therapeutic antibody was measured prior to the first 3 courses and at the end of therapy. *Results.* Brentuximab vedotin and MMAE clearance and volume were significantly correlated with weight (p<1e-10) and accounting for weight explained 75%, 84%, 61%, and 94% of the inter-individual variability in the ADC clearance, ADC volume, MMAE apparent clearance, and MMAE apparent volume respectively. The ADC clearance and volume differed by gender; clearance and volume were higher in male *vs* female patients (17%; p=0.08, and 17%; p=0.03, respectively) and explained an additional 11% and 36% of the inter-individual variability in the ADC clearance and volume respectively compared to the weight-normalized model. The ADC AUC and Cmax in our pediatric study were lower compared to those reported in adult studies (25% and 11%, respectively at 1.2 mg/kg and 35% and 16%, respectively at 1.8 mg/kg). Toxicity was comparable to that published for the standard of care backbone. All 16 patients remained negative for anti-therapeutic antibodies during and at the end of therapy. *Conclusions.* As in previous studies, weight continues to be the most significant factor explaining brentuximab vedotin pharmacokinetic variability in pediatric patients. Exposure with weekly dosing appeared safe and tolerable in pediatric patients. Given the promising clinical results of brentuximab vedotin, more studies are warranted to demonstrate safety and allow for increased use in the pediatric population.

P068

APPROACH AND FEASIBILITY OF PATIENT-REPORTED OUTCOMES IN A PHASE III CLINICAL TRIAL FOR ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA IN CHILDREN AND ADOLESCENTS

S.M. Castellino*, T.O. Henderson*, F. Keller, K. Kelly, R. Curtis, R.M. Conti, S.K. Parsons

Emory University, Children's Healthcare of Atlanta, Atlanta, GA, USA; The University of Chicago, Chicago, IL, USA; University of Buffalo School of Medicine, Buffalo, NY, Roswell Park Cancer Institute; Tufts Medical Center, Boston, MA, USA

**Co-first authors*

Objectives. We describe the feasibility of embedding PROs for chemotherapy-induced peripheral neuropathy (CIPN) and cost effectiveness (CEA) in a randomized, multi-institutional Phase III study (NCT02166463), evaluating the efficacy of the novel agent, Brentuximab vedotin, for advanced cHL in children and adolescents. *Methods.* Recruitment for PROs of interest is targeted for 250 of the planned 600 trial participants. Participation in the trial includes prospective collection of patient- and parent proxy-reported outcomes. CIPN is evaluated with the 11- item FACT-GOG-NTX and paired with the 9-item CHRIs-Global to serially evaluate health-related quality of life (HRQL) consequences of CIPN from initial diagnosis to 12 months off therapy. For CEA, US-based participants are queried from diagnosis through 36 months off therapy with the 4-item Stanford Healthcare Utilization Questionnaire (parent-report), the Health Utilities Index (HUI) 2/3, and the 23-item Caregiver Work Limitations Questionnaire (parent-report) as a measure of productivity loss. A study-designated research assistant is charged with contacting site personnel at study entry and at each scheduled assessment. All data are tracked for completion and uploaded into a web-based relational database for future analysis. Units of healthcare utilization will be monetized with unit costs from US-based administrative databases, including claims from public and private payers, based on site of care and diagnostic and/or procedure codes. Total costs will be calculated by study arm and expressed as cost per quality-adjusted life year, derived from the HUI 2/3. *Results.* The clinical trial, activated in March 2015, has enrolled 137 participants; accrual is ongoing at 170 participating institutions. Among participants 95% have completed the baseline CIPN and CEA assessments and >90% have completed subsequent measures. Monetization of significant adverse events and utilization is in progress. *Discussion.* We demonstrate feasibility of embedding PROs evidenced by high acceptance and completion rates of assessments for prospective evaluation of CIPN, HRQL, and healthcare utilization in a multi-institutional trial of children with advanced HL. Our experience serves as a proof of principle to cooperative groups regarding the resources and the feasibility of incorporating necessary PRO and health utilization outcomes into Phase III clinical trials as a component of cancer care delivery research.

P069

PREDICTION OF PRIMARY TREATMENT RESPONSE AND OUTCOME IN PEDIATRIC HODGKIN LYMPHOMA USING DIGITAL GENE EXPRESSION PROFILING

A. Mottok[1,2], R.L. Johnston[1,3], F. Chun Chan[1,3], D.W. Scott[1,4], D. Friedman[5], C.L. Schwartz[6], K. Kelly[7], T.M. Horton[8], C. Steidl[1,2]

[1]Department of Lymphoid Cancer Research and Centre for Lymphoid Cancer, British Columbia Cancer Agency, Vancouver, Canada; [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada; [3]Bioinformatics Training Program, University of British Columbia, Vancouver, BC, Canada; [4]Department of Medicine, University of British Columbia, Vancouver, Canada; [5]Vanderbilt Ingram Cancer Center, Nashville, TN, USA; [6]University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [7]Department of Pediatrics, Roswell Park Cancer Institute and University at Buffalo, Buffalo, NY, USA; [8]Baylor College of Medicine and Texas Children's Cancer Center, Houston, TX, USA

Introduction. Hodgkin lymphoma (HL) is a common pediatric malignancy, and although considered highly curable, treatment success comes at a high cost in the form of long-term toxicity and morbidity. To overcome this challenge clinical trials have evaluated risk-adapted treatment regimens aiming to maintain high survival rates and reduce treatment-related toxicity. However, risk stratification is currently limited to the use of clinical factors as there are no validated molecular biomarkers that can be employed as predictors for treatment outcome in pediatric HL. Therefore, we aimed to perform gene expression profiling (GEP) to uncover disease biology underlying treatment response and develop a prognostic model to tailor first-line therapy in pediatric HL. *Methods.* We selected specimens from patients enrolled in a phase 3 clinical trial (AHOD0031) of the Children's Oncology Group (COG) randomizing patients dependent on CT imaging-based early response criteria (slow early response, SER; rapid early response, RER). We performed intermediate density GEP (784 genes) using NanoString on RNA extracted from pre-treatment formalin-fixed, paraffin-embedded tissue biopsies. *Results.* Of the 206 tissue samples obtained, 185 (89.8%) passed quality assurance testing. We applied our previously published 23-gene predictor - developed to predict OS in adult HL patients - to the pediatric cohort. This assay failed to predict outcomes, with patients in the "high-risk" group, as assigned by the assay, trending to have superior outcomes than the "low risk" patients. Therefore, we sought to develop a novel EFS predictive model for pediatric patients. Using penalized Cox regression, we developed a 16-gene model to predict EFS in a training cohort. This model was applied to an independent cohort of 117 specimens from the same clinical trial which were enriched for treatment failure (no EFS event to EFS event ratio=1:1). Using this validation cohort, the 16-gene model separated high-risk and low-risk groups with significantly different EFS in the SER (p=0.034), but not in the RER group (p=0.81). *Conclusions.* Failure of the GEP-based model developed in adult HL suggests distinct biology underlies treatment failure in the

pediatric age group, although differences in therapy may also be a contributing factor. We describe the development of a novel predictive model for EFS in intermediate-risk pediatric HL patients which successfully risk-stratifies patients in the SER subgroup.

P070

DOES INVOLVED FIELD RADIOTHERAPY IMPROVE SURVIVAL RATES IN PEDIATRIC CLASSIC HODGKIN'S LYMPHOMA? A RETROSPECTIVE STUDY OF 694 CHILDREN

M.S. Zaghloul, H. Akoush, A. El Haddad, E. Attia, H. Taha, M. El Wakeel, W. Omar, S. El Sayed

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

Background. Pediatric Hodgkin's lymphoma represents survival success story, however late toxicity remains as a big consideration issue. *Patients and Methods.* During the period July 2007 and December 2014, 694 pediatric classic Hodgkin's lymphoma patients were treated according to risk-adapted protocol consisted of 4-8 ABDV chemotherapy courses and involved field radiotherapy (IFRT). Out of them 543 (78.2%) received IFRT with a dose of 19.8 Gy, while the other 151 (21.8%) did not receive radiotherapy for different reasons. *Results.* The 5-year overall (OS) and event-free survival (EFS) for the low risk patients were 99.7% and 92.6% respectively. These rates were 93.1% and 83.9% for the intermediate risk and 95.4% and 75.3% for the high risk respectively. The 5-year OS and EFS for those received IFRT were 98.0% and 86.9% respectively, while those who receive chemotherapy only were 92.9% and 77.8% respectively (p 0.001 for each). Radiotherapy could improve the 5-year EFS in the advanced (intermediate and high-risk) patients from 76.6% to 79.4% with marginal statistical significance (0.073). On the other hand, the OS improved from 94.5% to 96.0% though this difference did not reach the level of significance. Only one out of 318 low-risk patients died and 14 relapsed and could be salvaged. Only 25 low-risk patients did not receive IFRT and those did not show OS nor EFS differences from the 293 patients who received IFRT. Two patients developed acute myeloid leukemia & one developed thyroid cancer as second primary (0.43%). All of them received chemotherapy and IFRT. *Conclusions.* Involved field radiotherapy marginally improved the EFS in intermediate and high-risk pediatric Hodgkin's lymphoma significantly, while its improvement in OS in such patients did not reach the significant statistical level. Low-risk patient needs prospective randomized trial to thoroughly investigate this issue.

P071

CHIPS AS A PREDICTOR OF OUTCOME IN RADIATED *VS* UNRADIATED HL

C.L. Schwartz[1], S. Wolden[2], L.S. Constine[3], L. Chen[4], D. Friedman[5]

[1]University of Texas M. D. Anderson Cancer Center, Houston, TX, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]University of Rochester Medical Center, Rochester, NY, USA; [4]Children's Oncology Group, Monrovia, CA, USA; [5]Vanderbilt University School of Medicine, Ingram Cancer Center, Nashville, TN, USA

Purpose. To evaluate the CHIPS (Childhood Hodgkin International Prognostic score) in patients with intermediate risk (IR) Hodgkin Lymphoma (HL) randomized to +/- 21 Gy of involved filed radiation (IFRT) after completing 4 cycles of ABVE-PC. These patients had achieved a rapid early response (RER) to 2 cycles of ABVE-PC (RER) and complete response (CR) at the end of chemotherapy. *Methods.* Patients enrolled on COG AHOD were <21 years with IR HL. The CHIPS score was derived from clinical data on 1103 patients who had received 4 ABVE-PC and radiation. Four factors (fever, low albumin, large mediastinal adenopathy, stage 4) were identified as independent predictors of EFS. CHIPS was then examined in the cohort of RER who achieved CR and were randomized to receive or not receive IFRT. *Results.* There were 664 RER/CR patients with CHIPS scores available; 329 were randomized to no RT and 335 were randomized to RT. 4 year EFS was similar between CHIPS cohorts except for CHIPS 1. CHIPS 1 patients showed an advantage to the addition of IFRT (p=0.035). CHIPS 0 patients did well with or without IFRT. CHIPS 3 patients had poor outcomes with or without RT (Table 1). *Conclusions.* CHIPS was derived based on patients treated on COG protocol AHOD0031 who received IFRT after ABVE-PC chemotherapy. For this report, we compared CHIPS in the RER/CR cohort randomized to IFRT *vs* no IFRT. Although the overall randomization to +/- RT (Friedman, JCO 2015) did not detect any advantage to the addition of IFRT, this sub-analysis shows that 1) CHIPS was predictive of outcome in both the radiated and the un-irradiated cohort and 2) there may be a benefit for IFRT in the CHIPS 1 cohort. As in the overall cohort, CHIPS 2 and 3 patients should be considered for augmented therapy.

Table 1.

CHIPS	No RT	IFRT	4 year EFS ± S.E.	
			No RT	IFRT
0	157	154	89.9 ± 2.5	93.9 ± 2.0
1	**116**	**114**	**83.8 ± 3.5**	**92.5 ± 2.6**
2	45	57	84.1 ± 5.5	76.1 ± 5.8
3	11	10	60.6 ± 15.7	58.3 ± 16.1

P072

CYCLOOXYGENASE-2 EXPRESSION AS A PROGNOSTIC FACTOR IN PEDIATRIC CLASSICAL HODGKIN LYMPHOMA

A.H. Algammal[1], Y. Elborai[1], A. Salama[2], M. Fawzy[1], E.D. El-Desouky[3], L.M. Shalaby[1]

[1]Pediatric Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt; [2]Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt; [3]Biostatistics and Cancer Epidemiology Department, National Cancer Institute, Cairo University, Cairo, Egypt

Introduction. Cyclooxygenase-2 (COX-2) is an inflammatory enzyme and it was proved to have a role in tumor initiation, angiogenesis, and proliferation. It has been demonstrated that COX-2 expression increases in many tumors as a negative prognostic parameter. *Objectives.* We investigated the prognostic value of COX-2 expression among pediatric Classical Hodgkin Lymphoma patients. *Methods.* It is a retrospective analysis of group of pediatric patients (n=131), who were diagnosed as Classical Hodgkin Lymphoma and treated in the Pediatric Oncology department, National Cancer Institute, Cairo University, Egypt during the period from January 2005 till June 2013. and all of them were followed up till August 2015. We analyzed the relation of COX-2 expression to the most recognized clinical variables and its impact on outcome. *Results.* COX-2 was expressed in Reed-Sternberg cells in 37.4% of the whole group. The frequency of expression was found to be more among patients with bulky disease in comparison to non-bulky and the same applies to B symptoms, high ESR, extranodal extension, and advanced stage without statistical significance. With a mean follow-up period of 54.4 months, 5-year overall survival and progression free survival was lower in COX-2 positive cases than that in COX-2 negative cases; 85.3% and 78.6% *versus* 96% and 84.3%; respectively but still without statistical significance. The impact on prognosis was observed in male group of patients. 5-year overall survival in COX-2 positive cases was lower than that in COX-2 negative cases (82.9% *versus* 100%) (P value: 0.045). And there was tendency for statistical significant regarding 5-year progression free survival (75.7% *versus* 90.2%) in positive and negative cases respectively (P value: 0.06) (Figures 1 and 2). *Conclusions.* COX-2 was expressed on Reed-Sternberg cells in 37.4% of pediatric C-HL patients. It was found to be an unfavorable prognostic factor in males and might be a therapeutic target. However, further studies including larger numbers of HL patients are needed to investigate that COX-2 may be a major prognostic variable in HL.

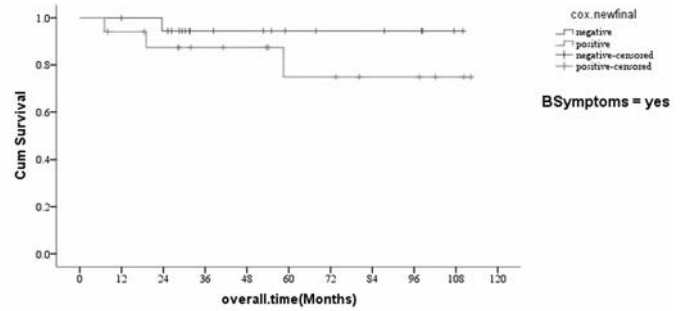

Figure 1. Five-year overall survival for cases with B symptoms in relation to COX-2.

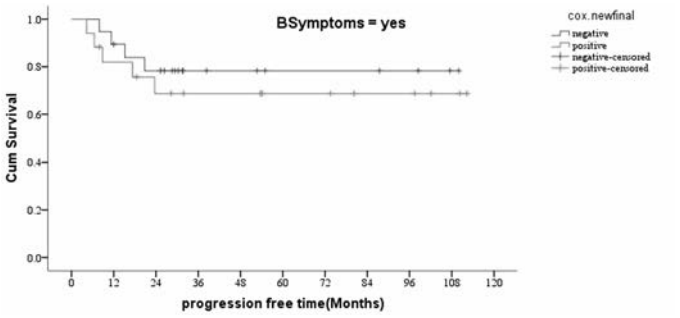

Figure 2. Five-year progression free survival for cases with B symptoms in relation to COX-2.

P073

HODGKIN LYMPHOMA IN ADOLESCENTS AND YOUNG ADULTS: RESULTS FROM A SINGLE-TERTIARY-CENTER PROSPECTIVE COHORT OF 349 PATIENTS

C. Bigenwald[1], J.E. Galimard[2], S. Amorim[1], C. Thieblemont[1], N. Boissel[1], M. Resche-Rigon[2], P. Brice[1]

[1]Hematology, Hopital Saint Louis APHP, Paris Diderot University, Paris, France; [2]Department of Biostatistics and Medical Information, CRESS INSERM U1153, Hopital Saint Louis, France

Background. Adolescents and young adults (AYA) represent one third of patients affected with Hodgkin lymphoma (HL). Clinical presentation at diagnosis differs among some subgroups of patient: children, adults, elderly, and patients with immunodeficiency. However, specific features of HL in AYA remain unclear. We conducted a single-center study to describe the characteristics of HL in AYA and to define associated factors with disease progression and/or death. *Methods.* All consecutive patients newly diagnosed with HL were prospectively recruited before the initiation of treatment from one tertiary academic center (Saint Louis Hospital, Paris, France). Clinical characteristics and outcomes of patients aged from 15 to 25 years old were retrospectively computed. The primary endpoint was the occurrence of an event defined as progression of the disease or death from any cause. June 2005 was chosen as threshold for the analysis as it constitutes the advent of TEP-TDM in current practice. Uni- and multivariate survival analyses were performed using a Cox model. *Results.* 349 patients were included between 1979 and 2013, with a median follow-up of 7 years. Nodular sclerosis was the most representative histologic subtype (86.3%). According to Ann Arbor classification, patients had a disseminated disease in 45% of cases. 289 (83%), 97 (28%) and 140 patients (56%) had a mediastinal lymph node, a bulky mediastinum and an extra-nodal involvement, respectively. No significant difference in terms of clinical presentation was noticed between patients younger than 21 year-old compared to older, except a more frequent EBV association after 21. Patients diagnosed after June 2005 presented more frequently a disseminated disease (36% *vs* 46.2%, p=0.04). 10 year-event free survival rate was estimated at 81% (95CI [76,7-85,5]). The first cause of mortality was HL. In multivariate analysis, stage 3 and 4 according to Ann Arbor classification were independently associated with the occurrence of event. Conversely, nodular sclerosis subtype was associated with a favourable outcome. *Conclusions.* Our large prospective cohort revealed interesting features of HL in AYA. Considering data from the literature, our study suggests a more frequent mediastinal involvement and a more advanced stage of disease in AYA compared to children and adults. Despite these pejorative features, relapse rate and mortality rates remain low.

P074

PROGNOSTIC VALUE OF 'INTERIM' POSITRON EMISSION TOMOGRAPHY AMONG CHILDREN WITH ADVANCED HODGKIN LYMPHOMA IN DEVELOPING COUNTRIES; CHILDREN CANCER HOSPITAL EGYPT EXPERIENCE

R. Khedr[1], A. Hamouda[1], S. Naguib[2], M. Khalaf[3], S. Fikry[4], A. El Sayed[5], H. Taha[6], M. Saad Zaghloul[7], I. Attia[1]

[1]Pediatric Oncology Department, National Cancer Institute, Cairo University Children, Cancer Hospital 57357, Cairo, Egypt; [2]Clinical Research Department, Children Cancer Hospital 57357, Cairo, Egypt; [3]Radiodiagnosis Department, National Cancer Institute, Cairo University Children, Cancer Hospital 57357, Cairo, Egypt; [4]Clinical Pharmacy, Children Cancer Hospital 57357, Cairo, Egypt; [5]Nuclear MedicineDepartment, National Cancer Institute, Cairo University Children, Cancer Hospital 57357, Cairo, Egypt; [6]Surgical Pathology Department, National Cancer Institute, Cairo University Children, Cancer Hospital 57357, Cairo, Egypt; [7]Radiation Therapy Department National Cancer Institute, Cairo University Children, Cancer Hospital 57357, Cairo, Egypt

Rationale and Aim of the Study. This is a retrospective, single center study was done to assess the prognostic role of 'interim' positron emission tomography (PET) performed during treatment of advanced stages HL with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) in pediatrics patients. *Patients and Methods.* Three hundred and eighty one patients with newly diagnosed Hodgkin lymphoma were enrolled. One hundred sixty five patients with early unfavorable and 216 with advanced-stage disease were treated with ABVD ± involved-field radiotherapy (IFR). PET scan was performed at baseline and after two cycles of chemotherapy. Treatment was not changed according to the results of the interim scan. PET scans reports was used using the Deauville five-point scale, blinded to treatment outcome. *Results.* Eighty-seven scans out of 336 were scored as positive (17.3%) and 249 (82.7%) as negative. The 5- years overall survival (OS) was 94% (95% Confidence Interval (CI) :91.5 – 96.6), 86.2% (95% CI :78.3 - 94) for patients with interim positive scans and 97% (95% CI:94.2 - 99.3) for patients with interim negative scans (P<0.0001). The 5-year Event-free survival (EFS) rate was 80% (95% CI :74.3 – 84.4) for the whole study population, 63.2% (95% CI :48.6 – 77.4) for patients with interim positive scans and 82.6% (95% CI :76.3 – 88.8) for patients with interim negative scans (P<0.0001). EFS in correlation with patients who received IFR was 82.4% (95% CI: 74.3-90.4) and in those who did not receive IFR was 71.9% (95% CI: 63.6-76.1) (Figure 1).

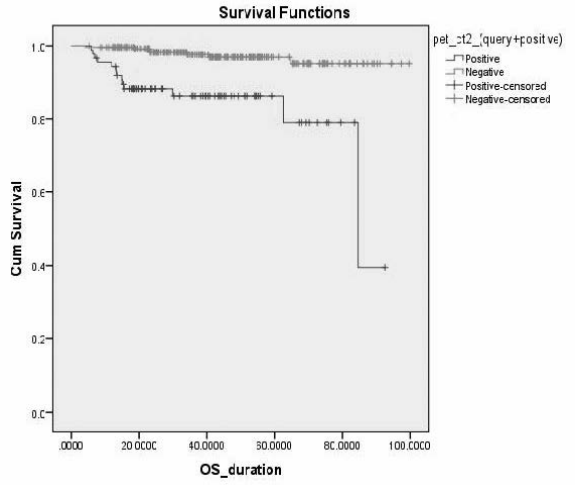

Figure 1.

Conclusions. The prognostic role and validity of using the interim PET scan response have been confirmed to be strongly related to treatment outcome by the present study. These results confirm that ABVD with or without IFR is an adequate treatment for more than 70% of patients in advanced stages HL.

P075

LONG-LASTING REMISSION IN AN ADOLESCENT WITH REFRACTORY HODGKIN LYMPHOMA AFTER BRENTUXIMAB VEDOTIN–CONTAINING TREATMENT. A CASE REPORT

A. Fedorova, A. Markavets, L. Hushchina, O. Aleinikova

Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Minsk, Belarus

Background. Despite the high cure rate of childhood Hodgkin lymphoma (HL) patients with refractory HL remain incurable with standard therapies. Autologous or allogeneic heamotopoietic stem cell transplantation (HSCT) is considered the most effective method of consolidation in relapsed or refractory HL treatment. Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate that has become the preferred therapy option for adults with HL who have relapsed after or are ineligible for auto HSCT, but data relating to pediatric patients are very limited. *Objectives.* We aimed to report a case of effective and tolerable BV-containing treatment in an adolescent with refractory HL. *Case Report.* A 17-year-old female with enlarged cervical, supra-/subclavicular, axillary, mediastinum lymph nodes and multiple lesions in both lungs was admitted to our hospital. FDG-PET/CT and lymph node biopsy were performed and nodular sclerosis HL stage IVA was diagnosed. Treatment was administered according to modified DAL-HD-95 protocol, and consisted of 6 courses of chemotherapy (2OPPA/4COPP) plus radiation therapy of the involved fields (20 Gy). Partial response was achieved after the 2nd cycle OPPA and stable disease was observing during the all remaining treatment. One month after the end of treatment the patient showed disease progression in mediastinum and lungs, confirmed by FDG-PET/CT and lung biopsy. Positive response was obtained after the two courses (IEP, ABVD) of second-line therapy, but patient remained PET-positive. Treatment was continued with 3 cycles VV (BV 1.8 mg/kg/bendamustine/dexamethasone), PET-negative complete remission was achieved and autoHSCT (conditioning regimen consisted of BEAM) with allogeneic bone marrow-derived mesenchymal stem cells cotransplantation was subsequently performed. Further the patient received adjuvant monotherapy with BV 1.2 mg/kg every 3 weeks (a total of 12 doses). The only evident side effect seen in BV treatment was deteriorating peripheral neuropathy. Patient remains in PET-negative complete remission for 14 months after autoHSCT and 4 months after the last dose of BV. *Conclusions.* Our experience should encourage to use BV in combination with chemotherapy or even alone in pediatric patients with refractory HL.

P076

OVERVIEW AND SURVIVAL OF PEDIATRIC ADVANCED STAGE HODGKIN LYMPHOMA TREATED IN DEVELOPING COUNTRIES; CHILDREN CANCER HOSPITAL EGYPT EXPERIENCE

A. Hamouda[1], R. Khedr[1], S. Naguib[2], M. Khalaf[3], S. Fikry[4], A. El Sayed[5], H. Taha[6], M. Saad Zaghloul[7], I. Attia[1]

[1]Pediatric Oncology Department, National Cancer Institute, Cairo University Children, Cancer Hospital 57357, Cairo, Egypt; [2]Clinical Research Department, Children Cancer Hospital 57357, Cairo, Egypt; [3]Radiodiagnosis Department, National Cancer Institute, Cairo University Children, Cancer Hospital 57357, Cairo, Egypt; [4]Clinical Pharmacy, Children Cancer Hospital 57357, Cairo, Egypt; [5]Nuclear Medicine Department, National Cancer Institute, Cairo University Children, Cancer Hospital 57357, Cairo, Egypt; [6]Surgical Pathology Department, National Cancer Institute, Cairo University Children, Cancer Hospital 57357, Cairo, Egypt; [7]Radiation Therapy Department National Cancer Institute, Cairo University Children, Cancer Hospital 57357, Cairo, Egypt

Background and Aim of the Study. The major challenge in advanced stage Hodgkin Lymphoma is to optimize the balance between overall survival and treatment related toxicity. The aim of the study was to describe the pediatric population with advanced Hodgkin lymphoma (HL) in our country and their treatment outcome. *Patients and Methods.* This is a retrospective single center study. Data analysis for children with advanced stage HL (IIB or IIIB with bulk disease, or stage IV) as done. Demographic data, staging, number of cycles (doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD)) received and whether or not consolidation radiotherapy (RTH) was administered. Positron emission tomography (PET) was performed baseline and after the second cycle to detect early response without any change to treatment plan. *Results.* Three hundred and eighty-one patients with newly diagnosed Hodgkin lymphoma were enrolled in the data analysis. Male (283) to female (98) ratio 3:1. B-symptoms was present in 60% of patients. Ann Arbor staging distribution was as follows; 68 (17.8%) IIB, 97 (25.5%) IIIA, 96 (25.2%) IIIB, 55 (14.4%) IVA, 65 (17.1%) IVB. the prevalent pathological subtype was the nodular sclerosis accounting for 54% (203/381) followed by the mixed cellularity 148/ 381 (39%) .One hundred sixty-five patients with early unfavorable and 216 with advanced-stage disease were treated with ABVD ± RTH. One hundred twenty- nine (34%) patient did not receive RTH. The Five-years Overall survival (OS) and the Event free survival (EFS) in these patients was 90.7 (95% CI: 85.4-95.9 and 71.9% (95% CI: 63.6-76.1) (p value 0.006) respectively. The OS and EFS of patient with advanced stage HL in the whole study population was 94.1 (95% CI: 91.5-96.6) and 79.4 (95% CI 74.3-84.4) respectively. *Conclusions.* More than 90% of patients are cured with risk-based combined-modality therapy, yet these therapies are frequently associated with risks for significant long term toxicities; innovative approaches are needed for those patients who have a high risk of failure with current therapies.

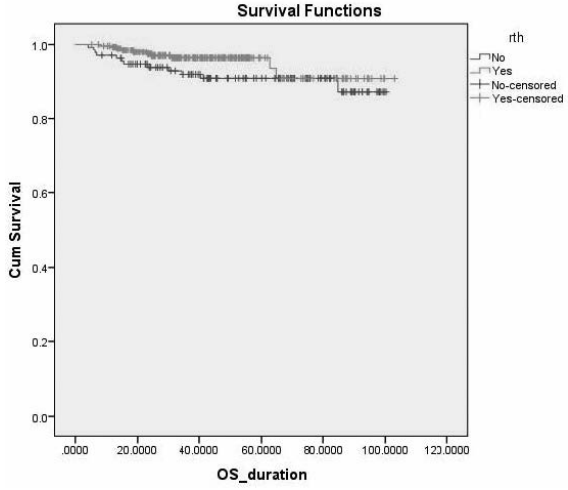

Figure 1.

Positron Emission Tomography

T019

ONLY FOCAL BONE MARROW FDG UPTAKE IN BASELINE FDG-PET SCAN HAS A DIAGNOSTIC AND PROGNOSTIC IMPACT IN HODGKIN LYMPHOMA: RESULTS FROM AN INTERNATIONAL COLLABORATIVE STUDY

C. Zwarthoed[1], T.C. El-Galaly[2], M. Canepari[3], M.J. Ouvrier[1], S. Viviani[4], L. Rigacci[5], L. Trentin[6], C. Rusconi[7], S. Luminari[8], M. Cantonetti[9], S. Bolis[10], A. Borra[3], F. Salvi[11], E. Subocz[12], J. Tajer[13], W. Kulikowski[14], B. Małkowski[15], J.M. Zaucha[16], M. Ettaiche[17], A. Gallamini[17], J. Darcourt[1]

[1]Nuclear Medicine Department, A. Lacassagne Cancer Center, Nice, France; [2]Hematology Department, Aalborg University Hospital, Denmark; [3]Hematology Department, S.Croce Hospital, Cuneo, Italy; [4]Hematology Department and Paediatric Onco-Haematology, National Tumour Institute, Milan, Italy; [5]Hematology Chair University of Florence, Policlinico Careggi,, Florence, Italy; [6]Hematology Section, Department of Medicine, Padua University, Padua, Italy; [7]Hematology Department Ca-Granda Niguarda Hospital, Milan, Italy; [8]Hematology Department Modena and Reggio Emilia University, Reggio Emilia, Italy; [9]Hematology Department Tor Vergata University, Rome, Italy; [10]Hematology Department San Gerardo Hospital Monza, Italy; [11]Hematology Department S. Antonio and Biagio Hospital, Alessandria, Italy; [12]Hematology Department, Military Institute of Medicine, Warszawa, Poland; [13]Lymphoproliferative Disease Department, Maria Sklodowska-Curie Memorial Institute, Warszawa, Poland; [14]Hematology Department, Interior Ministry Hospital, Warmia and Mazury Medical University, Olsztyn, Poland; [15]Nuclear Medicine Department, Oncology Center, Bydgoszcz, Poland; [16]Gdynia Oncology Center and Department of Oncological Propaedeutic, Medical University of Gdansk, Gdansk, Poland; [17]Research, Innovation and Statistics Department, A. Lacassagne Cancer Center, Nice, France

Background. PET/CT-ascertained bone marrow involvement (BMI) is the most frequent reason for Hodgkin Lymphoma (HL) upstaging by baseline PET/CT (PET-0). However, shared rules for BMI detection in PET/CT still lack. This study analyzed the diagnostic and prognostic value of BM FDG uptake pattern in PET-0. *Patients and Methods.* 186 early unfavorable and advanced stage HL patients (pts), enrolled in two International studies on the role of interim PET (PET-2) in HL, were analyzed. Treatment (Tx) was ABVDx6 cycles (advanced) or x4 cycles plus IF radiation (early unfavorable). No Tx adaptation on PET-2 was allowed. Two reviewers blinded to Tx outcome independently reviewed PET-0; discordant results were jointly discussed. Focal BM lesions (fPET+) were defined as focally increased FDG-uptake >liver uptake (with or without CT abnormalities), visible in ≥2 slices of fused images. Diffusely increased FDG-uptake was defined as a diffuse uptake >liver (dPET+). No uptake (nPET+) was defined as absent or faint (<liver) diffuse uptake. *Results.* After a median follow-up of 33.8 (16.6 – 109.4) months, 40 pts (21.5%) progressed or relapsed, and 9 (4.9%) died. The 3-Y OS and PFS was 98.0% and 83.8%, respectively. In 33/40 (82.5%) pts with a fPET+ all the PET-0 focal lesions had disappeared in PET-2. Half of pts (90/186: 48.4%) had a nPET+. dPET+, recorded in 56 (30.1%) pts, correlated with younger age, low hemoglobin, leukocytosis, low albumin and diffuse FDG spleen uptake. Notably, dPET+ had an identical 3-Y PFS to nPET+ pts: 83.2% and 81.6%, respectively (p=0.732). Out of 40 (21.5%) fPET+ pts, 11 had unifocal and 29 multifocal (≥2) lesions, with a 3-y PFS of 70.1% and 67.0%, respectively. Multifocal fPET+ pts had a worse PFS compared to dPET+ p. (p=0.05). BM biopsy (BMB) was positive in 6/40 (15%) of fPET+ and 0/56 (0%) of dPET+ pts. In univariate analyses, bulky disease (HR 2.4, p=0.008), IPS (HR 3.4, p=0.0001), and PET-2 (HR 11.0, p<0.0001) were significantly associated with PFS, but only PET-2 was still significant in multivariate analysis (p<0.0001). The kappa-value for inter-observer agreement was 0.83 for focal and 0.78 for diffuse uptake. *Conclusions.* The study confirms that (1) FDG-PET scan is a reliable tool for BMI assessment in HL; (2) only focal FDG uptake in PET-0 has an adverse prognostic value and should be considered to represent BMI; (3) BMI could be detected with high accuracy and inter-observed agreement in routine HL staging with PET/CT.

T020

STRONG PREDICTIVE VALUE OF PET BASED METABOLIC TUMOR VOLUME ON SURVIVAL AFTER AUTOLOGOUS HCT FOR HODGKIN LYMPHOMA

V. Procházka[1], R.R. Gawande[2], Z. Cayci[2], J.W. Froelich[2], Q. Cao[3], V. Bachanova[4]

[1]Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic; [2]Department of Radiology, University of Minnesota Twin Cities, MN, USA; [3]CTSI Biostatistics, University of Minnesota Twin Cities, MN, USA; [4]Division of Hematology, Oncology and Transplantation, University of Minnesota Twin Cities, MN, USA

Background. High-dose chemotherapy with autologous hematopoietic cell transplant (AHCT) is a standard treatment for relapsed/refractory Hodgkin lymphoma patients (R/R HL); however, 40-50% fail therapy. Metabolic FDG-PET is a powerful tool to predict treatment responses in HL. The value of more precise quantitative measurements combining volume with the metabolic activity in patients having residual HL before AHCT is unknown. *Aim.* To determine the predictive value of total metabolic volume (TMV) and total lesion glycolysis (TLG) in R/R HL patients undergoing AHCT. *Methods.* We analyzed 96 consecutive patients with R/R HL undergoing AHCT in 2004-2014. All had PET/CT ≤4 weeks before AHCT. Two independent radiologists assessed PET images using semi-quantitative Deauville (D) 5-point scale and selected all hypermetabolic sites to determine regions of interests. Analytic software was used to calculate TMV and TLG. *Results.* Median age at transplant was 33.1 years (range 18.0-71.3); 51% of patients were males. Patients were limited stage (60%) or advanced, commonly with extranodal (32%) and bone marrow (11%) disease. Nodular sclerosis (86%) was most common. Most patients (69%) relapsed in <1 year or were refractory to front-line therapy. PET negativity (neg) was achieved in 61 patients (63.5%), whereas 35 remained PETpos, with D1-2 (n=61), D3 (n=11), D4 (n=19), and D5 (n=5). Median TMV was 8.0 cm^3 (range 1.3-102.1), median TLG was 23.7 (range 4.0-813.1), and median SUVmax was 5.2 (range 2.7-23.2). Two-year PFS in PETneg patients (63%; 95% CI 50-74%) was significantly better than in PETpos patients (35%; 19-51%; p=0.014). In Cox regression analysis, D4-5 was associated with a 3.7-fold increased risk of failure compared to D1-3 (HR 3.73; 95% CI 1.92-7.28; p<0.01). PETpos patients with high TMV (>8 cm^3) had significantly lower 2-year PFS than those with low TMV (11% *vs* 53%; p=0.03). High TLG (>24) identified patients with poor 2-year PFS (12% *vs* 57%; p=0.04). *Conclusions.* Patients with R/R HL and low MTV and TLG prior to AHCT have similar outcomes to PETneg patients. Quantitative pretransplant PET may identify subgroups of very poor AHCT responders in whom alternative therapies should be considered.

Support. Supported by the Fulbright commission grant.

T021

SEMI-QUANTITATIVE PARAMETERS TO IMPROVE THE INTERIM FDG-PET/CT POSITIVE PREDICTIVE VALUE IN HODGKIN LYMPHOMA

A. Cuccaro[1], S. Annunziata[2], E. Galli[1], S. Bellesi[1], F. D'Alò[1], M.L. Calcagni[2], A. Giordano[2], V. Rufini[2], S. Hohaus[1]

[1]Institute of Hematology; [2]Institute of Nuclear Medicine, Catholic University of the Sacred Heart, Rome, Italy

Interim FDG-PET/CT (iPET), according to the 5-point Deauville score (5p-DS) is the strongest predictor for outcome in Hodgkin Lymphoma (HL). In PET-guided treatment approaches, iPET-positive patients are candidates for more intensive and potentially more toxic treatments. Nevertheless, recent studies have shown that the positive predictive value (PPV) of iPET visual analysis with 5p-DS has still some limitations to optimally identify patients at different prognosis. Semi-quantitative parameters could improve PPV of iPET. Aim of this retrospective study is to compare PPV of visual and semi-quantitative analysis of iPET in HL patients treated with ABVD. We studied 67 HL patients (median age 39 years; 30 females, 37 males; 38 limited Stage, 29 advanced) at

our Institution between 2007 and 2013, who were treated with ABVD. iPET was performed after 2 cycles of ABVD. For visual analysis, the 5p-DS was used, setting different cut-points at 5p-DS>3 and 5p-DS>4 as positive. For semi-quantitative analysis, we evaluated the ratio between lesion and liver SUVmax (rPET); the ratio between lesion and mediastinal blood pool SUVmax (mPET); the ratio between lesion SUV-peak and liver SUVmean (qPET). Primary endpoint was two-year progression-free survival (PFS). ROC analysis was used to determine the best cut-point of semi-quantitative parameters to identify treatment failures. In visual analysis, 25/67 patients had 5p-DS >3, and 5p-DS was >4 in 14/67 patients. PFS according to 5p-DS>3 and 5p-DS>4 was 53% and 27%, respectively and their PPV was 40% and 57%, respectively. The semi-quantitative parameters between residual lesion and the different backgrounds rPET, mPET and qPET were prognostic factors in our population (p<0.01). The most accurate cut-point in predicting adverse events for rPET, mPET and qPET were 1.14, 2 and 1.46, respectively. For values higher than these cut-point, PFS were 15%, 25% and 20% and the PPV were 70%, 63% and 80%, respectively. iPET semi-quantitative parameters appear to perform better than visual analysis for outcome prediction in HL. In particular, ratios between residual lesion and background SUV (liver or mediastinal blood pool) could improve the predictive value of relapse or progression.

P077

THE IMPORTANCE OF BONE MARROW 18F-FDG UPTAKE AND FOCAL SKELETAL LESIONS ON SURVIVAL IN PATIENTS WITH NEWLY DIAGNOSED HODGKIN LYMPHOMA

M.A. Pedersen[1], L.C. Gormsen[1], P. Kamper[2], A. d'Amore[2], G. Enblad[3], D. Molin[3], C. Wassberg[4], F. d'Amore[2]

[1]Department of Nuclear Midicine & PET-centre. Aarhus University Hospital, Denmark; [2]Department of Haematology. Aarhus University Hospital, Denmark; [3]Department of Immunology, Genetics and Pathology. Uppsala University Hospital, Sweden; [4]Consultant Radiologist and Nuclear Medicine. Karolinska University Hospital, Huddinge, Stockolm, Sweden

Background. 18F-FDG-PET/CT is an established method for staging patients with newly diagnosed Hodgkin Lymphoma (HL). It has a high ability to detect skeletal and bone marrow involvement. It has been discussed whether diffusely increased bone marrow uptake (BMU) of 18F-FDG indicates bone marrow involvement or not. In addition, the importance of unifocal *versus* multifocal bone lesions on survival is under debate. Thus, the aim of our study was to examine the prognostic value of BMU and compare it with that of uni- and multifocal lesions.

Materials and Methods. 217 patients from Aarhus and Uppsala university hospitals (mean age 42, range 8-83) with newly diagnosed HL were included. BMU was calculated as SUVmax in the vertebral column (L3/L4) divided by liver SUVmax. In case of focal 18F-FDG-uptake in bone, patients were categorized as having uni- or multifocal lesions. For survival analysis, patients were divided into four groups: Patients with BMU below the median and no focal lesions (lowBMU), patients with BMU higher than the median and no focal lesions (highBMU), patients with a single bone lesion (unifocal), and patients with multifocal bone lesions (multifocal). *Results.* Median BMU was 1.15 (range 0.52–5.56). 42/217 (19.4%) patients had either unifocal (21/217) or multifocal lesions (21/217). With a median follow-up time of 41 months, 3-year PFS was 87% (lowBMU), 88% (highBMU), 67% (unifocal), and 58% (multifocal). The presence of focal bone lesions (uni- or multifocal) was associated with a significantly inferior PFS (log-rank p=0.00046), but no significant difference in PFS between unifocal and multifocal lesions was observed (log-rank p=0.35). Multivariate analysis (Cox regression) on a subset of patients (n=183), showed that presence of bone lesions, age, and leukocyte count were independent predictors of PFS whereas gender, haemoglobin, albumin, and sedimentation rate were not (Figure 1). *Conclusions.* Diffusely increased BMU at initial staging was not associated with a poor prognosis. The presence of focal bone lesions was associated with significantly inferior prognosis, regardless of whether they were uni- or multifocal, and should therefore be considered equally important risk factors. Whether this bone lesion-associated clinical picture of HL also correlates to specific biological features, remains to be clarified.

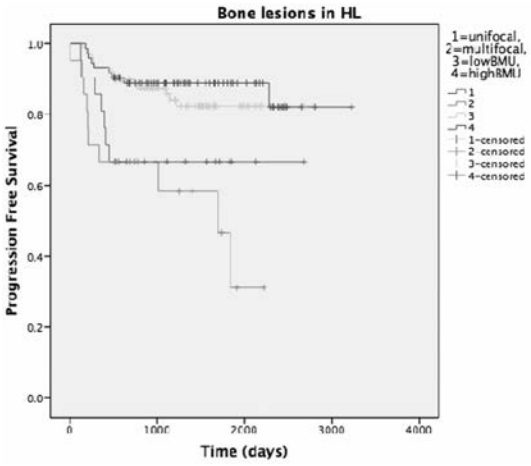

Figure 1.

P078

INTERIM PET POSITIVITY IN HODGKIN LYMPHOMA: CLINICAL FEATURES AND OUTCOMES

F. Gaudio[1], T. Perrone[1], P. Sindaco[1], F.E. Laddaga[1], C. Pasciolla[1], A. Franco[1], A.N. Asabella[2], P. Pedote[3], G. Specchia[1]

[1]Hematology, University of Bari, Bari, Italy; [2]Nuclear Medicine, University of Bari, Bari, Italy; [3]Radiology, University of Bari, Bari, Italy

Introduction. Hodgkin's lymphoma (HL) is a highly curable disease and 5-year survival is improving, being currently 86%. Cure rates of more than 90% for early HL and more than 70% for those with advanced HL are expected. Performing a positron emission tomography (FDG-PET), after two cycles of therapy, has proven to be a reliable tool in the prediction of patients' outcomes, but not all patients with positive interim PET have poor outcomes. *Patients and Methods.* In this single center retrospective study we collected clinical data of positive interim PET cases among all the 213 patients with a diagnosis of classic Hodgkin lymphoma admitted to our unit from 2006 to 2015. *Results.* A positive interim PET was reported in 48/213 patients (22.5%); 24 (50%) patients were classified as having 3-4 stage disease. Median age was 29 years (14-79); 20 (42%) patients were male. The presence of B symptoms was described in 25 (53%) patients and 23 (47.9%) patients had bulky disease. ESR was high in 33 (68.8%) patients; 2 (4.2%) patients had an infiltrated bone marrow biopsy; 15 (31.3%) patients presented with extranodal disease. After the first line therapy, 17 (35%) patients experienced disease progression or a relapse. Progression Free Survival at 40 months was 62.2% (Figure 1); Overall Survival was 95,7%, with a median follow-up of 38 months. 65% of our patients with a positive interim PET did not develop relapse/refractory disease, in contrast with the known prognostic value. We focused on clinical features in this population. A scleronodular histotype was present in 96% of patients, 7 (26.9%) were male. ESR was high in 20 (76.9%) patients. 24 patients (92%) had no disease at bone marrow biopsy. 6 (23.1%) patients had extranodal disease; 18 (69.2%) were younger than 45. Stages 3 or 4 were present in 11 (42.3%) patients, 14 (53.8%) presented with B symptoms, and 14 (53.8%) patients had bulky disease. We performed chi square test to compare clinical features of positive/negative PET populations, but none demonstrated a statistically relevant difference. *Conclusions.* Patients with interim PET positive in 65% of cases presented a responsive disease. Further studies could identify a series of clinical features in the interim PET positive population which may predict a better outcome. Novel approaches aim to individualise therapeutic choices, and to minimise toxicity while maximising response, above all in the era of new immunological and molecular targeting agents.

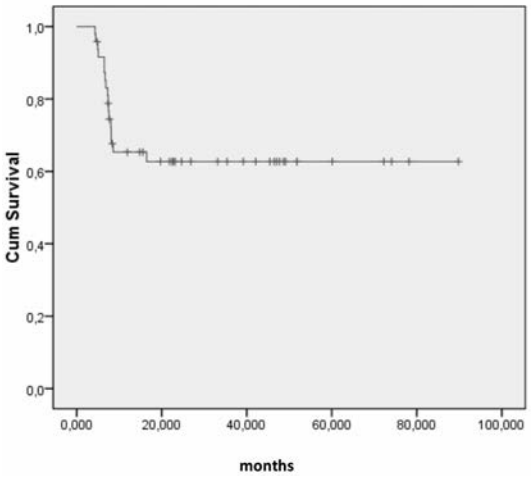

Figure 1. Progression free survival in patients with Hodgkin's lymphoma and Interim PET positivity.

P079

IS FDG-PET THE MOST SENSITIVE TOOL TO DIAGNOSE BLEOMYCIN INDUCED PNEUMONITIS IN HODGKIN'S LYMPHOMA?

E. Öztürk, O. Falay, Y. Bölükbaşı, T. Gümü, S. Örnek, M. Özbalak, O. Demirkol, B. Ferhanoğlu

Clinic of Hematology, Koç University Hospital Istanbul, Istanbul,Turkey; Clinic of Nuclear Medicine, Koç University Hospital Istanbul, Istanbul,Turkey; Clinic of Radiaton Oncology, Koç University Hospital Istanbul, Istanbul,Turkey; Clinic of Radiology, Amerikan Hospital Istanbul, Istanbul,Turkey

Bleomycin is an antineoplastic agent which may cause fatal pulmonary toxicities where early diagnosis of bleomycin induced pneumonitis (BIP) is crucial. In clinical practice, formal pulmonary function testing with inclusion of carbon monoxide diffusion capacity, is quite unpredictable at isolating patients at risk for major bleomycin toxicity. In small numbered case series, FDG PET/CT scan have shown to be helpful to reveal the inflammation secondary to the BIP, but FDG is not known to be specific to diagnose this fatal side effect. We analyzed FDG-PET/CT scans of 77 Hodgkin Lymphoma (HL) patients retrospectively to evaluate BIP. Thirteen patients have augmented abnormal FDG activity at their lungs after the exclusion of lymphoma involvement of the lung or pleura, radiation pneumonitis, infection, or cardiogenic pulmonary edema. Median age of the study population was 41 years and the average bleomycin dose was 134 mg. The FDG activities on the lungs were predominantly diffuse, bilateral, and mostly localized at the lower lobes and subpleural places. Interim PET revealed BIP in 8 of these 13 patients. Six of the 13 patients (46%) were asymptomatic during PET imaging. One of the patients without any clinical symptoms related to BIP continued to take bleomycin despite findings of FDG-PET, and ultimately lost secondary to bleomycin toxicity. The rest of the patients that bleomycin was omitted from the treatment regime and methylprednisolone was administered as routine approach demonstrated a favorable clinical course. Clinical and radiologic findings of BIP have been completely resolved. This study results suggest that routine interim or end of treatment PET/CT scan could have an additional benefit in clinic by alarming the diagnosis of asymptomatic BIP patients.

Relapsed Hodgkin Lymphoma

T022

CHECKMATE 205 COHORT C: NIVOLUMAB IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA AFTER PRIOR BRENTUXIMAB VEDOTIN AND AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

P.L. Zinzani[1], A. Engert[2], A. Younes[3], A. Santoro[4], S. Ansell[5], J. Timmerman[6], G. Collins[7], P. Armand[8], K.J. Savage[9], M. Trneny[10], M. Fanale[11], J. Kuruvilla[12], J.B. Cohen[13], M. Shipp[8], S. Rodig[14], K. Kato[15], A. Sumbul[15], B.A. Farsaci[15], V. Ratanatharathorn[16]

[1]Institute of Hematology "L. e A. Seràgnoli", University of Bologna, Bologna, Italy; [2]University Hospital of Cologne, Cologne, Germany; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Humanitas Cancer Center, Humanitas University, Rozzano (MI), Italy; [5]Mayo Clinic, Rochester, MN, USA; [6]University of California, Los Angeles, CA, USA; [7]Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, UK; [8]Dana-Farber Cancer Institute, Boston, MA, USA; [9]British Columbia Cancer Agency, Vancouver, British Columbia, Canada; [10]Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic; [11]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]University of Toronto and Princess Margaret Cancer Center, Toronto, Ontario, Canada; [13]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [14]Brigham and Women's Hospital, Boston, MA, USA; [15]Bristol-Myers Squibb, Princeton, NJ, USA; [16]Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA

Background. Nivolumab (nivo), a fully human IgG4 immune checkpoint inhibitor monoclonal antibody targeting programmed death receptor-1 (PD-1), is approved in the USA for classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (ASCT) and post-transplantation brentuximab vedotin (BV). CheckMate 205 is a multicohort international phase 2 trial (NCT02181738) of nivo that treated 243 pts with cHL after failure of ASCT in 3 cohorts: A (BV-naïve pts), B (pts with BV treatment after ASCT), and C (pts who received BV prior to and/or after ASCT). With a minimum 6-mo follow-up in Cohort B, ORR per independent radiologic review committee (IRRC) was 66% and 6-mo PFS was 77%, with an acceptable safety profile (Younes *et al.* Lancet Oncol 2016 [in press]) Here we present preliminary results of pts from Cohort C, with a minimum follow-up of 6 mo. *Aim.* Assess efficacy and safety of nivo in previously unreported Cohort C pts, including those who received BV prior to ASCT (not tested in Cohort B).

Table 1.

	Cohort C (n=100)		
ORR per IRRC, n (%) [95% CI]	73 (73.0) [63.2, 81.4]		
CR, n (%) [95% CI]	17 (17.0) [10.2, 25.8]		
PR, n (%) [95% CI]	56 (56.0) [45.7, 65.9]		
6-month PFS rate per IRRC, % [95% CI]	76.6 [66.3, 84.2]		
Median PFS, months [95% CI]	11.2 [8.5, NA]		
Median DOR, months [95% CI]	7.0 [6.7, NA]		
Cohort C subgroups			
	BV only before ASCT (n=33)	**BV only after ASCT (n=57)**	**BV before + after ASCT (n=8)**
ORR per IRRC, n (%) [95% CI]	23 (69.7) [51.3, 84.4]	41 (71.9) [58.5, 83.0]	7 (87.5) [47.3, 99.7]
CR, n (%) [95% CI]	6 (18.2) [7.0, 35.5]	7 (12.3) [5.1, 23.7]	3 (37.5) [8.5, 75.5]
PR, n (%) [95% CI]	17 (51.5) [33.5, 69.2]	34 (59.6) [45.8, 72.4]	4 (50.0) [15.7, 84.3]
6-month PFS rate, % [95% CI]	83.7 [65.1, 92.9]	71.2 [56.7, 81.6]	83.3 [27.3, 97.5]
Median PFS, months [95% CI]	11.2 [8.5, NA]	8.9 [8.3, NA]	NA [5.6, NA]
Median DOR, months [95% CI]	7.0 [6.7, NA]	NA [5.4, NA]	NA [3.3, NA]
NA, not achieved Median and rates computed using Kaplan-Meier method			

Methods. Pts in Cohort C received nivo 3 mg/kg IV q2 wk until disease progression, unacceptable toxicity, or investigator-assessed complete response (CR) lasting 1 yr. Pts who discontinued nivo with CR could re-initiate nivo if they relapsed ≤2 yr from discontinuation. The primary endpoint was ORR per IRRC using 2007 International Working Group criteria, based on CT and PET imaging. Pts were divided into subgroups by timing of prior BV treatment relative to ASCT. *Results.* 100 pts were treated, with a median age of 32 (range 19-69), and a median of 4 (range 2–9) prior lines of therapy. ORR by IRRC after a median follow-up of 8.8 mo was 73% overall, and >69% in all BV subgroups (Table 1). 6-mo PFS was 77% overall, and >71% in all subgroups (Table 1). Median time to response in the entire cohort was 2.1 mo (range 0.8–6.5), and median duration of response was 7.0 mo (95% CI 6.7, NA). 6-mo OS was 93.9% (95% CI 86.9%, 97.2%). 68% of pts had drug-related AEs between first dose and 30 days after last dose of nivo, most commonly fatigue, diarrhea, and infusion reactions (11% each). 19% had G3-4 drug-related AEs. At present, no pt has discontinued study therapy due to persistent CR lasting 1 yr. *Conclusions.* Nivo had clinically meaningful antitumor activity and acceptable safety in heavily pretreated cHL pts, regardless of the timing of prior BV relative to failure of ASCT.

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T023

PEMBROLIZUMAB FOR RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA: MULTICOHORT, PHASE 2 KEYNOTE-087 STUDY

C. Moskowitz,[1] P.L. Zinzani,[2] M.A. Fanale,[3] P. Armand,[4] N. Johnson,[5] V. Ribrag,[6] J. Radford,[7] B. von Tresckow,[8] A. Tomita,[9] M. Shipp,[4] Y. Wang,[10] A.D. Ricart,[10] A. Balakumaran,[10] R. Chen[11]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]Institute of Hematology "Seràgnoli", University of Bologna, Bologna, Italy; [3]The University of Texas MD Anderson Cancer Center, Houston, USA; [4]Dana-Farber Cancer Institute, Boston, USA; [5]Jewish General Hospital, Montreal, Canada; [6]Gustave Roussy, Villejuif, France; [7]Christie Hospital NHS Foundation Trust, Manchester, UK; [8]Uniklinik Koln, Cologne, Germany; [9]Fujita Health University School of Medicine, and Nagoya University, Toyoake, Japan; [10]Merck & Co., Inc., Kenilworth, USA; [11]City of Hope National Medical Center, Duarte, USA

Background. In the phase 1b KEYNOTE-013 study, PD-1 blockade with pembrolizumab demonstrated high antitumor activity (65% ORR) in heavily pretreated cHL patients. KEYNOTE-087 (NCT02453594) is a phase 2 study designed to further evaluate the clinical activity of pembrolizumab in patients with R/R cHL. *Methods.* Patients were enrolled into 3 cohorts: R/R cHL after autologous stem cell transplantation (ASCT) and subsequent brentuximab vedotin (BV) therapy (cohort 1); ineligible for ASCT because of chemotherapy resistance (no response to salvage chemotherapy) and BV therapy failure (cohort 2); or R/R cHL after ASCT, but not treated with BV after ASCT (cohort 3). Patients received pembrolizumab 200 mg Q3W. Primary end point was ORR, with response assessed Q12W according to Revised Response Criteria for Malignant Lymphoma. A prespecified interim analysis, based on investigator-assessed response, was performed after 30 patients in cohorts 1 and 2 reached the first response assessment. *Results.* At the time of data cutoff (April 8, 2016), 90 patients were enrolled (30 in each cohort). Median (range) age was 36 (19-64) years in cohort 1, 33 (20-71) years in cohort 2, and 30 (18-67) years in cohort 3. 42% had primary refractory disease (no response to frontline therapy), and 57% received >3 prior lines of therapy. By investigator review, ORR was 73% (95% CI, 54%-88%) in cohorts 1 and 3, and 83% (95% CI, 65%-94%) in cohort 2. Complete remission rates (residual mass permitted if PET negative) were 27% in cohort 1 and 30% in cohorts 2 and 3. With a median of 9 treatment cycles, the most common treatment-related AEs (TRAEs) were pyrexia (13%), diarrhea (10%), and cough, fatigue, and neutropenia (8% each). There were 8 grade 3-4 TRAEs occurring in 4 patients (grade 3 neutropenia, colitis, diarrhea, cytokine release syndrome, herpes zoster infection, increased amylase, lichenoid keratosis, and grade 4 increased lipase). There were no treatment-related deaths. *Conclusions.* Pembrolizumab showed frequent responses in heavily pretreated patients with cHL, and provided a high ORR (83%) in patients who were not candidates for ASCT and failed previous BV therapy.

T024

TRANSPLANT BRaVE:COMBINING BRENTUXIMAB VEDOTIN WITH DHAP AS SALVAGE TREATMENT IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA. A PHASE 1 DOSE-ESCALATION STUDY

A. Hagenbeek[1], J.M. Zijlstra[2], P. Lugtenburg[3], G. van Imhoff[4], M. Hutchings[5], R. Liu[1], M. Spiering[1], H. van Tinteren[6], M.J. Kersten[1]

[1]Academic Medical Center, Amsterdam, The Netherlands; [2]Free University Medical Center, Amsterdam, The Netherlands; [3]Erasmus Medical Center, Rotterdam, The Netherlands; [4]University Medical Center Groningen, Groningen, The Netherlands; [5]Rigshospitalet, Copenhagen, The Netherlands; [6]Netherlands Cancer Institute, Amsterdam, The Netherlands

Achieving a PET-negative CR with salvage chemotherapy prior to ASCT in r/r HL is a strong predictor for longterm progression-free survival (PFS). This phase 1 dose-escalation study explored the toxicity and feasibility of adding Brentuximab Vedotin (BV) to DHAP and established the recommended Dose Level (DL) for a phase 2 study. Final objective: to increase the metabolic CR rate after BV-DHAP and to make more patients eligible for auto-SCT with curative intent. BV was given at the standard dose of 1.8 mg/kg and combined with 3 courses of DHAP q 3 weeks at 3 DL in 3 patients per DL (3+3 design), *i.e.* dexamethasone 40 mg iv d1-4, Cisplatin (CP) and Cytarabine at 75%=DL1; CP75% and Cytarabine 100%=DL2 and CP 100 mg/m iv d1 and Cytarabine 2x2g/m iv d2 (full dose DHAP)= DL3 (6 patients). Out of 12 patients (8 F, median age 30.5 yr) 2 were primary refractory and 10 were in 1st relapse. 1st line induction: ABVD (n=9) or BEACOPPesc (n=3). Median time between response to 1st line treatment and the first course of BV-DHAP: 9.2 mo (range:2-134.5). Neutropenia grade 4 more than 10 days (causing 1 week delay of BV-DHAP): 2 out of 3 patients at DL1. Neulasta became mandatory after course 1 and 3, reducing the duration of neutropenia. Stem cells were harvested after the 2nd course (median yield:5.3x10E6 CD34+/kg;range:3.0-25.9). Seven AE's gr3-4 were observed: neutropenia gr4 (n=2), neutropenia gr3 and trombopenia gr4 (n=1), thromboembolism gr3 (n=1), elevated transaminases gr3 (n=1) and hypokalemia gr4 (n=1). SAE's occurred in 4 patients, all at DL3: CVC-related infection gr3, zoster infection gr3, fever gr3 (n=1), elevated transaminases gr3 (n=1), reduced kidney function gr3, pneumonitis gr3 (n=1), hypokalemia gr4, fever gr3, acute liver failure gr4 lasting longer than 14 days (likely related to antibiotics), atrial fibrillation gr3 (unlikely related;n=1).These last two SAE's were classified as DLT's. Sensory PNP gr1-2 was seen in 4 patients which fully resolved in 2. 11/12 patients reached a PET- complete metabolic remission after 3x BV-DHAP. In one PET+ PR a biopsy did not show HL. Thus, 12/12 achieved a CR. With a median FU of 15.4 mo (range:8.4-22.7) all patients are alive and in CR. In conclusion, BV-DHAP given at full doses is feasible with acceptable toxicity with G-CSF support and this dose will be used in the phase 2 part of the study. The CR rate, although assessed in only 12 patients, is 100%.

Support. This study is supported by Takeda,USA.

P080

A PHASE I STUDY WITH AN EXPANSION COHORT OF THE COMBINATION OF IPILIMUMAB AND BRENTUXIMAB VEDOTIN IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA: A TRIAL OF THE ECOG-ACRIN CANCER RESEARCH GROUP (E4412)

C.S.M. Diefenbach[1], F. Hong[2], R.F. Ambinder[3], J.B. Cohen[4], M.J. Robertson[5], T.S. Fenske[6], R. Advani[7], B.S. Kahl[8], S. Ansell[9]

[1]New York University Perlmutter Cancer Center, New York, USA; [2]Dana Farber Cancer Institute, Boston, MA, USA; [3]Johns Hopkins University, Baltimore, MD, USA; [4]Emory University, Atlanta, GA, USA; [5]Indiana University Hospital, Indianapolis, IN, USA; [6]Medical College of Wisconsin, Milwaukee, WI, USA; [7]Stanford University, Stanford, CA, USA; [8]Washington University, Saint Louis, MO, USA; [9]Mayo Clinic, Rochester, MN, USA

Background. Despite advances in chemotherapy, relapsed/refractory (R/R) Hodgkin lymphoma (HL) remains an unmet medical need. HL has a unique biology in which a small number of malignant Hodgkin Reed-Sternberg (HRS) cells propagate an immunosuppressive microenvironment. We hypothesized that using immune checkpoint inhibitor therapy to activate the immune microenvironment, and concurrently targeting HRS cells with the CD30 antibody-drug conjugate brentuximab vedotin (BV), could overcome tumor cell resistance. E4412 is a phase 1 ECOG-ACRIN sponsored study of the combination of BV and ipilimumab (IPI) and nivolumab (NIVO) in patients with R/R HL. Here we present the updated safety and response data on the full cohort of patients treated with BV+IPI. *Methods.* Patients were treated with BV 1.8mg/kg and IPI: 1 mg/kg or 3mg/kg, followed by an expanded cohort of BV+IPI 3mg/kg. BV was administered every 21 days for 16 cycles; IPI every 21 daysx4 and then every 3 months for one year. *Results.* As of 5/26/16: 23 planned patients have been treated; 21 patients were eligible for response assessment. The median age was 32 years (range: 20-49). Patients were heavily pretreated with a median of 4 prior therapies (1-13). Four patients had prior treatment with BV; 10 had prior SCT. BV+IPI was well tolerated, with no DLTs noted. The most common treatment-related adverse events (AEs) were: rash, diarrhea, and peripheral sensory neuropathy. Grade 3 and 4 AEs included: grade 3 infusion reaction, rash, vomiting, peripheral sensory neuropathy, and 1 grade 4 thrombocytopenia. For 21 evaluable patients, the overall response rate (ORR) for BV+IPI was 71% with a complete response (CR) rate of 48%. An additional 2 patients had stable disease (SD). The median progression free survival (PFS) is 1.02 years with a median follow-up of 0.48 years; the median overall survival (OS) has not been reached with a median follow-up of 1.16 years (Figure 1). *Conclusions.* Our data confirms the tolerability and activity of BV+IPI in a heavily pretreated R/R HL patient population. Optimization of this combination strategy is ongoing with accrual to cohorts receiving BV+NIVO, and BV+IPI+NIVO.

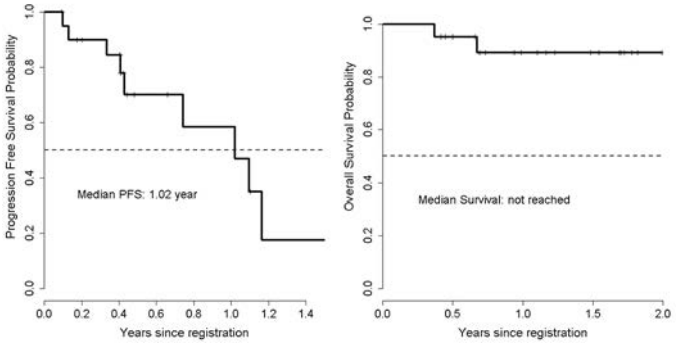

Figure 1.

P081

BENEFIT OF TANDEM STEM CELL TRANSPLANTATION FOR HIGH RISK RELAPSED/REFRACTORY HODGKIN LYMPHOMA PATIENTS: A FRENCH PROSPECTIVE MULTICENTER OBSERVATIONAL STUDY ON 120 PATIENTS

B. Deau[1], S. Amorim[2], A. Perrot[3], P. Quittet[4], J. Cornillon[5], D. Chaoui[6], J.P. Marolleau[7], L.-M. Fornecker[8], M. Robin[2], P. Brice[2]

[1]Hopital Cochin, Paris, France; [2]Hopital Saint Louis, Paris, France; [3]CHU Nancy, Vandœuvre-lès-Nancy, France; [4]CHU Montpellier, Montpellier, France; [5]Institut Cancerologique de la Loire, Saint-Priest-en-Jarez, France; [6]CH Argenteuil, Argenteuil, Francia; [7]CH Amiens, Amiens, France; [8]CHU Strasbourg, Strasbourg, France

Tandem stem cell transplantation (SCT) is an option for High Risk relapsed/refractory Hodgkin Lymphoma (HR R/R HL) patients. We conducted a prospective multicenter observational study to evaluate the feasibility of tandem SCT in the routine clinical practice. HR R/R HL patients have primary refractory disease, or stage III/IV disease with early (<12 months) relapse. Inclusion criteria were : HR R/R HL, age 55 or younger, eligibility for salvage chemotherapy and SCT. 18FDG PET CT/scan (PET) performed after 2 or 3 cycles of salvage chemotherapy, stem cell harvesting after the first cycle of salvage chemotherapy, and investigation for HLA-matched donor were required. We included 120 HL patients over a 5 years period. Median age was 26 (14-56 y) and 57% of patients were female. 61 (51%) patients had refractory disease and 59 (49%) had relapsing HL. 60 (50%) had a HLA-matched donor including 27 (47%) with sibling donors. Among our patients, 39 (33%) had chemosensitive disease as defined by PET negativity (Deauville score 1-2-3) after 2-3 cycles of first line salvage therapy. Before transplant, complete metabolic remission (CR) was achieved in 72 (60%) patients, partial response occurred in 38 (32%) patients, and PET positivity concerned 10 (8%) patients. Overall, 50 (66%) patients received Brentuximab Vedotin (BV) before SCT. 115 (96%) patients received high-dose chemotherapy by BEAM followed by autologous SCT. 73 (61%) patients received a second SCT : 42 (58%) had a reduced-intensity conditioning allogenic SCT and 29 (40%) had a second autologous SCT conditioned by BAM. Reasons for not performing a second transplant were: progression (n= 22), stem cell mobilization failure (n= 5), patient decision (n=4), toxicity (n= 4) and investigator decision (n=7). The median follow-up was 43 months (4,8-73,7). Progression-Free Survival (PFS) was 57% (95% CI 47-66%) at 2 year. Disease control before the first SCT (CR and PR) was associated with a better 2-y-PFS of 59,3% (95% CI : 49-68%) compared to 20% (95% CI 3,1-47,5%) for stable or progressive disease (p=0,007). Patients who underwent two SCT had a 2-y-PFS of 69% compared to 31% for patients treated with a single transplant (HR: 0.30; 95% CI 0.17-0.52; p<0.001). The 2-year overall survival of our patients was 82% (95% CI: 73-88). 29 (24%) patients died and 91 (76%) were alive. Causes of death were : GVH (n=2), LEMP (n=1), sepsis (n=5), allo toxicity (n=2), SDRA (n=1), progression (n=7) (missing n=11) (Figure 1).

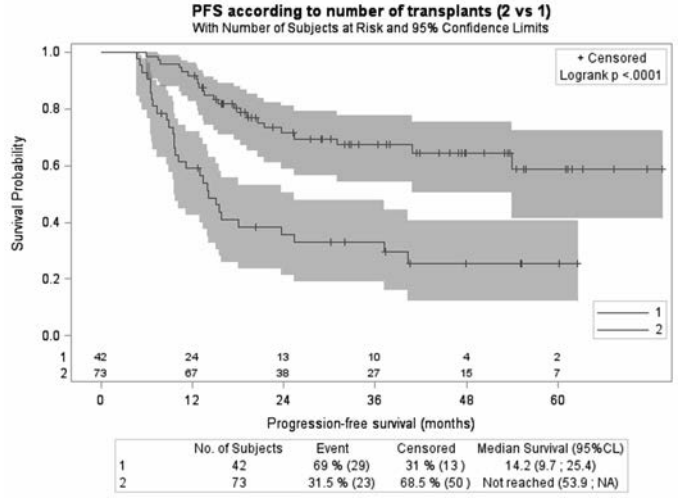

Figure 1.

P082

BRENTUXIMAB VEDOTIN PLUS BENDAMUSTINE AS A SALVAGE TREATMENT REGIMEN FOR PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

A. LaCasce[1], G. Bociek[2], A. Sawas[3], P. Caimi[4], E. Agura[5], J. Matous[6], S. Ansell[7], H. Crosswell[8], M. Islas-Ohlmayer[9], C. Behler[10], E. Cheung[11], A. Forero-Torres[12], J. Vose[2], O.A. O'Connor[3], N. Josephson[13], R. Advani[14]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]University of Nebraska Medical Center, Omaha, NE, USA; [3]Columbia University Medical Center, New York, NY, USA; [4]University Hospitals Case Medical Center, Cleveland, OH, USA; [5]Charles A. Sammons Cancer Center, Dallas, TX, USA; [6]Colorado Blood Cancer Institute, Denver, CO, USA; [7]Mayo Clinic, Rochester, MN, USA; [8]St. Francis Hospital, Greenville, SC, USA; [9]The Jewish Hospital-Mercy Health, Cincinnati, OH, USA; [10]Pacific Hematology Oncology Associates, San Francisco, CA, USA; [11]The Oncology Institute of Hope & Innovation, Whittier, CA, USA; [12]University of Alabama at Birmingham, Birmingham, AL, USA; [13]Seattle Genetics, Inc., Bothell, WA, USA; [14]Stanford Cancer Institute, Stanford, CA, USA

Conventional salvage therapy for patients (pts) with relapsed/refractory (R/R) Hodgkin lymphoma (HL) is associated with variable complete remission (CR) rates (19%-60%) and substantial toxicity. Brentuximab vedotin (BV) and bendamustine are active as single agents in pts with R/R HL (34% and 33% CR rates, respectively), with manageable safety profiles. This phase 1/2 open-label study was designed to evaluate the safety and efficacy of BV in combination with bendamustine in pts with primary refractory disease or in first relapse (NCT01874054). Pts received BV (1.8 mg/kg on Day 1) plus bendamustine (90 mg/m^2 on Days 1 and 2) in 3-week cycles (up to 6 cycles total). Pts could undergo autologous stem cell transplant (ASCT) any time after Cycle 2 and could receive BV monotherapy (up to 16 total doses) post-ASCT, or after completion of combination therapy if not proceeding to ASCT. Response was assessed by the investigator per Cheson 2007. A total of 55 pts (51% refractory; 49% relapsed) were enrolled. Median age was 36 years (range 19-79), 56% were female, and median time from HL diagnosis was 14 months (range 3-98). Pts received a median of 2 cycles (range 1-6) of the combination and 11 cycles (range 1-14) of BV monotherapy. Infusion-related reactions (IRRs) were reported in 58% of pts; however, a protocol amendment requiring premedication with corticosteroids and antihistamines during combination therapy reduced the IRR-related discontinuation rate from 24% (6/25 pts) to 7% (2/30 pts). Common IRR symptoms (≥10%) were pyrexia (26%), chills (20%), dyspnea (16%), nausea and flushing (15% each), and hypotension and pruritus (11% each). The CR rate of the combination was 74% (39/53 pts evaluable for response); objective response rate (CR and partial remission) was 93% (49/53 pts). Stem cell mobilization succeeded with 1st-line agents in 39/41 pts (95%); median yield was 4.2x10^6 CD34+ cells/kg. Median follow-up was 19 months (range 1-33). To date, 17 progression events have occurred in 53 pts: 11 in 40 pts who underwent ASCT and 6 in 13 pts who did not. The estimated 24-month progression-free survival was 68% for the ASCT population (95% CI: 48%, 82%) and 61% for the overall population (95% CI: 44%, 75%). Of 3 deaths, 2 were attributed to HL progression and 1 to septic shock after ASCT. Overall, these data demonstrate that the outpatient regimen of BV plus bendamustine is an active salvage therapy for pts with HL in first relapse and can be used prior to ASCT (Figure 1).

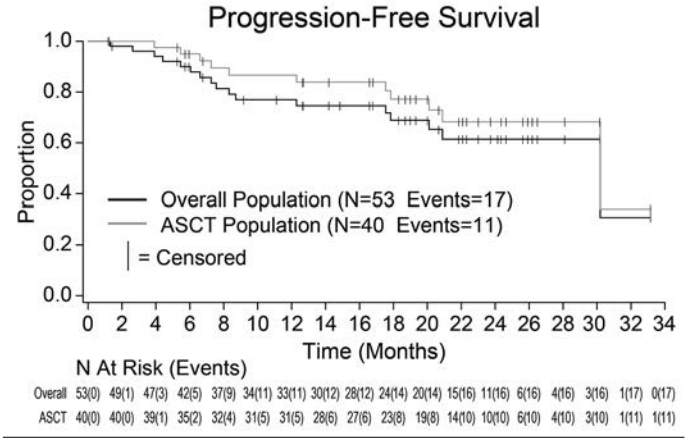

Figure 1.

P083

PET ADAPTED DOSE ESCALATION OF BRENTUXIMAB VEDOTIN AS FIRST LINE SALVAGE THERAPY IN RELAPSE/REFRACTORY HODGKIN LYMPHOMA

R. Chen, J. Palmer, A. Herrera, B. Chen, N. Tsai, S. Armenian, N. Kennedy, J.-L. Cai, A. Nademanee, M. Mei, L. Kwak, S. Rosen, S. Forman

City of Hope National Medical Center, Department of Hematology and Hematopoietic Cell Transplantation, Duarte, CA, USA

Background. Brentuximab vedotin (BV), an antibody drug conjugate, selectively induces apoptosis of CD30+ cells. We previously conducted a phase II trial using 1.8 mg/kg dose showing an ORR of 68% and CR of 36% in Hodgkin Lymphoma (HL) patients as first line salvage therapy. We observed that all patients who achieved CR did so after 2 cycles of therapy. However, 3 patients who achieved PR after 2 cycles progressed after 4 cycles of BV. We hypothesize that dose escalation from 1.8 mg/kg to 2.4 mg/kg after cycle 2 CT/PET may convert patients in PR/SD to CR or prevent disease progression. *Patients and Methods.* This is an additional feasibility cohort added to a prospective phase II trial in patients with relapsed/refractory HL. All patients had biopsy proven relapsed/refractory HL post induction therapy. Patients were treated with 1.8 mg/kg of BV intravenously every 3 weeks for 2 cycles followed by CT/PET. Patients in CR after 2 cycles received 2 additional cycles at 1.8 mg/kg. Patients in PR/SD after 2 cycles received dose escalation of 2.4 mg/kg of BV for 2 cycles. The primary endpoint was the CR rate according to Revised Cheson Criteria. Secondary endpoints were toxicities assessment according to NCI CTCAE v 4.0. *Results.* 20 patients were accrued and evaluable for response. See Table for baseline characteristics. The ORR with 1.8 mg/kg dose at cycle 2 was 85%, CR was 55%, PR was 30%, SD was 10%, and PD was 5%. 8/20 patients were in PR/SD after cycle 2 and received 2.4 mg/kgx2 doses. 1/6 patients in PR converted to CR and the rest stayed in PR. 2/2 patients in SD stayed in SD. At the end of study, ORR was 85%, CR was 60%, and PD was 5%. Treatment was well tolerated at both the 1.8 mg/kg and 2.4 mg/kg cohort. There were no significant differences in toxicities between the two cohorts and there were also no grade 4/5 toxicities. The only grade 3 possibly-related toxicity was maculopapular rash that occurred in 2 patients (at 1.8 mg/kg). In the 2.4 mg/kg cohort, grade 2 possibly-related toxicities >20% included fatigue (n=3), back pain (n=2), pruritis (n=2), and rash (n=2). There were no transfusions required and no neutropenic fevers. *Conclusions.* Dose escalation from 1.8 mg/kg to 2.4 mg/kg was able to convert 1/8 (12.5%) patients into CR. No patients developed progressive disease while receiving 2.4 mg/kg. The dosage of 2.4 mg/kg was well tolerated. Dose escalation of BV based on PET 2 is feasible and merits further investigation.

Table 1.

Characteristics	N (%)or Median (Range)
Gender	
Female	12 (60%)
Male	8 (40%)
Age	25 (15-57)
KPS	
80	4 (20%)
90	9 (45%)
100	7 (35%)
Stage at Diagnosis	
I-II	10 (50%)
III-IV	10 (50%)
Prior XRT	5 (25%)
B symptoms	12 (60%)
Bulky Disease	15 (75%)
Best Response to Induction	
Primary Refractory	10 (50%)
Relapsed (within 7 months)	10 (50%)

P084

VERY LATE RELAPSE >5 YEARS AFTER FIRST DIAGNOSIS OF HODGKIN LYMPHOMA: AN ANALYSIS OF THE GERMAN HODGKIN STUDY GROUP HD7-HD12 TRIALS

P.J. Bröckelmann, H. Görgen, C. Kohnhorst, M. Fuchs, P. Borchmann, A. Engert

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

Background. Patients free of HL >5 years after first diagnosis are usually considered cured. Nevertheless, VLR occur and biology, clinical characteristics, therapeutic approaches and prognosis are currently

poorly understood. *Methods.* Cumulative incidence of VLR was retrospectively estimated in 5149 patients of the GHSG HD7-HD12 trials, who were observed and relapse-free for >5 years; risk factors were analyzed using Gray's test and Cox regression. Standardized incidence ratio (SIR) was estimated using age- and sex-specific reference values for the German population. Overall and progression-free survival were estimated according to Kaplan-Meier from first diagnosis (OS/PFS) and date of relapse (OSr/PFSr), Hazard Ratios (HR) were obtained from Cox regressions adjusted for relevant risk factors such as age, sex and initial stage. Relapse localizations and therapies, OSr and PFSr were compared with a group of 487 patients having earlier relapse. Patient characteristics were analyzed descriptively. *Results.* With a median observation time of 10.3 years, a total of 169 relapses >5 years were observed. Cumulative incidences at 10, 15 and 20 years were 2.8%, 5.1% and 8.6%, respectively, with an SIR of 97.1 (95% CI: 83.0-112.9). VLR were more frequently observed in patients with early-stage favorable than early-stage unfavorable or advanced-stage disease at first diagnosis (15-year cumulative incidence 8.0%, 4.4%, 4.2%, respectively, p<0.001). Male patients and those with nodular-lymphocyte predominant subtype were also found at increased risk for VLR. VLR occurred more frequently outside initially involved areas and radiation fields than earlier relapse. OS was significantly worse compared to non-relapse survivors (10-year OS: 95.9% *vs* 88.5%, HR: 2.4, 95% CI: 1.7-3.4, p<0.001). For earlier relapse, we observed inferior 5-year PFSr and OSr compared to VLR (55.7% *vs* 64.3% HR: 1.6, 95% CI: 1.1-2.4, p=0.03; 63.0% *vs* 76.3%, HR: 2.1, 95% CI: 1.3-3.4, p<0.01, respectively). *Summary.* Besides therapy-associated side effects, survivors after initially successful HL-therapy are at a 100-fold increased risk of re-occurrence of disease compared to German reference values. After modern risk-adapted treatment strategies especially in early-stage favorable HL, thorough regular follow-up is hence needed for timely detection. Prognosis of VLR seems favorable when compared to early relapses.

P085

AN INTERNATIONAL MULTICENTER PHASE I/II STUDY OF BRENTUXIMAB VEDOTIN AND BENDAMUSTINE IN PATIENTS WITH HEAVILY TREATED RELAPSED OR REFRACTORY HODGKIN LYMPHOMA AND ANAPLASTIC LARGE T-CELL LYMPHOMA DEMONSTRATES MARKED DURABLE RESPONSES

O.A. O'Connor[1], A. Sawas[1], J.M. Connors[2], I. Turenne[1], C. Rojas[1], R. Lichtenstein[1], C. Deng[1], J.E. Amengual[1], D. Villa[2], M. Crump[3], J. Kuruvilla[3]

[1]Center for Lymphoid Malignancies, Columbia University Medical Center, New York, NY, USA; [2]BC Cancer Agency, BC Cancer Research Centre Vancouver, BC, Canada; [3]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Patients with HL or ALCL who relapsed post or are ineligible for autologous stem cell transplant (ASCT) are incurable with standard therapies. The anti-CD30 ADC BV is approved for such patients. B is also active and tolerable HL. This phase I/II study evaluated the safety and efficacy of brentuximab vedotin with bendamustine for patients with R/R HL or ALCL. (ClinicalTrials.gov #NCT01657331). *Methods.* Patients received IV BV on Day 1 with B on Days 1 and 2 of a 3-week cycle for up to 6 cycles. In the Phase 1 portion 4 dose levels were evaluated: (1) Bv=1.2mg/kg; B=70mg/m^2; (2) Bv=1.2mg/kg; B=80mg/m^2; (3) Bv=1.8mg/kg; B=80mg/m^2; and (4) Bv=1.8mg/kg; B=90. Accrual followed a classic Fibonacci dose escalation, with 3 patients being treated at each dose level. Dose Limiting Toxicity (DLT) led to expansion of the dose cohort. The recommended phase II dose was Bv 1.8 mg/kg on Day 1 and B 90 mg/m^2 on Days 1 and 2. Response was assessed by the investigator per Cheson 2007 after cycles 2 and 6. Enrollment is nearly complete (n=3 remaining) . In addition, plasma and serum biomarkers are being prospectively collected for correlation with toxicity and response. *Results.* Sixty-one patients (66% male) with a median age of 36 years (range, 18-70) were enrolled. Fifty-nine patients had HL and 2 ALCL; the median number of prior systemic therapies was 5 (range 1-16); with 36 patients having had prior ASCT and 25 patients receiving prior radiation therapy. The predominant all grade toxicity observed with the combination was nausea (62%, grade 1-2). The observed grade 3-4 toxicities in the phase I were: neutropenia (19%), thrombocytopenia (19%), anemia (15%) and rash (11%). The observed phase II grade 3-4 toxicities include neutropenia (8%). No DLT was observed at dose level 4 (Bv 1.8 mg/m^2 and B 90 mg/m^2). The maximum tolerated dose (MTD) was not reached. A decision was made not to explore further doses that exceeded the standard single agent doses of both drugs. Patient's received a median of 6 cycles (range, 1-6). To date, 52/59 patients are evaluable for response. The overall response rate is 73%, with 10 patients (19%) attaining a complete response (CR). Nine patients had stable disease. Among the 11 patients who received prior Bv, 6 responded (55%) (CR= 2, PR=4, SD=3, PD=2), and of the 4 patients who had prior B, 2 responded (50%) (PR=2, SD=1, PD=1). Two patients had received both Bv and B as single agents prior to initiation of study; one patient achieved a PR and the other experienced PD. The ALCL patient achieved a PR. *Conclusions.* In this heavily treated population of HL and ALCL, the combination of brentuximab vedotin 1.8 mg/kg on Day 1 with bendamustine 90 mg/m^2 on Days 1 and 2 of 3-week cycles represents a very effective and tolerable outpatient regimen. The regimen has an ORR of 73% with responses ≥50% in patients who had received either agent separately supporting the potential clinical synergy of the combination.

P086

POST TRANSPLANT OUTCOMES IN A MULTICENTER PHASE II STUDY OF BRENTUXIMAB VEDOTIN AS FIRST LINE SALVAGE THERAPY IN RELAPSED OR REFRACTORY HODGKIN LYMPHOMA PRIOR TO AUTOLOGOUS STEM CELL TRANSPLANTATION

A. Herrera[1], J. Palmer[2], P. Martin[3], S. Armenian[4], N.-C. Tsai[2], M. Mott[1], F. Sahebi[1], J.-L. Cai[1], T. Siddiqi[1], L. Popplewell[1], A. Nademanee[1], S. Rosen[1], L. Kwak[1], S. Forman[1], R. Chen[1]

[1]City of Hope National Medical Center, Department of Hematology and Hematopoietic Cell Transplantation, Duarte, CA, USA; [2]City of Hope National Medical Center, Department of Information Sciences, Division of Biostatistics, Duarte, CA, USA; [3]Weill Cornell Medical College, Department of Hematology/Oncology, New York, USA; [4]City of Hope National Medical Center, Department of Population Sciences, Duarte, CA, USA

Background. Standard of care treatment for patients with relapsed or refractory (rel/ref) Hodgkin lymphoma (HL) is salvage chemotherapy followed by autologous stem cell transplantation (ASCT) in chemosensitive patients. Brentuximab vedotin (BV) is an antibody drug conjugate that selectively induces apoptosis of CD30+ HL cells. Here we present updated post-ASCT follow-up in a previously reported multicenter phase II trial evaluating BV as first line salvage therapy prior to ASCT. *Patients and Methods.* We conducted a prospective, multicenter (City of Hope, Cornell) phase II trial of BV as first line salvage therapy prior to ASCT in patients with rel/ref HL after induction therapy. Patients received 1.8 mg/kg of BV intravenously every 3 weeks for 4 cycles. This analysis is limited to patients who underwent ASCT. Endpoints include toxicities, stem cell collection, engraftment, and 2-yr post-ASCT progression-free and overall survival (PFS, OS). *Results.* 37 patients were accrued and 36 were evaluable. The overall best response (CR+PR) rate to BV was 69% with 36% CR. 32 (89%) patients proceeded to ASCT. All 13 CR patients proceeded to ASCT without additional chemotherapy. 3/12 PR patients proceeded directly to ASCT, while 9 received additional chemotherapy. All patients with SD/PD received additional chemotherapy except for 1 patient who received XRT. 23 patients were in CR, 8 were in PR, and 1 patient had SD at ASCT. All patients were primed with cyclophosphamide/G-CSF and 9 patients received plerixafor per institutional guidelines. The median stem cell collection days was 2 and median CD34 cells collected was 5.97x10^6. 19 patients received BEAM conditioning, 11 received CBV, and 2 received BEAM plus yttrium-90 labeled anti-CD25. The median time to neutrophil and platelet engraftment was 11 and 20 days, respectively. There were no

Gr 3 or 4 post-ASCT toxicities through d+30. With a median follow up of 25.7 months, the 2-yr PFS was 72%, OS was 94%, and NRM was 3%. Patients who received only BV had 2-yr PFS of 80% *vs* 69% in patients who received BV followed by chemotherapy. Patients in CR at ASCT, had 2-yr PFS of 78% *vs* 56% for non-CR patients (Table 1). *Conclusions.* 89% of patients who received BV as first-line salvage therapy successfully underwent ASCT. Outcomes compare favorably with historical data, including patients who received BV salvage alone without chemotherapy. BV is a promising first-line salvage therapy for rel/ref HL patients undergoing ASCT.

Table 1. Patient characteristics.

Characteristics	N (%) or Median (Range)
Age	34 (11-67)
Institution City of Hope Weill Cornell	31 (84%) 6 (16%)
Stage at Diagnosis I-II III-IV	19 (51%) 18 (49%)
B symptoms	23 (62%)
Bulky Disease (> 5 cm)	32 (86%)
Induction Chemotherapy ABVD ABVD/BEACOPP ABVE-PC	34 (92%) 2 (5%) 1 (3%)
Prior XRT	9 (24%)
Best Response to Induction Primary Refractory Relapsed (within 7 months)	24 (65%) 13 (35%)

P087

T CELL REPLETE HAPLOIDENTICAL TRANSPLANTATION WITH POST-INFUSION CYCLOPHOSPHAMIDE IN POOR PROGNOSIS HODGKIN LYMPHOMA

L. Castagna[1], S. Bramanti[1], R. Devillier[2], R. Crocchiolo[1], S. Furst[2], J. El Cheikh[2], B. Sarina[1], A. Granata[2], C. Faucher[2], S. Harbi[2], L. Morabito[1], P.J. Weiller[2], C. Chabannon[3,4,5], J. Mokart[6], C. Carlo-Stella[1], A. Santoro[1], D. Blaise[2,4,5]

[1]Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano (MI), Italy; [2]Department of Hematology, Transplantation Program; [3]Cell Therapy Unit, Institut Paoli Calmettes, Marseille, France; [4]Aix-Marseille Université, Marseille, France; [5]Centre de Recherche en Cancérologie de Marseille, Institut Paoli-Calmettes, Aix-Marseille Université, CNRS UMR, Marseille, France; [6]Intensive Care Unit, Institut Paoli Calmettes, Marseille, France

In advanced Hodgkin lymphoma, allogeneic hematopoietic stem cell transplantation can represents a potential curative option. In this study, we analyzed the outcome of advanced HL patients who received haplo-HSCT using the unmanipulated stem cell and PT-Cy. 62 consecutive HL patients undergoing T-cell replete haploidentical transplantation with PT-Cy. ANC and platelets engraftment was observed in 94% and 82% of patients. The 100-day cumulative incidence (CI) of grade 2-4 and 3-4 aGVHD was 23% and 4%, respectively and the CI of cGVHD (overall) was 16. The median follow-up was 32 months. The 3-year OS, PFS, relapse rate was 63%, 59%, and 21%, respectively. The 1-year NRM was 20%. In multivariate analysis, factors negatively associated with OS were uncontrolled disease status and higher than 2 HCT-CI. PBSC was an independent protective factor. The same factors were predictive for PFS, except for HCT-CI 1. Disease status other than CR was predictive of relapse. Haplo-HSCT with PT-Cy looks particularly effective against HL cells, and it seem to work better than other donors. However, prospective studies are needed to confirm the these *results.*

P088

PET-ADAPTED THERAPY WITH BRENTUXIMAB VEDOTIN AND AUGMENTED ICE FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA – LACK OF IMPROVEMENT WITH 3 *VERSUS* 2 CYCLES OF WEEKLY BRENTUXIMAB VEDOTIN

A.J. Moskowitz, H. Schöder, J. Yahlom, S.J. McCall, S.Y. Fox, J. Gerecitano, R. Grewal, P.A. Hamlin, S. Horwitz, R. Kobos, A. Kumar, M. Matasar, A. Noy, M.L. Palomba, M.-A. Perales, C.S. Portlock, C. Sauter, N. Shukla, P. Steinherz, D. Straus, T. Trippett, A. Younes, A. Zelenetz, C. Moskowitz

Lymphoma Disease Management Team, Memorial Sloan Kettering Cancer Center, New York, USA

Introduction. PET-adapted salvage therapy with brentuximab vedotin (BV) and augmented ICE (augICE) produced a PET-negative (neg) rate of 76% (Moskowitz, AJ. Lancet Oncology 2015). In this study, 45 patients (pts) received 2 cycles of BV (1.2mg/Kg weekly, 6 doses over 8 weeks) and those with residual PET-avidity received 2 cycles of augICE (ifosfamide 5000mg/m^2 x2 doses, carboplatin AUC 5, etoposide 200mg/m^2 x3 doses) prior to ASCT. With a median follow-up of 40 months, 44 of 45 patients proceeded to ASCT and 3-year event free survival (EFS) and overall survival (OS) were 80% and 93%, respectively. 27% achieved PET-neg status following BV and received no additional chemotherapy before ASCT. We enrolled a second cohort aimed at improving the PET-neg rate to BV by administering 3 rather than 2 cycles. *Methods.* On cohort 2, pts received 3 cycles of weekly BV (1.2mg/Kg weekly, 9 doses over 12 weeks). PET-neg pts (by Deauville 1-2) proceeded to ASCT while those with residual PET-avidity received augICE for 2 cycles before ASCT. Transplant conditioning included involved field radiation for eligible patients. *Results.* 20 pts enrolled onto cohort 2. Characteristics appear in the Table 1.

Table 1. Summary of patient characteristics and outcomes according to treatment cohort.

	Cohort 1 (n=45)	Cohort 2 (n=20)
Characteristics		
Females, n (%)	20 (44%)	14 (70%)
Age, median (range)	31 (13-65)	35 (19-59)
Stage, n (%) Early Advanced	 23 (51%) 22 (49%)	 13 (65%) 7 (35%)
Refractory	25 (56%)	9 (45%)
B Symptoms	9 (20%)	1 (5%)
Extranodal disease	19 (42%)	5 (25%)
Bulk (>5cm)	12 (27%)	4 (20%)
Outcomes		
Completed all planned BV cycles*	45 (100%)	16 (80%)
PET-CR to BV (Deauville 1-2)	12 (27%)	6 (30%)
Pre-ASCT PET-status PET-negative (Deauville 1-2) PET-negative (Deauville 1-3)	 34 (76%) 36 (80%)	 16 (80%) 18 (90%)
Proceeded to ASCT	44 (98%)	20 (100%)
Median follow-up for survivors	40 months	24 months
EFS**	80%	85%
OS**	93%	100%

*Cohort 1: 2 cycles of weekly BV (1.2mg/Kg IV, 6 doses over 8 weeks); Cohort 2: 3 cycles of weekly BV (1.2mg/Kg IV, 9 doses over 12 weeks). In cohort 2, reasons for not completing BV included disease progression (1), grade 3 rash (1), grade 2 infusion related reaction (1) and poor tolerance (1).
**EFS and OS reported at 3 years for cohort 1 and 2 years for cohort 2.

After BV, 6 (30%) pts were PET-neg (by Deauville 1-2) and 7 (6 Deauville 2, 1 Deauville 3) proceeded directly to ASCT. 13 pts received additional treatment before ASCT; 10 received augICEx2, 2 received ICEx2, and 1 received ICEx1 and augICEx1. All patients proceeded to ASCT and pre-transplant PET was negative by Deauville 1-2 for 16 (80%) pts. The median follow-up for cohort 2 was 24 months and 2-year EFS and OS were 85% and 100%, respectively. For cohorts 1 plus 2, the PET-neg rate following BV and before transplant were 28% and 78%, respectively. The 2 year EFS was 82%. By multivariate analysis, factors predictive of EFS included age>40 (p<0.001), advanced stage (p=0.001), refractory disease (p=0.001), and pre-transplant PET (0.003). *Conclusions.* PET-adapted salvage therapy with BV followed by augICE produces a PET-neg rate of 78%. With this treatment program, 28% patients achieved PET-neg status and proceeded to ASCT following BV alone. Increasing the number of weekly BV cycles from 2 to 3 did not improve the PET-neg rate achieved with single-agent BV. Pre-transplant PET remains an important prognostic factor for relapsed/refractory HL and achievement of PET-negative status should continue to be the primary objective of studies evaluating novel salvage regimens.

P089

BRENTUXIMAB VEDOTIN AFTER AUTOLOGOUS STEM CELL TRANSPLANT YIELDS THE STRONGEST BENEFIT IN HODGKIN LYMPHOMA PATIENTS WITH ≥2 RISK FACTORS: RESULTS OF A MULTIVARIATE ANALYSIS

C. Moskowitz[1], J. Sweetenham[2], A. Chen[3], E. Ayala[4], T. Masszi[5], J. Holowiecki[6], P. Stiff[7], A. Carella[8], S. Viviani[9], V. Bachanova[10], A. Sureda[11], D. Huebner[12], S.-Y. Lee[12], N. Hunder[13], L. Thomas[13], M. Uttarwar[13], J. Walewski[14]

[1]Memorial Sloan-Kettering Cancer Center, New York, New York, USA; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA; [3]Oregon Health and Science University, Portland, Oregon, USA; [4]H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA; [5]Szent Istvan & Szent Laszlo Corporate Hospital Hematology & Stem Cell Dept., Budapest, Hungary; [6]Department of Bone Marrow Transplantation & Oncohematology, Maria Sklodowska-Curie Institute of Oncology, Gliwice, Poland; [7]Loyola University Medical Center, Maywood, Illinois, USA; [8]IRCCS Azienda Ospedaliera Universitaria San Martino-IST, Genoa, Italy; [9]Istituto Nazionale dei Tumori, Milano, Italy; [10]University of Minnesota Medical Center, Minneapolis, MN, USA; [11]Institut Català d'Oncologia, Hospital Duran i Reynals, Barcelona, Spain; [12]Millennium Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceuticals Limited; [13]Seattle Genetics, Inc., Bothell, WA, USA; [14]Maria Sklodowska-Curie Institute and Oncology Center, Warszawa, Poland

Background. In the phase 3 AETHERA trial, PFS was significantly improved with brentuximab vedotin (BV) *versus* placebo (PB) (HR=0.57, P=0.001) in HL patients at high risk of progression post-ASCT[1]. In a previous MVA of the study population, consolidation treatment with BV was significantly associated with improved PFS compared with placebo after adjustment for clinical factors[2]. Here we present an MVA assessing interactions between established risk factors and treatment (BV *versus* PB) to identify patients who may benefit most from consolidation therapy. As eligibility was limited to high-risk patients, identification of risk factors for a general population was not explored. *Methods.* To identify qualitative treatment-subgroup interactions, Martingale residuals from a null Cox proportional hazard (CPH) model were used as a continuous outcome variable for a qualitative interaction tree (QUINT[3]); 18 covariates were used to define potential subgroups. Some subgroups were based on number of established risk factors present in a patient, including relapse <12 months or refractory to frontline therapy, best response of partial remission or stable disease to salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, and ≥2 prior salvage therapies. As a sensitivity analysis, a multivariate CPH model with treatment-covariate interactions was developed to identify the most significant interaction (smallest p-value <0.05). This interaction was retained in the model, and a second-round analysis was performed to identify the next most significant interaction among the remaining covariates. *Results.* The most significant qualitative treatment-subgroup interaction identified in the QUINT model was in the subgroup of patients with 1 *versus* ≥2 risk factors, with greater treatment benefit for patients with ≥2 risk factors. The sensitivity analysis confirmed this outcome (P=0.0006) and, after adjusting for this interaction, found no other interaction among the covariates tested to be significant. Analysis details will be presented with updated PFS and safety data after ~4 years since last patient enrolled. *Conclusions.* Treatment with BV appears to have the strongest impact for patients with ≥2 risk factors.

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P090

NIVOLUMAB RE-TREATMENT IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA: SAFETY AND EFFICACY OUTCOMES FROM A PHASE 1 CLINICAL TRIAL

S. Ansell[1], P. Armand[2], J. Timmerman[3], M. Shipp[2], M. Popa Mckiver[4], L. Zhu[4], A.M. Lesokhin[5]

[1]Mayo Clinic, Rochester, MN, USA; [2]Dana-Faber Cancer Institute, Harvard Medical School, Boston, MA, USA; [3]Jonsson Comprehensive Cancer Centre, UCLA, Los Angeles, LA, USA; [4]Bristol-Myers Squibb, Princeton, NJ, USA; [5]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA

Background. In classical Hodgkin lymphoma (cHL), malignant Reed–Sternberg cells almost uniformly overexpress the programmed death receptor-1 (PD-1) ligands, PD-L1 and PD-L2, through genetic amplification at 9p24.1[1]; therefore, cHL may be particularly sensitive to PD-1 blockade. Nivolumab (nivo), a fully human anti–PD-1 IgG4 monoclonal antibody checkpoint inhibitor, showed acceptable safety and high efficacy in a phase 1 trial (NCT01592370) of patients (pts) with relapsed/refractory cHL-a group with limited treatment options. Among 23 pts treated with nivo, investigator-assessed ORR was 87% and PFS at 24 weeks was 86%[2]. Median duration of response was not reached after 101 weeks[3]. Pts who progressed after stopping nivo were eligible for re-treatment. *Aim.* Assess the safety and efficacy of nivo re-treatment in pts with progression after initial response. *Methods.* In this phase 1 trial, adults with relapsed/refractory cHL were treated with nivo until progression, CR, or for a maximum of 2 years[3]. Pts with ongoing disease control (CR, PR, or stable disease) after discontinuation entered a protocol-specified follow-up period. Pts with PD <1 year after discontinuing nivo were eligible for re-treatment for ≤1 year. Toxicity, treatment response, and duration of response were assessed during re-treatment. *Results.* In total, 3 pts (age 26, 35, and 43 at baseline; 2 female) were re-treated with nivo. All had prior systemic treatment (4, 3, and 15, therapies, respectively) and had undergone autologous stem cell transplantation; 2 had prior treatment with brentuximab vedotin. ECOG performance status was 0 or 1. Nivo treatment course and outcomes are summarized in the Table 1. All 3 pts achieved a response with re-treatment. All experienced treatment-related AEs during the initial treatment period (1 grade 3 lymphopenia; all others grade 1–2). During re-treatment, 1 pt experienced treatment-related grade 2 neutropenia after 18 re-treatment cycles. *Conclusions.* All 3 pts re-treated with nivo responded to treatment, with 2 achieving PR and 1 discontinuing due to CR. These data provide preliminary evidence that re-treatment with nivo after progression may be an option for further treatment response.

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Previous presentation. Preliminary data on 1 patient presented at ASH 2015.

Table 1.

	Patient		
	1	2	3
Initial treatment period			
Best response	PR	CR	CR
Duration of therapy (weeks)	102	85	37
Off therapy time to progression (weeks)	12	37	44
Re-treatment			
Best response	PR	PR	CR
Time to best response (weeks)	9	16	18
Duration of therapy upon re-treatment (weeks)	30	24	52
Remaining on re-treatment	Yes	Yes	No (discontinued due to CR)
Total time from start of nivo treatment to last re-treatment dose (weeks)	148	149	135

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P091

STEM CELL COLLECTION AFTER FAILURE OF UPFRONT ABVD OR BEACOPP IN PATIENTS WITH HIGH RISK ADVANCED STAGE III-IV HODGKIN'S LYMPHOMA

D. Ghez[1], C. Fortpied[2], N. Mounier[3], P. Carde[1], A. Perrot[4], H. Khaled[5], S. Amorim[6], S. Ramadan[2], F. Le Bras[7], M. Erlanson[8], C. Herbaux[9], J.P. Marolleau[10], E. Nicolas-Virelizier[11], O. Casasnovas[12], A. Stamatoullas-Bastard[13], C. Fermé[1] on behalf of EORTC, LYSA, LYMG and NLG cooperating groups

[1]Department of Hematology, Gustave Roussy, Villejuif, France; [2]EORTC Headquarters, Brussels, Belgium; [3]Onco-Hematology Department, CHU l'Archet, Nice, France; [4]Department of Hematology CHU Nancy-Brabois, Vandoeuvre Les Nancy, France; [5]Department of Medical Oncology, National Cancer Institute, Cairo, Egypt; [6]Hopital Saint-Louis APHP, Université Paris Diderot, Paris, France; [7]Unité Hémopathies Lymphoïdes, AP-HP CHU Mondor, Creteil, France; [8]Department of Oncology, Umea Universitet, Sweden; [9]Clinical Hematology, Hôpital Claude Huriez, Université de Lille 2, Lille, France; [10]Department of Hematology CHU Amiens, Université Picardie Jules Verne, Amiens, France; [11]Department of Hematology, Leon Bérard Cancer Center, Lyon, France; [12]Department of Hematology, CHU Dijon, Dijon, France; [13]Department of Hematology, Centre Henri Becquerel, Rouen, France

Treatment of relapsed/refractory (R/R) Hodgkin's lymphoma (HL) usually relies on high dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT). Whether the myelotoxicity of BEACOPP may have consequences on stem cell harvest in patients with R/R HL has not been evaluated. *Methods.* Among 549 patients enrolled in the 20012 Intergroup randomized phase III trial, which compared a4 cycles of escalated BEACOPP followed by 4 cycles of BEACOPP with 8 cycles of ABVD in high risk stage III-IV HL., we identified, 91 patients (67 ABVD and 24 BEACOPP arm) with R/R HL. Additional data on stem cell collection, transplantation and engraftment outcome was obtained in 64/91 patients, 46 in the ABVD and 18 in the BEACOPP arm.

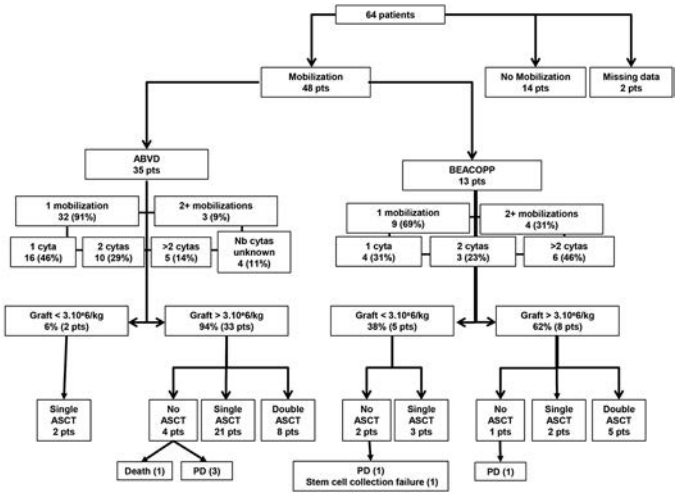


Figure 1.

Results. Mobilization was carried out in 48 patients (35 ABVD and 13 BEACOPP arm). 14 patients had no mobilization (death, refractory disease, ineligibility for HDT). Data were incomplete in 2 patients who were excluded from analysis. One mobilization was sufficient in 91% of ABVD and 69% of BEACOPP patients. 3 (9%) ABVD patients required 2 mobilizations, and 31% of BEACOPP patients had ≥2 mobilizations (2-5). Stem cell collection required one, two or >2 cytaphereses (3-5) in 52%, 32% and 16% of cases In the ABVD arm and 31%, 23% and 46% In the BEACOPP arm. A graft >3.10e6 CD34+ cell/kg was obtained in 33 (94%) patients in the ABVD and 8 (61%) in the BEACOPP arm. In this group, ASCT was not performed in 5 (12%) because of refractory disease or death. In the 36 patients (88%), it proceeded as initially planned. Eight (24%) patients in the ABVD arm and 5 (63%) in the BEACOPP arm had a double ACST. One patient was considered unfit for a second transplant (ABVD arm). Two patients (6%) in the ABVD arm and 5 (39%) in the BEACOPP arm had a graft <3.10e6 CD34+ cell/kg. In this group 5 patients proceeded to single ASCT and 2 did not because of death (BEACOPP arm) or insufficient graft (ABVD arm). Two patients had engraftment failures (ABVD arm). At the time of analysis, median overall survival from the date of randomization was 5.8 years in the ABVD and 4.3 years in the BEACOPP arm (Figure 1). *Conclusions.* Stem cells harvest is more difficult after first line BEACOPP, requiring more mobilizations and more cytaphereses. This is consistent with the greater bone marrow toxicity of BEACOPP. Remarkably, this had very limited impact on the strategy salvage treatment strategy as nearly all patients could proceed to transplantation as initially planned.

P092

COMPLETE RESPONSES TO IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA PREVIOUSLY TREATED WITH 5-AZACITIDINE: A POSSIBLE ROLE FOR EPIGENETIC PRIMING?

L. Falchi[1], A. Sawas[1], C. Deng[1], J.E. Amengual[1], D.S. Colbourn[1], E.A. Lichtenstein[1], H.J. Dials[1], K.A. Khan[1], L.H. Schwartz[2], O.A. O'Connor[1]

[1]Center for Lymphoid Malignancies, Department of Medicine, Division of Hematology/Oncology, Columbia University Medical Center, New York, NY, USA; [2]Department of Radiology, Columbia University Medical Center, New York, NY, USA

Background. Patients with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) after brentuximab vedotin (Bv) and autologous stem cell transplantation (ASCT) have limited treatment options. Immune checkpoint inhibitors (ICI) are active in this population, but rarely induce complete response (CR). Evidence suggests that exposure of tumor cells to 5-azacitidine may activate a T-cell-mediated immune responses, thus enhancing the efficacy of ICI. We reviewed our experience with ICI in patients with R/R cHL, and compared responses between those who had been exposed to 5-azacitidine to those not previously esposed to a hypomethylating agent. *Methods.* Eleven patients with R/R cHL received pembrolizumab at the dose of 2 mg/kg every 3 weeks (N=9), or nivolumab at the dose of 3 mg/kg every 2 weeks (N=2). Response was assessed by positron emission tomography/computerized tomography (PET/CT). *Results.* The patient population was very heavily treated, with a median of 12 [3-16] prior treatments. All had received ASCT and Bv. Six had been exposed to 5-azacitidine on a Phase 1 study. Four of them had received it immediately prior to ICI, all of them within 14 months. Grade ≥3 adverse events (AE) included: infusion reaction (N=1) thrombocytopenia (N=1), grade-5 respiratory failure (N=1), myelodysplastic syndrome (N=2, one pre-existent), and acute kidney injury (N=1, pre-existent). Nine patients were evaluable for response: 7 (78%) achieved CR, one PR, and one a reduction of tumor burden. All five evaluable patients who received 5-azacitidine prior to ICI achieved CR (one is pending evaluation and will be reported), while only 2 of 4 who did not receive prior 5-azacytidine achieved CR. At a median follow-up of 9.0 months [0.5-14.3], 9 patients are alive and 6 are still receiving treatment. *Conclusions.* We documented an unprecedented rate of CR to ICI in patients with heavily pre-treated R/R cHL. The most serious AE's were unrelated to ICI therapy. We believe this experience supports the notion of epigenetic priming, as shown in lung cancer studies, and is now being studied in the context of a clinical trial.

P093

BRENTUXIMAB VEDOTIN IN PATIENTS WHO ARE INELIGIBLE FOR AUTOLOGOUS STEM CELL TRANSPLANT WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA: A UNITED KINGDOM AND GERMANY RETROSPECTIVE STUDY

P.J. Bröckelmann[1], E.A. Zagadailov[2], S. Corman[3], M. Hagan[4], V. Chirikov[3], C. Johnson[3], C. Macahilig[4], B. Seal[2], M.R. Dalal[2], T. Illidge[5]

[1]Department I of Internal Medicine and German Hodgkin Study Group (GHSG), University Hospital of Cologne, Germany; [2]Millennium Pharmaceu-

ticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, USA; [3]Pharmerit International, Bethesda, MD, USA; [4]Medical Data Analytics, Parsippany, NJ, USA; [5]Institute of Cancer Sciences, University of Manchester, Christie Hospital, Manchester, UK

Background. Brentuximab Vedotin (BV) is an anti-CD30 antibody-drug conjugate indicated for the treatment of CD30+ rrHL following Autologous Stem-Cell Transplantation (ASCT) or following at least two prior therapies in patients who are ASCT-ineligible. Clinical outcomes in the ASCT-ineligible population have not yet been evaluated in a real-world study. We aimed to describe outcomes in real-world ASCT-ineligible patients with relapsed/refractory Hodgkin Lymphoma (rrHL) in two countries known to have different practice patterns in rrHL. *Methods.* This was a retrospective medical chart review study that enrolled patients at 45 clinical sites representative of routine practice in Germany and the UK. The study included patients ≥18 years old at the time of HL diagnosis, who progressed after multi-drug chemotherapy regimens between 1 January 2008 and 30 June 2014 and were not ASCT candidates as identified by their clinicians, were subsequently treated with BV, and were not enrolled in an HL-related clinical trial. Patient demographics, clinical characteristics, and treatment characteristics were described. Clinical outcomes included best response to treatment, progression-free survival (PFS), overall survival (OS), and adverse events (AEs). All outcomes were descriptive, and reported in the full study population and by country. *Results.* A total of 136 patients were included in this analysis (78 in Germany and 58 in the UK). The median age of study patients at HL diagnosis was 70 years, and 58% were male. Nearly all patients had classical HL (96%), and over half had non-bulky (<5 cm) disease (55%). The most common reasons for ASCT ineligibility were comorbidities (74%), age (57%), and disease progression (12%). Coronary artery disease (39%), diabetes (38%), and chronic pulmonary disease (24%) were the most common comorbidities among study patients. Eighty-five percent of patients received at least 2 lines of treatment prior to initiating BV. At the time of BV initiation, 24% of patients had stage IV disease and 21% had extranodal involvement. The median duration of follow-up was 3.2 years from the time of HL diagnosis. Three fourths of patients had a partial or complete response (Table 1). Other events of interest included leukopenia (13%; of which 53% were serious), neuropathy (10%; 8% serious), and anemia (9%; 42% serious). *Conclusions.* Progression-free and overall survival in ASCT-ineligible patients receiving BV were 15.1 and 17.8 months, respectively, after initiation of therapy.

Table 1. Treatment, response, and survival in ASCT-Ineligible patients receiving Brentuximab Vedotin.

Outcome	ASCT-Ineligible Patients Receiving BV N=136
Median cycles administered (range)	8 (1-16)
Response	
Complete response	35%
Partial response	40%
Stable disease	13%
Progressive disease	12%
PFS from start of BV (months), median (95% CI)	15.1 (8.9-22.0)
OS from start of BV (months), median (95% CI)	17.8 (13.7-33.5)

P094

REAL-WORLD EFFECTIVENESS OF BRENTUXIMAB VEDOTIN *VS* OTHER TREATMENTS IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA POST AUTOLOGOUS STEM-CELL TRANSPLANTATION

E.A. Zagadailov[1], S. Corman[2], M. Hagan[3], V. Chirikov[2], C. Johnson[2], C. Macahilig[3], B. Sea[1], M.R. Dalal[1], P.J. Bröckelmann[4], T. Illidge[5]

[1]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [2]Pharmerit International, Bethesda, MD, USA; [3]Medical Data Analytics, Parsippany, NJ, USA; [4]Department I of Internal Medicine and German Hodgkin Study Group (GHSG), University Hospital of Cologne, Germany; [5]Institute of Cancer Sciences, University of Manchester, Christie Hospital, Manchester, UK

Background. Brentuximab Vedotin (BV) is an anti-CD30 antibody-drug conjugate indicated for the treatment of CD30+ rrHL following Autologous Stem-Cell Transplantation (ASCT) or after ≥2 prior therapies in patients who are ASCT-ineligible. We aimed to compare effectiveness in post-ASCT patients with relapsed/refractory Hodgkin Lymphoma (rrHL) receiving BV to those receiving other or no treatment in clinical settings in Germany and the UK. *Methods.* This retrospective medical chart review enrolled patients at 45 clinical sites in Germany and the UK. The study included patients ≥18 years old at HL diagnosis, who received ASCT between 1 January 2008-30 June 2014, had ≥12 months of available clinical data from the start of post-ASCT treatment, and were not enrolled in an HL-related clinical trial. This analysis included randomly selected post-ASCT patients who subsequently relapsed, and an augmented sample of patients who relapsed post-ASCT. Patients were grouped according to the subsequent line of therapy (LOT) received after post-ASCT relapse (BV, salvage chemotherapy, or no treatment). Patient demographics, clinical, and treatment characteristics were described, and clinical outcomes included progression-free survival (PFS), OS, and best response. Median PFS and OS were calculated using Kaplan-Meier methods; other outcomes were summarized using descriptive statistics. *Results.* A total of 360 patients were included in the study (161 in Germany, 199 in the UK). Of these, 213 received BV, 128 received other treatments, and 19 received no treatment for post-ASCT relapse. Groups were similar in age at diagnosis, gender, and HL type. The most commonly applied chemotherapy regimens were gemcitabine-based (38% and 42% in Germany and UK) and ICE (17% and 8%, respectively). Patients in the BV group received a median of 7 of the recommended 16 treatment cycles (Table1). Median PFS was 11.7 months longer in patients receiving BV compared to those receiving salvage chemotherapy. Median OS from start of therapy was 32.0 months in the salvage chemotherapy group and was not estimable in the BV group due to >50% of patients surviving at last follow-up (P=0.014). Other events that occurred during treatment include leukopenia (12%) and peripheral neuropathy (10%) for BV and leukopenia (12%), anemia (6%), and diarrhea (6%) for salvage chemotherapy. *Conclusions.* In this real-world study, rrHL patients receiving BV as the first post-relapse LOT after ASCT relapse tended to have longer PFS and OS than patients receiving salvage chemotherapy; however, confidence intervals were wide.

Table 1. Treatment and survival outcomes in patients with Relapsed/Refractory Hodgkin Lymphoma after Autologous Stem-Cell Transplantation relapse.

Outcome	Brentuximab vedotin N=213	Salvage chemotherapy N=128
Median cycles administered (range)	7 (1-16)	4 (1-8)
Best response to therapy, N (%)		
Complete response	93 (43.7)	60 (37.3)
Partial response	76 (35.7)	36 (22.4)
Stable disease	26 (12.2)	18 (11.2)
Progressive disease	17 (8.0)	46 (28.6)
Ongoing treatment	1 (0.5)	1 (0.6)
PFS from start of post-relapse therapy (months), median (95% CI)	27.0* (19.9-NE)	15.3 (8.0-NE)

NE, not estimable

* *P*=0.0129 vs. salvage chemotherapy

P095

RISK FACTORS FOR RELAPSE IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA AFTER AUTOLOGOUS STEM CELL TRANSPLANT: A REAL-WORLD ANALYSIS IN GERMANY AND THE UNITED KINGDOM

E.A. Zagadailov[1], S. Corman[2], M. Hagan[3], V. Chirikov[2], C. Johnson[2], C. Macahilig[3], B. Seal[1], M.R. Dalal[1], T. Illidge[4], P.J. Bröckelmann[5]

[1]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [2]Pharmerit International, Bethesda, MD, USA; [3]Medical Data Analytics, Parsippany, NJ, USA; [4]Institute of Cancer Sciences, University of Manchester, Christie Hospital, Manchester, UK; [5]Department I of Internal Medicine and German Hodgkin Study Group (GHSG), University Hospital of Cologne, Germany

Background. With the advance of novel therapeutic options, RFs for post-ASCT outcomes in patients with rrHL are of immediate interest. Several RFs for relapse have been previously documented; however, there are limited data with respect to the prevalence and distribution of RFs in post-ASCT rrHL patients who have and have not had a subsequent relapse. We aimed to describe the prevalence and distribution of RFs after ASCT in patients with rrHL in a sample of real-world patients in Germany and the UK. *Methods.* We retrospectively evaluated patients who were ≥18 years old at the time of HL diagnosis, received ASCT between 1 January 2008 and 30 June 2014, were not enrolled in an HL-related clinical trial and treated under real-world setting at 45 clinical sites in Germany and the UK. This analysis included randomly selected post-ASCT patients, and was augmented by patients who relapsed post-ASCT. RFs of interest included patient age, sex, B symptoms, extranodal disease, bulkiness, clinical stage, ECOG performance status, erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, lymphocyte count, hemoglobin (Hgb), and lactate dehydrogenase (LDH) at the time of relapse preceding ASCT (ie, pre-ASCT relapse), number of salvage regimens prior to ASCT; response to salvage treatment; and time to relapse after front-line treatment. *Results.* A total of 398, predominantly male patients, with a median follow-up of 2.2 years post-ASCT were included (196 in Germany, 202 in the UK). The mean age at diagnosis was 43 years. In total, 329 (83%) had a relapse during the follow-up period. A greater proportion of patients who relapsed were ≥45 years old, had stage IV disease, B symptoms, bulky disease, ECOG ≥1, anemia, and elevated LDH at the time of pre-ASCT relapse (Table 1). The median number (range) of RFs present was 3 (0-7) in patients who relapsed and 1 (0-5) in patients who did not relapse. *Conclusions.* This real-world study demonstrates the prevalence and distribution of a myriad of RFs in patients post-ASCT rrHL. RF profiles are different in patients who did and did not have a subsequent relapse, and, as such, clinical evaluation of RFs is critical to identify patients at a truly increased risk of subsequent relapse.

Table 1. Table. Prevalence of risk factors in patients who did and did not relapse after Autologous Stem-Cell Transplantation.

Risk factor, N (%)	Relapsed N=329	Did not relapse N=69	P-value
Male	186 (56.5)	37 (53.6)	0.658
Age ≥45 years	173 (52.6)	13 (18.8)	<0.001
B symptoms at the time of ASCT	43 (13.1)	2 (2.9)	0.028
Extranodal disease at the time of ASCT	116 (35.3)	24 (34.8)	0.94
≥2 salvage regimens prior to ASCT	19 (5.8)	2 (2.9)	0.341
Non-response to salvage therapy (stable or progressive disease)	43 (13.1)	4 (5.8)	0.098
Bulkiness (>5 cm) at pre-ASCT relapse	265 (80.5)	54 (78.3)	0.665
Clinical stage at pre-ASCT relapse			0.016
I	11 (3.3)	2 (2.9)	
II	109 (33.1)	26 (37.7)	
III	103 (31.3)	30 (43.5)	
IV	95 (28.9)	10 (14.5)	
Not assessed	11 (3.3)	1 (1.4)	
ECOG status ≥1 at pre-ASCT relapse	233 (70.8)	36 (52.2)	0.003
Time to relapse <3 months after front-line therapy	56 (17.0)	7 (10.1)	0.155
ESR >50 mm/h at pre-ASCT relapse	63 (19.1)	15 (21.7)	0.798
WBC >15 x 10^9/L at pre-ASCT relapse	12 (3.6)	0 (0)	0.909
Anemia at pre-ASCT relapse	116 (35.3)	10 (14.5)	0.001
LDH >250 IU/L at pre-ASCT relapse	217 (66.0)	28 (40.6)	<0.001

P096

VERY LATE RELAPSES OCCURING AT LEAST 5 YEARS AFTER THE INITIATION OF TREATMENT WITH CHEMOTHERAPY OR COMBINED MODALITY THERAPY IN PATIENTS WITH HODGKIN: INCIDENCE, RISK FACTORS AND OUTCOME

T.P. Vassilakopoulos[1], G.A. Pangalis[2], M.N. Dimopoulou[1], M.P. Siakantaris[3], M. Dimou[4], G. Boutsikas[1], M. Moschogiannis[2], V. Telonis[1], K. Petevi[1], T. Tzenou[4], X. Yiakoumis[2], A. Kanellopoulos[1], G. Gainaru[1], L. Papageorgiou[1], K. Koutsi[1], J. Asimakopoulos[1], N. Giannakopoulou[1], M. Arapaki[1], G. Dryllis[1], T. Yiannikos[1], E. Konstantinou[1], E. Pessach[4], T. Iliakis[1], S. Sachanas[2], V. Komninaka[1], P. Tsaftaridis[1], E. Plata[1], M.C. Kyrtsonis[4], P. Tsirkinidis[2], E. Variamis[3], N.A. Viniou[3], P. Panayiotidis[4], K. Konstantopoulos[1], M.K. Angelopoulou[1]

[1]Department of Haematology; [2]Department of Haematology, Athens Medical Center, Athens, Greece; [3]1st Department of Internal Medicine; [4]1st Propedeutic Department of Internal Medicine of National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece

Introduction. Most relapses in HL patients (pts) occur within 5 yrs from diagnosis. However, there are pts who do relapse later on, even after decades. The exact incidence of VLRs, especially after CT/CMT, is not well established. Similarly, there are very limited data on baseline disease features associated with VLRs as well as the outcome of these pts. *Aim.* The estimation of the probability of VLR in pts with HL who remain in 1st complete remission (CR1) for 5 years after institution of CT/CMT, the identification of risk factors for VLR and the evaluation of the outcome of VLRs. Pts/*Methods.* Retrospective study of 764 HL pts in CR1 for ≥5 years. Initial CT was anthracycline-based in 87% of pts [mainly A(E)BVD] and MOPP-like in 13%. The Kaplan-Meier method and Cox's model were used for univariate and multivariate survival analysis. *Results.* Among 764 pts, 44 had a VLR (2/44 had a composite HL and non-Hodgkin lymphoma): 24, 13, 4 and 3 between 5-10, 10-15, 15-20 and beyond 20 years from diagnosis. Starting from diagnosis, the 10-year and 15-year VLR rate were 3.7% and 8.0%. In univariate analysis, higher risk for VLR was observed for pts treated with CT only *vs* CMT (p=0.0006), non-nodular sclerosing histologies (non-NS) (p=0.002) and age ≥45 yrs (p=0.02). In multivariate analysis, independent predictors of VLR were non-NS (HR 2.39, p=0.006) and CT *vs* CMT (HR 2.56, p=0.003). At 15 yrs from diagnosis, the probability of VLR was 3.0%, 10.3% and 24.0% (p<0.0001) for pts with 0, 1 and 2 risk factors (RFs). Among 663 anthracycline-treated pts, independent predictors for VLR were non-NS histologies (HR 2.56, p=0.02) and age ≥45 yrs (HR 2.29, p=0.04). At 15 yrs from diagnosis, the probability of VLR was 2.7%, 10.8% and 27.3% (p<0.0001) for patients with 0, 1 and 2 RFs. Conventional salvage therapy was given to 37 pts (mostly non-cross resistant), 4 received salvage RT only, 2 salvage with autoSCT, while 1 pt has not received salvage therapy yet. The 5- and 10-yr survival after failure was 70% and 42%. *Conclusions.* Among pts with HL who remain in CR1 at 5 years following CT w/wo RT, approximately 3-4% relapse within the next 5 yrs and even more thereafter. This observation if important when counselling pts in CR1 regarding their chance of ultimate cure. Younger pts with NS who receive CMT have the lowest risk for VLR. AutoSCT should not be spared solely on the basis of a very long CR1, since the results of conventional salvage do not appear satisfactory.

P097

LONG-TERM OUTCOME OF REDUCED-INTENSITY ALLOGENEIC TRANSPLANT IN RELAPSED/REFRACTORY HODGKIN'S LYMPHOMA: THE TIMING OF RELAPSE AFTER AUTOLOGOUS TRANSPLANT AND PRIMARY REFRACTORY DISEASE DO NOT IMPACT THE LONG-TERM SURVIVAL

F. Spina[1], S. Dalto[1,2], C. De Philippis[1,2], A. Dodero[1], L. Farina[1], V. Montefusco[1], S. Viviani[1], P. Corradini[1,2]

[1]Division of Hematology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [2]Chair of Hematology, Università degli Studi di Milano, Milan, Italy

This study analyzed a cohort of consecutive patients with relapsed/refractory Hodgkin's lymphoma (RR-HL) receiving reduced intensity allogeneic transplant (alloSCT) in a single center to understand whether the timing of relapse after autologous transplant (ASCT) or primary refractory disease would change the survival after allograft. Of 243 patients with HL referred to our division from 2001 to 2014, 105 had RR-HL (64 primary refractory). After salvage treatment, 62 patients (59%) underwent alloSCT with thiotepa-based conditioning, 43 patients did not receive alloSCT due to progressive disease (31), age >65 years (3) or complete remission after third line chemotherapy and ASCT (9 patients). Multivariate analysis of alloSCT outcomes included disease pre-transplant status (CR *vs* PR *vs* resistant [SD or PD]), donor type (HLA identical, matched unrelated

[MUD], or T-depleted or T-repleted haploidentical), primary refractory disease (yes *vs* no) and timing of relapse after ASCT (<12 months after ASCT *vs* >12 months *vs* no ASCT). Allografted patients had a median of 33 years, 76% had a primary refractory disease, 25% had persistent disease at alloSCT. Donors were HLA identical siblings (42%), MUD (29%) or haploidentical (29%); 74% of patients relapsed <12 months, 15% relapsed >12 months after ASCT, and 11% had not received ASCT. After a median follow-up of 5.4 years, 5-year OS was 59% (CI95% 47-71%), PFS and relapse incidence were 46% (CI95% 34-58%) and 38% (CI95% 26-50%). Non-relapse mortality (NRM) was 10% at 100 days (CI95% 3-17%), 17% at 1 year (CI95% 8-26%) and subsequently for the entire follow-up. In multivariate analysis, the timing of relapse after ASCT and primary refractory disease did not impact the outcome after alloSCT. OS was reduced by resistant disease at alloSCT (HR=4.01, CI95% 1.34-11.97, p=0.012) and by T-depleted haploidentical graft (HR=3.81, CI95% 1.36-10.66, p=0.010). PFS and relapse incidence were impacted only by resistant disease (HR=5.54, CI95% 2.13-14.37, p<0.001, and HR=6.75, CI95% 2.07-21.96, p=0.001, respectively). NRM was significantly increased in the T-depleted haploidentical transplant (HR=7.63, CI95% 1.07-54.31, p=0.042). In conclusion, only the disease pre-transplant status, not the timing of relapse after ASCT or primary refractory disease, influenced OS, PFS and relapse of alloSCT. The deepest response should be pursued before alloSCT to have the best results from it and this might be possible in the era of novel agents.

P098

THE PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF BRENTUXIMAB VEDOTIN IN A PATIENT UNDERGOING HEMODIALYSIS

C. Liu[1], G. Jang[2], R. Ramchandren[1]

[1]Department of Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA; [2]Seattle Genetics, Bothell, WA, USA

Abstract. Brentuximab Vedotin (BV) is an antibody drug conjugate (ADC) approved for the treatment of relapsed classical Hodgkin lymphoma (cHL) and systemic anaplastic T cell lymphoma. BV consists of a CD30 directed antibody cAC10 conjugated by a protease-cleavable linker to a microtubule disrupting agent, monomethyl auristatin E (MMAE). Prior studies analyzing the pharmacokinetics (PK) of BV in normal and impaired renal function patients indicate that the elimination of the ADC and unconjugated cAC10 are through proteolytic degradation into amino acids with the elimination of MMAE occurring through the liver and kidney. However, to date no data evaluating the PK of MMAE in the hemodialysis (HD) population is available. Therefore, we serially obtained serum MMAE levels in a 75 year old female patient diagnosed with relapsed cHL undergoing HD and BV therapy to evaluate the PK and PD behavior of ADC in this population. *Methods.* BV was administered at a dose of 1.2 mg/kg every 21 days. Serum samples were obtained within 15 minutes pre and post HD (Mon,Wed, Fri) and pre and post BV. The samples were then analyzed for MMAE drug levels. Concentrations of unconjugated MMAE were measured in plasma, by liquid chromatography and tandem mass spectrometry(LC MS/MS). *Results.* The maximum observed plasma MMAE level (Cmax) of 3110 pg/ml and overall decline in plasma concentrations post dosing were similar to phase I studies evaluating the 1.2 mg/kg dose in patients with normal renal function. Areas under the curve (AUC) levels over 21 days also were similar to non HD patients with normal renal function. In addition, pre and post dialysis plasma MMAE levels were similar, indicating that the effect of HD on MMAE levels was negligible. *Conclusions.* In a single patient analysis of MMAE levels undergoing HD, levels were consistent with non HD patients suggesting that BV may have similar PK, PD and clinical activity profiles in this population. In addition, HD had minimal effect on MMAE levels indicating little effect of HD on potential efficacy or toxicity. Further studies of BV in patients undergoing HD are warranted to further characterize drug behavior in this population.

P099

IMMUNE SYSTEMS ENGAGEMENT RESULTS IN NON-CLASSICAL ANTIBODY-DRUG CONJUGATE ANTITUMOR ACTIVITY OF BRENTUXIMAB VEDOTIN

S.J. Gardai, R. Heiser, A. Cao, F. Li, C. Leung-Law

Seattle Genetics, Bothell, WA, USA

Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) approved for the treatment of relapsed Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL). Brentuximab vedotin is comprised of a chimeric IgG1-directed antibody against CD30 and the small molecule, MMAE, a microtubule-disrupting agent covalently attached to the antibody via a cleavable linker. The primary anticancer activity of BV is believed to be the binding of the ADC to CD30-expressing cells, followed by internalization, release of MMAE which results in microtubule network disruption, cell cycle arrest, and apoptotic death. In addition to classical ADC activity, the antibody and auristatin drug payload components of BV have additional and distinct modalities that may contribute to its overall function and antitumor activity in the heterogeneous and complex immune microenvironment of lymphoma. In addition to classical ADC activity, recent evidence elucidates new functionality of BV including antibody-dependent cellular phagocytosis (ADCP); bystander-killing of nearby CD30-negative tumor cells in the tumor microenvironment due to MMAE release from CD30-expressing tumor cells and macrophages; and immunogenic cell death driven by endoplasmic reticulum (ER) stress that can promote an antigen specific T-cell response. Decoration of CD30-expressing cells with BV mediates macrophage recognition and phagocytosis promoting the removal of tumor cells independent of antibody internalization and release of the auristatin payload (MMAE). This activity occurs *in vitro* and contributes to *in vivo* activity seen with the antibody backbone. Furthermore, cell-permeable MMAE released from proteolytic processing of BV by macrophages within the tumor microenvironment or CD30-expressing tumor cells is able to kill antigen-negative tumor cells in a variety of *in vivo* tumor models. Additionally, *in vitro* characterization has demonstrated that MMAE-mediated disruption of microtubules not only drives tumor cell apoptosis but results in ER stress leading to surface exposure of immune-activating molecules that can drive innate and adaptive immune response that may contribute to the overall and long-term antitumor activity of BV. Taken together, these data provide rationale for the activity of BV in tumors with low and heterogeneous CD30 expression and for ongoing combinatorial trial with immuno-oncology agents.

P100

THE LONG-TERM OUTCOME OF PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA AND NEGATIVE INTERIM PET FAILING ABVD MIGHT BE WORSE THAN THAT OF INTERIM PET POSITIVE PATIENTS UNDERGOING EARLY TREATMENT INTENSIFICATION WITH ESCALATED BEACOPP

J.M. Zaucha[1], B. Małkowski[2], E. Subocz[3], J. Tajer[4], W. Kulikowski[5], M. Panebianco[6], J. Grad[7], J. Rybka[8], R. Kroll-Balcerzak[9], A. Romanowicz[10], A. Chamier-Ciemińska[11], P. Kurczab[12], G. Cimino[6], S. Chauvie[13], W. Knopinska-Posluszny[5], J. Walewski[4], A. Gallamini[14]

[1]Gdynia Oncology Center, Gdynia and Department of Oncological Propedeutics, Medical University of Gdansk, Gdansk, Poland; [2]Nuclear Medicine Department, Oncology Center, Bydgoszcz, Poland; [3]Department of Hematology, Military Institute of Medicine, Warszawa, Poland; [4]Department of Lymphoproliferative Diseases, Maria Sklodowska-Curie Memorial Institute, Warszawa, Poland; [5]Clinical Department of Hematology, Interior Ministry Hospital, Warmia and Mazury Medical University, Olsztyn, Poland; [6]Department of Cellular Biotechnology and Hematology, University "La Sapienza" of Rome, Italy; [7]Hematology Unit, Regional Hospital, Opole, Poland; [8]Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland; [9]Department of Hematology, University Medical School, Poznan, Poland; [10]Department of Hematology, Central Clinical Hospital MSW, Warszawa, Poland; [11]Department of Clinical Oncology, Oncology Center, Bydgoszcz, Poland; [12]Medical Center Mrukmed with Outpatient Chemotherapy

Unit, Rzeszów, Poland and Department of Clinical Oncology, Sub-Carpathian Oncology Centre, Brzozow, Poland; [13]Medical Physics Department Santa Croce e Carle Hospital, Cuneo, Italy; [14]Research, Innovation and statistics department, Lacassagne Cancer Center, Nice University, Nice, France

Purpose. Despite high NPV of negative iPET in patients with HL about 10% of them relapse/progress after completion of ABVD. Here we present clinical characteristics and outcome of such patients comparing them to patients with positive iPET and interim treatment escalation [iPET(+)&TE]. *Patients and Methods.* Data of the Polish patients were retrieved from the prospective observational study of the Polish Lymphoma Research Group on the predictive role of iPET after 1 ABVD cycle. Briefly, intermediate and advanced stage (IIB-IVB) HL patients were treated with ABVD followed by iPET after each of the first 2 ABVD cycles. iPET(-) patients continued with ABVD, while some iPET2(+) had at the discretion of a local physician treatment intensification with BEACOPP esc. with a median of 6 (2-8) cycles. iPET(-) patients failing ABVD had second line treatment with ICE(3), IGEV(6), DHAP(7),ESHAP(5), BEACOPP esc(3), ABVD/MOPP(2) Brentuximab(1), IVOX(1), ASCT(1). iPETs were interpreted according to the Deauville scale as negative(-)(score 1,2,3) and positive (+)(score 4,5). The primary endpoints were: overall survival (OS) and time (EFS2) to the second event (no complete remission or allogeneic HCT at the day of last follow-up), respectively. The secondary endpoint: time to first event (2^nd progression for iPET1(-) or 1^st one for iPET(+)&TE after treatment escalation). *Results.* After a median follow-up of 48.8 (range 15 – 84) months 29 iPET(-) failing ABVD and 26 iPET(+)&TE patients were identified. (Table 1).

Table 1. Demographics and treatment outcome of patients.

		Interim PET(-) failing ABVD	Interim PET(+) with treatment escalation	p
No.		29	26	
Age	Years	33,8	32,4	0,71
Sex	Female/Male	13/16	7/19	0,17
Histological type	NS	20	19	
	MC	5	1	
	LR	3	2	0,11
	LD	0	4	
	Unknown	1	0	
Clinical stage	I-IIA	7	4	
	IIB-IV	22	22	0,9
	IPS:0-2/>2*	8/13	8/14	1,0
B-symptoms	No/Yes	8/21	4/22	0,27
Bulky disease	No/Yes	12/17	10/16	0,82
Extranodal disease		12/17	12/14	0,82
Lymphocyte count	No/ul	1319	1556	0,09
Lymphocyte/Monocyte	Ratio	2,15	1,97	0,61
Type of relapse	Primary refractory	18(62%)	7(70%)	
	Early 3-12 months	7(24%)	1(10%)	0,61
	Late>12 months	4(14%)	2(20%	
Brentuximab	Yes(%)	2(7%)	3(12%)	
Auto SCT	Yes(%)	19(66%)	5(19%)	
Allo SCT	Yes(%)	2(7%)	3(12%)	
1st treatment failure	Yes(%)	15(51%)	11(42%)	0,48
	EFS1@3 years	0,46	0,57	0,054**
	95%CI	0,26-0,66	0,38-0,76	
2nd treatment failure	Yes(%)	12 (41%)	8(30%)	0,41
	EFS2@3 years	0,53	0,69	0,04**
	95%CI	0,34-0,73	0,51-0,86	
Alive	Dead	6(21%)	4(15%)	
	OS@3years	0,74	0,84	0,09
	95%CI	0,56-0,92	0,70-0,98	

*-advanced patients ** land mark analysis- cut off 25 months

The two cohorts were not different with regard to sex, age, stage, histological subtype, presence of: B symptoms, bulky mass and extranodal disease, absolute number of lymphocytes, lymphocyte to monocyte ratio, and type of relapse. Six(21%) iPET(-) and 4(15%) iPET(+)&TE died. However, in the former group deaths occurred during the longer follow-up, whereas in the latter occurred in the 25 months after treatment onset (Figure1). Similarly more patients experienced S2 events in iPET(-) group (12-41% *vs* 8-31%) that tended to occur within longer time in iPET(-) patients. This translated to a significant difference (p=0,04) in the probability of EFS2 events between the two cohorts as shown by the landmark analysis @25 months. *Conclusions.* Patients with iPET(-) interim BEACOPP escalation despite iPET(+) may experience better long-term OS and significantly better EFS than patients with iPET(-) failing ABVD. Markers to improve NPV of iPET are warranted.

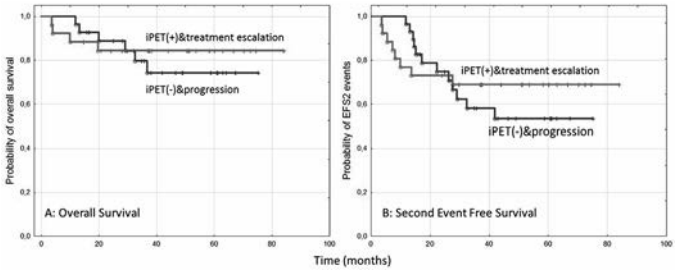


Figure 1. The probability of overall survival (Panel A) and second event free survival (Panel B) in patients with iPET(-) and subsequent progression, and iPET(+) and interim treatment escalation.

P101

THE VALUE OF BRENTUXIMAB VEDOTIN IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA PATIENTS BASED ON POOLED-ANALYSIS

R. Dada[1,2], J. Zekri[1,2], M. Bayoumy[1], R. Al Saadi[1]

[1]King Faisal Specialist Hospital and Research Center, Jeddah, Kingdom of Saudi Arabia; [2]College of Medicine, Al-Faisal University, Riyadh, Kingdom of Saudi Arabia

Objectives. Based on excellent data of Results of the Pivotal phase II study (Younes *et al.*, J Clin Oncol. 2012 Jun 20;30(18):2183-9), the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved BV for the treatment of patients with HL who have either failed autologous stem cell (ASCT) or had at least two prior multi-agent chemotherapy regimens and who are not candidates for ASCT. Since the approval several study groups published the results of their experience in treating refractory/relapsed HL patients with BV. This meta-analysis evaluated the effect of single agent brentuximab vedotin (BV) in patients with relapsed/refractory Hodgkin lymphoma (HL). *Patients and Methods.* A systematic literature search was performed and included studies published from 1st January 2012 to 1st July 2015 investigating BV in patients with relapsed/refractory HL. Data was extracted and reviewed by two investigators then analyzed using the comprehensive meta-analysis version 3 software. Heterogeneity of studies was identified according to I2 value. Studies are regarded homogenous if I2 ≤25% and the fixed effect model of meta-analysis is used. *Results.* 22 out of 4048 screened records met the eligibility criteria. These records included 903 patients. The median age of the cohort was 31 year (range: 26-45). 86% received ≥3 previous lines of systemic therapy. 529 (58.7%) and 232 (25.7%) underwent high dose chemotherapy and autologous and/or allogeneic stem transplantation prior of BV respectively. The overall response rate to BV was 62.7% (range: 30-100%) (Figure 1).

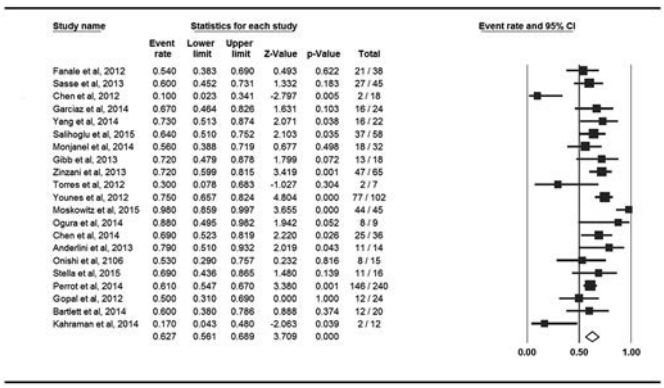


Figure 1. Pooled overall response rate to Brentuximab Vedotin (Random effect).

The complete response, partial response, stable disease and progressive disease rates were 31.8% (Figure 2), 35.1%, 19.5% and 11.7% respectively.

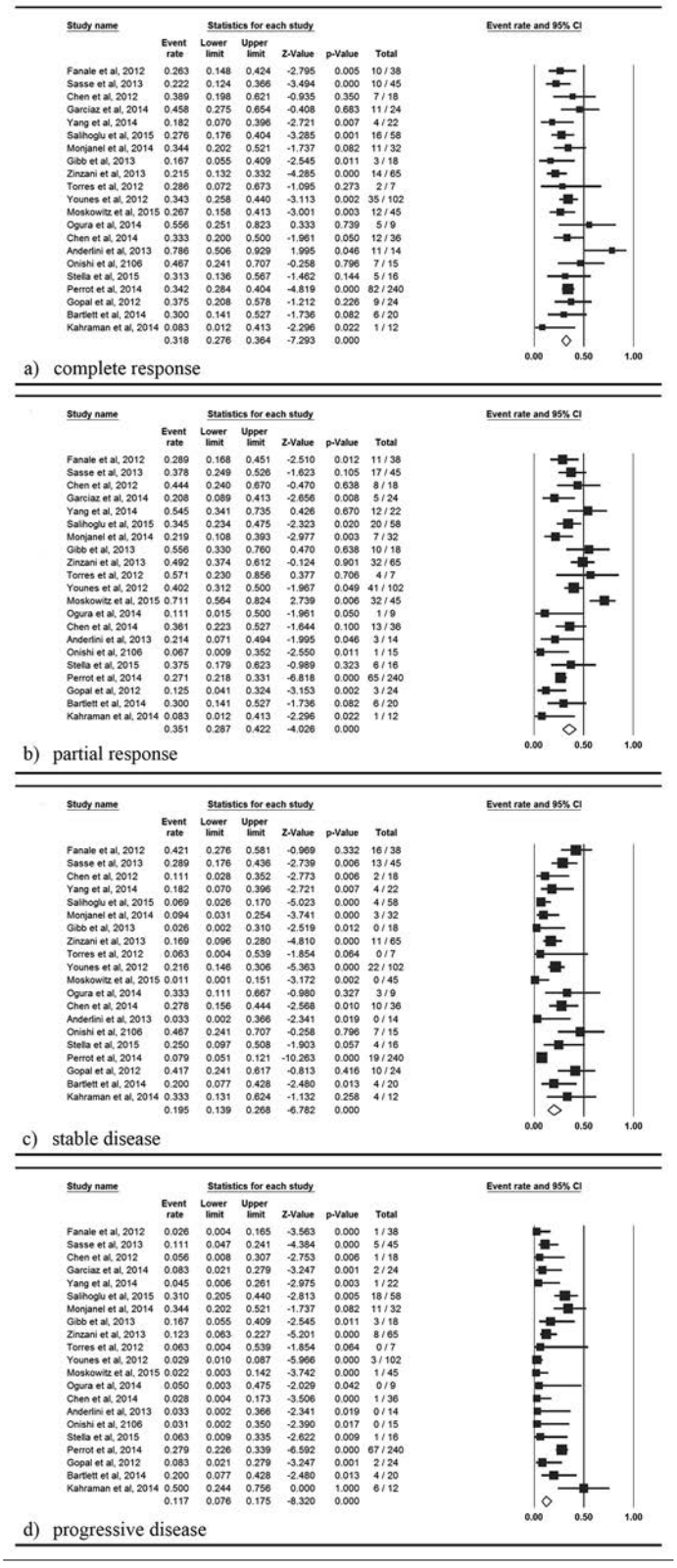


Figure 2: Pooled response rate to Brentuximab Vedotin (Random effect).

The one year progression free survival and estimated one year overall survival were 47.6% (Figure 3) and 79.5% (Figure 4) respectively. Additional fixed effect model meta-analysis showed similar results (difference: <2%) except for progressive disease (difference: 9.3%) and progression at one year (difference: 5.2%) (Table 1). *Conclusions.* In this largest published pooled cohort BV produces high responses with encouraging progression free and overall survival in relapsed/refractory HL patients. Our results enhance the role of BV in heavily pretreated HL patients.

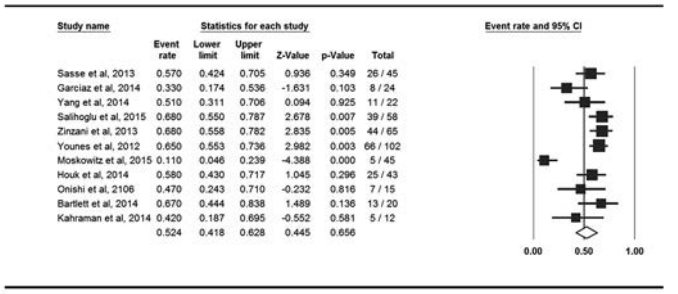


Figure 3: Pooled rate of disease progression one year after treatment with Brentuximab Vedotin (Random effect).

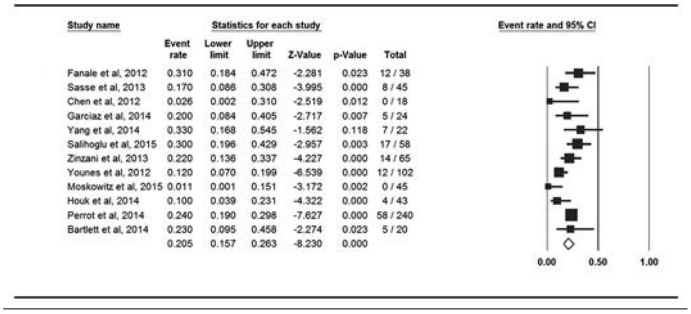


Figure 4: Pooled rate of mortality events one year after treatment with Brentuximab Vedotin (Random effect).

Table 1. Results of random and fixed effect meta-analysis models.

Outcome	Result of random effect model (95% CI)	Result of fixed effect model (95% CI)	I^2
Overall response rate	62.7% (56.1-68.9)	63.4% (59.9-66.7)	61%
Complete response	31.8% (27.6-36.4)	32.1 (29-35.4)	34%
Partial response	35.1% (28.7-42.2)	35.7% (32.4-39.1)	68%
Stable disease	19.5% (13.9-26.8)	20.1% (17.2-23.4)	72%
Progressive disease	11.7% (7.6-17.5)	21% (18-24.4)	72%
Progression at 1 year	52.4% (41.8-62.8)	57.6% (52.7-62.4)	76%
Mortality (death)	20.5% (15.7-26.3)	22% (19-25.4)	53%

P102

A ROLE FOR ALLOGENEIC STEM CELL TRANSPLANTATION IN THE ERA OF NOVEL AGENTS FOR HODGKIN'S LYMPHOMA?

C. Scheid, J. Chemnitz, M. Herling, N. Pflug, S. Theurich, A. Burst, S. Leitzke, M. von Bergwelt-Baildon, M. Hallek, U. Holtick

Stem Cell Transplantation Program, Dept. I of Medicine, University of Cologne, Cologne, Germany

Patients with relapsed Hodgkins lymphoma (HL) can achieve long term remission after high-dose chemotherapy and autologous stem cell transplantation (SCT). However the prognosis is dismal for patients relapsing after autologous SCT. The advent of novel agents such as brentuximab vedotin or checkpoint-inhibitors has enabled a

large proportion of patients to achieve responses, but these remissions are often not durable. On the other hand there have been several attempts to use allogeneic SCT as a potentially curative treatment modality in HL. While progress has been made to reduce the transplant-related mortality, relapse after transplant remains the biggest challenge for allogeneic SCT. In order to investigate how the availability of novel agents may have influenced the results of allogeneic SCT we performed a retrospective single centre analysis in our institution. Thirty seven patients with relapsed/refractory HL were transplanted between 2005 and 2016. Median overall survival (OS) after transplant was 4.4 years with 57% OS at 3 years. There was no difference in OS in patients transplanted before or after 2010. Remission status before allogeneic SCT had a significant impact on 3 yr OS which was 75% in patients transplanted in CR, 63% in PR, 66% in SD and 22% in patients with progressive disease. Of the 20 patients in CR or PR before transplant 2 (10%) died from transplant-related causes. Eight patients (40%) in this group relapsed after transplant. While four patients eventually died from relapsed HL, four patients are long term survivors 5 – 6.6 years from transplant after being treated with novel agents such as brentuximab, everolimus or ruxolitinib. In the era of novel agents performing allogeneic SCT in patients with relapsed HL at the time of maximum response may provide long term survival with acceptable transplant-related risks. In addition using these agents to treat relapse after transplant can further improve the long term prognosis. While more and more options are available to optimize the remission status before transplant, new approaches will incorporate novel agents in the early post-transplant phase before day 100, such as everolimus in our current single-centre OCTET-Ever protocol or brentuximab vedotin in a planned multi-centre protocol by the German Hodgkin Study Group.

P103

SALVAGE TREATMENTS FOR RELAPSED CLASSICAL HODGKIN LYMPHOMA IN CHILDREN AND ADOLESCENTS: A 10-YEAR EXPERIENCE IN A SINGLE CENTRE

V. Fiaccadori[1], J. Roskin[1], V. Sana[1], B. Carpenter[1], R. Hough[1], V. Grandage[1], P. Humphries[2], M. Klusmann[2], L. Menezes[3], S. Daw[1]

[1]Children and Young People's Cancer Services, University College Hospital London, UK; [2]Department of Radiology, UCLH, London, UK; [3]Department of Nuclear Medicine, UCLH, London, UK

Background. The optimal treatment for paediatric relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) is undefined. Standard salvage treatment is re-induction chemotherapy followed by consolidation with high dose chemotherapy (HDCT) / autologous stem cell transplantation (ASCT). However some patients may be salvaged with chemo-radiotherapy only thereby avoiding toxicity of transplant while in others the standard HDCT/ASCT would be predicted to fail and allogeneic transplant has been proposed as an alternative approach.

Purpose: To evaluate outcomes of risk and response adapted salvage strategies in R/R cHL in our centre. *Patients and Methods.* A retrospective study between 2005-16 identified 23 first relapse patients; median age 14 (3-19) years; M:F ratio 1.6:1; median time to relapse 10 months (1 month - 180). First line treatment was multi-agent chemotherapy with (n=5) or without radiotherapy (n=18). Salvage was re-induction chemotherapy in all patients followed by consolidation treatment which was selected based on an assessment of prognostic factors and assessment of response to salvage chemotherapy. RT consolidation was used in 4 patients with later relapse who achieved a complete metabolic remission (CMR) with one line of salvage. HDCT/ASCT was used in 13 patients, all in a CMR after one (n=5), two (n=7) or four (n=1) lines of salvage. Allo-SCT was used in 6 patients, five in CMR [after one (n=1), two (n=2), three (n=1) or four (n=1)] lines of salvage. *Results.* 4/4 consolidated with RT only (no transplant) remain well in second remission, median follow-up 66 months. 11/13 consolidated with HDCT/ASCT (conditioning BEAM/LEAM) remain in second remission, median follow-up 18 months. Only 2/6 consolidated with allo-SCT (conditioning regimen BEAM-Campath in 5 and FMC in 1) remain in second remission, median follow up of 24 months while 2/6 relapsed and 2/6 died of early treatment toxicities. *Conclusions.* Only 4/23 patients experienced a second relapse. 0/4 in the RT group, 2/13 in the HDCT/ASCT group, 2/6 in the Allo-SCT group. Two patients died of infection / toxicity post allo-SCT. The disease free survival (DFS) by consolidation group was 100% in the RT group, 85% in the HDCT/ASCT group, and 33% in the allo-SCT group. A risk and response adapted salvage approach achieved excellent outcomes with RT or HDCT/ASCT consolidation but the outcomes with allogeneic transplant are less encouraging due to relapse and toxicity in this small study.

P104

SINGLE-ARM STUDY OF BRENTUXIMAB VEDOTIN IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA WHO ARE INELIGIBLE FOR STEM CELL TRANSPLANTATION OR MULTIAGENT CHEMOTHERAPY

J. Walewski[1], A. Hellmann[2], N. Siritanaratkul[3], G.H. Ozsan[4], M. Ozcan[5], S. Chuncharunee[6], A.S. Goh[7], W. Jurczak[8], J. Koren[9], B. Wang[10], S. Singh[10], D. Huebner[10], A. Engert[11]

[1]Maria Sklodowska-Curie Institute and Oncology Centre, Warsaw, Poland; [2]Medical University of Gda sk, Gda sk, Poland; [3]Siriraj Hospital, Bangkok, Thailand; [4]Dokuz Eylul University, Izmir, Turkey; [5]Ankara University School of Medicine, Ankara, Turkey; [6]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [7]Hospital Pulau Pinang, Pulau Pinang, Malaysia; [8]Jagiellonian University, Kraków, Poland; [9]Charles University, Prague, Czech Republic; [10]Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Ltd, Cambridge, USA; [11]University Hospital Cologne, Cologne, Germany

Background. CD30 is a cell surface antigen expressed on malignant HL Reed-Steenberg cells and targeted by the antibody-drug conjugate (ADC) brentuximab vedotin (ADCETRIS®), which comprises a CD30-targeted monoclonal antibody conjugated to the microtubule disrupting agent monomethyl auristatin E via a protease-cleavable linker. Brentuximab vedotin has received US and European approval for treatment of RRHL following failure of autologous SCT (ASCT) or following ≥2 prior therapies when ASCT or multiagent chemotherapy is not a treatment option. Treatments are limited for patients ineligible for ASCT or multiagent chemotherapy; results of this ongoing Phase 4 trial (NCT01990534) will further investigate the anti-tumor activity of brentuximab vedotin in this difficult-to-treat population. *Methods.* Eligible patients are ≥18 years of age with Eastern Cooperative Oncology Group performance status 0–1, RRHL after ≥1 prior therapy, and considered ineligible for SCT or multiagent chemotherapy due to progression within 90 days of complete response (CR) or unconfirmed CR to multiagent frontline chemo/radiotherapy, progressive disease (PD) during frontline multiagent chemotherapy, or relapse after ≥2 prior treatments (including salvage). Patients must have measurable disease (≥1.5 cm) by CT scan. Patients will receive an intravenous infusion of brentuximab vedotin 1.8 mg/kg on day 1 of 21-day cycles for up to 16 cycles or until disease progression or unacceptable toxicity. The primary objective is overall response rate (ORR) assessed by an independent review committee; secondary objectives include duration of response, CR rate, progression-free survival (PFS), overall survival (OS), pharmacokinetics, immunogenicity, safety and tolerability, and proportion of patients receiving ASCT or allogenic SCT following brentuximab vedotin treatment. CT scans of chest, neck, abdomen, and pelvis will be performed at baseline and cycles 2, 4, 7, 10, 13, and 16; PET scans at baseline and cycles 4 and 7. Post treatment follow-up for PFS and OS will be performed every 3 months, for 18 months after end of treatment. OS assessment will continue thereafter every 6 months until death or study closure. Incidence and severity of adverse events will be evaluated according to NCI CTCAE v.4.03. Enrollment has finished with 60 patients across 20 international sites. Final data will be provided at the congress.

P105

OUTCOME OF VERY LATE RELAPSE IN HODGKIN LYMPHOMA – A REPORT FROM DEBRECEN, HUNGARY

L.I. Pinczés, Z. Miltényi, Á. Illés

Department of Hematology, University of Debrecen, Faculty of Medicine, Debrecen, Hungary

Introduction. With modern risk-adapted treatment modalities 80-90% of Hodgkin lymphoma (HL) patients can be cured, however, 30% of the patients may relapse after the first line treatment. Late relapses, that occurred 5 or more years after first diagnosis are rare. Neither clinical characteristics, nor risk factors, nor optimal treatment are well described for very late relapse (VLR) patients. *Aim.* To describe the incidence, clinical presentation, treatment and outcome of VLR in HL patients between 1970 and 2010 at our institute. *Results.* Of 669 consecutive HL patients treated at our institute between 1970 and 2010, 617 (92.2%) patients achieved complete remission after the first line treatment. Relapse occurred in 188 (28.1%) patients, 26 (3.8%) of them 5 or more years after the first diagnosis. VLR were more frequently observed in patients with mixed cellularity histological subtype and stage II/III disease at first diagnosis. In 15 (57.7%) patients, the histologic subtype remained the same at VLR, in 8 (30.8%) cases the region of the relapse was also identical. 24 (92.3%) patients with VLR received polychemotherapies, 5 (20.8%) of them also received involved-field radiotherapy. Primary diagnosis before the age of 20 and treatment with radiotherapy alone at first diagnosis was associated with a higher risk of VLR (p=0.009 and p=0.004 respectively). Compared to early relapse we observed superior OS after VLR. At a median of 244 (91 - 360) months of follow-up, 22 (84.6%) patients with VLR are still alive and disease free. In addition, relapse characteristics, therapeutic approaches, and changes in histologic subtype will be presented. *Conclusions.* VLR occurs in a small number of patients diagnosed with HL. Besides the rarity of these cases, with adequate treatment, late relapse of HL appears to have a favorable prognosis to early relapse HL cases. Subgroup analyses suggest that treatment with radiotherapy alone and first diagnosis before adulthood conveys worse prognosis. Continuous investigations are needed in this setting to determine further risk factors of VLR in HL.

P106

LIMITED EFFICACY OF BRENTUXIMAB VEDOTIN IN A HEAVILY PRE-TREATED HODGKIN LYMPHOMA POPULATION

F. Pierdomenico[1], A.L. Pinto[2], J. Coutinho[3], S. Chacim[4], J. Raposo[5], A. Neves[6], M. Fevereiro[7], F. Principe[8], M.H. Vitória[9], J.P. Fernandes[10], S. Carvalho[11]

[1]Instituto Portugues de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; [2]Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [3]Centro Hospitalar do Porto, Porto, Portugal; [4]Instituto Portugues de Oncologia do Porto Francisco Gentil, Porto, Portugal; [5]Centro Hospitalar de Lisboa Norte, Lisboa, Portugal; [6]Hospital São Bernardo, São Bernardo do Campo, Brasil; [7]Centro Hospitalar Lisboa Centro, Lisboa, Portugal; [8]Centro Hospitalar São João, Porto, Portugal; [9]Centro Hospitalar Tondela Viseu, Tondela, Portugal; [10]Hospital da CUF, Porto, Portugal

Although HL is highly curable, 10-30% patients (pts) are refractory or relapse after treatment. Salvage second line chemotherapy with autologous stem cell transplant (ASCT) usually achieves 50% responses. Refractory pts and those who relapse after ASCT have a poor prognosis. BV is an anti_CD30 antibody-drug-conjugate with significant activity against refractory/relapsed HL. We report a multicentric retrospective analysis of 34 Portuguese pts receiving BV monotherapy for refractory/relapsed HL between 9/2011 and 2/2016 at 10 centers. BV (1.2 or 1.8 mg/Kg) was administered every 3w. Response was evaluated by PET-CT. Overall (OS) and progression-free-survival (PFS) were estimated using the Kaplan-Meier method; chi-square text was used to evaluate relation between clinical variables and response. Pts (53% female) were diagnosed between 1997 and 2015; 62% had advanced disease. First-line treatment was ABVD in 91% with a 74% overall response rate (ORR). Twenty-eight pts (82%) received salvage chemotherapy with intent to perform ASCT, and 64% underwent transplant. Median age at BV was 34.5 yo (23-69), 76% had advanced disease and 1/3 B symptoms. Median time from initial diagnosis was 44 mo; median number of prior treatments was 4 (2-6), with 79% pts refractory to last one. Median number of BV cycles was 7.5. In 18 pts with early evaluation of response (at cycles 2 to 4), ORR was 67% and CR 33%. At the end of treatment, ORR was 21% (5 CR, 15%), while 76% had either stable or progressive disease. Pts with ≤3 prior lines had ORR 47% as compared to none in pts with >3 (p<0,001). No difference in ORR was noted according to gender, refractory/relapsed state and number of involved nodal areas. Ten pts (29%) were transplanted after BV, only 4 in response; 18 started subsequent treatment after BV. After a median follow-up of 12 mo 11 pts died, mostly of progressive disease. OS and PFS at 12 months were 73.5% and 19% respectively. BV was well tolerated with 18% peripheral neurotoxicity, 33% at least one hematological toxicity and 9% grade 3-4 infections in all pts. In a real-life setting, with a heavily pre-treated and mainly refractory population, responses to BV were lower than previously described. In agreement to others we observed loss of responses with prolonged treatment, suggesting a benefit for early evaluation and treatment consolidation to maximize the benefit of BV. Better ORR was observed after ≤3 prior treatments, suggesting that BV should be offered early.

P107

THE ROLE OF STEM CELL TRANSPLANTATION IN HODGKIN'S DISEASE; PERSPECTIVES FROM RETROSPECTIVE ANALYSIS

P. Mazza[1], N. Cascavilla[2], P. Galieni[3], G. Palazzo[1], A.M. Carella[2], S. Falcioni[3], G. Pisapia[1], E. Merla[2], B. Amurri[1], S. Angelini[3]

[1]Hematology and Bone Marrow Transplantation Unit "SS Annunziata" Hospital, Taranto, Italy; [2]Hematology and Bone Marrow Transplantation Unit "Opera Padre Pio", S. Giovanni Rotondo (FG), Italy; [3]Hematology and Bone Marrow Transplantation Unit "Mazzoni" Hospital, Ascoli Piceno, Italy

Purpose. To disclose the prognostic value of status of disease and lines of therapy at transplantation (SCT) either autologous or allogeneic in Hodgkin lymphoma we did a retrospective evaluation. *Patients and Methods.* We accrued all patients who did a stem cell transplant (SCT) procedure following resistance, residual disease, or relapse after previous conventional therapy. The accrual started in October 1998 when we did the first autologous SCT with the use of peripheral stem cells (PSC) and included patients up to December 2015. One hundred eighty one patients with Hodgkin lymphoma did autologous and 40 patients did allogeneic SCT and analyzed for prognosis according to status and number of lines of therapy at transplant. Five categories of patients were identified according the status at transplant: primary resistant, with residual disease, in first relapse, in second relapse and more than second relapse. Autologous SCT was done as II, III, IV line and more than IV line of therapy. High dose therapy followed by autologous PSCT represented a line of therapy for almost all patients who did allogeneic SCT. The analysis included the evaluation of survival according to groups identified and see if there are significant differences. *Results.* Worse chances of survival were for patients primary resistant, 6% at 138 months, and for those with more than two relapses,10% at 120 months; better chance were for patients with residual disease, 88% and those who did transplantation following I relapse, 96% at 194 months (p<0.0001) (Figure 1). In addition better survival was for patients who received autologous SCT as II line of therapy, 93% survival at 194 months, and worse those with more than IV line of therapy, 12% at 146 months (p<0.0001). Allogeneic SCT was done in 38 (95%) patients following autologous SCT; survival was 16% at 175 months and relapse-free survival (RFS) was 18% at 174 months. The stratification of survival in the setting of allogeneic SCT was worse for patients resistant and with previous more lines of therapy. *Conclusions.* Our study demonstrates that Hodgkin lymphoma may be cured by high-dose ther-

apy and a procedure of SCT following failure to conventional therapies. However, different outcomes were recorded according the status of disease and the line of therapy at transplant; differentiated therapeutic approaches to various patients categories will be discussed.

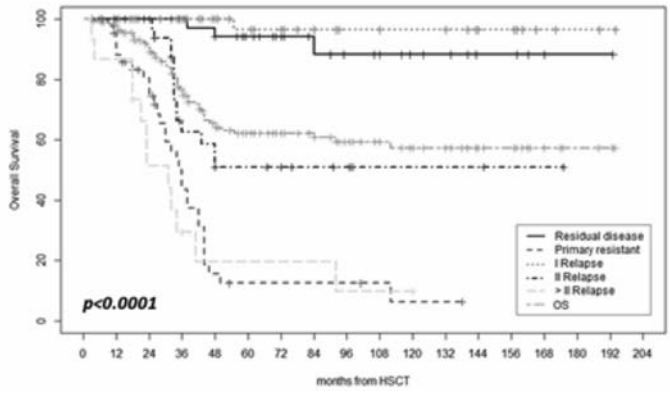


Figure 1.

P108

AUTOLOGOUS STEM CELL TRANSPLANTATION IN HODGKIN LYMPHOMA: EXPERIENCE OF TWO CENTERS IN BRAZIL

J. Sobreira de Almeida[1], M. Seo Gomes Pinto[2], S. Costa Fortier[1], T.M. Bueno da Silveira Rocha[1], R.M. Augusto Passos[3], L. de Lourdes Martins Perobelli[3], R. Rabelo Chiattone[1,2], C.S. Chiattone[2,4]

[1]Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, Brasil; [2]Hospital Samaritano, São Paulo, Brasil; [3]Hospital de Transplantes Doutor Euryclides de Jesus Zerbini, São Paul, Brasil; [4]Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo, Brasil

Introduction. Hodgkin Lymphoma (HL) is considered a potentially curable neoplasm in which most patients respond well to initial treatment. However, 10-15% of patients with localized disease and 25-30% with advanced disease experience treatment failure or relapse. In this patient group, high-dose chemotherapy followed by salvage with hematopoietic stem cells (HSCT) is considered the standard treatment. Objectives: Analysis of Overall Survival (OS) and Progression-Free Survival (PFS) in patients with HL submitted to HSCT, and identification of possible predictors of poor prognosis. *Materials and Methods.* A retrospective study of HL patients submitted to HSCT at two Brazilian centers was conducted. *Results.* A total of 106 patients were analyzed with mean follow-up time of 28.6 months (0.37 – 154.23). Regarding pre-HSCT disease status, 38 (40.9%), 45 (48.4%) and 10 (10.7%) patients had Complete Remission (CR), Partial Remission (PR) and were refractory, respectively. Response after HSCT was CR, PR and refractory in 51 (68.9%), 13 (17.6%) and 10 (13.5%) individuals, respectively. Of the 44 patients in PR before HSCT, 17 (38.6%) evolved to CR after HSCT. Three-year GS and PFS were 84.7% and 74%, respectively. Pre-HSCT influenced OS (p=0.012) and PFS (p=0.007). *Conclusions.* We confirmed in a Brazilian population that HSCT should be considered as a therapeutic option for patients with refractory or recurrent HL since it can promote long-term responses. Factors associated with poor prognosis were determined, allowing an individualized approach to improve response rates and minimize toxicity.

P109

PD1-INHIBITION WITH NIVOLUMAB AFTER ALLOGENEIC HAEMATOPOIETIC CELL TRANSPLANTATION FOR HODGKIN'S LYMPHOMA

S. Schulze[1], N. Jaekel[1], A. Monecke[2], S. Leiblein[1], P. Schirmacher[3], D. Niederwieser[1], H.K. Al-Ali[1]

[1]University Hospital of Leipzig, Division of Hematology and Oncology, Leipzig, Germany; [2]University Hospital of Leipzig, Department of Pathology, Leipzig, Germany; [3]University Hospital, Institute of Pathology, Heidelberg, Germany

Allogeneic hematopoietic cell transplantation (allo-HCT) is an option for patients with Hodgkin's lymphoma (HL) who relapse after autologous HCT. Recently, response rates of 87% after treatment with nivolumab (a monoclonal IgG4 anti-PD-1 antibody) in relapsed/refractory HL even after autologous HCT were published (Ansell *et al.*, NEJM 2015). Yet, the impact of nivolumab with its immune-related mechanism of action after allo-HCT is unknown. We report the use of nivolumab after allo-HCT for relapsed HL. *Patient and Methods.* The patient is a 52-year-old female with HL, stage IVLA in 5th relapse. Earlier treatments were standard chemotherapies prior to and after autologous HCT. In 2010, the patient received an allo-HCT from an HLA-identical unrelated donor. She developed extensive graft *versus* host disease (GvHD) of the skin and liver. The patient suffered further relapses and was treated with brentuximab, and gemcitabine. Immunosuppression could be discontinued in 2014. Peripherally, NK- and T-cells were 100% of donor origin. A PET-CT prior to nivolumab displayed a generalized lymph node, pulmonary and bone involvement by HL. Immunohistochemical staining of a tissue biopsy revealed that the Hodgkin- and Reed-Sternberg cells expressed the PD-L1 protein. *Results.* Nivolumab was started (3mg/kg at week 1 and 4, and then every 2 weeks) in July, 2015. A PET-CT at week 5 revealed a complete remission which is now maintained for 8 months. Two weeks after the first infusion, an upsurge in eosinophils, NK- and T-cell populations occurred (Table 1). CD279 (PD-1) was expressed on 21% of the T-cells. A grade 3 hepatotoxicity at week 6 necessitated an interruption of nivolumab for 5 weeks and treatment with prednisolone 25 mg QD. Nivolumab was resumed and prednisolone tapered without evidence of further immune-mediated adverse events or GvHD. *Conclusions.* A fast and complete remission with immunologic checkpoint blockade is possible even after allo-HCT. However, a therapeutic blockade of the PD-1 pathway may influence the function of lymphocytes and NK-cells. Thus, further data are needed to establish the impact of PD-1/PD-L1 blockade after allo-HCT.

Table 1. Peripheral WBC counts under nivolumab.

	Prior to nivolumab	*2 weeks after the start of nivolumab*	*5 months under nivolumab*
Eosinophils (%)	6	27	2
Lymphocytes (x10^9/L)	0.7	1.5	1.6
CD3+ cells (x10^9/L)	0.4	1	1
CD3+/HLA-DR+ cells (x10^9/L)	0.1	0.3	0.2
CD3+/CD4+ cells (x10^9/L)	0.3	0.6	0.7
CD3+/CD8+ cells (x10^9/L)	0.1	0.3	0.3
CD3-/CD16/CD56+ cells (x10^9/L)	0.2	0.4	0.2

P110

EFFICACY OF BRENTUXIMAB VEDOTIN IN THE TREATMENT OF RELAPSED HODGKIN LYMPHOMA AND CONCOMITANT MYCOSIS FUNGOIDES

E. Meli[1] C. Rusconi[1], V.R. Zilioli[1], P. Minga[1], M. Zancanella[1], M. Anghilieri[2], R. Cairoli[1]

[1]ASST Grande Ospedale Metropolitano Niguarda, Niguarda Cancer Center, Milan, Italy; [2]ASST Lecco, Ospedale Alessandro Manzoni, Lecco, Italy

Background. Brentuximab Vedotin (BV) is currently used for the treatment of relapsed/refractory Hodgkin Lymphoma (HL). Accordingly to preliminary data, BV might be useful also against Mycosis Fungoides (MF), even in patients with weak CD30 expression. Here we describe a case of relapsed HL and concomitant MF treated with BV. *Case Report.* A 73-year-old man was referred to our Center in September 2015 for relapsed HL and simultaneous MF. Medical history included hypertension, moderate chronic renal impairment and acute heart failure secondary to atrioventricular block. MF was diagnosed

in 1987 and UVA, UVB and PUVA were delivered, with short term partial remissions. Classical HL, clinical stage IIIB, was diagnosed in 2004 and patient obtained complete remission (CR) after 6 ABVD cycles. After 7 years (68 years-old), HL relapse was histologically documented and clinical stage was IIIA. Three cycles of IGEV chemotherapy obtained a second CR and 30 Gy involved-field radiotherapy was given as consolidation. A third HL relapse, biopsy proven with strong CD30 expression, occurred 3 years later and clinical stage was IIIA. At time of HL relapse MF was in stage III and patient presented scaly erythematous plaques distributed over most of his body. Patient started BV therapy at the reduced dose of 1.2 mg/kg/3ws due to creatinine-clearance of 53 ml/min. A significant regression of the skin lesions was observed after the first BV dose, and after 4 BV cycles both MF and HL achieved a CR, documented by clinical examination and PET scan, respectively. Twelve of the 16 BV planned doses have been administered, with no significant toxicity and no recurrence of both HL and MF. *Conclusions.* This case confirms that BV is a well tolerated and effective treatment for HL; the quick response of the concomitant MF that we observed encourages further investigations on the role of BV also in this setting.

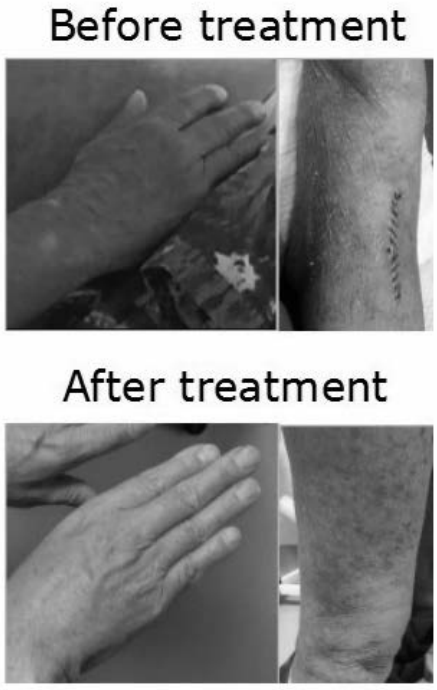


Figure 1.

P111

PROGRAMMED DEATH 1 BLOCKADE WITH NIVOLUMAB AS SALVAGE THERAPY FOR HEAVILY PRE-TREATED CLASSICAL HODGKIN'S LYMPHOMA RELAPSING AFTER ALLOGENEIC STEM CELL TRANSPLANTATION: A CASE REPORT

A. Comai, E. Domingo-Domenech, A. Sureda

Clinical Hematology Department, Institut Català d'Oncologia, Hospitalet, Barcelona, Spain

Introduction. Monoclonal antibody nivolumab (NIVO) blocks Programmed Death-1 ligands avoiding overstimulation of T-cell activity therefore preventing autoimmunity. On May 2016, US Food and Drug Administration granted its accelerated approval in patients with Hodgkin's lymphoma (HL) relapsed after both autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV), based on the overall response rate (ORR) of 65% from the combined analysis of phase I CheckMate-039 and phase II CheckMate-205 trials. In the setting of allo-SCT, NIVO seems to be associated with increased transplant related toxicity and mortality, *e.g.* higher incidence of veno-occlusive disease and graft *versus* host disease (GVHD). *Case Report.* A 43 years-old male was diagnosed of classical HL stage IIA with bulky mediastinal disease in June 2008. After achieving a PET negative complete remission (CR) with ABVD x6 cycles and involved field radiotherapy, the patient presented an early relapse with stage IIIA disease. He was then treated with salvage second-line therapy with DHAP x3 cycles and consolidated with ASCT with BEAM as conditioning regimen. He achieved a second PET negative CR but experienced a second early relapse (<1 year) after the ASCT that was treated with NOVPx6 cycles and consolidated with an allo-SCT from his HLA-identical brother in November 2009. In spite of developing clinical significant acute and chronic GVHD, the patient experienced two more relapses treated with BV (1.8 mg/kg iv every 21 days up to 10 cycles – disease progression) and bendamustine single drug (120 mg /m^2 iv x2 days, 3 cycles) with disease progression. In September 2015, NIVO was requested through the name patient program in our country. At that time, the patient had progressive disease, stage IVA (bone marrow), no clinically relevant GVHD and no need for active immunosuppression. NIVO was started in October 2015 at a dose of 3 mg/kg iv every 2 weeks with very good tolerance and no reactivation of the prior history of GVHD. The patient achieved a PET negative CR after 6 cycles and nowadays has an excellent performance status under NIVO treatment, in continuous CR by PET CT 8 months after starting this latter therapy. *Conclusions.* Our patient, treated in the absence of immunosuppression and almost 6 years after allo-SCT, has significantly benefited from NIVO with no relevant toxicity. Further studies on the role of NIVO before and after allo-SCT should be pursued.

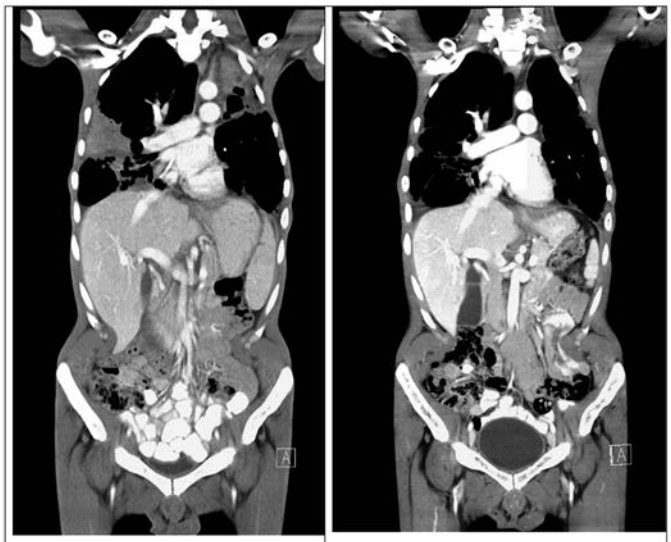
P112

MAJOR RESPONSE OF HEAVILY PRETREATED HODGKIN LYMPHOMA TO NIVOLUMAB: THE IMMUNE SYSTEM RELOADED

R. Dada[1,2], J. Zekri[1,2]

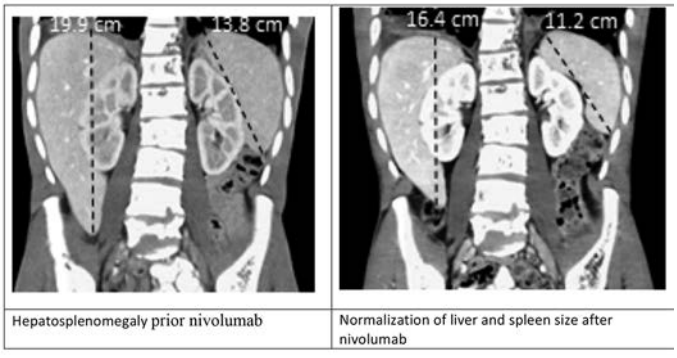
[1]King Faisal Specialist Hospital and Research Center, Jeddah, Kingdom of Saudi Arabia; [2]College of Medicine, Al-Faisal University, Riyadh, Kingdom of Saudi Arabia

Background. Cancer can escape the immune system through different mechanisms. One of which is the expression of program death ligand-1 (PD-L1). This ligand binds to PD-1 receptor on activated T cells, subsequently leading to inhibition of the immune response. Nivolumab is novel antibody that binds to PD-1 and prevents such immune tolerance. Several recently published clinical trials confirmed the clinical efficacy of single agent Nivolumab in pretreated patients with different cancer types. Publications on Nivolumab in Hodgkin lymphoma (HL) are very scares. The available literature is limited to only one phase 1 clinical study with 23 pretreated patients (Ansell eta l., N Engl J Med 2015;372:311-9). Case description: We report on a 30 year-old man with stage IVB HL. He failed 9 lines of prior therapy including: ABVD, ICE, radiation, ESHAP and high dose BEAM chemotherapy and autologous stem cell transplantation, IGEV, Brentuximab vedotin,. Brentuximab and Ifosfamide, GVD and Bendamustine. The patient has multiple visceral involvement including lung and liver proven by histopathology. He was wheelchair bound (ECOG 3) and oxygen dependent. He received Nivolumab achieving a major radiological response after 4 cycles (Figure 1 and 2). The lung involvement by the HL has nearly completely disappeared. The involved liver has markedly decreased in size, in addition to improvement of splenomegaly. This radiological response was associated with significant clinical improvement. The performance status improved to ECOG 1and became oxygen independent. No treatment related significant side effects were observed. *Conclusions.* Pre-treated HL is amenable to novel immunotherapy. Nivolumab induces clinically meaningful responses with excellent tolerance. The drug enriches our treatments options by reloading the immune system response against cancer. Further clinical studies are needed to determine the effectiveness on large patients' cohort.



Computer tomography prior nivolumab shows multiple lung lesions	Computer tomography after nivolumab shows complete resolution of the lung lesions

Figure 1.



Hepatosplenomegaly prior nivolumab	Normalization of liver and spleen size after nivolumab

Figure 2.

P113

TREATMENT OF A PATIENT WITH PRIMARY REFRACTORY HODGKIN LYMPHOMA AND CONCURRENT CENTRAL NERVOUS SYSTEM INVOLVEMENT

H. Móciková, Ľ. Gahérová, T. Kozák

Department of Internal Medicine and Haematology, University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University in Prague, Czech Republic

Background. The incidence of CNS involvement in Hodgkin lymphoma (HL) is 0.05% and it can occur at the time of initial diagnosis or in a relapsed/refractory disease. *Case Report.* 32-year-old female immunocompetent patient with classical HL (mixed cellularity) in initial clinical stage IIB was treated in Lybia between 2011-2014 (6xABVD, 3x ICE, 4x ASHAP, involved field irradiation of 36Gy on cervical lymph nodes, 2 cycles of Gemcitabine and Navelbine, steroid treatment) without achieving a sustained remission and HL was considered primary refractory. The patient was admitted to our hospital with headache, blurred vision and with disseminated disease in clinical stage IVA (2015): PET/CT confirmed involvement of lymph nodes on both sides of diaphragm, liver, diffuse skeletal and muscle infiltration. MRI of the brain revealed involvement of paranasal sinuses, focal lesions in the right temporal lobe with perifocal oedema and dislocation of the right lateral ventricle. A new biopsy of the cervical lymph node confirmed HL- nodular sclerosis. Cerebrospinal fluid and bone marrow examinations were negative for HL involvement. She was treated with two cycles of brentuximab vedotine and bendamustine (BVB) in combination with dexamethasone. Two cycles of BVB alternated with two cycles of high-dose methotrexate 3,5g/m^2 with procarbazine and dexamethasone. She achieved a partial remission according to PET/CT and MRI of the brain after above mentioned treatment. The patient received conditioning regimen BCNU/etoposide/thiothepa followed by autologous stem cell transplantation (ASCT) in February 2016. Neutrophil and platelet engraftment was reported on day+10 after ASCT. Currently, consolidation treatment with brentuximab vedotine is ongoing since day +30 after ASCT. *Conclusions.* BVB combination is a highly effective salvage chemotherapy for relapsed/refractory systemic Hodgkin lymphoma, and additional effect of bendamustine on CNS involvement in combination with high-dose methotrexate, procarbazine and dexamethasone can be anticipated. Conditioning regimen directed against CNS and systemic HL involvement CNS may further potentiate the effect of salvage chemotherapy.

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P114

PEMBROLIZUMAB *VERSUS* BRENTUXIMAB VEDOTIN IN RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA: RANDOMIZED, PHASE 3 KEYNOTE-204 STUDY

M.A. Fanale[1], J. Kline[2], R. Chen[3], V. Ribrag[4], G. Salles[5], I. Matsumura[6], Y. Zhu[7], A.D. Ricart[7], A. Balakumaran[7], P.L. Zinzani[8]

[1]The University of Texas MD Anderson Cancer Center, Houston, USA; [2]University of Chicago, Chicago, USA; [3]City of Hope National Medical Center, Duarte, USA; [4]Gustave Roussy, Villejuif, France; [5]Centre Hospitalier Lyon-Sud, Lyon, France; [6]Kinki University, Osaka, Japan; [7]Merck & Co., Inc., Kenilworth, USA; [8]Institute of Hematology "Seràgnoli", University of Bologna, Bologna, Italy

Background. The PD-1 ligands, PD-L1 and PD-L2, are frequently overexpressed in relapsed or refractory classical Hodgkin lymphoma (R/R cHL), and this is typically associated with chromosome 9p24.1 amplification. In the phase 1b KEYNOTE-013 study, PD-1 blockade with pembrolizumab demonstrated high antitumor activity (65% ORR) in heavily pretreated patients with cHL. KEYNOTE-204 (NCT02684292) is a randomized, international, open-label phase 3 study designed to compare the efficacy and safety of pembrolizumab *versus* brentuximab vedotin (BV) in patients with R/R cHL. *Methods.* This study will enroll patients aged ≥18 years with R/R cHL who (1) have failed to achieve a response or progressed after autologous stem-cell transplantation (auto-SCT) and have not had previous treatment with BV; or (2) are not auto-SCT candidates because of chemotherapy-resistant disease (unable to achieve complete remission or partial remission to salvage chemotherapy), advanced age, or comorbidities, and have received at least 2 prior multi-agent chemotherapy regimens that did not include BV. ~300 patients will be randomized 1:1 to receive either pembrolizumab 200 mg Q3W or BV 1.8 mg/kg Q3W. Treatments will continue for up to 35 cycles or until documented disease progression, unacceptable adverse events (AEs), or investigator decision. Response will be assessed Q12W by PET/CT scans per International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma by central imaging vendor review. After the end of treatment, patients will be followed for 30 days for AE monitoring (90 days for serious AEs and events of clinical interest). All patients will be followed for overall survival until death, withdrawal of consent, or the end of the study, whichever comes first. Primary end points are PFS and OS; secondary end points are ORR and complete remission rate (CRR). Exploratory end points include PK profile, duration of response, and comparison of ORR in patients with PD-L1–positive *versus* PD-L1–negative lymphoid tumors. Assessment of primary efficacy end points are based on blinded independent central review according to IWG criteria; secondary/exploratory efficacy analyses are based on investigator assessment. Enrollment to KEYNOTE-204 is ongoing.

Survivorship

T025

PATIENT PREFERENCES - SURVEY OF HL SURVIVORS ON TREATMENT-ASSOCIATED BURDENS AND SIDE EFFECTS

C. Buerkle, H. Goergen, H. Müller, P.J. Bröckelmann, S. Kreissl, M. Fuchs, A. Engert, P. Borchmann, K. Behringer

German Hodgkin Study Group (GHSG), University Hospital of Cologne, Germany

Hodgkin lymphoma (HL) survivors often report impaired quality of life due to side effects. For evaluation of the relevance of efficacy outcomes and side effects from the patient's point of view, we created a questionnaire for HL long-term survivors. The questionnaire was sent to randomly selected patients (male and female 150 each) of every trial of our 5th trial generation (HD13, HD14, HD15) with no documented refractory disease or relapse (N=900) and to all patients with documented refractory disease or relapse (R/R) (N=249). 52% of contacted patients participated and median follow up time was 106 month. R/R was reported by 16% of the participants. Chemotherapy was a great or very great burden for 77% of the participants, independent of stage of disease, treatment and study. In early favorable (HD13) and early unfavorable stages (HD14) treatment standard included radiotherapy (RT) of 30 Gy. For 64% of participants this was a great or very great burden. In advanced stages (HD15) RT was only performed in patients with PET-positive residual tissue after chemotherapy. 26% of them rated RT as great or very great burden. Most frequent side effect was fatigue reported by 87% during and 41% after treatment. About of patients who experienced fatigue consider it as a great or very great burden. Most long-term side effects were significantly more frequent for participants with R/R. At time of first diagnosis >50% had concerns about acute and long-term side effects, relapse and death due to HL. Most frequently the concern about relapse is mentioned. At time of survey, ≈25% without R/R worried much or very much about side effects or death because of HL and ≈40% about long-term effects or possibility of relapse. Of those participants with R/R, concern of side effects or death because of HL was present in ≈35% and about long-term effects or another relapse in ≈60%. Cure of HL was rated as the most important treatment goal by 72% of patients. Only 9 participants (2%) would have chosen a slightly less effective therapy to avoid side effects. Chemotherapy is a great burden independent of duration and intensity of administered regimen. HL Survivors are more concerned about relapsing than dying from HL, which could be interpreted as fear of another treatment. Results suggest that avoidance of relapse should be the primary therapy goal and cure is above possible side effects. Thus, progression-free survival is an important patient-relevant endpoint in clinical trials.

T026

CHANGE IN PERIPHERAL BLOOD LYMPHOCYTE TELOMERE LENGTH IN RELATION TO MORTALITY AND MORBIDITY IN HODGKIN LYMPHOMA PATIENTS

R. M'kacher[1,2], T. Girinsky[3], B. Colicchio[4], M. Ricoul[1], A. Dieterlen[4], E. Jeandidier[5], L. Heidingsfelder[6], C. Cuceu[1], J. Bourhis[3,7], W. Hempel[1], S. Koscielny[8], J.F. Paul[9], L. Sabatier[1], P. Carde[10]

[1]Radiobiology and Oncology laboratory, CEA, DSV/iRCM, Fontenay-aux-Roses, France; [2]Cell Environment Oncology Section, Paris, France; [3]Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France; [4]Laboratoire MIPS, Groupe TIIM3D Université de Haute-Alsace, Mulhouse, France; [5]Department of genetics, CHU, Mulouse, France; [6]MetaSystems GmbH, Altlussheim, Germany; [7]Laboratory of Radiation Sensitivity and Radio-carcinogenesis, Villejuif, France; [8]Biostatistics and Epidemiology Unit, Institut Gustave Roussy, Villejuif, France; [9]Department of Radiology, Marie Lannelongue, Chatenay- Malabry, France; [10]Department of Hematology, Institut Gustave Roussy, Villejuif, France

Background. Short telomeres in peripheral blood lymphocytes are associated to an increased cancer risk as well as age-related diseases. Our previous studies demonstrated the significant correlation between telomere dysfunction in peripheral blood lymphocytes of retrospective cohorts of Hodgkin lymphoma (HL) patients and the high risk of late complications, in particular secondary cancers and cardiovascular disease. In this study, we investigate telomere length in a prospective cohort of HL patients followed more than 12 years after diagnosis. *Patients and Methods.* Telomere length measurements were performed at several time points in a prospective cohort of 220 HL survivors patients (95.9% stage I and II). Patients were diagnosed between 1997 and 2005 with a median follow-up 11.2 years. All patients were treated with a combination of chemotherapy and radiation therapy. We evaluated the association between telomere length measured at diagnosis, after treatment and during follow-up. The dynamics of telomere change between those time points in relation to HL cancer specific and all-cause mortality and morbidity was assessed using Cox proportion hazards models. Cardiovascular evaluation has been described previously (Girinsky *et al.* 2014). *Results.* Fifty-seven patients developed cardiovascular disease, 19 a secondary cancer and 10 died. Telomere length at baseline and follow-up after treatment were associated with all-cause mortality (p=0.02 and p=0.008, respectively). A stable telomere length was associated with the absence of late complication. Changes in telomere length were associated to the occurrence of a late complication, either cardiovascular or secondary cancer (p<10-3). A high variation of telomere length and the presence of a sub population of cells with drastic telomere shortening was observed during follow-up preceding a secondary cancer (p<10-3). Telomere dysfunction was related to the presence of complex chromosomal exchanges. *Conclusions.* Telomere shortening was associated with an increased risk of the occurrence of secondary cancer and all-cause mortality. Changes in telomere length in circulating lymphocytes over time may represent valid biomarkers for the prognosis. Telomere dysfunction may play a significant role in the initiation of genomic instability during carcinogenesis. Further investigation to determine causes of telomere change is needed.

T027

THE IMPACT OF TREATMENT TYPE AND AGE ON OVARIAN TOXICITY IN THE RATHL STUDY

R.A. Anderson, R. Remedios, A.A. Kirkwood, P. Patrick, L. Stevens, T. Roberts, A.M. Carella, M. Federico, A. Fossa, C. Hatton, N. Kalakonda, D.W. Milligan, P. McKay, J. Radford, C. Rowntree, F. Scott, P. Smith, P.W.M. Johnson

MRC Centre for Reproductive Health, The University of Edinburgh, Edinburgh, UK; Cancer Research UK & UCL Cancer Trials Centre University College London, London, UK; Cancer Research UK Centre, Southampton, UK

This analysis examined the differential effects upon ovarian function of the treatment strategies within the international RATHL study (NCT00678327). Women with newly diagnosed advanced HL (stages IIb to IV, IIa with bulk or ≥3 involved sites) had two cycles of ABVD followed by PET/CT scan. Those with negative scans were randomised to ABVD or AVD for 4 more cycles, those with positive scans were escalated to either BEACOPP-14 or escalated BEACOPP for 8-9 weeks. Reproductive hormones were measured in women in the main cohort of the trial (n=390) with additional samples taken in a sub-group for measurement of anti-Müllerian hormone (AMH) as a marker of the ovarian reserve (n=63). There were no differences between the ABVD and AVD groups. AMH fell markedly from baseline to end of treatment, but equally in all 3 groups. Thereafter, there was a return to concentrations not different from pre-treatment in the ABVD/AVD groups within 1 year, but no recovery in the BEACOPP groups over 3 years. An FSH threshold of >25IU/L was used to indicate premature ovarian insufficiency (POI). The prevalence of this threshold was substantially higher for women treated with BEACOPP than those treated with ABVD/AVD (see Table 1), with longer and less complete recoveries. Patients aged over 35 were more likely to exhibit POI, especially after BEACOPP

therapy. Pre-treatment AMH was associated with post-chemotherapy ovarian damage in all groups. ABVD/AVD regimens are regarded as low risk to fertility, and these results confirm the absence of detectable ovarian damage in women aged <35, although there was some evidence of ovarian toxicity in older women. Pre-treatment AMH may be of value to predict early POI and loss of fertility following treatment by identifying those women at particular risk who may wish to consider fertility preservation strategies.

	ABVD/AVD	BEACOPP	p-value
FSH>25 at end of treatment, % women over 35	66	100	0.026
FSH>25 at end of treatment, % women under 35	14	89	<0.001
FSH>25 at 2 years, % women over 35	10	70	<0.001
FSH>25 at 2 years, % women under 35	0	20	0.007
Median time to recovery of FSH, women over 35 (days)	516	824	0.008*
Median time to recovery of FSH, women under 35 (days)	209	664	<0.001*

*logrank test

Table 1.

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OSTEONECROSIS AFTER TREATMENT FOR HODGKIN LYMPHOMA: THE GERMAN HODGKIN STUDY GROUP EXPERIENCE

S. Borchmann[1], H. Müller[1], H. Haverkamp[1], C. Baues[2], J. Marková[3], A. Hüttmann[4], A. Glunz[4], M. Fuchs[1], P. Borchmann[1], A. Engert[1]

[1]First Department for Internal Medicine, University Hospital of Cologne, Köln, Germany; [2]Department of Radiooncology, University Hospital of Cologne, Köln, Germany; [3]Department for Internal Medicine and Haematology, University Hospital Kralovske Vinohrady and 3rd Faculty of Medicine, Charles University, Prague, Czech Republic; [4]Clinic for Hematology, Essen University Hospital, Essen, Germany

Background. Osteonecrosis (ON) has been reported as an infrequent but sometimes debilitating late effect of HL therapy. The goal of this study is to provide a detailed analysis of ON as a late effect after treatment for HL. *Methods.* 12,083 patients treated within first-line GHSG trials between 05/98 and 07/14 were evaluated. ON cases were identified and information on patient characteristics, localizations, interventions and outcomes was collected. Risk factors for ON were analyzed by multivariate logistic regression. *Results.* 66 patients had a total of 140 ON. The cumulative incidence of ON was 0.16% [CI: 0.08-0.30] in early (favorable or unfavorable) stage HL (esHL) (n=10) and 0.93% [CI: 0.71-1.21] in advanced stage HL (asHL) (n=54). 75% of ON cases were male. 71% of patients had more than one area affected and in 73% ON of the femoral head was present. 54% of patients needed surgical intervention and 66% had lasting symptoms despite treatment. Peak incidence (41%) was observed in the second year after diagnosis and 83% of cases occurred within 3 years after HL diagnosis. In a multivariate logistic regression comprising all patients, male gender (OR 2.1; CI: 1.2-3.7) and asHL (OR 3.9; CI: 2.3-6.9) were identified as risk factors for ON. Because ON was a rare complication in esHL, the following results focused on survivors of asHL. The median cumulative prednisone dose in ON cases after asHL was 8,400mg (range: 3,920-10,800) *versus* 7,350mg (range: 0-16,800) in not affected patients. In a multivariate logistic regression model including only asHL patients, young age (OR 0.7 for each additional 10 years; CI: 0.5-0.9) and a higher cumulative dose of prednisone during therapy (OR 1.3 for each additional 1gr; CI: 1.1-1.5) were identified as additional risk factors. Nodal pain after alcohol ingestion (p=0.78), radiotherapy (p=0.29), a large mediastinal tumor (p=0.13), international prognostic score (IPS) (p=0.09) and body-mass-index (BMI) (p=0.99) did not influence ON risk. *Conclusions.* We provide the most comprehensive analysis of ON after HL therapy performed so far. ON after HL therapy is infrequent but often leads to significant disease burden in affected patients. The described risk factors and peak incidence timeframe could help to identify patients at high risk for ON. Early evaluation of patients with suggestive symptoms is recommended. Decreasing the cumulative corticosteroid dose in future regimens might reduce the incidence of ON after HL therapy.

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LONGITUDINAL EVALUATION OF HEALTH-RELATED QUALITY OF LIFE IN HODGKIN LYMPHOMA PATIENTS AND SURVIVORS: RESULTS FROM THE GERMAN HODGKIN STUDY GROUP

I. Hude[1], H. Müller[2], H. Görgen[2], C. Bürkle[2,3], K. Behringer[2,3], V. Diehl[2], A. Engert[2,3], P. Borchmann[2,3], on behalf of the German Hodgkin Study Group

[1]Department of Internal Medicine, Division of Hematology, University Hospital Center Zagreb, Zagreb, Croatia; [2]German Hodgkin Study Group (GHSG), University Hospital of Cologne, Cologne, Germany; [3]Department of Internal Medicine I, University Hospital of Cologne, Cologne, Germany

Background. One of the most commonly used patient reported outcome (PRO) measures in oncology is the European Organisation for Research and Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30). In a recent publication by EORTC Quality of Life Group, global HRQoL (gHRQoL), a single higher order measurement model for QLQ-C30, was found to be robust and is recommended to supplement the traditional 15-outcome profile. Aim of this study is to evaluate longitudinal gHRQoL from diagnosis to year 5 after end of treatment (y5EOT) in GHSG clinical trials for early-stage favorable (HD13), early-stage unfavorable (HD14) and advanced-stage (HD15) HL. *Methods.* 5,306 qualified patients of the HD13-HD15 trials (ISRCTN63474366, ISRCTN04761296, ISRCTN32443041) ≤60 years at study entry were eligible for evaluation; 4,110 provided HRQoL data. Patients were treated with different risk-adapted therapies . EORTC QLQ-C30 was used to evaluate gHRQoL from diagnosis to y5EOT with means and 95% confidence intervals. Treatment effects on gHRQoL in y2EOT and y5EOT were tested with multiple linear regression analyses adjusting for age, gender and baseline-gHRQoL. *Results.* Analysis showed significantly worse baseline-gHRQoL with higher stage (means [95%-CI]: HD13 80.6 [79.5-81.8], HD14 76.1 [75.2-77.0], HD15 71.0 [70.0-71.9]). During chemotherapy, gHRQoL worsened in all stages (means [95%-CI]: HD13 63.5 [62.2-64.8], HD14 62.8 [61.9-63.8], HD15 62.7 [61.9-63.6]), rapidly improving thereafter. Compared to baseline, gHRQoL in the early-stage group recovered and remained stable from y1EOT, whereas in higher stages it improved significantly above baseline value, also remaining stable during follow up (y5EOT means [95%-CI]: HD13 82.6 [80.8-84.4], HD14 83.9 [82.6]85.1, HD15 82.5 [81.4-83.7]) (Figure 1). Age- and gender-adjusted German reference values of gHRQoL (93.5-93.9 in HD13-HD15) were not reached at any time point. Comparison of standard *vs* successful experimental treatments showed that treatment intensity had no significant influence on long-term gHRQoL. Age and baseline gHROoL were predictive of gHRQoL in y2EOT and y5EOT. *Conclusions.* Global HRQoL is largely impaired among HL patients. Despite significant baseline differences, gHRQoL after therapy seems independent of initial stage or treatment regimen and does not recover to normal values, warranting further investigation. QLQ C30 summary score seems like a promising tool for PRO evaluation, encouraging further testing.

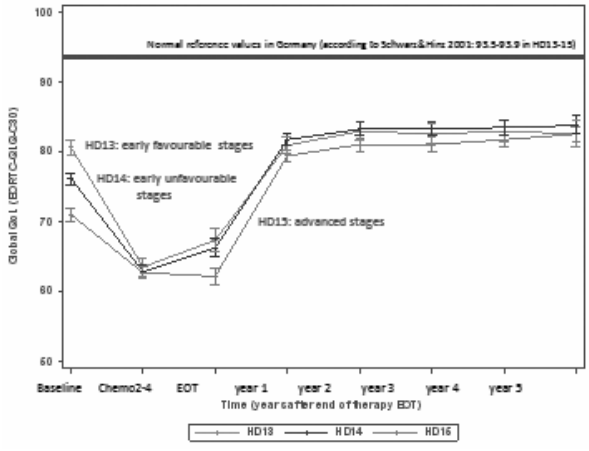

Figure 1.

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BREAST CANCER AFTER HODGKIN LYMPHOMA: INFLUENCE OF ENDOGENOUS AND EXOGENOUS GONADAL HORMONES ON THE RADIATION DOSE-RESPONSE RELATIONSHIP

B.M.P. Aleman[1], I.M. Krul[2], A.W.J. Opstal van Winden[2], C.P.M. Janus[3], A.M. van Eggermond[2], M.L. De Bruin[4], M. Hauptmann[2], A.D.G. Krol[5], M. Schaapveld[2], A. Broeks[6], K.R. Kooijman[2], S. Fase[2], M. Lybeert[7], J.M. Zijlstra[8], R.W.M. van der Maazen[9], A. Kesminiene[10], I. Diallo[11], F. De Vathaire[11], N.S. Russell[1,*], F.E. van Leeuwen[2,*]

[1]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [2]Department of Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [3]Department of Radiation Oncology, Erasmus University MC Cancer Institute, Rotterdam, The Netherlands; [4]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands; [5]Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands; [6]Division of Experimental Therapy and Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [7]Department of Radiotherapy, Catharina hospital, Eindhoven, The Netherlands; [8]Department of Hematology, VU University Medical Center Amsterdam, Amsterdam, The Netherlands; [9]Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands; [10]Section of Environment and Radiation, International Agency for Research on Cancer, Lyon, France; [11]Department of Clinical Research, Gustave Roussy, Villejuif, France

**Authors contributed equally to this work*

Background. After chest radiotherapy (RT) for Hodgkin lymphoma (HL), women experience a dose-dependent increase of breast cancer risk. It is unknown whether endogenous and exogenous gonadal hormones affect the radiation dose-response relationship. *Methods.* We conducted a case-control study nested within a cohort of female 5-year HL survivors treated before age 41 years between 1965 and 2000. Detailed data on HL treatment, reproductive factors and hormone use were collected through medical records and questionnaires for 174 breast cancer cases and 466 matched HL controls who did not develop breast cancer. RT charts, simulation films and mammography reports were used to estimate the radiation dose to the location of the breast tumor (and similar location for matched controls). *Results.* The median interval between HL diagnosis and breast cancer diagnosis was 21.9 years. Ninety-eight percent of the cases received supradiaphragmatic RT and 3% pelvic RT (without successful oophoropexy) compared with 92% and 9% of the controls respectively. We observed a linear radiation dose-response relationship for risk of breast cancer with an adjusted excess odds ratio (EOR) of 5.4%/Gray (95%CI:1.8%-13.3%). Women who reached menopause before age 30 years (caused by high dose of procarbazine or pelvic RT) had a lower risk (OR 0.13; 95%CI:0.03-0.54) than women who reached menopause at age ≥50 years when adjusted for RT dose. Breast cancer risk increased by 7.4% for each additional year of intact ovarian function after RT (P<0.001). Among women with an early menopause (<45 years), the use of hormone replacement therapy (HRT) for ≥2 years did not increase breast cancer risk (OR 0.81, 95%CI:0.30-2.21), while this risk was non-significantly increased among women who became menopausal at ages ≥45 years (OR 1.91, 95%CI:0.70-5.20). Moreover, endogenous and exogenous hormones did not statistically significantly modify the slope of the linear radiation dose-response relationship. *Conclusions.* Among female survivors of HL treated with chest RT, a therapy-induced premature menopause reduces their radiation-associated breast cancer risk. However, hormone replacement therapy use did not appear to increase breast cancer risk in these women. There was no evidence for interaction between RT dose and number of years with intact ovarian function or HRT use.

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LAUNCH OF THE BREAST SCREENING AFTER RADIOTHERAPY DATASET - AN ENGLAND WIDE INITIATIVE TO IMPROVE SCREENING FOR BREAST CANCER IN 9,000 WOMEN AT HIGH RISK FOLLOWING RADIOTHERAPY TO BREAST TISSUE UNDER AGE 36

J. Radford[1,2], S. Howell[1,2], K. Vaughan[1,2,4], V. Goode[2], D. Worthington[3], N. Yates-Bolton[3], E. Payne[4], J. Jenkins[4], M. Sibbering[4], A. Swerdlow[5], R. Cowan[1,2]

[1]The University of Manchester, Manchester, UK; [2]The Christie NHS Foundation Trust, Manchester, UK; [3]Consumer Representatives; [4]Public Health England; [5]Institute of Cancer Research, Sutton, UK

Introduction. Women who received radiotherapy (RT) involving breast tissue when aged 36 yrs most usually for Hodgkin lymphoma are at high risk of developing breast cancer. UK national guidelines published in 2003 recommend that breast screening should start 8 years after RT or at age 25 whichever is later. Screening depends upon individual haemato-oncologists referring at-risk women to breast screening centres and this is prone to delay/error leading to survivor anxiety/frustration and time consuming troubleshooting to correct. A decision was therefore taken to develop a single national dataset of at-risk women (BARD) from which annual screening appointments could be generated. *Methods.* 3 at-risk cohorts were identified: Cohort 1 women irradiated pre-2003 identified from a national recall exercise in 2003 to inform about risk and advise screening in accordance with national guidelines (n~6,500); Cohort 2 women irradiated 2003-2016 identified from National Cancer Registry and Radiotherapy Centre Records (n~2,500); Cohort 3 women irradiated from now into the future identified prospectively at the time of consent for RT. Prior to registration with BARD family physicians were contacted to enquire whether a screening appointment was still appropriate for each survivor. *Results.* Project sign-off from NHS England and Public Health England occurred January 2016. A pilot phase across 4 RT centres in the northwest of England is currently completing (May 2016) and once any learning from this has been incorporated into the processes a national rollout will occur with planned completion in Q4 2016. The NHS Breast Screening Programme will use BARD to identify women irradiated under age 30 years who require screening in any given year. Screening of women irradiated aged 30-35 years will be arranged by their family physician. *Discussion.* An England wide dataset of ~9,000 women who have received RT involving breast tissue when aged 36 yrs has been launched to optimise breast screening in this high risk group. It is hoped that as a result the service to women will be enhanced and breast cancer outcomes improved. A BARD research group has also been formed to undertake relevant research; this will include qualitative assessments of the user experience, evaluation of the effectiveness of current screening with a view to improving the screening regime, studies of the biological characteristics of RT induced *vs* sporadic breast cancers and risk reduction trials.

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MANAGED LOCAL FOLLOW-UP OF LONG TERM LYMPHOMA SURVIVORS – THE ADAPT PROGRAMME

J. Radford[1,2], V. Goode[1], E. White[1], R. Monkhouse[1], R. Cowan[1,2]

[1]The Christie NHS Foundation Trust, Manchester, UK; [2]The University of Manchester, Manchester, UK

Introduction. A high proportion of patients treated for Hodgkin lymphoma and diffuse large B cell lymphoma are cured following chemotherapy/radiotherapy but long term quality of life and survival are undermined by the late toxicities of treatment including second cancers, cardiovascular disease and hormonal disorders. For best outcome these need to be anticipated/well managed and survivors/health care professionals made aware of how best to achieve this. The aim of ADAPT is to improve the management of patients likely cured of lymphoma by increasing survivor/primary care physician awareness of late treatment toxicities whilst reducing the burden on survivors of attendance at hospital clinics and maintaining accurate outcomes data. *Methods.* After 5 yrs of hospital follow-up, likely cured patients are offered a final "ADAPT consultation" focused on the future low risk of recurrence and potential for late treatment toxicity. An individualised treatment summary and late toxicity management plan (LTMP) is given to survivors and copied to their primary care physician. The LTMP is constructed by selecting from a menu of pre-written paragraphs describing the possible late toxicities of each treatment, their symptoms, manage-

ment and key points (cardiac key points; don't smoke, take exercise, check blood pressure). These paragraphs were all reviewed and approved for relevance and readability by a panel of 25 lymphoma survivors. Following the ADAPT consultation, survivors receive no further routine hospital appointments but can access the service immediately if the need arises. An annual questionnaire is issued by e-mail or letter according to survivor preference enquiring about quality of life, new diagnoses, new medication or surgical interventions and this information added to the survivor database. *Results.* 600 survivors have so far been ADAPTed and anecdotal evidence suggests satisfaction with the service. On the basis that the average time for a return journey from home or work, waiting and consultation is 3 hours, 600x3=1800 survivor hours or 1800/40=45 working weeks have been saved per year.

Conclusions. The ADAPT programme provides long term lymphoma survivors and their primary care physician with individualised information about late treatment toxicity, shifts the focus of management of this from the hospital to primary care and saves time whilst maintaining accurate long term outcomes data. Formal evaluation of this new service is planned.

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THE ROLE OF WATCH AND WAIT IN NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA: SINGLE CENTRE DATA FROM THE MODERN ERA

A. Navarro-Bailón[1,2,*], J.G. Taylor[1,3,*], J. Matthews[3], S. Montoto[1,3], J.G. Gribben[1,3]

[1]Haemato-Oncology, St Bartholomew's Hospital, London, UK; [2]Hematology, Hospital General Universitario Marañón, Madrid, Spain;[3]Barts Cancer Institute, Queen Mary University of London, UK

**Contributed equally*

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) is an indolent lymphoma with excellent overall survival (OS) and distinct clinicopathological characteristics reclassified as separate to Classical Hodgkin Lymphoma (CHL). Debate is ongoing as to optimum management. Guidelines differ in approach, particularly around watch and wait (W+W); ranging from selected use in all stages (B J Haem 2015), to advanced disease (NCCN 2015) to not at all (ESMO 2014). Few studies have assessed W+W, with discordant *results.* All were retrospective and include cases diagnosed before reclassification. We conducted a retrospective analysis to investigate outcomes of adults with NLPHL diagnosed and managed at St Bartholomew's hospital from 1994 (reclassification) to 2014. This represents the largest single centre study reporting data obtained since reclassification. Clinical characteristics, treatment, OS, progression free survival (PFS) and Disease Free Survival (DFS) were collected. Forty-four patients were included. 82% had limited (stage IA or IIA) disease, 73% were male. Median age was 38. Patients of Black (25%) and Asian (39%, mainly Bangladeshi) origins were overrepresented compared to CHL cases (7% Black, 13% Asian) or any haematological malignancy (8% Black, 10% Asian) managed during this period. Initial management consisted of W+W +/- excision (32%), Radiotherapy +/- excision (29%) and Chemotherapy (mostly ABVD; in 2 cases R-ABVD) or Combined Modality (39%). W+W was used in 36% of patients with limited and 25% with advanced disease. Median follow-up was 63 months. 10-year OS and PFS estimates were 100% and 60% respectively. Two transformation events were observed, none in the W+W group. One patient died from an unrelated cause. 80% of W+W patients remained untreated at median follow up of 29 (5-198) months. No significant differences were seen in PFS, DFS or OS between W+W and immediate treatment. Our data is consistent with an increased incidence seen in African-Americans. Raised incidence in Asian groups has not previously been reported. The differing racial demographic profile to CHL supports NLPHL's separate classification. The relatively good PFS and excellent OS support consideration of W+W as a management option, given that most patients remained treatment free after long follow up. Our data support the need for a clinical trial to assess W+W *versus* immediate treatment. Given the rarity of NLPHL this would require an international collaborative study.

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NEURO-BEHAVIORAL CHANGES IN HODGKIN LYMPHOMA SURVIVORS

E. Trachtenberg[1], T. Mashiach[2], J. Aharon-Peretz[1,3], E.J. Dann[1,4]

[1]Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel; [2]Quality Assurance Unit; [3]Department of Cognitive Neurology; [4]Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel

Background. Hodgkin lymphoma (HL), frequently diagnosed at the young age, is currently treated with chemotherapy and/or radiotherapy (RT). The combination of malignancy and chemotherapy is often associated with neuro-behavioral impairment (NI), reported in up to 75% of adult survivors in various malignancies. NI involves fatigue and cognitive changes such as slowness and impairment of memory, concentration and executive functioning. NI is particularly dramatic for young adult HL survivors (YAHLS), given their age at diagnosis, long life expectancy and high curability. The current research aimed to assess the incidence and characteristics of NI in YAHLS. *Methods.* The study evaluated YAHLS, who completed first-line therapy (chemo±RT) and remained in complete remission (CR) for 6 months-5 years after the end of treatment. All participants completed questionnaires evaluating fatigue (MFI-20), depression (BDI-II), anxiety (HA), quality of life (QLQ-C30) and cognitive function (FACT-cog), and underwent neuropsychological evaluation. The test battery included California verbal learning test, Digit span (WAIS-III), Trail making test A+B, subtests from the Computerized Battery (CANTAB), Stroop and Raven progressive matrices tests. Processing speed, memory, and executive functions were assessed and calculated for each subject. Test and subtest results were presented in standard scores. *Results.* We report results of 21 YAHLS, aged 19-47 years (median 28), with mean education duration of 14.4±2.2 years. No significant depression or anxiety was observed in study participants. Severe fatigue was reported in 33% of patients. Impairment in executive functions, with scores below 1.5SD in at least 2 parameters, was observed in 33% of patients (76% below 1SD). Scores below 1.5SD in at least 2 parameters of memory were found in 19% of patients (53% below 1SD). Slow processing speed was depicted in 38% of patients (TMT-B). No correlation was found between NI and fatigue. *Conclusions.* NI and fatigue were observed in one third of patients. An impairment score above 1SD and especially above 1.5SD below that expected for age and education is usually regarded significant. Our results were unexpected. Given the enormous impact of these symptoms on all aspects of life, they need to be taken into consideration while assessing the efficacy of therapeutic protocols applied in YAHLS.

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HEALTHCARE USE AMONG YOUNG HODGKIN LYMPHOMA SURVIVORS IN THE ERA OF INTENSIFIED CHEMOTHERAPY AND LIMITED RADIOTHERAPY

S. Eloranta[1], K.E. Smedby[1,2], S. Ekberg[1], E. Chang[3], M. Neovius[1], I. Glimelius[1,4]

[1]Department of Medicine, Clinical Epidemiology Unit, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; [2]Department of Medicine, Division of Hematology, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden; [3]Center for Epidemiology & Computational Biology, Health Sciences Practice, Exponent, Inc., Menlo Park, California, USA and Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California, USA; [4]Department of Immunology, Genetics and Pathology, Clinical and Experimental Oncology, Uppsala University and Uppsala Akademiska Hospital, Sweden

Purpose. With today's excellent cure rates for Hodgkin lymphoma (HL), the number of long-term survivors is increasing. This study provides a global assessment of late effects for working-age HL survivors treated with contemporary protocols (intensive chemotherapy and lim-

ited radiotherapy). *Patients and Methods.* From Swedish nationwide registers we identified 1017 HL survivors diagnosed in 2000-2009, aged 18-60 years (median 32) and surviving at least one year post-diagnosis, and 4031 age-, sex- and calendar-year-matched population comparators. Incidence rate ratios (IRR) and 95% confidence intervals (95%CI) for hospital outpatient visits and hospital bed-days after the first year and up to 2013 (maximum 14 years post-diagnosis) were estimated across treatment subgroups, considering relapse-free time and using negative binomial regression. Scheduled outpatient visits for HL were excluded but inpatient visits for HL were included in analysis of bed-days. *Results.* The rate of outpatient visits among relapse-free survivors was nearly double (IRR=1.8, 95%CI: 1.6-2.0) and the rate of bed-days was more than triple that among comparators (IRR=3.6, 95%CI: 2.7-4.7). The higher rates of outpatient visits persisted up to 10 years and bed-days up to four years post-diagnosis. However, absolute numbers of extra visits were low (mean=2 outpatient visits and 2 bed-days, respectively, during follow-up). Patients requiring 6-8 chemotherapy courses had higher rates of outpatient visits (IRR=1.4, 95%CI: 1.1-1.7) and bed-days (IRR=4.7, 95%CI: 2.9-7.8) than patients treated with 2-4 courses+radiotherapy. Established late effects including heart disease and second malignancies accounted for a minority of outpatient visits. Previously unstudied reasons for excess healthcare use included diabetes mellitus, keratitis, chest pain, and asthma (Figure 1). *Conclusions.* Chemotherapy, but not radiotherapy, appears to drive the slight excess healthcare use among contemporarily treated HL survivors. The diagnoses of healthcare visits reflected a broad panorama of disorders, indicating the need of comprehensive care in addition to specific screening programs.

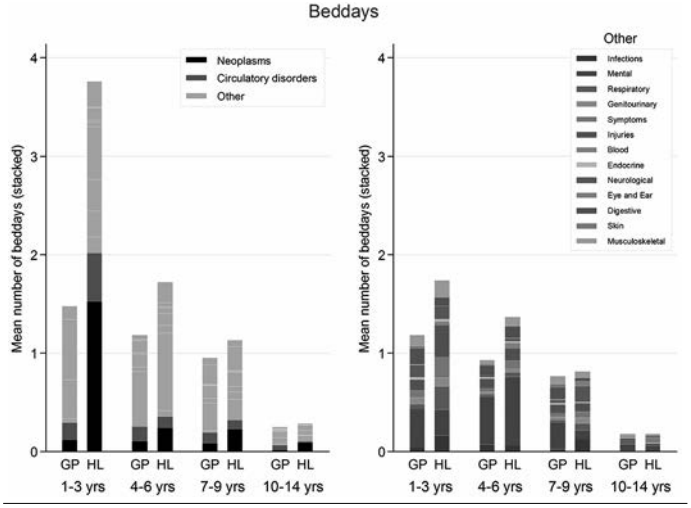

Figure 1.

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HIGH BURDEN OF MORBIDITY FROM SECOND MALIGNANT NEOPLASMS AND CARDIOVASCULAR DISEASE IN LONG-TERM HODGKIN LYMPHOMA SURVIVORS

S. de Vries[1], F.A. van Nimwegen[1], M. Schaapveld[1], P. Lugtenburg[2], A.D.G. Krol[3], J.M. Roesink[4], J. Raemaekers[5], B.M.P. Aleman[6], F.E. van Leeuwen[1]

[1]Department of Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [2]Department of Hematology, Erasmus University MC Cancer Institute, Rotterdam, The Netherlands; [3]Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands; [4]Department of Radiotherapy, University Medical Center Utrecht, Utrecht, The Netherlands; [5]Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands; [6]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Background. Hodgkin lymphoma (HL) survivors are at increased risk to develop late treatment-related complications, including second malignant neoplasms (SMNs) and cardiovascular disease (CVD). Research to date has focused on separate risk estimates for these outcomes. We aimed to examine the combined risk of SMN and CVD, providing more insight into the total burden of morbidity from these severe late effects. *Methods.* Our multicenter cohort comprised 2,908 5-year HL survivors, treated before age 51 between 1965 and 2000. CVD endpoints (coronary heart disease, cardiomyopathy and congestive heart failure, and valvular heart disease) were assessed through general practitioners. Data on SMNs were obtained from linkage with the Netherlands Cancer Registry, including all invasive cancers except basal cell carcinomas. Cumulative incidences of SMN and/or CVD were calculated with death from other causes as competing risk. Treatment-specific risks of developing SMN and/or CVD were quantified using Cox regression analysis. The mean cumulative count (MCC) will be calculated as the average number of events per individual in our cohort over a given follow-up period (results will be available in October 2016). *Results.* After a median follow-up of 22 years, we identified 874 SMNs and 1044 CVDs. 1249 patients developed ≥1 major event; of those 240 developed both an SMN and CVD. After a follow-up of 40 years, at a median attained age of 60 years, the cumulative incidence of SMN or CVD was 67.4% (95%CI: 64.6-70.0), with 22.5% (95%CI: 19.8-25.3) of patients being diagnosed with both events. Both supradiaphragmatic RT (Hazard Ratio [HR]: 2.5, 95%CI: 2.1-3.1) and anthracycline-containing CT (HR: 1.2, 95%CI: 1.0-1.4) independently increased the risk of SMN or CVD. Supradiaphragmatic RT was associated with a 4.1-fold increased (95%CI: 2.3-7.3) risk of developing both SMN and CVD. *Conclusions.* HL survivors experience a high disease burden from SMN and/or CVD during follow-up. The cumulative incidence of SMN and/or CVD in our HL population treated between 1965 and 2000 amounted to 67% after 40 years from initial treatment. Supradiaphragmatic RT most strongly increased the risk developing SMN and/or CVD.

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THE IMPACT OF FERTILITY PRESERVATION ON TREATMENT DELAY AND PROGRESSION-FREE SURVIVAL IN WOMEN WITH LYMPHOMA: A SINGLE-CENTER EXPERIENCE

P.B. Allen[1], M.E. Pavone[2], K.N. Smith[2], R.R. Kazer[2], A. Rademaker,[5] A.K. Lawson,[2] M.B. Moravek[6], R. Confino[2], L.I. Gordon[1], J. Winter[1]

[1]Division of Hematology/Oncology, Department of Medicine and Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [2]Division of Reproductive Endocrinology and Fertility, Department of Obstetrics and Gynecology, Northwestern University; [3]Division of Biostatistics, Department of Preventive Medicine, Northwestern University. Chicago, IL, USA; [6]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA

Background. Lymphoma affects many women of childbearing age. Fertility preservation (FP) prior to chemotherapy offers women an opportunity for future pregnancy if fertility is compromised. Fear of treatment delay is one factor contributing to low rates of referral for fertility preservation. *Methods.* We performed a retrospective review of female lymphoma patients who contacted a fertility preservation patient navigator (FPPN) at Northwestern University from May 2006 until August 2015. Our primary objective was to assess the median treatment delay associated with FP. Our secondary objective was to assess progression free survival (PFS). Patients who underwent FP were compared to women that contacted a FPPN but did not undergo preservation. *Results.* Thirty-three subjects who underwent FP and 50 controls were analyzed. Among FP patients, 21 had Hodgkin lymphoma, 12 had non-Hodgkin lymphoma; 25 presented for upfront treatment and 8 with relapsed/refractory disease. Controls had a higher median age (29 in control *versus* 26 in FP, p=0.001); however, there was no difference between groups in histology, treatment setting, or stage. Median follow-up was 39.3 (1.5 – 103.4) months, and did not differ between controls and those undergoing FP (p=0.16). Median time to treatment among FP patients was 28 days (range: 18-76) *versus* 15.5 days (range: 0-74) for controls, resulting in a median delay of 12.5 days (p<0.001).

The median time to first contact with a fertility specialist was 0 days (range -15 to +11) from hematology consult, with several patients having contact prior to their hematology visit. There was no difference in 5 year PFS between FP patients and controls (71.4% *vs* 83.7%, respectively, p=0.11). Median time to complete the stimulation protocol was 11 days (range: 5-14). A median of 14 oocytes (range: 0-37) was retrieved per patient. In 2 women, no oocytes could be successfully retrieved. Five women achieved pregnancy following fertility preservation. Of these, 3 were spontaneous, and 2 required reproductive assistance, one from frozen embryos and one from frozen oocytes. Of three women returning to use their frozen gametes, 2 were successful, and one was unsuccessful. *Conclusions.* This study demonstrates that fertility preservation is feasible and results in a small delay in therapy. This approach does not significantly impact PFS in our series.

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COMORBIDITY ASSESSMENT USING THE CIRS IN ELDERLY PATIENTS WITH HODGKIN LYMPHOMA: PREDICTION OF SURVIVAL

A. Cuccaro, E. Galli, E. Maiolo, S. Bellesi, F. D'Alò, S. Hohaus

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

The ABVD regimen is the standard of care for patients with Hodgkin lymphoma up to 70 years. This regimen has been considered to be too toxic for elderly patients, and alternative regimens have been proposed, that are often associated with a reduced efficacy. The evaluation of comorbidity has not been extensively studied in HL. We reasoned that evaluation of comorbidity according to a standardized approach, the Cumulative Illness Scaling Rate (CIRS) might be a predictor for overall survival (OS). We studied 62 consecutive elderly patients with HL (median age 68 years, range 60-83 years), who had been treated in our institution between 1999 and 2016. Chemotherapy was ABVD in 47 (76%) patients, COPP in 12 (19%) patients, and other in 3 (5%) patients. OS at 2 years was 70% (95% C.I., 55-81%). Comorbidity was rated on the 4-point CIRS scale for 13 main organ systems. 36 patients had no severe comorbidity (score >3) and were considered fit (58%), while 26 patients had at least one severe comorbidity and were considered frail (42%). Patients with at least one severe comorbidity were more likely to be >70 years old (p=0.03), to have advanced stage disease (p=0.02) and not to receive ABVD (p=0.01). Patients with at least one severe comorbidity had a 2-year OS of 17% (95% C.I. 3-41%) *versus* 89% (95% C.I., 73-96%) in fit patients (p=0.001). We next restricted the analysis to ABVD-treated patients. Frail patients still had a significant worse 2-year OS (65%; 95% C.I., 25%-88%) with respect to fit patients (97%; 95% C.I., 79-99%) (p=0.02), that was however better than for patients treated with MOPP (2-year OS: 11%). We conclude that a significant proportion of elderly HL patients has severe comorbidity on the CIRS scale, that impacts on prognosis. Prospective studies including comprehensive geriatric assessment are warranted to better tailor therapy in the often frail elderly patients with HL.

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RISK ADAPTED ABVD BASED PROTOCOL WITH RESTRICTED RADIOTHERAPY TO BULKY DISEASE FOR HODGKIN LYMPHOMA: A 20 YEAR FOLLOW UP MULTICENTER ANALYSIS

R. Vallansot[1], C. Talarn[1], L. Escoda[1], M. Cervera[1], J. Do Nascimento[1], J. Gumà[2], X. Ortin[3], M.J. Herranz[4], M.J. Miranda[2], F. Martínez[2], M. Prats[4], R. Aguinaco[1], M.T. Giménez[1], C. Araguás[1], A. Esteban[1], A. Martínez[1], J. Sarrà[1]

[1]Hospital Universitari de Tarragona Joan XXIII, ICO-Tarragona, IISPV-Universitat Rovira i Virgili, Tarragona, Spain; [2]Hospital Universitari Sant Joan de Reus, IISPV-Universitat Rovira i Virgili, Tarragona, Spain; [3]Hospital Verge de la Cinta de Tortosa, Tarragona, IISPV-Universitat Rovira i Virgili, Tarragona, Spain; [4]Hospital Sant Pau i Santa Tecla, Tarragona, IISPV-Universitat Rovira i Virgili, Tarragona, Spain

Introduction. The combination of radio and chemotherapy in HL has led to the greatest advances in disease response. The benefit in terms of overall survival (OS) has been jeopardized by long term toxicity related to second malignancies and cardiovascular events. *Aim.* Analyze the risk factors associated with survival and asses the frequency of secondary malignancies with an ABVD based regimen that restricted radiotherapy only to bulky disease. *Materials and Methods.* We retrospectively analyzed HL patients diagnosed in 4 centers in Tarragona area (Catalonia, Spain), between 1995 and 2015 treated uniformly according to a local protocol. Patients were assigned into 4 groups: G1: favorable early stage: ABVDx6 cycles, G2: Bulky early stage without other risk factors: ABVDx6+IFRDT. G3: unfavorable early stage (B symptoms) and advanced stage without bulky disease: ABVDx8, G4: Bulky advanced stage: AVBDx8+IFRDT. *Results.* A total of 183 patients were analyzed with a median follow up of 82 months [range 1-244]. Male/female ratio was 1,29. Median age was 36 years [range 16-82]. Complete response was achieved in 160 patients (87,4%). The estimated OS at 20 years for the whole group was 62.7%. In univariate analysis, worse OS was found in patients with increased LDH, non-NS subtype, albumin <3,5 g/d, B symptoms, HIV+, advance stage and ESR >50 mm (log rank p=0,012; p=0,049; p=0,024; p=0,002; p=0,005; p=0,004 and p=0,001 respectively). The multivariate Cox regression analysis identified B symptoms and ESR >50 mm as independent prognostic factors for OS (p=0,002; p=0,006 respectively). Furthermore, B symptoms was also found as an independent prognostic factor for OS when patients were analyzed according to disease stage (localized and advanced) (p=0,018; p=0,014) while ESR >50 mm was an independent prognostic factor for the advanced disease group only (p=0,038). Secondary malignancies were observed in 18 patients (9,8%). The most frequent were hematological in 6 patients (3 myelodysplastic syndrome, 3 non Hodgkin lymphoma), gynecological 4 patients (2 breast cancer, 2 adnexal carcinoma) and colorectal 2 patients. Two patients developed 2 malignancies. *Conclusions.* Our risk adapted protocol showed a good rate of response and overall survival with low rate of secondary malignancies. B symptoms and elevated ESR were independently associated with OS in the whole group.

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INFRADIAPHRAGMATIC HODGKIN LYMPHOMA: A LARGE SERIES OF PATIENTS STAGED WITH PET-CT. A PARTICULAR SUBSET OF HL?

C. Rossi[1,2], M. Mounier[3], P. Brice[4], H. Ghesquières[5], V. Safar[5], E. Nicolas-Virelizier[5], C. Sebban[5], A. Stamatoullas-Bastard[6], M. Alcantara[6], A. Chauchet[7], E. Reboursière[8], L. Filiattre-Legras[9], A. Perrot[9], G. Salles[10], B. Coiffier[10], O. Casasnovas[1]

[1]Hématologie Clinique, CHU Le Bocage, Dijon, France; [2]INSERM UMR1037 - Cancer Research Center of Toulouse, Toulouse, France; [3]Registre des Hémopathies Malignes de Côte d'Or, EA4184, Université de Bourgogne, Dijon, France; [4]Hématologie clinique, CHU Paris-GH St-Louis Lariboisière F-Widal - Hôpital Saint-Louis, Paris, France; [5]Hématologie clinique, Centre Régional de lutte contre le Cancer Léon Bérard, Lyon, France; [6]Hématologie Clinique, Centre Henri Becquerel, Rouen, France; [7]Hématologie Clinique, CHU Besançon, France; [8]Hématologie Clinique CHU Caen, France; [9]Hématologie Clinique, CHU Nancy, France; [10]Hématologie Clinique, Centre Hospitalier Lyon Sud, Pierre-Bénite, France.

Introduction. Infradiaphragmatic Hodgkin Lymphoma (IDHL) accounts for 3-11% of adult cases of stage I-II Hodgkin Lymphoma. While the treatment strategy of most clinical subsets of HL has been improved and standardized along the last decades, it remains more heterogeneous in IDHL. Moreover, previous studies considered IDHL, patients on the basis of CT-scan staging which could underestimated advanced disease compared to the more sensitive PET-CT staging currently widely available. Thus, this study aimed to evaluate the characteristics of PET-staged IDHL patients compared to patients with an IDHL disease defined on the basis of CT scan assessment, and to analyse the outcome of patients with PET-defined disease. *Methods.* The baseline clinical, biological data, and the outcome of patients with a first diagnosis of stage I-II of IDHL treated with ABVD +/- radiotherapy were retrospec-

tively collected in 8 french departments of hematology. Patients with a positive HIV serology and those treated with radiotherapy alone were excluded. *Results.* From 1986 to 2014, 99 patients were included whose 65 (66%) of them were staged with PET-CT. PET-CT staged patients were older (53 years *vs* 47 years, p=0.043), had lower ESR (27 *vs* 58 mm, p= 0.022), higher haemoglobin level (13.6 *vs* 12.8g/dL, p=0.015), less frequent Ann Arbor stage II (74% *vs* 91%) and less frequently central adenopathy involvement (60% *vs* 80%, p=0.024). The median follow-up of 99 patients was 3.8 years. For the PET-CT staged patients, at five years, PFS was 78% (IC95% 0.64-0.87) and OS was 88% (IC95% 0.73-0.95). Thirteen relapses occurred (20%) whose eleven (16%) within the five-years after diagnosis, and five patients died (8%), 3 from HL progression and 2 from toxicity of chemotherapy. In univariate analysis, patients with crural adenopathy involvement and treated with chemotherapy alone (p=0.026) had a poorer PFS. The treatment modality retained significance (p=0.036) in the modelisation analysis and also performans status (0.045) and crural involvement (0.005). *Conclusions.* This multicenter study of IDHL shows that CT-scan defined IDHL patients have more unfavorable characteristics than PET-CT staged patients which might be related in some cases to more advanced diseases specifically in younger patients. So, PET-CT is required for better defining IDHL diseases. The present study suggests that chemo-radiotherapy combined modality provides a better PFS than chemotherapy alone in these patients.

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A RETROSPECTIVE ANALYSIS OF FERTILITY IN FEMALE PATIENTS WITH ADVANCED STAGES OF HODGKIN LYMPHOMA TREATED WITH BEACOPP ESCALATED CHEMOTHERAPY (20 YEAR EXPERIENCE OF A SINGLE CENTRE)

J. Marková[1], H. Mócziková[1], Ľ. Gahérová[1], T. Jančárková[1], Z. Vernerová[2], K. Dědečková[3], T. Kozák[1]

[1]Department for Internal Medicine, Haematology, University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University in Prague, Czech Republic; [2]Institute of Pathology, University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University in Prague, Czech Republic; [3]Proton Therapy Center and Institute of Radiation Oncology, Na Bulovce Hospital and 1st Faculty of Medicine, Charles University, Prague, Czech Republic

Background. BEACOPP escalated includes alkylating agents and its gonadal toxicity has been reported in prospective and retrospective studies. This retrospective study analyzed fertility of 98 female patients (pts) with initial diagnosis of Hodgkin lymphoma (HL) in advanced stages treated with BEACOPP escalated. *Patients and Methods.* Overall 98 women aged 18 – 34 years (median age at diagnosis was 27 years) were treated with BEACOPP escalated between 1997 and 2015: 8 cycles received 57 pts (58%), 6 cycles 39 pts (40%) and 4 cycles 2 pts (2%). Additional radiotherapy was indicated in 33 pts (32%). Forty nine pts (48%) received GnRH analogue (Diphereline) during chemotherapy to preserve their ovarian function. Median follow-up after the end of treatment was 144 months (range, 57 – 210). *Results.* Overall 26 women delivered 33 babies including 7(27%) women with 2 deliveries. Median age at diagnosis HL was 24 years (range, 19 – 32). Number of all delivered healthy babies was 32 and only one baby was born with small cleft lip. All pregnancies were spontaneous except of 2 women that undewent *in vitro* fertilization . Another 5 female pts are still pregnant. Median time from the end of chemotherapy until the delivery of the first baby was 78 months (range, 21 – 169). Two pregnancies were terminated prematurely (week 20 and 22) due to congenital malformations: monosomy 45,X0 Turner syndrome and serious cleft lip. Despite the low number of pts and a relatively short-term follow-up we assume, that we can expect a higher rate of pregnancies and deliveries after the reduction from 8 to 6 cycles of BEACOPP escalated. *Conclusions.* New strategies for the protection of fertility should be offered to young female HL patients treated with BEACOPP escalated therapy. Reduced number of cycles of BEACOPP escalated may further contribute to preservation of their fertility.

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CAUSE-SPECIFIC MORTALITY AMONG HODGKIN LYMPHOMA PATIENTS UP TO 40 YEARS AFTER TREATMENT

M. Schaapveld[1,2], A.M. van Eggermond[1], C.P.M. Janus[3], A.D.G. Krol[4], J. Raemaekers[5], E.J. Clevers-Petersen[6], P. Lugtenburg[7], J.M. Zijlstra[8], G. van Imhoff[9], R.W.M. van der Maazen[10], J.M. Roesink[11], M. Beijert[12], P.M.P. Poortmans[10], L.C.M. Kremer[13], M.W.J. Louwman[2], M. Lybeert[14], J.P. de Boer[15], B.M.P. Aleman[16], F.E. van Leeuwen[1]

[1]Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam; [2]Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam; [3]Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam; [4]Department of Radiation Oncology, Leiden University Medical Center, Leiden; [5]Department of Hematology, Radboud University Medical Center, Nijmegen; [6]Department of Hematology, University Medical Center Utrecht, Utrecht; [7]Department of Hematology, Erasmus MC Cancer Institute, Rotterdam; [8]Department of Hematology, VU University Medical Center Amsterdam, Amsterdam; [9]Department of Hematology, University Medical Center Groningen, Groningen; [10]Department of Radiation Oncology, Radboud University Medical Center, Nijmegen; [11]Department of Radiotherapy, University Medical Center Utrecht, Utrecht; [12]Department of Radiation Oncology, University Medical Center Groningen, Groningen; [13]Department of Pediatric oncology, Emma Children's Hospital, Academic Medical Center, Amsterdam; [14]Department of Radiotherapy, Catharina hospital, Eindhoven; [15]Department of Hematology, The Netherlands Cancer Institute, Amsterdam; [16]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Background. Hodgkin Lymphoma treatment is associated with high risk of treatment-related morbidity, including second cancers and cardiovascular diseases. However, only few studies examined long-term excess mortality. *Methods.* We studied cause-specific mortality in a multicenter cohort comprising 3,575 5-year HL-survivors, diagnosed before age 51 and treated between 1965 and 1995. Follow-up was complete until at least January 2010 for 96% of the patients. For 93% of deaths, the cause was known. Mortality after HL was compared with mortality in the general population by calculating standardized mortality ratios (SMRs) and absolute excess mortality (AEM), expressed per 10,000 person-years. Treatment-specific SMRs were compared by Poisson regression. *Results.* After a median follow-up of 21.6 years since HL treatment 1,328 patients had died (19.5% from HL, 32.5% from solid tumors, 15.5% from cardiac diseases, 7.0% from NHL/leukemia). The SMR for causes other than Hodgkin Lymphoma was 8.2-fold that of the general population. The cohort experienced 149.2 excess deaths per 10,000 patients per year. The SMR and AEM for causes of death other than Hodgkin Lymphoma increased throughout follow-up: after ≥35 years the SMR was 19.2, translating to 505.9 excess deaths per 10,000 patients per year. Solid tumors accounted for the largest part of the excess mortality (overall SMR 5.6, AEM 56.1). While the SMR for solid tumors remained stable, the SMR for cardiac diseases (overall SMR 9.8, AEM 29.4) increased during follow-up (SMR at ≥35 years 28.8, p-trend<0.001)). Adjusted for sex, age and follow-up time, risk of death from cardiac diseases was increased for patients treated with supradiaphragmatic radiotherapy (Relative Risk (RR) 4.8, p<0.001) or anthracyclines (RR 1.5, p=0.044). The SMR for infectious causes (2.9% of all deaths, including deaths due to influenza/pneumonia) was 6.5-fold increased. Both splenectomy (RR 2.1, p=0.041) and spleen radiotherapy (RR 3.2, p=0.001) were associated with increased risk of death due to infectious causes compared to patients not receiving such treatment. *Conclusions.* Even 35 years after treatment, HL Hodgkin Lymphoma patients experienced elevated SMRs and AEMs from solid tumors and cardiac diseases. Both splenectomy and spleen radiotherapy increased mortality due to infections.

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ELDERLY HODGKIN LYMPHOMA – MULTICENTER RETROSPECTIVE DATA ANALYSIS FROM THE CZECH HODGKIN LYMPHOMA REGISTRY

A. Sýkorová[1], H. Móciková[2], V. Procházka[3], M. Lukášová[3], P. Štěpánková[1], D. Belada[1], K. Klásková[2], Ľ. Gahérová[2], Z. Král[4], L. Martinková[5], T. Nečasová[6], E. Koriťáková[6], J. Marková[2]

[1]Fourth Department of Internal Medicine - Haematology, Charles University Hospital and Faculty of Medicine, Hradec Kralove, Czech Republic; [2]Department of Internal Medicine and Haematology, Faculty Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University in Prague, Czech Republic; [3]Department of Haemato-Oncology, Faculty of Medicine and Dentistry, Palacky University and University Hospital Olomouc, Czech Republic; [4]Department of Internal Medicine and Haematooncology, University Hospital, Brno, Czech Republic; [5]Department of Haematooncology, University Hospital Ostrava and Medical Faculty of the Ostrava University; [6]Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic

Background. The proportion of elderly Hodgkin lymphoma (HL) patients (age ≥60 years) ranges between 15% and 35%. Outcome of this group of patients (pts) is significantly inferior compared with younger pts. Management of therapy is still unclear, standard treatment is not yet defined. Purpose of this study was to analyze treatment and outcome of elderly HL pts prospectively registered in Hodgkin Lymphoma Project in the Czech Republic. *Patients and Methods.* The proportion of elderly patients in the Czech HL Registry was 11%. We analyzed 151 pts ≥60 years with classical HL (pts with nodular lymphocyte predominant HL were excluded) diagnosed between 2000 and 2016. Median age was 67 (60-83) years, 68.9% of them were 60-69 years old and male gender represented 55% (83 pts). Histological subtype mixed cellularity occured in 55%. Advanced clinical stage (CS) was confirmed in 60.9%. Chemotherapy (CT) alone was used in 66.2% of pts (initial/intermediate CS 23 pts, advanced CS 76 pts). Combined modality of treatment (CT and radiotherapy, RT) was used in 40 pts (intial/intermediate CS 27 pts, advanced CS 13 pts). Anthracycline – based CT received 79.4% of pts (86 pts). Five pts (4%) were treated with RT alone, three pts received supportive care only and treatment in three pts was not reported to the Registry. *Results.* Overall response rate after the first-line treatment was observed in 70.9% (57.6% CR), SD in 0.7% and primary disease progression in 7.3% of pts. Treatment response was not evaluable in 21.2% of pts. Relapses occured in 12.6% (19 pts) and 3 pts underwent high dose CT and autologous stem cell transplantation (age 61, 63, 64 years). Median PFS and OS was 7.9 years (y) and 10.2y, respectively. Two – year PFS and OS was 73.1% and 81.5%, respectively. Overall 53.6% pts are alive and 31.8% (48 pts) of pts died: HL progression 11 pts, toxicity of treatment 14 pts, others causes 13 pts. *Conclusions.* Outcome of our retrospectively analyzed pts with classical HL compares favorably with other reported data in the group of elderly pts. Long-term survival of our pts depended on te use of anthracycline-containing CT. Prospective clinical studies are still needed to determine an optimal effective regimen with low toxicity in elderly pts.

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INCIDENCE OF HYPERLIPOPROTEINEMIA IN LONG-TERM SURVIVORS OF HODGKIN LYMPHOMA IN CHILDHOOD OR ADOLESCENCE AND IN HEALTHY CONTROLS

M. Cepelova[1], V. Jerabkova[1], J. Kruseova[1], J. Stary[1], P. Cepela[2], P. Kraml[2]

[1]Department of Pediatric Hematology and Oncology, 2nd Medical Faculty Charles University and University Hospital in Motol, Prague, Czech Republic; [2]2nd Department of Internal Medicine, 3rd Medical Faculty Charles University and University Hospital Kralovske Vinohrady, Prague, Czech Republic

Background. The development of curative therapies has led to a growing population of chilhood Hodgkin lymphoma survivors. Approximately 75% of survivors experience some adverse event. Cardiac events are among most important adverse events, causing long-term morbidity and early mortality. Seriousness of these cardiovascular late adverse events could be reduced only by their early recognition and also by recommendations of preventive measurements for modifiable cardiovascular risk factors - hyperlipoproteinemia, hypertension, overwight or obesity, smoking. *Methods.* The aim of our prospective observation study is 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 more than 10 years after the treatment and the matched group of healthy volunteers at the age of 25-40 years. *Results.* Forty-seven long-term survivors of childhood Hodgkin lymphoma (29 males, 18 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. Preliminary results are available in forty-four long-term survivors - abnormal levels of blood lipids were found in 52,3% of them. Elevated cholesterol levels (LDL and total cholesterol) were detected in 12 pts. (in three of them also with elevated levels of triglycerides), elevated level of triglycerides was found in four pts., hyperglycemia was found in 12 patients (in 7 patients together with elevated cholesterol or triglycerides levels). Plaques in main carotid artery were found by ultrasonography in two patients, both of them have elevated cholesterol levels. Recruitment of the long-term survivors will continue and of matched group of healthy volunteers will start soon. *Conclusions.* Our results will give us insight into atherosclerosis development in this specific population and potential impact of hyperlipoproteinemia. It will help us to introduce appropriate guidelines for follow-up and examinations of long-term survivors in the field of specialized health care providers, but also in primary care together with the recommendation of therapeutic interventions in this population.

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SURVIVORS OF ADULT HODGKIN LYMPHOMA: A FRAIL POPULATION. THE EXPERIENCE OF THE SURVIVORSHIP CLINIC FOR ADULT HL SURVIVORS AT ISTITUTO NAZIONALE TUMORI OF MILAN, ITALY

V. Simonetta[1], M. Soldarini[1], I. Arendar[2], N. Cieri[1], A. Guidetti[1,3], A. Busia[2], P. Matteucci[1], A. Gianni[1], P. Corradini[1,3]

[1]Department of Hematology and Pediatric Onco-Hematology; [2]Division of Cardiology and Pneumology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Department of Oncology and Onco-Hematology, University of Milan, Italy

Background. Nowadays more than 80% of adult patients (pts) diagnosed with HL have a long-life expectancy. Pts diagnosed from late 1960' to 2000's are at risk of developing long-term complications from chemotherapy (CT) and radiation therapy (RT), The majority of data on iatrogenic late effects are derived from registries or self-reported interviews and only a few data on clinical outcome of suvivors followed in survivorship clinics (SC) are available. *Aim.* To evaluate the incidence of long-term complications among pts, in complete remission (CR) for >5 years from the end of first-line treatment (EOT), followed in the SC for adult HL survivors at INT. *Methods.* Medical records of 359 AHLS, who underwent a routine visit, were analyzed to evaluate data on demographic characteristics, treatment and incidence of late complications. Descriptive statistics were calculated. *Results.* From May 2014 to April 2016, 359 AHLS (168 males, 191 female) diagnosed at a median age of 31 (range, 17-71), underwent a routine visit at SC. Median time from EOT and last follow-up visit was 17 years (range, 5-41 years). Late complications were reported in 116 pts (32%), the majority of whom had been treated with CT+RT. After a median of 19 years (range,1-35) from EOT, 23 pts (6%) developed 29 second cancers (9

breast, 2 bladder, 2 renal, 3 prostate, 1 lung, 4 melanoma, 1 pleural mesothelioma, 1 non Hodgkin lymphoma, and 6 skin basal cell carcinoma). Cardiovascular disease (CVD) was documented in 39 pts (11%), after a median of 13.5 years (range, 3-32), and 10 pts had multiple CVDs. Among CVD, myocardial infarction occurred in 8 pts, ischemic heart disease in 4, heart failure in 4, moderate or severe valvular disease in 15 and cerebrovascular disease in 4 pts. Conventional CVD risk factors were observed in 58 pts (16%). Hypothyroidism occurred in 9% of pts. *Conclusions.* Results of our study confirm that a substantial proportion of survivors of adult HL develop late complications. Specific health resources should be addressed for prolonged follow-up programs, lifestyle advices as well as prompt and aggressive management of risk factors to improve health in this frail patient population.

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ELDERLY PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA HAVE HIGH RATES OF SECONDARY B-CELL NON-HODGKIN LYMPHOMA

M. Gilbertson[1], K. Maclaughlan[1], G. Gregory[1], S. Ratnasingham[1], I. Simpson[1], B. Kumar[1], G. Grigoriadis[1,2], S.S. Opat[1,2], J. Shortt[1,2], S. Patil[1,3], E. Hawkes[4,5], F. Ha-he[5]

[1]Monash Haematology, Monash1 Health, Australia; [2]School of Clinical Sciences at Monash Health, Monash University, Australia; [3]Department of Haematology, Alfred Health, Australia; [4]Department of Clinical Haematology & Oncology, Olivia Newton John Cancer Centre, Austin Health, Australia; [5]Eastern Health, Australia

Introduction. Elderly patients (>60 years old) with Hodgkin lymphoma have inferior rates of survival compared to patients <60 years old due to multiple factors including treatment toxicity and comorbidities influencing the intensity of chemotherapy that can be successfully delivered. Hodgkin lymphoma is derived from germinal centre B-cells and contributed to by latent Epstein Barr Virus (EBV) infection in a number of patients. *Aims.* To examine the incidence and treatment outcomes of B-cell NHL following completion of treatment for CHL in elderly patients compared with younger patients. *Methods.* Adult patients diagnosed with CHL at our institutions from 2000-2015 were followed prospectively following initial treatment for survival and toxicity outcomes. Any subsequent diagnosis of B-cell NHL was confirmed by two expert lymphoma anatomical pathologists consistent with WHO 2008 diagnostic criteria. *Results.* 165 adult patients were available for analysis, of which 56 (34%) patients were >60 years old. There was no significant difference between elderly and young cohorts in the number of patients with early stage favourable, unfavourable or advanced stage CHL. Less elderly patients received ABVD-like chemotherapy (71% *vs* 95%). There was a higher number of relapses of CHL in elderly patients (31% *vs* 20%). At a median follow-up of surviving patients at 2.7 years, there was a much higher incidence of secondary malignancy in elderly patients n=11 *vs* n=2 (24% *vs* 2%), of which there were far more haematological compared to solid malignancies n=8 (17%) *vs* n=3 (6%). Specific histologies included Diffuse Large B-cell Lymphoma (5), Follicular lymphoma (1), Lymphoplasmacytic lymphoma (1) and Chronic lymphocytic leukaemia (1). Patients with DLBCL were treated with R-CEOP and resulted in 2 patients achieving long-term relapse free survival. *Conclusions.* There is a high incidence of B-cell NHL in elderly patients with CHL, suggestive of a common germinal centre derived progenitor cell of origin. Comparative genomic annotation of such cases is required to better understand the lymphoma initiating events in this cohort to enable selection of treatment which may reduce this complication.

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ANALYSIS OF HODGKIN LYMPHOMA IN OLDER ADULTS IN A SINGLE CENTER

L. Cuevas[1], A. Uranga[1], I. López[1], I. Zubicaray[1], N. Robado[1], A.N. Bizjak[1], A. Garcia[2], M. Leturia[2], I. Urreta[3], H. Arrizabalaga[1], N. Caminos[1], M. Sirvent[1], E. Perez[1], P. Romero[1], T. Artola[1], C. Lobo[4], M. Araiz[1], I. Ceberio[1]

[1]Hematology; [2]School of Medicine, EHU/UPV (University of the Basque Country); [3]Epidemiology and Statistics; [4]Department of Pathology, University Hospital Donostia (H.U.D)

Introduction. Due to demographic changes, it is expected that the incidence of the HL will increase in patients(pts) over 65 years(y), highlighting the need for therapeutic strategies designed specifically for the geriatric population. The objective of this review is to evaluate our everyday life practice and analyze the characteristics, prognostic factors and survival of pts over 65y diagnosed of HL in our center. *Methods.* This is an observational, retrospective review. A total of 44pts over 65y and diagnosed of HL from May 2005 to December 2015 were included. The Charlson Comorbidity Index (CCI) was used to evaluate the comorbidities. Pts's and disease's characteristics are listed in Table 1.

Table 1.

Characteristics	No. of patients (%)
No. of patients	44
Median age (years)/range	75/64-91
-<80	29 (67%)
-≥80	15 (33%)
Sex	
-Male	22 (50%)
-Female	22 (50%)
Histology:	
Classical HL:	
- Nodular esclerosis (NE)	16 (36%)
- Mixed cellularity (MC)	18 (41%)
- Lymphocyte-Rich (LR)	4 (9%)
- Lymphocyte-depleted (LD)	1 (2%)
Nodular lymphocyte predominant (NLP)	1 (2%)
No specified	4 (9%)
Comorbidity index	
<3	34 (77%)
≥3	10 (23%)
Stage (Ann Arbor)	
I-II	17 (39%)
III-IV	27 (61%)
B symptoms	
-Present	18 (41%)
-No present	26 (59%)
Bulky	
- Yes	1 (2%)
- No	39 (89%)
- No specified	4 (9%)
Treatment	
-Yes	36 (82%)
-No	8 (18%)
Regimen	
-ABVD	26 (59%)
-Others	11 (25%)
-Not applicable	7 (16%)
RT	
-Yes	14 (32%)
-No	30 (68%)
Treatment response	
-Complete response (CR)	25 (58%)
-Partial response (PR)	3 (7%)
-Progression	7 (16%)
-Not valuable	8 (19%)
Relapse	
-Yes	2 (5%)
-No	25 (58%)
-Not applicable	16 (37%)
Exitus	
-Yes	24 (54,5%)
-No	20 (45,5%)

Results. The treatment and the response rate are shown in Table 1. 58% of pts achieved CR and there were only 2 relapses recorded in this group. 16% progressed during treatment (most of them had an advanced stage at diagnosis). 18% did not receive any treatment owe to comorbidities or denial by the pt. The estimated 5y overall survival (OS) was 45%. Mortality rate was 54.5%: half due to the disease itself, 27% as a result of the treatment's toxicity (60% of this group owe to pulmonary involvement), 14% by other neoplasia and 9% due to comorbidities. In the univariate analysis factors associated with lower survival were a CCI ≥3 and the age >80y, with a 5 y-OS of 28% *vs* 51% (p=0.003) and 8% *vs* 60% (p=0.0002), respectively. Because of the low sample size it is not rentable to assess a multivariate analysis. *Conclusions.* Despite the limitations of a retrospective analysis, our study confirms the data published in the literature: elderly patients frequently present mixed cellularity subtype, achieve lower rates of CR and OS, but relapse-free survival is less impaired and present high-

er toxicity associated with treatment compared to young patients. The fundamental cause of death remains being the disease. The age over 80 years and CCI≥3 are associated with a worse prognosis. The management of patients over 80 years represents a major therapeutic challenge because of the high toxicity and low efficiency of current treatments. It is important to include these patients in clinical trials covering new drugs. The new drugs and new easy geriatric assessment tools, which detect frailty, should assist in the better management of these elderly patients. Our hospital intends to initiate a care protocol that covers the assessment using the CIRS-C and GAH scales.

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AN UPDATE ON BETER, THE DUTCH NATIONWIDE SURVIVORSHIP CARE PROGRAMME FOR HODGKIN LYMPHOMA SURVIVORS

A. Nijdam[1], B.M.P. Aleman[1], M.B. van 't Veer[1,2], C.P.M. Janus[3], R. de Weijer[4], L.A. Daniëls[2], F.G. Stedema[5], J.M. Zijlstra[6], R.W.M. van der Maazen[7], J.H. Borger[8], K. Verschueren[9], J. Manenschijn[10], E.F.M. Posthuma[11], J. Raemaekers[7,12], F.E. van Leeuwen[1], on behalf of the BETER consortium

[1]The Netherlands Cancer Institute, Amsterdam, the Netherlands; [2]Leiden University Medical Center, Leiden, the Netherlands

3Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands; [4]University Medical Center Utrecht, Utrecht, the Netherlands; [5]University Medical Center Groningen, Groningen, the Netherlands; [6]VU University Medical Center, Amsterdam, the Netherlands; [7]Radboud University Medical Center, Nijmegen, the Netherlands; [8]MAASTRO clinic, Maastricht, the Netherlands; [9]Institute Verbeeten, Tilburg, the Netherlands; [10]Isala Clinics, Zwolle, the Netherlands; [11]Reinier de Graaf Group, Delft, the Netherlands; [12]Rijnstate Hospital, Arnhem, the Netherlands

Background. Survivors of Hodgkin lymphoma (HL) are at increased risk of various late adverse effects of treatment, leading to substantial excess morbidity and mortality. The Dutch BETER consortium (Better care after Hodgkin lymphoma: Evaluation of long-term Treatment Effects and screening Recommendations) aims at improving life expectancy and quality of life for HL survivors. *Methods.* The BETER consortium has developed: (1) evidence-based follow-up guidelines for HL survivors according to (inter)national standards; (2) a nationwide infrastructure for survivorship care clinics in which risk-based care is provided to ≥5-year survivors of HL, who were treated after 1965 at ages 15-60 years. Moreover, the BETER consortium aims at improving knowledge about late adverse effects of HL treatment in patients as well as health care providers, *e.g.* through the website www.beternahodgkin.nl. *Results.* BETER-guidelines for second malignancies, cardiovascular disease, thyroid disease, osteoporosis and fertility, functional asplenia, neck muscle weakness and other problems (quality of life, weight, dental health, neurological problems, and pulmonary disease) are expected to be approved soon by the respective medical societies. Currently, 11 out of 23 centres participating in the BETER consortium have established a BETER Survivorship Care Clinic. Other centres are planning to start shortly. The proportion of HL survivors still under medical surveillance varied substantially across BETER clinics. For these patients follow-up care is adapted to the new screening guidelines. Among the HL survivors who were discharged from follow-up care, there was a large variation in attendance rate between BETER clinics, varying from 25% to 90%. Five to 35% of patients did not respond to the invitation and 5 to 40% did not wish to attend. Most common reasons to not attend were: undergoing screening or treatment for late effects elsewhere, not wanting to be reminded of HL, emotional burden and financial reasons. We will evaluate reasons for non-attendance in more detail in the near future. *Conclusions.* Clinical attendance rates of HL survivors who were previously discharged from follow-up, vary substantially between BETER clinics. Evaluation of reasons for non-attendance will be used to improve survivorship care.

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PROSPECTIVE EVALUATION OF PULMONARY TOXICITY IN FIRST LINE TREATMENT OF HODGKIN LYMPHOMA PATIENTS

Á. Jóna, Z. Ujj, M. Szilasi, S. Póliska, B.L. Bálint, I. Garai, Z. Miltényi, Á. Illés

Department of Hematology and Pulmonology, Genomic Medicine and Bioinformatic Core Facility, University of Debrecen, Faculty of Medicine; Scanomed Ltd, Debrecen , Hungary

Introduction. Bleomycin (bleo) containing first-line therapy ± irradiation may cause pulmonary toxicity in Hodgkin lymphoma (HL) patients.

*Patients and Methods.*Pulmonary function of newly diagnosed HL patients were assessed, by using St. George Respiratory Questionnaire (SGRQ), dynamic inhalation lung scintigraphy, diffusion capacity of the lung for carbon monoxide (DLCO) and spirometry before, during and after treatment, prospectively. Bleo hydrolase (BLMH) SNP A1450G genotype polymorphism was determined by TaqMan genotyping assay. *Results.* A total of 50 classical HL pts. data were available for analysis, treated between February 2012 and March 2016 in our Institution. 38 pts. received ABVD (median cumulative bleo dose: 120 mg/m^2) chemotherapy, 18 pts. received bleo intramuscularly (im.) and 20 intravenously (iv.). As control group, 12 pts. were treated with brentuximab vedotin (BV)-AVD. Chest irradiation was involved in 11 pts.' treatment. Pulmonary complains measured by SGRQ slightly improved over treatment. Lung scintigraphy results of bleo-treated pts. significantly worsened over treatment. More interestingly, results of BV-treated pts. not only significantly worsened over treatment, but was significantly inferior to bleo treated patients. By excluding smoker pts., difference became not significant, but still inferior to bleo treated pts. DLCO much less explicitly confirmed these *results.* Spirometry parameters improved over treatment in both groups, with no significant differences. Chest irradiation did not significantly worsen pulmonary function. Pts. receiving iv. bleo had significantly worse results measured with lung scintigraphy at the end of treatment and during treatment with DLCO, than those receiving im.. BLMH SNP A1450G didn't distinguished in this short run of bleo treated pts. *Discussion.* Pulmonary function test results of bleo treated pts. worsened over treatment as previously reported, however we found these results only with lung scintigraphy. DLCO was much less supportive. Moreover, only one patient was found with acute bleo induced lung injury in contrast with the literature (20-46%). Surprisingly, BV-AVD, which is considered non-pulmonary toxic, produced inferior results to bleo treated pts.. We have to compliment, that these results were only seen with lung scintigraphy, which has no literature, and data lacks of confirmation with gold-standard DLCO. Nevertheless, lung scintigraphy is supposed to measure earlier epithelial damage.

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HODGKIN LYMPHOMA AND PREGNANCY - DILEMMAS OF HOW TO TREAT?

E. Lampka[1], J. Tajer[1], W. Osiadacz[1], B. Brzeska[1], M. Dębska[2], M. Rubach[1], R. Dębski[2]

[1]The Maria Sklodowska-Curie Memorial Cancer Center and Institute, Warsaw, Poland; [2]The Medical Centre of Postgraduate Education, II Department of Obstetrics and Gynecology, Warsaw, Poland

Introduction. The incidence of malignant neoplasms in women at reproductive age has increased dramatically over the past decade and is still rising. Hodgkin's lymphoma (HL) is one of the most frequent hematological malignancies in young women. When diagnosed HL during pregnancy,it represents a major clinical dilemma and there is a lack of established standards defining its optimal treatment during gestation. The coincidence of HL and pregnancy poses an unusual challenge for the mother and the medical team. *Materials.* 102 patients with Hodgkin lymphoma(HL) were treated at the MSCMCC Warsaw between 01/1986 and 12/2015. Age: range (mean): 16-39 (29). Most patients

Hodgkin's lymphoma (HL) in the second stage of clinical Ann Arbor (CS), histopathological type of NS (nodular sclerosis) and in the second trimester of pregnancy. B symptoms- 51%, tumor mass -41%, MMR>1/3 -38%. Methods of treatment: I trimester :therapeutic abortion or radiotherapy (IF) upper cervical or axillary lymph nodes or miscarriage (7-8 Hbd), III trimester : method "watch and wait" and delivery 37-39 Hbd or chemotherapy scheme EVA (1-2 cycles before delivery) (Etoposide 100mg/m^2 days 1-3, Vinblastine 6 mg/m^2 day 1, Doxorubicin 50mg/m^2 day 1 repeated every 28 days) before delivery. II trimester method "watch and wait" or radiotherapy (IF) total dose between 20-44 Gy before delivery and chemotherapy LOPP, MOPP, MOPP/ABV after delivery or radiotherapy (IF) total dose 30-35 Gy and chemotherapy scheme EVA (2 cycles) before delivery or chemotherapy scheme EVA (3-4 cycles) before delivery and radiotherapy (IF) total dose 30-40 Gy after delivery. *In vivo* dosimetry before delivery during radiotherapy by irregular fields Thermoluminescent dosimetry HARSHAW 100 or Thomson and Nielsen t.MOSFET TN –RD 51 and individually blocks of the abdomen and fetus were used. The dose of the fetus was estimated individually in all. Total dose 0 cGy -19.19 cGy.*Results.* Out of 102 treated women now live 94 (92%).Most of the living patients in complete remission. In 2 patients after childbirth was made a full panel of diagnostic tests. They remain in partial remission and continued treatment regimen ABVD. Cause of death in 8 patients: relapse or primary refractory disease. Was born 90 children. Parturition and postpartum correct. All bearings were subjected to histopathological examination. There was no cell lymphoma in the tested material. There were no developmental or genetic defects in children. Children are under constant medical care. Physical and mental development correct. One infant developed acute respiratory distress syndrome and died 6 days after delivery. Age surviving children 6 months - 29 years.

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SECOND CANCER RISKS IN PATIENTS WITH SUPRADIAPHRAGMATIC HODGKIN LYMPHOMA

S. Shahtarina, A. Danilenko, V. Pavlov

The Tsyb Medical Radiological Research Center, Obninsk, Russian Federation

Background. Second cancer s (SC) developing in Hodgkin Lymphoma (HL) patients after treatment significantly affect survival. The studies defining relative risc (RR) of SC in the cohort s of HL patients treated with similar radiotherapy (RT) target volumes and total tumor doses (TTD) are rare. *Purpose.* The aim was to evaluate RR of SC in HL patients treated with RT alone or chemoradiotherapy (CRT) when irradiation was limited to the lymphatic areas above diaphragm and the spleen. *Methods.* The study included 1789 initial HL pts, stages I, II, IV (supradiaphragmatic, age 13-69 (87% under 40). Women 1177 (66%), men 612 (34%). The treatment period was between 1968 and 1998. Patients were given either RT alone limited to the lymphatic areas above diaphragm and the spleen, TTD 40 Gy (363 pts, 20.3%) or 6 cycles of chemotherapy COPP+similar RT (1426 pts, 79.7%). The incidence of SC was compared with the data from Cancer Register of Russian Federation. *Results.* Follow-up was 6 mnths - 36 years (median 18 years). The overall follow-up for the cohort was 18949 patients/years (men 5917, women 13032). SC developed in 80 (4.5%) patients: after RT in 27 (7.4%) of 363 pts, after CRT in 53 (3.7%) of 1426 patients. One tumor occurred in 74 pts, two tumors, two tumors successively in 5 patients and three tumors in 1 patient. The total number of tumors was 87, including 85 (97.7%) solid tumors, 2(2.3%) hemoblastoses. The time of SC occurrence was 1-31 years (median 18). SC RR: overall for the cohort - 2.85 (95% confidence interval (95% CI) 1.85-2.98); in women - 3.02 (95% CI 1.9-3.12); in men - 2.46 (95% CI 1.23-2.91). After RT alone: in women - 3.22 (95% CI 2.11-4.75); in men - 2.51 (95% CI 0.9-4.63). After CRT: in women - 2.9 (95% CI 1.48-3.02); in men - 2.4 (95% CI 1.04-2.96). The prevailing tumors were mammal, thyroid, gastric. The RR of mammal cancer was 4.01 (95% CI 2.46-5.98); gastric cancer: in women - 7.95 (95% CI 3.2-14.4), in men - 4.03 (95% CI 1.0-9.0); thyroid cancer: in women - 7.8 (95% CI 3.47-13.9), in men - beyond 95% CI. 19 (21.8%) of 87 tumors occurred within irradiation fields. *Conclusions.* In our study the RR of SC in HL patients was 2.85, which is lower than reported by other authors. This probably could be explained by the fact that the study included HL patients in whom irradiation was limited to supradiaphragmatic areas and spleen.

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PROGNOSTIC VALUE OF CLINICAL, TREATMENT AND SOCIO-DEMOGRAPHIC RESULTS OF PSYCHOLOGICAL DISTRESS AMONG HODGKIN LYMPHOMA SURVIVORS IN HUNGARY

F. Magyari[1], Z. Miltényi[1], S. Simon[1], K. Kósa[2], R. Berecz[3], Á. Illés[1]

[1]Department of Hematology, Faculty of Medicine; [2]Department of Behaviour Sciences, Faculty of Public Health; [3]Department of Psychiatry, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

Objectives. Due to risk and response adapted treatment strategies, more than 80% of newly diagnosed classical Hodgkin lymphoma (HL) patients can be cured, and are expected to be long-term survivors. A remarkable number of HL survivors suffer from treatment related long-term side effects, such as secondary malignancy, organ failure, persistent fatigue and psychological distress. *Purpose.* The aim of this study was to evaluate the frequency of psychological distress and it's risk factors among HL survivorsin Hungary. *Patients and Methods.*163 (88 female and 73 male) adult HL survivors were identified between 1st January 2012 and 31st March 2015 in our outpatient centre. The patients were asked and agreed to completestandardized, self-administeredquestionnaires: Hospital Anxiety and Depression scale (HADS14), General Health Questionnaire (GHQ12), Perceived Stress Scale (PSS4) and sociodemographic questions. Disease and treatment data were based on the hospital records. *Results.*The mean age at thetime of diagnosis was 32.16±12.97 years, at the completion of the survey was44.84±14.51 years. A total of 25% had caseness scores with HADS14. Anxiety caseness scores were high infemale patients (p=0.003), and were strongly associated with lack of employment (p=0.011) and treatment related long-term side effects (p=0.001). Depression caseness scoreswere increasedamong female patients (p=0.020), and were related to baseline comorbidities (p<0.001), lack of employment (p<0.001), higher ECOG scores at the time of diagnosis (p=0.036) and treatment related long-term side effects (p<0.001). 14.11% of HL survivors had abnormal levels of distress with GHQ12, which were significantly associated with baseline comorbidities (p=0.041), lack of employment (p<0.001), higher ECOG score at diagnosis (p=0.020) and treatment related long-term side effects (p=0.001). The PSS4 scale results were found significantly lower among employees (p<0.001), and in subjects without comorbidities (p=0,008) and with bulk tumor (p=0,026). There was a tight correlation between the questionnaires and the time of survey completion. *Conclusions.* Related to the literature and our own results, the majority of cured HL patients survive without distress at caseness level. Based on our experience HL survivors should be closely followed up by clinicians. If mental health disorder is suspected further psychologic or psychiatric treatment is strongly recommended.

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HODGKIN LYMPHOMA IN ELDERLY PATIENTS - A SINGLE CENTER EXPERIENCE

M. Santos, A. Pinto, D. Mota, R. Guilherme, M. Gomes, L. Ribeiro

Clinical Hematology Department, Coimbra University Hospital Center, Coimbra, Portugal

Background. Classical Hodgkin lymphoma occurs in 20% of patients aged over 60 years. Survival rates for elderly patients with Hodgkin Lymphoma (eHL) are disproportionately inferior compared with younger patients. In eHL poor outcome is related with biologically more aggressive disease, treatment toxicity and comorbidities. Although ABVD is regarded as standard of care for most eHL patients, adjusted treatment strategies are lacking for this particular population and innovative approaches are awaited. *Aims.* Characterize an elderly population

with HL and analyze the impact of different treatment approaches (response to treatment, long-term outcome and occurrence of secondary neoplasms). *Methods.* We performed a retrospective analysis of elderly patients with HL (≥60 years) treated between 1991 and 2015, in a tertiary center. *Results.* Forty-six eHL patients were considered, mainly males (58.7%) with a median age of 70 years (60-80). The most prevalent histological subtype was nodular sclerosis (n=30; 65.2%). Ann Arbor stage III/IV was observed in 31 patients (67.4%), B symptoms in 34 (73.9%) and bulky disease in 2 (4.3%). The risk stratification (GHSG) was: limited n=4 (8.7%), intermediate n=10 (21.7%) and advanced n=32 (69.6%). ABVD was performed in 19 patients (41.3%); MOPP/MOPP like in 11(23.9%); other regimens in 8 (21.7%) and radiation alone in 2. Six patients had an early death event before starting chemotherapy. Overall response rate (ORR) was 72.5% (complete response - CR 67.5%); with ABVD, ORR was 73.7% (all with CR). With a median follow-up of 34.6 months (0.3-273.4), 5-year overall survival (OS) and progression free survival (PFS) were 46.1% and 35.9%, respectively. Among 33 patients who died, 20 were due to HL. Median OS and PFS were superior in patients treated with ABVD when compared with other approaches (156.6 *vs* 22.5 months, p=0.047 and 156.6 *vs* 20.3 months, p=0.035). Using a univariate analysis most International Prognostic Score factors didn't show prognostic value, although multivariate analysis identified hemoglobin as a predictive factor of OS (HR 0.59; 95%CI 0.40-0.87, p=0.007) and PFS (HR 0.11; 95%CI 0.45-0.90, p=0.011). Four patients presented late second malignant neoplasms (n=2, ABVD; n= 2, other regimens). *Conclusions.* ABVD remains a standard of care in eHL. In our cohort we observed that this regimen was effective and can improve survival. We concluded that hemoglobin level is an independent predictor of survival in this population.

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ARE WE AWARE OF NUTRITIONAL STATUS AND VITAMIN D LEVEL IN HODGKIN LYMPHOMA PATIENTS?

V. Djurasinovic[1], B. Andjelic[1,2], M. Saric[3], S. Ignjatovic[2,3], M. Todorovic Balint[1,2], D. Antic[1,2], V. Vukovic[1], J. Jelicic[1], A. Sretenovic[1], B. Mihaljevic[1,2]

[1]Clinic for Hematology, Clinical Center of Serbiaal, Belgrade, Serbia; [2]Medical Faculty, University of Belgrade, Belgrade, Serbia; [3]Clinic for Biochemistry, Clinical Center of Serbia, Belgrade, Serbia

Background. Patients with Hodgkin lymphoma ussualy have weight loss at the diagnosis of disease. None of the prognostic parameters so far did not evaluate prognostic significance of weight loss. Also, vitamin D is not ussualy assed in lymphomas. *Aim.* Evaluation of nutritional status and level of vitamin D in *de novo* patients with Hodgkin lymphomas. *Methods.* 22 *de novo* pts diagnosed from january 2014. At Clinic for hematology, Clinical center of Serbia, median age 34,5(19-60)years. Initial clinica stage (CS) was: I in 1/22; II in11/22; III in 4/22 ans IV5/22..ECOG PS: 0 in 5/22pts, 1 in 12/22, 2 in 5/22. All pts were treated initialy with ABVD. Nutritional status was screened by NRS 2002 and vitamin D was assesed with the chemiluminescent immunoassay for the quantitative determination of total serum 25-hydroxyvitamin D (25(OH) vitamin D). Pts were followed for median18,5 (12-26) months. *Results.* Mean BMI was 24,08±3,39 while 3/22 pts had BMI less than 20,5kg/m^2. 7/22 pts have lost ≥10%body weight (BW) during previous 6mts. 9/22pts had NRS 2002≥3. Median 25-OH vitamin D 26,7(10,2-62,05)nmol/l and none of pts had normal level. 9/22 had severe defitiency <25nmol/l, 9/22 defitiency 25-50nmol/l and 4/22 had unsufitient level 50-75nmol/l. 7/22 pts progressed within one year. Median PFS 8(3-12) months. Pearson correlation between pts with weight loss over 10% BW and progression is 0,4, p=0,66, while for 25-OH vitamin D lower than 25nmol/l and progression was 0,589, p=0,005. In binary logistic model only severe defitency 25-OH vitamin D was significant for progression while CS, NRS and ECOGPS over were not significant. *Conclusions.* Around 40%pts are malnourished or in nutritional risk. Any of pts had normal 25-OH vitamin D, there was a significant correlation between severe defitiency and progression. Supportive care along with chemotherapy may obtain better treatment *results.*

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MENTAL DISORDERS IN HODGKIN'S DISEASE PATIENTS

D. Vybornykh, L. Olexenko, S. Khrushchev, S. Kravchenko, I. Shitareva, T. Moiseeva

National Research Center for Hematology, Moscow, Russia

Background. Data on mental disorders, manifesting in Hodgkin's disease patients are rather limited. Such disorders are considered as within somatogenic psychoses and adjustment disorders. Among described psychoses identified isolated cases of delusional disorders, delirium, oneiric. Among the adjustment disorders described is mainly anxiety, depression, or combinations thereof. Systematic studies of psychiatric disorders in patients with Hodgkin's disease have not been conducted. *Aim.* To identify the structure of mental disorders in patients with Hodgkin's disease. *Materials and Methods.* There were examined 95 patients with Hodgkin's disease by clinical-psychopathological method. Results of the study were subjected to statistical analysis using Stat for Windows 5.5 licensing programs. *Results and Discussion.* It was revealed that endogenomorphical psychoses (hallucinatory-paranoid and depressive-delusional states) and somatogenically provoked schizophrenia attacks in Hodgkin's disease patients are much more likely (17 and 6, respectively) than delirium, unlike other hematological malignancies, in which be present (or was found observed) the opposite trends. In addition, Hodgkin's disease is the only hematological malignancy in the studied sample, in which the schizophrenia attacks are detected (were detected). Among adjustment disorders in Hodgkin's disease patients were identified as follows: anxiety and dissociative (n=29) (anxiety and dissociative reactions occur with symptoms of the phenomenon of alienation of real hematological disease and signs of latent somatization of anxiety, accompanied by abnormal behavior in the disease), hypomanic (n=4), dissociative (n=25) (dominated by the phenomenon of alienation of the hematological malignancy, reaching the degree of total denial of the fact of the blood system diseases, revealed gross cognitive disorders characterized by distinct partial peculiar syndrome pseudodementia) and anxiety-koenestopathical (n=14) (somatogenically and / or psychogenic provoked polymorphic functional symptoms, abnormal bodily sensations). *Conclusions.* The study results show that in a sample of Hodgkin's disease patients schizoid spectrum disorders accumulate, what could serve as a reason for further studies of this phenomenon, involving both clinical and biological research methods.

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ANALYSIS OF ACCESS TIME TO CARE FOR PATIENTS WITH HODGKIN'S LYMPHOMA IN PUBLIC HOSPITAL IN SÃO PAULO

N. Amaral, T. Fisher, S. Fortier, T. Silveira da Rocha, C.S. Chiattone

Santa Casa Medical School, Samaritano Hospital Center, Sao Paulo, Brazil

Introduction. Cancer is responsible for over 12% of all causes of death in the world, where more than 7 million people die each year from this evil. Early diagnosis coupled with existing therapeutic methods allow higher survival rates for cases considered incurable before. *Objectives.* To analyze the time spent on the access of patients with Hodgkin's disease in philanthropic Hospital in São Paulo (SP) to the specialized service. *Methods.* query the records with tabulation and analysis of data of 67 patients. *Results.* male Majority N=35 (52.2%) aged between 15 and 75 years and frequency of single N=33 (50.0%). As for the disease, 25 (37.3%) were in stage IVB and the waiting time interval until the first examination (p=0.035). Gender variations, age and education were significant in the elapsed time of the first signs and symptoms until the first examination (p=0.008) and attendance at the Santa Casa to consultation with a specialist (p=0.012). Younger patients (15 and 35) sought the first faster service, and the time was 31 days; older (56 and

75) took more average time: 304 days. *Conclusions.* The most economically disadvantaged patients were in advanced stage. There is an increased time interval to access health services, especially regarding the type of service for the first visit. The variables showed significant when analyzed "type of service" and "age" over time.

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THE USE OF COPING STRATEGIES AND SOCIAL SKILLS IN YOUNG ADULT PATIENTS WITH HODGKIN'S LYMPHOMA: CORRELATION WITH ANXIETY AND/OR DEPRESSION SYMPTOMS

A. Silva, W. Bruscatto, T. Fisher, S. Fortier, T. Silveira da Rocha, C.S. Chiattone

Santa Casa Medical, Samaritano Hospital Center, Sao Paulo, Brazil

Introduction. The oncologic disease exposes the patient into a dynamic and complex treatment process along different steps of the disease, requiring him/her adaptive coping answers; in other words, the patient with cancer needs to mobilize psychosocial resources to deal with the stress due to this illness. The Hodgkin's lymphoma is a type of cancer potentially curable, and the age range of this type of disease, presents a bimodal distribution, having its first incidence peak between 15 and 35 years olds. *Objectives.* This study aimed to evaluate the coping strategies and social skills in young adults against the oncologic treatment and the correlation of these variables with anxiety and/or depression symptoms. *Materials and Methods.* The sample was composed of 44 patients with Hodgkin's lymphoma diagnosis between the ages of 18-35 years old. There have been used as research tools: Socio-demographic Record, Ways of Coping Scale - EMEP, Social Skills Inventory – HIS, Hospital Anxiety and Depression Scale – HAD. *Results.* By a quantitative analysis of data, it has been possible to conclude that the coping strategy focused on the problem presented higher scores in this population, while the coping strategy focused on the emotion presented lower scores. The correlation of coping strategy focused on the emotion showed symptoms (p=0,000) and depression (p=0,002). It has been verified that in this population, the social skills factors related to the self-affirmation in expression of positive affection, conversation and social resourcefulness, and self-exposure to unknown or new situations, are above the average if compared to the general population of the validation study. These factors might be associated to the oncologic treatment, environmental factors involved in this process, which favor the development of these skills. There has not been significant statistically correlation among these social skills and anxiety and depression symptoms.

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QUALITY-OF-LIFE OUTCOMES IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA TREATED WITH NIVOLUMAB MONOTHERAPY IN CHECKMATE 205 (COHORT B), A PHASE 2 STUDY

A. Engert[1], I. Hirji[2], F. Taylor[3], B. Bennett[4], K. Cocks[4], K. Kato[2], D. Cella[5]

[1]University Hospital of Cologne, Cologne, Germany; [2]Bristol-Myers Squibb, Princeton, NJ, USA; [3]Adelphi Values, Boston, MA, USA; [4]Adelphi Values, Bollington, Cheshire, UK; [5]Northwestern University, Chicago, IL, USA

Background. Nivolumab (nivo), a fully human IgG4 immune checkpoint inhibitor targeting PD-1, showed encouraging efficacy in relapsed/refractory cHL in a ph1 study (Ansell *et al.* NEJM 2014). Cohort B of CheckMate 205 ph2 study investigated nivo in cHL pts who had failed autologous hematopoietic stem cell transplantation (auto-HSCT) and brentuximab vedotin (BV): ORR per independent radiologic review committee was 66% and 6-m PFS was 77% (Engert *et al.* EHA 2016; abstr S793). Due to limited treatments there is a need to provide durable efficacy while maintaining/improving QoL. *Aim.* Evaluate QoL in pts receiving nivo in CheckMate 205 cohort B. *Methods.* This ongoing ph2 study (NCT02181738) assessed QoL in cHL pts receiving nivo 3 mg/kg IV q2w. Pt-reported QoL was assessed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and EuroQol Five Dimensions Questionnaire (EQ-5D) q4 cycles on treatment. EQ-5D visual analog scale (VAS) scores range 0–100 and EQ-5D utility index scores –0.6–1 (higher scores=better health state). A 7- and 0.08-point change from baseline (BL) in VAS and utility index score, respectively, represent a clinically meaningful improvement (CMI). QLQ-C30 scores range 0–100 (high scores=higher level of function/global health status [GHS]; for symptom scales, higher level of symptom burden); 10-point change represents a CMI. Changes from BL estimates are based on a mixed model with time point as a fixed effect. Missing data was investigated to assess possible bias. *Results.* BL and subsequent QoL assessment was completed by 72 treated pts (90%) from cohort B (n=80). Most pts with an on-treatment study visit through wk33 (n=47/72) completed both questionnaires (n=42). CMI in mean EQ-5D VAS scores were maintained over time on treatment (VAS mean change BL–wk33: 19.6, $p \leq 0.001$). Changes of the utility index least squares were significant ($p \leq 0.005$) at all treatment time points. For the QLQ-C30, significant improvements from baseline were observed from wk9 for: fatigue, dysnpena, appetite loss, physical function, role function and global health status. No QoL scale indicated deterioration during treatment. *Conclusions.* In cHL pts who had failed auto-HSCT and BV, nivo resulted in a trend towards QoL improvement in this small cohort. An improvement in GHS (EQ-5D VAS) was observed by wk9 and maintained over time on treatment.

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