Thieme

ISCAYAHL 2020

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Congress Chairs:
Prof. Christine Mauz-Körholz, Prof. Monika Metzger

S-I | Session I: Translational Biology

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S-I-01 Introduction

DOI 10.1055/s-0040-1701807

S-I-02 Single cell RNA-sequencing of the Hodgkin lymphoma tumor microenvironment

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S-I-03 Deregulated transcription factor networks in HRS cells

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S-I-04 RNA-seq analysis of plasmatic exosomal miRNAs in pediatric Hodgkin Lymphoma

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DOI 10.1055/s-0040-1701810

Introduction Hodgkin lymphoma (HL) represents around ~10% of all cases of lymphoid neoplasms. Although current risk-adapted and response based treatment approaches can cure >90% of the children, treatment of relapsed/resistant patients remains a challenge [1].

In the last years, a large body of evidence proved the functional involvement of exosomes in cancer progression and spreading, induction of angiogenesis, as well as in chemoresistance and immune response evasion during tumor development 2.

The aim of our study is to characterize miRNA in plasmatic exosomes of pediatric HL patients, for the identification of new non-invasive biomarkers and disease mechanisms, which might be used to improve diagnosis, treatment and prognosis of the affected children.

Methods The study cohort included 36 HL patients treated according to EuroNet-PHL-C2 trial and 7 plasma samples from healthy donors (D) as controls. Exosomes were isolated from 0.5 ml plasma at diagnosis by exoEasy Midi Kit (Qiagen) and validated by Nanoparticle Tracking Analysis (NTA, Malvern Nanosight), Atomic Force Microscopy (ATM) and Western Blotting. Total exosomal RNA was obtained using exoRNeasyMidi Kit (Qiagen) and sequencing libraries were prepared from 10 ng RNA by using the NEBNext® Multiplex Small RNA Library Prep Kit for Illumina® (New England Biolabs). RNA-seq analysis was performed on an Illumina HiSeq 4000 with target depth of 15 M reads per sample. RNA-seq data were analyzed using the software miR&moRe [3]. Differential expression analyses were performed with DESeq2 [4].

Results Overall, >200 expressed miRNAs were identified. Comparing HL and D exosome samples, 11 differentially expressed miRNAs were disclosed. When patients were grouped based on Early Response Assessment (ERA), 15 miRNAs differentially expressed were identified between patients with adequate and inadequate response.

Conclusion Differentially expressed miRNAs will be prioritized based on their functional significance in cancer and/or previous reports in lymphoid malignancies. The most promising candidates will be validated by quantitative real-time PCR in an extended cohort of both HL and D and functionally characterized by *in vitro* experiments.

These results are expected to provide insights on the role of exosomal miRNAs in HL disease aggressiveness and response to therapy.

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S-I-05 Molecular Mechanisms in the Pathogenesis of Composite Lymphomas

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Introduction If two distinct lymphomas occur concurrently in a patient this is named composite lymphoma. Such lymphomas often involve a classical Hodgkin lymphoma (HL) and a B cell-Non-Hodgkin lymphoma (B-NHL). In most instances such composite lymphomas are clonally related and originate from a common germinal center B cell, which can be detected by identical rearranged immunoglobulin variable region genes. Several studies analysing selected candidate genes have identified shared as well as distinct transforming events in single genes of clonally related composite lymphomas, indicating that the malignant cells developed separately from a common precursor cell. Thus, composite lymphomas are elegant models to study the multi-step transformation process in lymphomagenesis. Moreover, there is indication that even composite or consecutive B- and T-cell lymphomas may share transforming events, as somatic genetic lesions can be already detected in hematopoietic precursor cells of lymphoma patients and elderly healthy individuals.

Methods We isolated lymphoma and non-tumor cells by microdissection from several composite lymphomas involving HL and B-NHL as well as by flow-cytometric cell sorting for two B- and T-cell-NHL combinations. For the composite HL and B-NHL their rearranged immunoglobulin were amplified. For all samples, whole exome sequencing was performed.

Results We analyzed composite lymphomas of HL combined with mantle cell lymphoma, splenic marginal zone lymphoma or follicular lymphoma, and two B- and T-cell-NHL combinations which included a plasma cell leukemia co-occurring with an anaplastic large cell lymphoma and a chronic lymphatic leukemia combined with a T-cell prolymphocytic leukemia. Analysis of the immunoglobulin variable region genes of combined HL and B-NHL showed that most HL were clonally related to the combined B-NHL. Whole exome sequencing of the two lymphoma components and of non-tumor cells revealed that in each of the cases shared somatic mutations were present. All cases also carried a substantial number of non-shared somatic mutations.

Conclusion Our preliminary evaluation of the whole exome sequencing data indicates that in all cases analyzed by us, numerous shared as well as distinct non-synonymous mutations are found. This supports the close relationship of HL to B-NHL, and eluminates ways how from a common pre-malignant precursor, two distinct lymphoid malignancies can develop.

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S-I-06 Genomic Landscape of Reed-Sternberg Cells of Hodgkin Lymphoma from Children, Adolescents, and Young Adults

Chairs Roshal M[2], Xiang JZ[1], Park S[3], Oberley M[4], Ruchdeschel E[5], Lim M[6], Wertheim G[6], Barth M[7], Horton TM[8], Bhinder B[1], Wha Eng K[1], He F[1], Zhang W[1], Tan A[1], Elemento O[1], Giulino-Roth L[1]
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DOI 10.1055/s-0040-1701812

Conflict of Interest: LGR: Janssen (consultant), ADC Therapeutics (consultant), Celgene (consultant), Merck (advisory board member)

Introduction Genomic evaluation of classical Hodgkin lymphoma (cHL) is challenging due to the scarcity of Hodgkin and Reed-Sternberg (HRS) cells within an extensive reactive microenvironment. To overcome this limitation our group has optimized flow-sorting to isolate HRS cells followed by exome sequencing using ultra low input DNA (Reichel et al, Blood 2015). This approach has been used to describe the exome of 10 cHL biopsies, most of which were from adult patients. To better understand the mutational landscape of cHL in children, adolescents and young adults, we performed whole exome sequencing (WES) on 54 cases and whole genome sequencing (WGS) on 9 cases.

Methods HRS cells and intra-tumoral T-cells were isolated from cHL biopsies as previously described (Reichel at al, Blood 2015). Library construction was performed using the Kapa Hyper Plus Kit (Roche). A portion of library constructs were used for WGS; the remaining libraries were captured/amplified using SeqCap EZ Human Exome v3.0 probes (Roche) for WES. Exomes were analyzed using the MC3 pipeline. Somatic copy number analysis was performed using TITAN.

Results WES was performed on 54 cases: 42 from children/AYAs (age 0-39yrs) and 12 from older adults (age ^{3}40yrs). Histology included nodular sclerosis (83%), mixed cellularity (13%) and lymphocyte rich (4%). EBV was positive in 18%. For WES, the mean coverage was 80x for tumor and 48x for germline; the mean tumor purity was 61%. The average tumor mutation burdern was 5.9 mutations/MB. A total of 46,635 variants across 14,579 genes were found including 2,194 indels and 16,909 misense mutations. The most common non-silent alterations were *SOCS1* (61%), *SYNE1* (39%), *DNHD1* (37%), *TNFAIP3* (37%), *B2M* (33%), *OTOG* (30%), *ITPKB* (28%), *RYR2* (28%), and *DNAH9* (26%). Recurrent copy number gains and losses were detected, including the *B2M* locus. WGS was performed on 9 cases with mean coverage of 71x in tumor and 34x in germline. Analysis of structural variants is ongoing and will be presented.

Conclusion Here we present the largest cohort of cHL to be analyzed by WES and the first WGS. The most common gene alteration was in *SOCS1*, which is also the most common alteration reported in primary mediastinal B-cell lymphoma (Mottok et al, Blood 2019). Additional alterations in cHL, however, suggest a unique molecular signature. This work highlights the genomic diversity of cHL, potential differences across the age spectrum, and opportunities to explore novel therapeutic targets.

S-I-07 A specific chromatin structure and increased RUNX3 expression contribute to the Hodgkin/Reed-Sternberg cell-specific phenotype

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Introduction Hodgkin Lymphoma (HL) is one of the most common lymphomas in the western world and frequent in children, teenagers and young adults. Hodgkin Reed/Sternberg (HRS) cells derive from germinal center (GC) B-cells with clonal immunoglobulin rearrangements which often carry function impairing crippling mutations that should cause apoptosis of GC B cells. HRS-cells, however, escape apoptosis.

Furthermore, they exhibit nearly no expression of typical B-cell markers. It is assumed that constitutive signaling (JAK-STAT, NFkB, PI3K-AKT), changes in the microenvironment and Epstein Barr Virus infection contribute to the HRS-cell survival. Another possibility could be the loss of the normal B-cell phenotype. The causes for the encompassing loss of the B cell phenotype of HRS cells are so far largely unclear. We hypothesized that changes of epigenetic features, which is a poorly explored field of HL research, could contribute to the loss of the B-cell phenotype.

Methods We characterized the chromatin landscape of HSR-cell lines in comparison to various non-Hodgkin lymphoma (NHL) cell lines by ATAC-Seq. RNA-Seq was performed to verify the Data. Computing analyses of the data allowed the identification of target factors.

Results We identified a HRS-cell specific chromatin structure. The pattern of differentially expressed RNAs was largely in concordance with changes in the chromatin structure, especially regarding the loss of the B-cell identity. Furthermore, we identified motives of DNA binding factors enriched in the open chromatin of HRS-cells as compared to NHL cells. The binding sites of these factors were mostly in intronic and intergenic regions of the genome, including cis-regulatory sequences like enhancer and isolators. One of the DNA binding factors which enriched binding sites in open chromatin is RUNX3 which binds to promotors and enhancers and also takes part in normal B-cell development in interplay with RUNX1. RUNX3 is strongly expressed in HRS-cells compared to NHL-cells and RUNX3 knock down caused a partial restoration of B-cell specific gene expression in HRS-cell lines.

Conclusion The Results indicates that the high RUNX3 expression could contribute to the HRS-cell specific chromatin landscape and the loss of the B-cell phenotype.

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S-I-08 Circulating tumor DNA in Genetic Profiling and Monitoring of Pediatric Hodgkin Lymphoma

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DOI 10.1055/s-0040-1701814

Introduction Hodgkin Lymphoma (HL) comprises 6% of all pediatric cancers. By using response-based therapies, the overall survival of HL is >90%; however, children remain at risk for long-term treatment-related morbidity. Currently, response to therapy in HL is assessed by PET-CT scan. However, a more sensitive and specific assessment method would have improved predictive value to more appropriately tailor therapy to prevent both relapse and long-term morbidity. We have developed an ultra-sensitive method for detecting circulating tumor DNA (ctDNA) called CAncer Personalized Profiling by Deep Sequencing (CAPP-Seq). CAPP-Seq uses selective sequencing of specific regions of DNA that are commonly mutated in a given malignancy to assess the presence and quantity of cell free DNA (cfDNA) that has tumor-associated mutations [1].

Methods For this study, we will use the CAPP-Seq selector that was developed for adult HL, which contains a library of genes curated using genomic studies of B-cell malignancies [1,, 2]. We will begin by performing CAPP-Seq analysis on a discovery set of 25 pediatric patients. We will extend to whole exome sequencing on a subset of patients to allow for the detection of additional mutations. We will use the results of this discovery set to refine our selector library and then expand our analysis to longitudinal ctDNA samples collected prospectively as part of the Pediatric Hodgkin Consortium cHOD17 study. Treatment response will be measured by fold ctDNA change from baseline. We will observe the dynamics of tumor response to treatment and correlate these to patient outcomes.

Results Preliminary results from a CAPP-Seq analysis on a cohort of 50 adult patients with HL undergoing treatment showed that ctDNA mean variant allele frequency (VAF) and mutation number did not differ between HL and other aggressive lymphoma histologies despite the relatively low presence of tumor cells in HL. CAPP-Seq was also used in genotyping single nucleotide variants and somatic copy number alterations. In longitudinal studies, patients with log fold decrease in ctDNA of 2 or greater after 2 cycles of chemotherapy had better outcomes [2,, 3].

Conclusion Targeted next-generation sequencing of ctDNA by CAPP-Seq allows for biopsy-free genotyping and disease monitoring in adults with HL. In order to demonstrate the fesability of this method in pediatrics, samples from pediatric patients with HL are currently being profiled and the results of the analysis will be presented at the meeting.

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S-II | Session II: Immune Checkpoint Inhibition and Drug Targets

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S-II-01 Introduction

DOI 10.1055/s-0040-1701816

S-II-02 Immune checkpoint inhibition in lymphoma

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DOI 10.1055/s-0040-1701817

S-II-03 Hodgkin lymphoma microenvironment: cross talk between HRS cells and the rosetting T cells

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DOI 10.1055/s-0040-1701818

Thieme

S-II-04 Interactive Case Presentation

DOI 10.1055/s-0040-1701819

S-II-05 Brentuximab Vedotin and Rituximab with Reduced Toxicity Chemotherapy in Children, Adolescents and Young Adults with Newly Diagnosed Hodgkin Lymphoma

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Conflict of Interest: The authors of the above mentioned abstract have no Conflict of Interest

Introduction Treatment regimens for Hodgkin Lymphoma remain limited by toxicity of chemotherapy and radiation [1,]. Immunotherapy has potential to reduce the burden of traditional treatment. Brentuximab Vedotin and Rituximab have both shown efficacy in Hodgkin Lymphoma [2,, 3]. We hypothesized that the addition of Brentuximab vedotin (Bv) and Rituximab (R) combined with risk-adapted chemotherapy will be well tolerated and effective in children, adolescents and young adults with all stages of newly diagnosed Hodgkin lymphoma.

Methods To evaluate the safety, tolerability and overall response rate of Brentuximab vedotin and Rituximab in combination with risk adapted chemotherapy in newly diagnosed Hodgkin Lymphoma. Patients 1-30 yrs with all stages newly diagnosed Hodgkin Lymphoma. Low risk given 3 cycles of Brentuximab with Doxorubicin, Vincristine, Prednisone and Dacarbazine. Intermediate and High Risk patients received 4 or 6 cycles of Brentuximab, Doxorubicin, Vinblastine, Dacarbazine and Rituximab. Early response measured by PET/CT scan. Slow responders received an additional 2 cycles of therapy. Radiation therapy given ONLY to patients with bulky disease at presentation and slow early response.

Results Total enrolled = 33. Median age = 15yr (range 4-23yr). Total 12 males, 21 females. Risk Assignment = 4 low, 17 intermediate, 12 high. Toxicity = 1 episode of GrIII mucositis, 1 episode of GrIII infusion reaction to Brentuximab, 2 episode GrIII peripheral neuropathy. All 33 patients achieved a complete response (100% CR). Twenty patients (61%) achieved a rapid early response. Four patients (only 12%) have required radiation therapy to date. Immune profiles at 18 month follow up show mean±SEM IgG level, CD19 and CD3 levels = 1097±63, 325±105, and 1273±290, respectively. No patient developed agammaglobulinemia or required hospitalization for systemic infection during or following treatment. The EFS and OS is 100% with a median follow up time of 4yrs (7-84 months).

Conclusion The addition of Brentuximab vedotin and Rituximab to combination risk adapted chemotherapy for newly diagnosed Hodgkin Lymphoma appears to be safe in children, adolescents and young adults. Our results show significant promise with a CR rate of 100%, 61% rapid early response and significant reduction in the use of radiation. The EFS/OS to date is 100% with a median follow up time of 4 years.

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S-II-06 Nivolumab monotherapy in childhood refractory and relapsed Hodgkin's lymphoma

Chairs Kozlov AV[1], Kazantzev IV[1], Iukhta TV[1], Tolkunova PS[1], Zvyagintseva DA[1], Gevorgian AG[1], Morozova EV[1], Schvecov AN[1], Baykov VV[1], Punanov YA[1], Mikhailova NB[1], Zubarovskaya LS[1], Afanasyev BV[1]
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DOI 10.1055/s-0040-1701821

Introduction Immune checkpoint inhibitors (ICIs) demonstrate substantial efficiency in Hodgkin's lymphoma (HL). Pembrolizumab was approved for the treatment of children with HL, but the role of other ICIs in pediatrics should only to be elucidated.

Methods Thirteen children and adolescents with refractory and relapsed (R-R) HL received nivolumab (nivo) monotherapy in Raisa Gorbacheva Memorial Research Institute of Children Oncology, Hematology and Transplantation, Pavlov First St. Petersburg State Medical University. Median age was 17 years (11 to 18). Histological forms of HL were as follows: nodular sclerosis was diagnosed in 11 patients (84.6%); mixed cellularity HL, 1 case (7.7%) and nodular lymphocyte predominant Hodgkin's lymphoma, 1 (7.7%). Median number of previous therapy lines was 4 (2-7) with autologous hematopoietic stem cell transplantation (HSCT) in 5 cases (38.5%). Prior to nivo therapy, 10 children (77%) had progression; 1 (7.7%), stabilization, and 2 (15.3%), partial remission according to Lugano criteria. Treatment schedule consisted of 3 mg/kg of nivo biweekly in 8 (61.5%) or 40 mg of nivo biweekly in 5 (38.5%). Median number of nivo cycles was 10 (5-24). Response to treatment was evaluated by the LYRIC criteria.

Results Nivo resulted in overall response of 92% (12 patients); complete response, in 61.5% (8), partial response, in 30.8% of cases (4) and indeterminate response, in 7.7% (1). Three-year overall survival (OS) was 100%. Progression free survival (PFS) rates according to Kaplan-Meier method at 1, 2 and 3 years were 80.8%, 69.3% and 34.6%, respectively. With median follow-up of 447 days (91-1137) nine patients (69.2%) remained in remission state. Median PFS was 30 months. Complications of nivo were registered in 1 adolescent (7.7%). This patient developed autoimmune thyroiditis which required hormone replacement therapy. It didn't lead to discontinuation of the drug. We did not observe any unacceptable toxicity of nivo.

Conclusion Nivo is effective in the majority of children and adolescents with R-R HL. However, many patients relapse after treatment. Therefore, it is important to improve the results by shifting to combination therapy, incorporation of ICIs earlier in treatment and consolidation with HSCT. Nivo is relatively safe with only one clinically significant adverse effect (autoimmune thyroiditis) observed in our study.

S-II-07 A randomized Phase III trial of Brentuximab vedotin (Bv) for de novo High-Risk Classical Hodgkin Lymphoma (cHL) in children and adolescents - Study Design and Incorporation of secondary endpoints in Children's Oncology Group (COG) AHOD1331

Chairs Castellino SM[1], Parsons SK[2], Pei Q[3], McCarten K[4], Kessel S[4], Punnett A[5], Horton TM[6], Henderson TO[7], Hodgson D[8], Dave H[9], Charpentier AM[10], Keller FG[1], Kelly KM[11]
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DOI 10.1055/s-0040-1701822

Introduction Among patients with high-risk cHL initial cure rates are suboptimal and rely on high cumulative doses of alkylating agents, anthracyclines and radiation therapy (RT). Our overarching goal is to improve disease control and minimize treatment burden by incorporating the targeted antibody drug conjugate Bv into the COG legacy chemotherapy backbone, thus facilitating omission of bleomycin and reduction of RT fields.

Methods Patients 2 to 21 years with newly diagnosed cHL of Stages IIB with bulk, IIIB, IV and adequate organ function were eligible for enrollment. Patients were randomized (1:1) to 5 cycles of either adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC) or Bv-AVEPC given on a 21-day interval compression schedule (NCT02166463). Response by FDG-PET after 2 cycles directed involved site RT (ISRT) based on central imaging review. Patients received GCSF support to neutrophil count recovery with each cycle. Protocol-prescribed dose reduction was designed to preserve Bv dose, based on mandatory clinical grading of peripheral neuropathy (PN) at each treatment cycle with the Balis Scale. The study has approximately 86% power to detect an 8% improvement in 3-year event-free survival (EFS) in the Bv arm with log-rank test. Secondary and exploratory endpoints include: characterization of pharmacokinetics of Bv in children < 13 years, expression of tumor-specific antigens and changes in immunogenicity, evaluation of reduction in normal tissue irradiation, patient-reported outcomes (PRO) of PN and health-related quality of life (HRQL), and assessment of resource use and cost.

Results 600 patients were enrolled across 192 COG institutions between March 2015 and August 2019.The PRO and cost effectiveness sub-studies met accrual of 310 in September 2017. PRO completion rates exceeded 90% throughout treatment and remain high through 36 months. Peripheral blood samples for immune function studies were received in 75% of patients. The majority of adverse events were as expected, associated with the known myelosuppression of the chemotherapy backbone. Stopping rules based on PN rates were never met.

Conclusion This trial will inform on the efficacy of Bv with a chemotherapy backbone other than AVD in pediatric patients with high-risk cHL, and on the impact of this targeted agent on important secondary outcomes including immune function, normal tissue volume reduction with ISRT, HRQL and cost-effectiveness.

S-II-08 Phase 2, open-label study of pembrolizumab in children and young adults with newly diagnosed classical hodgkin lymphoma (cHL) with slow early response (SER) to frontline chemotherapy: KEYNOTE-667

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DOI 10.1055/s-0040-1701823

Conflict of Interest: Dr. Mauz-Körholz declares no conflicts. Drs. Kelly Giulino have received research grants from Merck & Co., Inc., to their respective institutions. Drs. Keller and Ramchandren have received research funding from Merck & Co., Inc. Mr Nahar is an employee of Merck & Co., Inc., and may own stock in the company.

Introduction High risk for relapse is observed in cHL patients (pts) with SER to initial chemotherapy and organ toxicities may be higher following dose intensification.

Methods The phase 2 KEYNOTE-667 (NCT03407144) study will enroll 440 pts aged 3-17 (children) or 18-25 years (young adults) with newly-diagnosed, confirmed stage IA, IB, or IIA cHL without bulky disease (Group 1 [low-risk]) or stage IIEB, IIIEA, IIIEB, IIIB, IVA, or IVB cHL (Group 2 [high-risk]); measurable disease; performance status per Lansky Play-Performance Scale ≥50 (age ≤16 years) or Karnofsky score ≥50 (age >16 years). Pts will receive induction with doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD; Group 1) or vincristine, etoposide/etoposide phosphate, prednisone/prednisolone, doxorubicin (OEPA; Group 2) for 2 cycles, then early response assessment by PET/CT/MRI. Pts with rapid early response (Deauville score 1-3) will receive non-study consolidation chemotherapy. Pts with SER (Deauville score 4-5) will receive consolidation with pembro 2 mg/kg Q3W to 200 mg (children) or 200 mg Q3W (young adults) plus 2 cycles AVD (Group 1) or 4 cycles cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine (COPDAC-28; Group 2). PET/CT for late response assessment (LRA) will be performed after consolidation. After LRA, Group 1 SER pts and Group 2 pts (Deauville score 4-5) will receive radiotherapy (RT). All pts will receive maintenance pembro Q3W concomitantly with RT. Pembro will continue for 17 administrations, with option to stop after 8-administrations due to CR, or until progression, unacceptable toxicity, or withdrawal. Primary endpoint: ORR per Cheson 2007 IWG criteria by group in SER pts. Secondary endpoints: SERs with PET negativity after consolidation, 2-yr event-free survival (EFS), OS, RT frequency and details by group, RERs with PET negativity after ABVD induction, 3-yr EFS by investigator, OS by risk group, serum TARC levels at screening in SERs by risk group. ORR with 95% CI will be estimated by Clopper-Pearson method. EFS and OS will be estimated by Kaplan-Meier method. Safety will be assessed in all-treated pts.

Results N/A

Conclusion N/A

S-III | Session III: Global Experiences

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DOI 10.1055/s-0040-1701824

S-III-01 Evolution of CLEHOP as a Cooperative Group and its Experience with the Latin American LH Protocol

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DOI 10.1055/s-0040-1701825

S-III-02 Hodgkin lymphoma: Trials and tribulations in a middle income country. The first inclusive prospective paediatric cancer study in South Africa

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DOI 10.1055/s-0040-1701826

S-III-03 Interactive Case Presentation

DOI 10.1055/s-0040-1701827

S-III-04 Epstein Barr Virus in children and adolescents with classical Hodgkin Lymphoma: analysis of a cohort of 299 patients

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DOI 10.1055/s-0040-1701828

Introduction To analyse the Epstein Barr Virus (EBV) part in biological and clinical characteristics of patients treated for a classical Hodgkin lymphoma (cHL) in France.

Methods Biopathological datas were centrally reviewed in 299 patients with cHL. Patients were treated in or according to the Euronet PHL-C1 trial between November 2008 to February 2013.

Results Median age at diagnosis was 14 [3-18], F/M ratio was 0,84; 0,47 between 3 to 10 years, and 0,9 from 11 to 18. CHL subtypes were nodular sclerosis (cHL NS) 265/299 (88,6%), mixed cellularity (cHL MC) 22/299 (7,4%), lymphocyte rich 2/299 (0,7%) and 10/299 (3,3%) were unclassified. 68/299 (22,7%) present a cHL EBV+, significantly more frequent in 3-10 years patients n=17/34 (50%), than in >11years n=51/265 (19,2%) p<0,001, and in cHL MC subtype n=15/22 (68,2%), than in cHL NS subtype n=49/265 (18,5%) p<0,001. EBV serology was recorded in 100/299 (33,4%) cases. Anti VCA-IgG were positive in 70/100 (70%) cases, anti EBNA-IgG were positive in 61/100 (61%) cases, and anti VCA-IgM were positive in 5/100 (5%) cases. In EBV+ cases, 22/23 (95,7%) were VCA-IgG+ (p=0,002), 19/23 (82,6%) were EBNA-IgG+ (p=0,01), and 2/23 (8,7%) were VCA-IgM+ (p=0,3). EBV PCR was recorded in 108/299 (36,1%) cases, and was positive in 22/108 (20,4%). In EBV+ cases, 13/28 (46,4%) had a PCR+ (p<0,001). No significant difference in sex distribution (p=0,12) and staging disease (p=0,84) was present in cHL EBV+/- . Immunostaining was: 284/284 (100%) CD30+, (no data for 15 patients); CD15 was + 242/284 (85,2%) cases and 55/62 (88,7%)in cHL EBV+ (p=0,38). CD20 was + 62/287 cases (21,6%) and 15/63 (23,8%) in cHL EBV+ (p=0,23). PAX5 was + 211/255 (82,7%) with cHL EBV+ 44/52 (84,6%) (p=0,69). Overall, no significant differences between immunostaining in cHL EBV+and negative distribution has been highlighted. No significant difference in overall survival (p=0,35) and event free survival (p=0,9) has been raised between EBV positive and negative population.

Conclusion In this cohort of 299 French children and adolescents with cHL, cHL MC subtype is present in only 12.4%. EBV cHL represent 22,7% of our cohort and is significantly associated with young age and cHL MC, without survival or relapse impact. Although EBV in cHL is well-known, EBV immune role in HL pathology need further research.

S-III-05 Lymphocyte-Predominant Hodgkin Lymphoma Variant: Long Term Outcome. Data From The Lh-2004 Protocol Of The Italian Association Of Pediatric Hematology And Oncology (Aieop)

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Introduction Lymphocyte-predominant Hodgkin lymphoma (LPHL) is a distinct lymphoid malignancy accounting for approximately 5% of all patients with HL. The clinical course is usually indolent, and most patients are diagnosed with early-stage disease. Because of the rare nature of the disease, few large-scale studies are available.

Aim of the study to evaluate the long term outcome of patients with LPHL enrolled in the AIEOP-LH 2004 protocol that represents the 4th Italian protocol for the pediatric HL therapy.

Methods This is a retrospective study. Patients were stratified in 3 risk groups: low risk G1 (stage I-IIA without: M/T ≥0.33 or ≥4 nodal sites or hilar adenopathy), intermediate risk G2 (patients not included in G1 and G3) and high risk group G3 (stages IIIB-IV and patients with M/T ≥0.33). GR1: 3 ABVD+25,2 Gy only to PR after CT. GR2: 4 COPP/ABV+14,4 Gy if CR achieved; PR pts received 2 cycles of IEP (Ifosfamide, Etoposide and Prednisone) and RT (14,4 Gy if CR, 25,2 if PR). GR3: 4 COPP/ABV and 2 further COPP/ABV+RT if CR was achieved. PR pts: 2 IEP+14,4 Gy if CR was obtained; if not, pts received 2 additional COPP/ABV+RT according to the quality of response.

Results From June 2004 to June 2017, 89 patients with LPHD were enrolled into the protocol, 61 in G1, 19 in G2 and 9 in G3. The stratification according to stage is: 23 pts stage I (no pts with B symptoms), 47 stage II (46 IIA, 1 IIB), 17 stage III (14 IIIA, 3 IIIB), 2 stage IV (1 IVA, 1 IVB). Patients were mostly male (83,5%). The median age at diagnosis was 11,9 years. The median observation time of follow up was 8,41 years. Mediastinal involvement occurred in 12/47 stage II pts, in 6/17 stage III and in 2/2 stage IV. Bulky disease was observed in 3 pts, all in stage II. Radiotherapy was performed in 41/61 pts of G1 patients. 11 relapses and 3 progressions of disease were registered; no case of second malignancy or death occurred. 8 pts were lost to follow-up. Median time to relapse was 3,06 years. The Event-Free Survival at 10 years of LPHL patients is 83,1% versus 78,25% of classical HL patients (p=ns).

Conclusion LPHL behaves as a distinct clinical entity, often in low stage without risk factors, with a good outcome, better than classical HL. For these reasons LPHL requires its own treatment approach, guided by various clinical and pathological factors, to optimize the management and improving their outcome.

S-III-06 The GATLA (Argentinian Collaborative Group) experience through international cooperation in Pediatric Hodgkin Lymphoma (HL)

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DOI 10.1055/s-0040-1701830
Conflict of Interest: The authors have no conflicts of interest.

Introduction The GATLA Cooperative Group has a 50 year (y) long experience of running cooperative trials for lymphomas in Argentina. Our aim is to describe the outcome of pediatric patients treated according to the international AHOPCA/GATLA strategy (11-EHP-12) adopting OEPA/COPDAC for high Risk (HR) and ABVD for Intermediate (IR) and Low Risk (LR) patients.

Methods 11-EHP-12: Risk assignment according to the Stanford/Danna-Farber/SJCRH consortium classification. LR: ABVD x 4 ± 20 Gy IFRT; IR: ABVD x 6 ± 20 Gy IFRT; HR: OEPA-COPDAC + 20/25 Gy IFRT. Response evaluation: LR after 4th cycle, IR and HR after the 2nd cycle. Complete Remission (CR): > 80% reduction and negative PET. Partial Remission (PR): >50% and <80% reduction and/or positive PET. 170 pediatric patients were enrolled since November 2012. 133 evaluable patients with 37 on treatment and/or follow up of less than 5 years. Sex: M/F: 85(64%)/48.Median age: 13 y (4-18 y). Histology: nodular sclerosis 91 (68%), mixed cellularity 31 (23%), lymphocyte rich 1 (0,7%), lymphocyte depleted 1 (0,7%), nodular lymphocyte predominant 8 (7%). Stage: I: 16 (12%), II: 51 (38%), III: 27 (20%), IV: 39 (29%). B Symptoms: 66 (50%). Distribution by risk groups: 77 (58%) HR, 35 (26%) IR, 21 (16%) LR. Only 109/133 (82%) patients had an interim PET, while 14 were evaluated only by TC.

Results 5y-OS was 94% (100% for LR and IR, and 91% HR) and 5y-EFS was 88% (100% for LR, 91% IR, and 84% HR). 95% of LR and 72% of the IR patients did not undergo radiotherapy; 70% of HR patients achieved CR after the 2nd OEPA and received 20 Gy IFRT. According to PR or CR after 2nd OEPA, the 5y-EFS for HR patients was 84% and 90% respectively.

Conclusion Thanks to this international cooperation we could significantly improve the results in Argentina compared to our previous experience (7-PHD-96: COPP-ABV x 6 + IFRT Bulky disease or PR (20/25Gy): 5y-OS 85%, 5y-EFS 67%), and reduce the number of patients who required radiotherapy as we reproduced the EuroNet experience for HR patients in a different context.

S-III-07 Assessment of Epstein-Barr Virus (EBV) status and its impact on outcomes in intermediate and high-risk childhood classic Hodgkin Lymphoma (cHL) treated at a tertiary cancer center in India

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Conflict of Interest: No conflict of interest

Introduction The prevalence of EBV positivity in childhood cHL in India has ranged from 60% to >95% in most studies which has mainly looked into the epidemiology of EBV positive(EBV+HL) and negative HL(EBV-HL), with limited data on outcomes.(1-4)We studied the EBV status of a large cohort of cHL patients and its impact on outcomes.

Methods Children(<15years) with cHL from July-2013 to December-2016 were retrospectively analyzed. EBV status was assessed by EBV LMP1 on immunohistochemistry performed on excision or trucut biopsy specimens. Staging was by Positron emission computerized tomography(PET-CT) with IAX,IBX,IIAX,IIE,IIIA assigned as Intermediate-risk(IR) and IIBX,IIBE,IIIX,IIIE,IIIB, IV High risk(HR). Patients received 2 cycles OEPA(vincristine,etoposide,prednisolone,doxorubicin) followed by early PET-CT. Complete metabolic responses(CMR) received 2 cycles COPDac(cyclophosphamide,vincristine, prednisolone,dacarbazine) for IR, and 4 for HR. Bulky sites(X) at baseline received involved field radiation(IFRT) post-chemotherapy.

Results Of the 107 eligible patients, EBV status was available in 85 patients with a M:F of 6.7:1 who were analyzed. Sixty-five patients had EBV+HL (76.5%) and 20 had EBV-HL(23.5%). B symptoms, bulky disease, histology, risk, bone-marrow disease, hemoglobin, serum albumin, LDH were not significantly different among the two groups. EBV+HL was significantly associated with age ≤10 years(p=0.03), bulky mediastinal disease(p=0.001) and early PET morphological CR(p=0.04), but not metabolic CR and showed a trend towards more incidence in males(p=0.06).

At a median follow-up of 28-months (range, 6-56 months), 3-year Event-Free Survival(EFS) and Overall Survival(OS) of the entire cohort was 88(95% CI:81%-95%) and 90.4%(95%CI:84%-97%), and of EBV+HL and EBV-HL were 90.7%(95%CI:84%-98%), 92.3%(95%CI:86%-99%) and 79.1%(95%:61%-98%), 84.1%(95%CI:68%-100%)(p=0.18,p=0.32) respectively. In EBV+HL, 3-year EFS and OS was significantly associated with gender, 94.9% in males vs 50% in females(HR-0.08,95%CI:0.017-0.415,p=0.002) and 94.9% vs 66.7%(HR-0.135,95%CI:0.023-0.810,p=0.028) respectively. In EBV-HL, 3-year EFS was significantly associated with early PET CMR(p=0.045) and OS showed a trend towards worse outcome in patients with serum albumin ≤3g/dl (p=0.06).

Conclusion EBV drives most of the intermediate and high risk childhood cHL, occurs in younger patients, and results in bulky mediastinal disease. Though overall outocmes were good, EBV+HL adversely impacted survival in females.

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S-III-08 Pediatric Hodgkin lymphoma: Characteristics, stratification,treatment and survival at a single institute in Lima-Perú.

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DOI 10.1055/s-0040-1701832
Conflict of Interest: no conflicts of interest

Introduction Lymphomas represent fourth most commom cancer in peruvian children (10% of all cases).Currently, different cooperative groups are reducing intensity of chemotherapy and radiotherapy with intension to improve survival and reduce sequelae. Limited data such as information on epidemiology and survival are available in peruvian pediatric population .This study aimed to describe clinical, histological characteristics, risk group distribution and survival in pediatric Hodgkin lymphoma(HL) patients

Methods Children (≤14 years old) diagnosed with histologically proven HL from 2009 to 2015 were retrospectively analyzed. . The Kaplan-Meier survival curves were used for survival analysis.

Results 117 patients were enrolled; predominantly male 3:1, mean age of 7.3 years, range 3 to 14 years and 72 % came from outside Lima. Disease time has a mean of 8 months, B symptoms were present in 45 %, 51.6% has bulky mass, primary site was neck in 47%, 52.8% of the patients were at high risk group. The histopathological diagnosis was mixed celular type in 52.9% and nodular sclerosis in 19.5% of the patients,64.9% express latent membrane protein 1 (LMP1) by inmunohistochemestry. We used ABVD chemotherapy to treat low/intermedate risk and ABVD/COPD for high risk group, 68% has good early response, 80% of slow early responders receive radiotherapy at mean dose 2600 cGy, 18.8% of patients left therapy, 11.7% relapse. With a median follow-up of 24 months, the 5-year overall and event-free survival rates were 94.2% and 92.7% respectively (abandonment is not included). Sex, treatment risk groups, presence of B symptoms, bulky mass and histology type had no significant effect on overall survival.

Conclusion Advanced disease, bulky mass, B symptoms, EBV expression and mixed celular histology are main characteristics in peruvian HL. We must to improve education and follow up to reduce high abandonment rates.

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S-III-09 Clinical course and prognosis of children with Hodgkin Lymphoma in Central and Southern Mexico areas. Results of the Mexican Association of Pediatric Hematology and Oncology

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DOI 10.1055/s-0040-1701833
Conflict of Interest: I declare any conflict of interest

Introduction In developed countries, the survival of children with Hodgkin Lymphoma is very high, the treatment according to risk groups has been able to reduce toxicity and long-term sequelae. Objective: To know the clinical course and prognosis of pediatric patients with Hodgkin Lymphoma at the central and southern areas from Mexico.

Methods We Included in a cohort, clinical records of pediatric patients with Hodgkin Lymphoma. Diagnosed and treated in 14 hospitals of the south and center zone. We analyzed clinical variables, demographics, histological variety, primary site, treatment scheme used, survival and the related factors.

Results 359 patients were assessed, 242 Male and 117 females, aged from 2 to 17 years average of 10±2 years old, primary site 78% cervical, followed by mediastinum, 60% with histological variety nodular sclerosis. 67% presented Symptoms B. The risk allocation was 15% low, mean 37% and high 57%. 90% treated with national protocol based on ABVD/CVPD, more radiotherapy to compromised fields. Presented Relapse 8%. The survival reported was 93% to 5 years for all patients. The variables that influenced the prognosis were the presence of symptoms B and stage of the disease, was performed TPH in 7 patients. Deaths were attributed in 50% to toxicity related to treatment. There were significant differences in the survival of patients in the south and center area, for stages III and IV with 50% vs. 75 % to 5 years respectively.

Conclusion In Mexico, multiple factors influence the results of treatment of children with cancer, in this series most of our patients are of high and intermediate risk, the presence of B symptoms and advanced stage to the diagnosis, involve a late diagnosis which are determinants in the survival. Multiple social and cultural circumstances can explain the discrepancy in the results of treatment in the different regions of our country.

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S-IV | Session IV: International Trial Workshop

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S-IV-01 Global nLPHL trial proposal

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DOI 10.1055/s-0040-1701835

S-IV-02 Proposal for a global Grey Zone Lymphoma Registry

DOI 10.1055/s-0040-1701836

S-IV-03 Regulatory Aspects roundtable discussion

DOI 10.1055/s-0040-1701837
Ways to improve PIP requirements/inform better study development

- Representatives of:
  - European Medicines Agency (EMA), Amsterdam, The Netherlands
  - Food and Drug Administration (FDA), USA
  - Pharmaceutic industries, USA, Europe,
  - China Net Childhood Lymphoma (CNCL) group Beijing, China

PW I-V | Guided Poster Walk

DOI 10.1055/s-0040-1701838

PW I-V-01 3′ untranslated region A>C (rs3212227) polymorphism of Interleukin 12B gene as a potential risk factor for Hodgkin's lymphoma in Brazilian children and adolescents

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Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Introduction Natural Killer (NK) cells represent a key component of the innate immune system against cancer. It was observed that patients with Hodgkin's Lymphoma (HL) exhibit inactivated peripheral NK cells due to high serum levels of MHC class I ligands for the Natural Killer Group 2D (NKG2D) protein. According to the literature, inactivation of NK cells may be associated with NKG2D blockade by these ligands, and consequently may interfere on your antitumor function. On the other hand, expression of NKG2D can be regulated by cytokines, such as IL-12. IL-12 plays an important role in immunoregulation between the Th1/Th2 helper lymphocytes and in the antiviral and antitumor immune response. The aim of the present study was to investigate the possible association between the interleukin 12B polymorphism rs3212227 and the risk to develop HL in childhood and adolescents.

Methods A total of 100 patients with Hodgkin's lymphoma and a group of 181 healthy controls aged 0 to 19 years were selected. DNA extraction from peripheral blood was performed by the ''Mini Salting out'' method. Genotyping was determined using Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR-RFLP). The 118 bp PCR product was digested by the enzyme TaqI (10 U/mL) for 4h at 65°C. Data analysis was performed using the BioEstat 5.0 program. The associations were considered significant when $p<0.05$.

Results The AA genotype was the most frequent in the controls (53.04%) and the AC genotype was the most frequent in the patients (54%). The AC genotype showed an association with the development of HL (OR = 2,091, 95% CI = 1,240-3,523, $p = 0.007$). When AC + CC genotypes were analyzed together, an increase in risk of 1.9 times more chances for HL development could be observed (OR = 1,923, 95% CI = 1,166-3,170, $p = 0.014$). However, there was no association between the AC and CC genotypes of the *IL-12B* polymorphism with the clinical risk group ($p = 0.992$, $p = 0.648$, respectively).

Conclusion Our results suggest that the presence of the C allele may be contributing to the development of HL in children and adolescents. Thus, the identification of this

polymorphism may help in the stratification of patients with HL according to the risk for the disease. This is the first study to analyze this type of association in children and adolescents with HL in Brazil. However, other studies in other populations are important to investigate this association, since the antitumor mechanisms of this interleukin are not yet fully understood.

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PW I-V-02 Assessment of tumor antigen specific T cell immunity and cytokine milieu at diagnosis in patients with high risk Hodgkin Lymphoma treated on Children's Oncology Group trial AHOD1331

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Conflict of Interest: No disclosures

Introduction The role of the immune system and the microenvironment in classical Hodgkin Lymphoma (cHL) has been established. However, little is known about the baseline plasma cytokine profile and tumor antigen specific T cell responses in pediatric and adolescent and young adults (AYA) patients. We examined the feasibility of evaluating tumor specific T cell responses and cytokines at diagnosis in children and AYA on a Phase III trial.

Methods AHOD1331 (NCT02166463) randomized newly diagnosed high risk cHL patients 2-21 years of age to standard or brentuximab containing chemottherapy. Between March 2015 and August 2019, peripheral blood was obtained at baseline from 441 of the 600 enrolled patients. Mononuclear cells and plasma were isolated within 24-72 hours of blood collection using Ficoll Density gradient and cryopreserved. Non-adherent T cells were stimulated *ex vivo* with autologous dendritic cells pulsed with HL specific pepmixes for the tumor associated antigens (TAA) MAGEA4, PRAME and Survivin and cultured in the presence of cytokines. T cell specificity to the TAAs was tested using Interferon-γ ELISPOT assay and considered positive if the number of spot forming counts (SFC) per 10^5 T cells was twice that of the control (Actin). Plasma samples were tested for 17 inflammatory cytokines using Luminex assay. Baseline immune response and cytokine levels were compared in univariate analysis for: age, gender, stage, B symptoms, bulk, EBER status and large mediastinal adenopathy.

Results In the 72 patients evaluated to date for tumor antigen specificity, in vivo T cell responses were detected to at least one of the three non-EBV tumor associated antigens in 58%. The mean SFC/ 10^5 T cells for MAGEA4, PRAME and Survivin was 6.2 (95% 2.7-9.7), 13.2(95% CI 4.2-16.3) and 5.9 (95% CI 2.4-9.5) respectively. T cell responses were associated with age >12 years(p=0.01) and higher stage (p=0.04).To date, 167 baseline plasma samples have been analyzed. Interleukin-10 was significantly elevated in patients < 12 years of age compared to >12 years(p=0.04) and mean Interleukin-5 levels were higher in patients without bulky disease (p=0.02).

Conclusion T cell responses to TAAs can be detected in patients with HL at diagnosis and differ by patient and disease factors. We are currently completing the cytokine analysis and T cell responses on all the patient samples received to date. Once completed, our study will provide baseline immune markers on one of the largest cohort of pediatric and AYA patients with HL.

PW I-V-03 The prognostic value of HLA-G genetic marker in paediatric Hodgkin lymphoma patients enrolled in the italian AIEOP-LH2004 trial

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Introduction We found HLA-G+3027 single nucleotide polymorphism (SNP) as a potential negative prognostic marker in pediatric Hodgkin lymphoma (HL) patients treated according to LH-2004 protocol[1]. However, its association with poor outcome could be validated. Our aim was to support the role of HLA-G+3027 in LH-2004 long term study and in association with hematochemical markers.

Methods The study included 104 HL patients, age range 3 to 18 years (y), who received LH2004 treatment. We identify 28 relapsed/progressive patients (26.9%), with a mean time of event 1.45 y ±SD1.14. Median follow up 5.16 y ±SD3.96. Analyses were conducted on even free survival (EFS) and overall survival (OS) based on the therapeutic risk groups (TG), histological classification, gender, HLA-G+3027 SNP, and hematochemical test (VES, albumin, ferritin, Hb, WBC, neutrophils, eosinophils, basophils, lymphocytes, monocytes, LUC, platelets) values at the time of diagnosis[2].

Results The mean age of the patients was 13.08 y ±0.32, 37.5% were female. Groups of algorithm (GR) combining HLA-G+3027 with TG (Y=-3.94+1.36 C/A +0.94 TG) was able to better identify patients with an inferior EFS (mean time at relapse/progression 7.69y ±SE1.76, 12.70y ± SE1.05, 14.5y ±SE0.50, for GR3, GR2, GR1, respectively, *p=0.0073)* than GT alone (12.63±SE1.0, 10.99y ±SE0, 13.46y ±SE1.03 for TG3, TG2 and TG1, respectively *p=0.015).* The cutoff value of GR was found as >-2.06, *p=0.0013.* The decrease lymphocyte value at the time of diagnosis was significantly related to the algorithm, r -0.475, p<0.0001 and with poor prognosis (EFS r=0.39, *p=0.0389).* Multivariate analysis for OS revealed mixed-cellularity histological subtype and increased platelets value as two worse independent factors (stepwise, *p=0.029).*

Conclusion Our findings show that including HLA-G+3027 SNP value in the TG score increases the prognostic EFS significance in a long follow-up of LH-2004 trial. An indication of an association between the lower number of lymphocyte cells at diagnosis and the GR with EFS was seen. Both histological classification and platelets counts were independent factors associated with OS.

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PW I-V-04 TARC is a specific and sensitive serum marker for classical Hodgkin's lymphoma in children

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Conflict of Interest: No conflict of interest.

Introduction Pediatric classical Hodgkin's lymphoma (cHL) is characterized by Hodgkin Reed-Sternberg (HRS) cells located in an inflammatory microenvironment. HRS cells and microenvironment communicate through active crosstalk. This results in secretion of blood biomarkers, which may serve as surrogate markers for lymphoma viability [1,, 2,]. One promising biomarker in adult patients with cHL is "Thymus and Activation-Regulated Chemokine" (TARC) [3,, 4]. So far, TARC levels in pediatric cHL patients have not been reported. The objectives of this study were to investigate TARC as a diagnostic marker in pediatric cHL patients and to define normal TARC values in non-cHL children.

Methods In thismulti-center prospective study, plasma and serum samples were collected of newly diagnosed cHL patients before start of treatment (n=43). To define normal values of TARC in children, samples were collected from non-cHL randomly selected patients from different outpatient clinics (n=80). TARC levels were measured by enzyme-linked immunosorbent assay (R&D systems, Human CCL 17/TARC Quantikine ELISA Kit). TARC levels of the cHL patients were compared to the non-cHL group to obtain ROC curves and calculate the AUC, to assess sensitivity and specificity and accuracy of TARC as a diagnostic marker. In addition, we assessed the association between TARC levels and disease characteristics.

Results The non-cHL patients had a median plasma TARC value of 71 pg/mL (range 18-762), compared to 13984 pg/mL (range 197-73174) in cHL patients (p<0.001). Serum TARC levels were 317 pg/mL (range 27-1300) in non-cHL patients versus 31110 pg/mL (range 826-176451) in cHL patients (p<0.001). For plasma, with a cut-off level of 942 pg/ml, TARC level provides a sensitivity of 98% (95% CI 88%-100%), specificity of 100% (95% CI 95%-100%). The area under the curve (AUC) was 0.999 (95% CI 0.998-1). For serum, with a cut-off level of 1300pg/ml, sensitivity was 97% (95% CI 85-100%), specificity 99% (95% CI 93%-100%), AUC 0.998 (95% CI 0.994-1). TARC levels were associated with treatment level according to the EuroNet-PHL-C2 protocol, bulky disease, the presence of B-symptoms and with ESR. TARC levels were not associated with Ann Arbor staging and CRP levels.

Conclusion TARC was found to be a specific and sensitive diagnostic marker for pediatric cHL. Moreover, this non-invasive marker could be of great value as screening test in the diagnostic work-up for pediatric patients with enlarges lymph nodes.

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PW I-V-05 Comparative proteomic profiling in recurrent pediatric/adolescent Hodgkin Lymphoma

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Introduction Inpediatric/adolescent Hodgkin lymphoma (HL) the discovery of protein(s) specifically associated with the presence/absence of relapse may contribute to optimize therapeutic approaches.

Methods Liquid chromatography-mass spectrometry (LC-MS) label-free quantitative proteomics on plasma collected at diagnosis from pediatric/adolescent HL patients was adopted firstly to validate a set of biomarkers predicting disease relapse, and secondly to identify additional candidate protein panels for disease relapse. Protein profiles of 3 not relapsing (NR) HL patients were compared with those of 3 relapsing (R) ones treated with LH-2004 protocol in one 'explorative' and two 'validation' cohorts.

Results The LC-MS approach validated some differential proteins we previously identified by Differential In Gel Electrophoresis (SERPINC1, SERPINA1, FGB and FGG) [1]. In each protein group belonging to either NR or R patients, bioinformatics functional enrichments showed several biological processes, which were manually grouped into 9 'biological classes'. The differential proteins were involved in several biological processes related to either the absence (e.g., regulation of protein metabolism, response and haemostasis) or the presence of relapse (e.g., immune system and cell and extra-cellular matrix architecture). Moreover, additional proteins were found as up-regulated in either NR or R plasma of HL patients, and data were validated with Western Blotting.

Conclusion Overall, our data depict a part of the different molecular scenarios occurring at diagnosis in plasma of HL pediatric/adolescent patients that could affect their different responses to therapy, and provide new evidence about these protein panels as promising biomarkers of relapse in HL pediatric/adolescent disease. Further studies are underway in the EURONET-PHL trial of pediatric/adolescent patients.

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PW I-V-06 Cell-free DNA as biomarker in Hodgkin lymphoma patients

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Introduction Treatment failure or relapse occurs in approximately 10% of early stage Hodgkin lymphoma (HL) patients and 20% of patients who have advanced stage HL. Identifying this group of refractory and relapsed HL patients is crucial in order to plan for effective first line treatment. Considering that genomic aberrations can be readily detected in cfDNA, this method may allow for a non-invasive method of monitoring disease load and serve as a prognostic marker. We aimed to study the genomic profile of HL and correlate these findings to the levels of the circulating biomarker TARC and to other clinical characteristics.

Methods Cell-free DNA was isolated from 1-2 ml of plasma with the QIAamp Circulating Nucleic Acid kit according to manufacturer's protocol. A targeted panel was designed including 46 genes commonly mutated in B cell lymphoma, genomic regions of immunoglobulin gene loci, MYC, BCL2 and BCL6 to detect chromosomal breaks and part of the EBV genome. Deep targeted sequencing (DTS) was performed with two hybrid capture-based next generation sequencing platforms, namely SureSelect$^{XT\ HS}$ Target Enrichment System and Twist Custom Panel Multiplex Hybridization Kit. Prior to target enrichment, a small fraction of the indexed libraries was aliquoted for low-pass whole genome sequencing (LP-WGS) to check for copy number aberrations (CNAs). Variant calling was performed with SNPPET SNP caller using SureCall Software. The R package, CNAclinic was used for CNAs analysis.

Results The total yield of cfDNA ranged between 23-429 ng (median 100 ng). There was no significant correlation between cfDNA levels and TARC in this cohort. Using an input varying between 18 and 124 ng, we successfully generated libraries for NGS. Copy number aberrations were detected in four out of eleven samples. In vitro size selection of cfDNA fragments <150bp to enrich for tumor cell derived DNA, resulted in detection of CNAs in three additional samples. Variant calling with SNPPET SNP caller, revealed a median of 130 variants after filtering out common variants (allele frequency (AF) >1% in 1000 Genomes). Hotspot mutations in STAT6 were detected in two HL samples and in one of these two samples we also observed a XPO1 E571k hotspot mutation. These mutations were validated by ddPCR in diagnostic FFPE tissue samples of the two patients.

Conclusion Despite the low percentage of tumor cells in HL tissue samples, somatic mutations with AF as low as 0.5% were detected in cfDNA using a minimal input of 18ng.

PW I-V-07 Expression of splice variants of the transcription factor ONECUT2 in Hodgkin lymphoma cells

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Introduction Like other members of the ONECUT family of transcription factors, ONECUT2 is characterized by the simultaneous presence of one CUT domain and one HOX domain. We discovered a new transcript variant of ONECUT2 in a cDNA library [1] from the Hodgkin lymphoma (HL) cell line L-

1236. This variant (ONECUT2s) uses an alternative second exon compared to the reference sequence.

Methods Expression of ONECUT2 and ONECTUT2s in different tissues and cell lines was assessed by quantitative real-time polymerase chain reaction (qRT-PCR). ONCUT2 specific siRNA was used for knock-down in HL cell lines. In addition, ONECUT2 and ONECUT2s were cloned into eukaryotic expression plasmids. Expression of ONECUT2/ONECUT2s in transfected cells was detected by immunofluorescence. RNA from transfected cells was analyzed by DNA microarray analysis.

Results The expression analysis indicated high expression of ONECUT2 and ONECUT2s in HL cell lines as well as in normal liver. The majority of normal tissues and cell lines expressed only low levels of ONECUT2 and ONECUT2s. In contrast, the cell lines Kasumi-1 and HL-60 as well as normal testis showed high expression of ONECUT2s only. We observed that knockdown of ONECUT2 lead to decreased ONECUT2s expression whereas transgenic overexpression of ONECUT2 had no impact on ONECUT2s. Interestingly, overexpressed ONECUT2 was located predominantly in the cytoplasm and not in the nucleus. By transgenic overexpression or knockdown of ONECUT2 and subsequent DNA microarray analysis we identified potential new ONECUT2 target genes.

Conclusion The data suggests that ONECUT2 as well as ONECUT2s play important roles in the gene regulation of HL cells. The fact that the transcription factor is not only located in the nucleus but predominantly in the cytoplasm suggest additional functions besides transcriptional activation.

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PW I-V-08 Increased Expression of Matrix Metalloproteinases 2 and 9 as Poor Prognosis Factor for Hodgkin's Lymphoma Patients

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Introduction Matrix metalloproteinases (MMPs) are zinc dependent endopeptidases that act on both renewal and remodeling of the extracellular matrix. Increased expression of these proteins is associated with neoplastic, invasive and metastatic processes. Studies show that in Hodgkin's Lymphoma (HL), strong expression of metalloproteinase 2 (MMP-2) correlates with a favorable prognosis, while expression of metalloproteinase 9 (MMP-9) showed an adverse outcome. Therefore, the aim of our study was to evaluate the expression of MMP-2 and MMP-9 as a prognostic factor in patients diagnosed with HL.

Methods In the present study, 45 paraffin biopsies from patients up to 19 years old diagnosed with HL were used in two referral hospitals in the state of Pernambuco, Brazil. The immunohistochemistry reaction used primary monoclonal antibodies directed to matrix metalloproteinases (MMP-2 and -9) to detect such proteins in the tumor microenvironment.

Results MMP-2 intensity pattern was stronger (> 10% of total field) in patients with stage III/IV and B symptoms. MMP-2 x Risk group showed significant value *(p=0,0388)*. That is, the stronger the MMP-2 marking, the greater the unfavorable risk. However for MMP-9 there was no difference in the stronger intensity pattern in relation to stages I/II and III/IV, only in the presence of symptoms B. The criterion MMP-9 x Symptoms B showed significant value *(p = 0.0411)*. Therefore, patients with B symptoms have higher MMP-9 expression.

Conclusion Thus, we believe that both MMP-2 and MMP-9 can be considered poor prognostic molecules for Hodgkin's lymphoma and the that RNA expression evaluation could confirm the results.

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PW I-V-09 HLA haplotype on outcomes in pediatric Hodgkin patients enrolled in the italian AIEOP-LH2004 trial

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Introduction The human leukocyte antigen (HLA) class I and class II genes are highly polymorphic and proteins encoded by them play an important role in self/non-self immune recognition. The identification of causal variants that modulate the susceptibility to a large number of infections and disease is

problematic due to linkage disequilibrium (LD) that extends both across multiple HLA genes and non HLA genes. In a previous study evaluating polymorphic sites 3′ Untranslated region (UTR) HLA-G and Hodgkin disease (HL) in pediatric patients, we found the positive association between +3027-A frequencies and progression/relapse. In order to investigate the relationship between 3′UTR HLA-G and negative treatment outcome, the extended HLA haplotypes were analyzed.

Methods DNA from 113 pediatric HL patients (27 with progression/relapse (P/R)) treated using the AIEOP LH-2004 protocol were typed for HLA-A, HLA-G, HLA-F and HLA-E. In addition, two probes located in 3′UTR HLA-F (rs1633096) and near the HLA-DRA region (rs6903608) were studied. For allele frequency and epitope analysis the SKDM HLA Tool beta was used. The results are shown as *P*-values and odd ratios (OR) in the text.

Results Our data showed the presence of a LD block within the HLA class I region. The haplotype was composed of HLA-A*11, HLA-G*01: 01: 03 with +3027-A and HLA-F*01: 01: 02 with an alternating presence of the two HLA-E alleles (E*0101 or E*10103). The comparison of HLA-A allele frequencies between patient P/R and HL showed an association between HLA-A*11 with progression/relapse. Moreover, the alignment of the amino acids (AA) composing the anchorage pocket of the epitope from the most represented HLA-A alleles showed a Tyrosine (Y) in position 9 in P/R patients (Y9, *P*=0,002674, OR=5,443). The presence of AA Y9 was statistically linked to the condition of heterozygosity and to the female gender (*P*=0,0045, OR=6,28; *P*=0,006222, OR=15,923 respectively). In a preliminary analysis of the class II marker, the rs6903608 T/C an association of the C allele with HL was observed suggesting that the HLA haplotype block structure could be further determined.

Conclusion We demonstrated that the HLA haplotype HLA-A*11, HLA-G*01: 01: 03 with +3027-A and HLA-F*01: 01: 02 was associated with progression/relapse in pediatric HL patients treated with the AIEOP LH-2004 protocol especially in female gender, however larger prospective studies will be necessary to confirm this relationship.

PW I-V-10 Expression of human endogenous retroviruses and associated transcripts in Hodgkin lymphoma cells

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Introduction During human evolution, germline infections by retroviruses have repeatedly occurred, integrating viral DNA into the host genome. As a result, the human genome consists of approximately 8% human endogenous retroviruses (HERV). Although most of this viral DNA is defective due to mutations, there are sequences with intact open reading frames for the generation of viral transcripts and proteins. In Hodgkin lymphoma (HL) the activation of HERV loci and expression of related transcripts has been observed.

Methods In order to characterize HL-associated HERV sequences that might play a role in HL biology we analyzed cDNA libraries, DNA microarray data and RNA sequencing data from HL cell lines. With different molecular-biological and computational approaches [1,–4] we identified expressed HERV loci that might be relevant for the origin of HL.

Results We observed increased transcriptional activity of several HERV related sequences in HL cell lines. Among these sequences, we discovered a new HERV-related transcript derived from the chromosomal region immediately upstream of the colony stimulating factor 1 (CSF1) region. The first exon of this Transcript From HL Cells (THOLE) is part of a member of the HUERS-P1/LTR8 family of endogenous retroviruses. High expression of THOLE was observed only in HL cell lines with an exceptionally high expression in the cell line L-1236.

Conclusion The expression of THOLE in L-1236 cell is an example for HERV/LTR-associated gene expression in HL. The influence of HERV/LTR-associated transcripts on gene expression might explain the characteristic phenotype of human HL and requires further investigations.

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PW I-V-11 An Intergroup Approach for Advanced Stage Classical Hodgkin Lymphoma (cHL) in Adolescents and Young Adults (AYA): SWOG S1826.

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Introduction Treatment approaches to pediatric and adult cHL have varied considerably. This has resulted in gaps in understanding risk prediction and optimal therapy for de-novo advanced stage disease across the adolescent and young adult (AYA) age spectrum. In collaboration with adult research groups through the U.S. National Cancer Institute's National Clinical Trials Network (NCTN), earlier access to novel agents such as immunotherapy could be facilitated for high risk AYA. The PD-1 inhibitor Nivolumab (Nivo) has safety and efficacy in relapsed and refractory disease in children and adults, but has not been evaluated in de-novo disease to date.

Methods Leaders in lymphoma, including all North American cooperative group chairs, Cancer Therapy Evaluation Program (CTEP) representatives and patient advocates met to establish consensus on the comparison arms and study design, based on recent historical approaches across adult and pediatric groups. Study champions were identified across all North American cooperative groups and included expertise in imaging, radiation oncology, biology and patient-reported outcomes. A therapeutic study was designed with the primary aim being to compare progression-free survival with novel targeted agents in advanced stage cHL.

Results The trial, led by SWOG Cancer Research Network, opened to accrual in July 2019. Eligibility criteria include patients ≥ 12 years of age with Stage III or IV disease. Patients are randomized (1:1) to 6 cycles of either Nivo-Adriamycin, Vinblastine, Dacarbazine (AVD) or Brentuximab vedotin (Bv)-AVD. Enrollment is being stratified by age, baseline International Prognostic Score, and provider intent to use involved site radiation therapy (ISRT). Protocol-prescribed ISRT is response-adapted, based on end of therapy imaging. The primary endpoint is a comparison of progression-free survival between arms. Secondary clinical endpoints include comparison of: overall survival, metabolic response at the end of therapy, physician-reported adverse events, patient-reported adverse events, and health-related quality of life (overall, and specific to fatigue and neuropathy).

Conclusion This unique intergroup collaboration demonstrates the process and the feasibility of consensus study designs toward early adoption of targeted therapies and harmonization of treatment approaches for AYA populations.

PW I-V-12 Phase I study of brentuximab vedotin (SGN-35) in Japanese children with relapsed or refractory CD30-positive Hodgkin's lymphoma or systemic anaplastic large cell lymphoma

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DOI 10.1055/s-0040-1701850

Conflict of Interest: YK, AI, and TM reports grants from Japan Agency for Medical Research and Development via Center for Clinical Trials Japan Medical Association, during the conduct of the study. MS reports grants from Japan Agency for Medical Research and Development via Center for Clinical Trials Japan Medical Association, during the conduct of the study; non-financial support from Pfizer Japan Inc., outside the submitted work. AK reports personal fees from Bayer Yakuhin, Ltd. as a member of an independent data monitoring committee of clinical trials, outside the submitted work. KH reports personal fees from Chugai Pharmaceutical Co., Ltd., Amgen Astellas BioPharma K.K., and Sumitomo Dainippon Pharma Co., Ltd, grants and non-financial support from Pfizer Japan Inc., outside the submitted work. The other authors have nothing to disclose.

Introduction Data on the treatment of pediatric patients with brentuximab vedotin are limited. The aims of this study were to assess the safety and tolerability of brentuximab vedotin in Japanese children with relapsed or refractory Hodgkin's lymphoma (HL) or systemic anaplastic large-cell lymphoma (sALCL). In Japan, a phase I/II study (TB-BC010088 study) involving patients with recurrent or refractory CD30-positive HL or sALCL was initiated in October 2011. Based on the results of the TB-BC010088, SG035–0003, and SG035–0004 studies, brentuximab vedotin was also approved for the treatment of patients with recurrent or refractory CD30-positive HL or ALCL in 2014 in Japan. We report here the safety and tolerability of brentuximab vedotin in Japanese children with relapsed or refractory CD30 positive HL or sALCL.

Methods Pediatric patients, aged 2–17 years, with relapsed or refractory HL or sALCL were recruited. Brentuximab vedotin were administered at 1.8 mg/kg via intravenous infusion once every 3 weeks. Primary endpoints were dose-limiting toxicities and safety.

Results Between September 2016, and March 2018, six patients (median age: 11.5, range 5–14 years), four with relapsed or refractory HL and two with relapsed or refractory sALCL were enrolled. Dose limiting toxicities were not observed in any of the six patients. Although three of six patients (50%) had at least one grade ≥3 adverse event, no patient had a serious adverse event. The pharmacokinetic profile of brentuximab vedotin in pediatric patients was comparable to that reported in adults. The proportion of patients who achieved overall response was 60% (95% confidence interval 14.7–94.7).

Conclusion Our study had two limitations, namely the small sample size and the heterogeneity of the patients. However, it also represents the first prospective trial to systematically investigate the use of brentuximab vedotin in Japanese children.

Our data suggest that brentuximab vedotin at 1.8 mg/kg might have a manageable toxicity profile for the treatment of children with recurrent or refractory HL or sALCL. Despite this, the optimal dose of BV in pediatric patients is unclear. Further research in pediatric patients with recurrent or refractory HL or sALCL is needed.

PW I-V-13 Prognostic Value of Interim and End of Treatment PET-CT Scan Results in Pediatric Hodgkin Lymphoma

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Introduction Treating Hodgkin lymphoma (HL) among children involves a tradeoff between cure and reducing long term radiotherapy toxicity like secondary malignancies, cardiac and endocrine dysfunction. Fluorodeoxyglucose positron emission tomography (PET) combined with computed tomography (CT) identifies patients with early response to chemotherapy, for whom radiotherapy may be avoided. The prognostic role of PET-CT in response–adapted treatment is evaluated in this study.

Methods Patients with HL of all treatment groups, who were younger than 18 years, were included. Interim PET-CT was performed after two chemotherapy cycles. Patients were stratified into three risk groups: group 1 (stage I or II with no unfavorable features); group 2 (stage I or II with bulky disease/B symptoms); and group 3 (stage III/IV). A vincristine,etoposide,prednisone and doxorubicin – based regimen was used in early disease. A Cyclophosphamide, Oncovin, Predinsone,Dacarbazine–based regimen was used in advanced disease.Patients who achieved complete response by interim PET-CT will avoid radiotherapy .

Results Sixty-five patients were included. Sixteen (24.6%), 27 (41.5%), and 22 (33.9%) patients were included in treatment groups 1, 2, and 3, respectively. On the basis of negative interim PET responses, 43 (66.1%) patients were treated without radiotherapy. The 5-year event-free survival for the entire cohort was 96 % and overall survival was 99%. Most of the PET-CT scans at the end of treatment were done in positive interim PET-CT cases, while in early responders; only CT scans were done.

Conclusion The number of pediatric HL patients who need to be treated with the expensive radiotherapy devices can be decreased in limited resources countries and replace it with the less costly modality like interim PET-CT. We can decrease the burden on PET-CT machines especially at the end of treatment after achieving CR by interim PET-CT.

PW I-V-14 A Case Report of Neutropenic Enterocolitis in Armenia

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Introduction Neutropenic enterocolitis (NE) also known as typhlitis is a severe condition usually affecting immunocompromised patients. Typhlitis is classically seen during neutropenia but also can be seen outside the

neutropenic periods. The true incidence of NE is unknown worldwide. The frequency of neutropenic enterocolitis appears to be increasing with the widespread use of cytotoxic agents, which cause gastrointestinal mucositis.

Methods This is a first documented case of NE in a patient with Hodgkin Lymphoma, in Armenia.

Results 12-years oldgirl was diagnosed with Hodgkin Lymphoma IIA in September of 2019 based on the histological and immunohistochemical investigations. She was hospitalized and chemotherapy with the following medications was initiated: prednisolone, vincristine, doxorubicin and etoposide. On the 9th day of chemotherapy she was complaining of abdominal pain, cramps, constipation. Laboratory findings were unremarkable. Gastroenterologist consultation was organized and she prescribed empiric eradication of Helicobacter Pylori (regimen with amoxicillin and clarithromycin). Chemotherapy has been suspended. 2 days later the patient started to complain of fever (up to 39 degrees of Celsius) and CBC showed profound neutropenia (WBC - 0.34**10^3/μL, neutrophil counts 0.06*10^3/μL). Meropenem and granulocyte colony-stimulating factor were started for the empiric treatment of febrile neutropenia. Despite the treatment symptoms were persistent. Besides, patient had a new complaint - diarrhea. Based on the symptoms (fever, neutropenia, abdominal pain, diarrhea) NE was suspected. The results of ultrasound of abdomen was unremarkable. CT scan of abdomen revealed the width of the intestinal mucosa 0.5-1.0 cm. Consequently, the diagnosis of NE was confirmed. Clarithromycin was switched to metronidazole accordingly. Pseudomonas aeruginosa was detected in blood culture and Proteus vulgaris was detected in stool culture. After 10 days of antibacterial therapy (Meropenem and Metronidazole) and diet the patient was recovered.

Conclusion As the true incidence of NE is still unclear, awareness of typhlitis and possible risk factors at local institutions might help to modify the incidence and consequences of typhlitis.

PW I-V-15 Retrospective Analysis of Baseline Prognostic Factors On the Outcome of Pediatric Hodgkin Lymphoma in a Tertiary Cancer Centre

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Introduction Pediatric Hodgkin's Lymphoma constitute 5 to 6% of all the children with cancer. Cure rates approach 80-90% due to combination of different chemotherapy drugs and low dose involved field radiotherapy however, 15-20% of patients have resustance to therapy or relapse after treatment. Prognostic factors help to define risk startified treatment and also identify patients at risk for faiure. The purpose of this our study was to see the impact of baseline prognostic factors on the outcome of Pediatric Hodgkin Lymphoma in our institute.

Methods Medical records were reviewed retrospectively from April 2010 to December 2015 after IRB approval with newly daignosed Hodgkin Lymphoma on histopathology in Shaukat Khanum Memorial Cancer Hospital . Data was collected on each pateint's age, gender, B symptoms, stage, bulk volume, ESR, albumin, hemoglobin, staging workup, re evaluation scans and followup.

Results A total of 357 patients with Hodgkin Lymphoma were included, the median followup of cohort was 40 months.All patients were treated with COPDac/ABVD chemotherapy and 54 (15%) patients received low dose involved field radiotherapy. Stage I patients were 26(7%), Stage II patients were 91(25.5%), Stage III patients were 148(41.5%) and Stage IV patients were 92(36%). B symptoms were positive in 71(20%) patients and negative in 286(80%) patients. ESR was more than 30 in 196 (55%) patients and less than 30 in 161(45%) patients.Three categories of bulk volume 0-100ml in 83(23%) patients, 101-200ml in 148 (49%) patients and above 200ml in 100 (28%) patients. Bone marrow involvement in 48(13%) patients, BM no involved in 297(83%) patients and BM was not done in 12(3.4%) patients. In multivariate analysis, three variables were identified as significant independant risk factors for advanced stage ESR (Above 30) (adjusted odd ratio) [AOR] 2.40; 95% confidence interval [CI](1.34 4.27), p- value was 0.003, Hemoglobin;(AOR 0.82; 95% CI(0.69 0.97), p-value 0.02 and albumin (AOR 0.47;95% CI (0.30 0.82), p-value 0.01.Further more paltelets were marginally significant (AOR 0.99; 95% CI (0.99 1.00), p -value 0.01.Median Event Free Survival and Overall Survival were 13±4.48 and 18 ±6.32 months respectively.

Conclusion There was significant impact of baseline prognostic factors on the survival of patients with Hodgkin Lymphoma. Further prospective trials needed for emerging biomarkers for risk stratification.

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PW I-V-16 Nodular Lymphocyte Predominant Hodgkin Lymphoma - experience of Polish Pediatric Leukemia/Lymphoma Study Group

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Introduction Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLP-HL) is a rare clinical entity. In order to investigate NLP-HL clinical course and treatment a survey was performed within Polish Pediatric Leukemia/Lymphoma Study Group participating centers.

Methods Questionnaire was sent to all participating centers and data regarding patients, diagnosis, treatment and treatment results were gained. Analysis of collected data was performed.

Results From 2010 to 2019, 28 pediatric patients with NLP-HL were registered in Poland. Two patients with inherited immune deficiencies and 3 patients who did not complete treatment were excluded from analysis. Age of patients was 5,5 – 17,8 (median: 12,2) years. NLP-HL occurred mainly in males (n=21). All stages of disease were observed but stage I (n=7) and stage II (n=10) were predominating. In most of patients (n=15) supradiaphragmatic localization was observed while mediastinal involvement was observed only in 2 patients.

7 patients presented with localized, resectable disease. In 3 patients total primary resection was performed. One of these patients relapsed and was treated with CVP chemotherapy. Two patients received further chemotherapy after total resection. Two patients were resected incompletely thus underwent CVP chemotherapy. No other relapses were observed.

Fourteen patients presented with unresectable disease, of these 8 received CVP chemotherapy, and 6 were treated with other chemotherapy regimens, three relapses were observed and these patients were further treated with chemotherapy and rituximab. One patient underwent auto-SCT. All patients remain alive. Three-years disease-free survival was 81%.

Conclusion NLP-HL treatment result are consistent with results noted in other countries, but still there is a need for improvement and coherent treatment of NLP-HL patients in Poland. Focus has to be made on primary resection eligible patients. In higher stages of disease consensus on treatment has worked out as many different chemotherapy schedules were in use.

PW I-V-17 Real-life experience of multisciplinary pediatric lymphoma tumor board: decision's impact on Hodgkin Lymphoma treatment choice and results

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DOI 10.1055/s-0040-1701855

Introduction In France, all classical Hodgkin Lymphoma (cHL) children and adolescents cases are presented in seven multidisciplinary pediatric regional tumor boards (RCPP) to define treatment plan. Between January 2013 and December 2016, no trial was open for recruitment and treatment recommendations were based on the preliminary results of the EuroNet-PHL-C1 protocol. This retrospective work aims to describe RCPP decisions, delivered treatment and outcome of cHL patients during this period for one region (Ile-de-France).

Methods Medical report, histology, biology, RCPP decisions, of all cHL presented at diagnosis in RCPP Lymphoma "Ile-de-France" with CT scan, MRI, abdominal ultrasound and PET-FDG-CT available were analysed.

Results Between January 2013 and December 2016, 157 patients were recorded, median age was 14 years; sex ratio was 0.87; and stratification in the treatment groups was as follows: TG1/2/3 respectively 10, 30 and 60%. Patients were treated according to amended EuroNet-PHL-C1 protocol in 123/157 (78%) cases; 34 received a different treatment plan: third cycle of OEPA, adjunction of one or more cycle of COPDAC, Brentuximab vedotin, ABVD, escalated BEACOPP. Complete metabolic response was define on Deauville Score, ie < or = 3. Radiotherapy indication was defined by the response after the first 2 cycles of OEPA: response was inadequate for 56/157 (36%) patients, 15/56 nevertheless did not received radiotherapy because young age (n=2), extensive disease (n=7), unclear response after 2 OEPA (n=3), medical condition (n=2), progression (n=2) and/or parental refusal (n=2). In 3 cases, patients with adequate response radiotherapy on residual disease. With median follow up of 39 months, 155/157 patients are alive, 2 patients died (1 unknown reason, 1 relapse treatment toxicity). With a median follow up of 35 months, 19 (12%) patients relapsed; median time between end of treatment and relapse was 4 months (0 to 33 months). Overall survival is 98%, estimated 5 years Event-Free-Survival is 86%, univariate analysis did not identified any significant difference between patients treated with or without radiotherapy. Inadequate response after 2 OEPA course and TG 2/3 were associated to inferior outcome.

Conclusion In a real life experience of tumor board decisions, survival is excellent and relapse cumulative rate in the range of expected result. Of note, the use of radiotherapy was limited to 26% of cases.

PW I-V-18 Hodgkin Lymphoma Cases in Mongolia

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DOI 10.1055/s-0040-1701856

Introduction Between 2014 and 2019, in the department of hematology and neoplasm, 11 children with Hodgkin lymphoma have been hospitalized and treated. The National Center for Maternal and Child Health is the leading center for maternal and child health. We have 1200 medical workers and 21 pediatric subspecialty department in the country. All pediatric serious cases come to our center. Pediatric Hematology is stablished on 2006. In 2016 our department is upgraded and included Pediatric Oncology. Now we give medical services as unified Pediatric Hematology and Oncology Department. Hematology and Oncology department is an only subspecialty department in the country. We have 7 medical doctors and 20 nurses. We are providing medical services with 30 patient beds and 5 palliative beds. We provide medical services to 1400 patients annually. I would like to like highlight that medical service for children aged from 0-18 is free in Mongolia.

Methods The study is based on 150 patient history which were treated in Pediatric Hematology and Oncology Department from 2014 to 2019. 11 children treated total 150 times between 2014 to 2019.

Results 11 children diagnosed with Hodgkin lymphoma between 2014 to 2019.

Gender ratio

Male: 64%

Female: 36%

Number of occurrences by year

2014: - 1

2015: - 1

2016: - 1

2017: - 5

2018: - 2
2019: - 1
Occurrences by age
0 - 05 years old: 0
06 - 10 years old: 7/63.6%/
11 - 15 years old: 4/36.4%/
16 - more years old: 0
Occurrences by Region
Central Region: 73%
Khangai: 18%
Eastern: 9%
Geographical regions of Mongolia: West, North, Kahngai, Central, Gobi, East Central is the region where Ulaanbaatar city is located with 40-50 percent of total population.
Average elapsed time for treatment 5 months
Conclusion Result of the treatment is going well. There is no death case up to date.

PW I-V-19 Result of therapy for Hodgkin Lymphoma (HL): a report from the Chilean pediatric National Cancer Program (PINDA)

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DOI 10.1055/s-0040-1701857
Conflict of Interest: Without conflicts of interest
Introduction
Objective the aim of this study was to analyze the event-free survival (EFS) and the overall survival (OS) of children with HL treated by the PINDA-99 protocol, based in the Children´s cancer group 1995 (CCG-5942)
Methods
Patients and Methods 119 patients were registered on this trail between January 1999 and April 2005 at our country (public health). Low risk (LR) were stages IA, IB and IIA (no bulky disease (<10 cm), < 4 involved ganglionar areas and no lung hilar nodes), high risk (HR) were stages II B, III A, III B, IV, bulky mediastinum and bulky disease (>10 cm). Chemotherapy for LR was 4 cycles of the COP/ABVD hybrid scheme (cyclophosphamide, vincristine, prednisone, doxorubicin, bleomycin, vinblastine and dacarbazine) and low-dose involved field radiotherapy (RT) only in case of partial remission (PR) at the end of chemotherapy (21 Gy in initially involved areas, plus 14 Gy boost on residual disease). The HR group was treated with 6 cycles of hybrid COP/ABVD, using RT only in PR and in patients with diagnosed bulky mediastinum.
Results
Results The male to female ratio was 2:1 (80 men and 39 women). The median age at diagnosis was 8,5 years old (range, 2.6 to 15 y). Histology was obtained in 112/119 patients: Mixed-cellularity 49 (44%) Nodular sclerosing 44 (39%) Lymphocyte-rich 9 (8%) Lymphocyte depleted 2 (2%) Not classifiable 8 (7%). 46 patients (41%) were assigned to LR: Stage IA 11/113 (10%) IB 5/113 (4%) IIA 30/113 (27%). 67 patients (59%) were assigned to HR, IIB 15/113 (13%), IIIA 18/113 (16%), IIIB 20/113 (18%), IVA 0 and IVB 14/113 (12%). B symptoms presents in 53/113 (47%). 61 patients (51%) received RT, 46 not achieved complete remission (CR) after chemotherapy (4 or 6 cycles LR or HR respectively) and 15 had bulky mediastinum. 9 relapsed (7,5%) and 5 of them remained in second CR after further therapy. 3 (2.5%) had a second cancer (one osteosarcoma and two thyroid cancer, all in irradiated site). 7 patients dead (5.8%), 5 for illness (1 did not respond to initial therapy and 4 died in relapsed), 1 for infection and 1 for second cancer (osteosarcoma in irradiated bone). OS was 94 % and EFS was 89% with a median follow -up of 10 years.
Conclusion
Conclusions Avoiding RT in patients that RC to chemotherapy COP/ABVD hybrid scheme had excellent results both LR and HR. In our protocol nearly half of the patients could be cured without RT. Second cancer were observed only in irradiated patients, and one of them died for that, being in remission of hodgkin disease.

PW I-V-20 Hodgkin's disease in children in Moroccan Hospital

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DOI 10.1055/s-0040-1701858
Conflict of Interest: No conflict of Interset.
Introduction Hodgkin's disease is a neoplastic disorder of lymphoid tissue. It remains the first model of malignant tumor curable and curable by combined multidrug therapy and radiotherapy.
The objective to carry out an epidemiological analysis, to study the clinical and histological aspects, to evaluate the therapeutic response and the evolutive aspects.
Methods This work is a retrospective study of cases of hodgkin's disease diagnosed in the department of hematology, pediatric oncology, CHU Mohammed VI Marrakech
Results As of 2011, 22 cases with Hodgkin's disease were collected. The mean age is 11.18 with a male predominance of 73%. Cervical adenopathies are affected in 90% of cases. According to the classification of Ann-Arbor stage II is found in 36% of the cases. The scleronodular histologic type is the most frequent (54.5%). All patients are treated according to the MA-MDH 2004 protocol. Complete clinical remission is obtained in 73% of cases. The rate of loss of sight is 18%.
Conclusion This rate can be reduced by the efforts undertaken in our service by sensitizing patients and their families to adherence to treatment and medical coverage.

PW I-V-21 High response rate to combined chemotherapy avoiding radiotherapy in children and adolescents with classical Hodgkin lymphoma. Preliminary results of GALOP LH 2017 Protocol

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DOI 10.1055/s-0040-1701859
Introduction Children with diagnosis of Hodgkin Lymphoma (HL) have achieved high rate of survival, and for this reason the aim of our current study is to decrease radiotherapy (RT) indications for avoiding late sequelae. To analyze

disease response rate to combined chemotherapy in children and adolescents with classical HL included in LH GALOP 2017 Protocol.

Methods From Sept 17 to Oct 19, 45 consecutive pediatric patients with HL were registered in LH GALOP 2017 Protocol. This is a non-randomized, multicenter, prospective pediatric HL treatment trial, stratified according to initial risk factors and response to chemotherapy (interim and late response), with reduced cumulative doses of antineoplastic agents and avoiding radiotherapy in good responders. Chemotherapy is based on ABVD and ESHAP regimes. No radiotherapy is delivered when complete response is achieved after chemotherapy in any risk groups. Patients who achieved partial response receive low dose (30Gy) involved node RT. Stable or progressive disease is assumed as a trial failure at any moment. (Further information ClinTrials.gov NCT NCT03500133

Results Forty-three of 45 patients (pts) were eligible for analysis. Misdiagnosis (1pt), additional radiotherapy off protocol (1pt). Males: 22pts Females: 21pts. Median age: 11.3 (range: 4.7–16.2) years. Median follow-up was: 10 months. Bulky mediastine: 14pts (32.5%),B-symptoms: 20pts (44.4%), extranodal invasion: 2pts (4.2%), systemic involvement: 17pts (39.5%), lung: 7pts (16.2%), liver: 4pts (9.3%), bone: 3pts (6.9%), bone marrow: 3pts (6.9%).Histology subtyping: Nodular Sclerosis: 34pts (79%), Mixed Cellularity: 5pts (11.6%), LR CHL: 4pts (9.3%). Autoimmune related initial disorders: 4 pts (9.3%). Initial staging: IA: 4pts, IIA: 11pts, IIB: 6pts, IIIA: 6pts, IIIB: 4pts, IVA: 2pts, IVB: 10pts. Initial risk assignment: Low: 8pts (18.6%), Intermediate: 15pts (34.8%), High: 20pts (46.5%). Early response assessment: CR: 23/42pts (54.7%). Late response assessment: CR: 32/34pts (94.1%)PD: 1pt, PR: 1pt. RT: 2 pts (5.8%). Acute therapy related toxicity was mild-moderate, mainly hematological. No relapses and deaths were observed.

Conclusion High rates of complete responders were found in the interim assessment and at the end of chemotherapy, even with high proportion of advanced disease, achieving a better treatment tailoring and avoiding RT in most of cases. At 10 months of median follow-up only one case of refractory disease was found as trial failure event for survival analysis.

PW I-V-22 Hodgkin lymphoma: results observed in an oncological center of the Ecuadorian Andes. Series of cases with follow-up

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DOI 10.1055/s-0040-1701860
Conflict of Interest: The authors declare no conflicts of interest

Introduction Hodgkin lymphoma (HL) is a clonal, lymphoproliferative cell neoplasm which mainly involves nodes with high chances of survival (SV).

Objective To determine differences in global survival (GS) and disease-free SV (DFSV) at 20 years according to risk.

Methods Case series with follow-up. Patients with HL from 1 to 18 years old, treated at the Institute of SOLCA-Cuenca (1999-2019) were included. The outcome variables were: histology, symptoms, stage, risk, complete remission (CR), GS and DFSV. Once their treatments were completed, patients underwent clinical follow-up. Descriptive statistics (measures of central tendency and dispersion) and analytical (Chi2, Fisher exact and continuity correction) were used. SV analyzes were performed with Kaplan Meier and log-rank curves.

Results

Results: 44 patients (56.8% men) were studied, with a median age of 9.8 years. 45.5% had mixed cellularity and 63.6% presented symptoms B. Stage IV (31.8%) and high risk (56.8%) were the most frequent. After the first line of treatment, 32 patients (72.7%) achieved CR. The GS and DFSV at 20 years were 77.5% and 71.1% respectively. When comparing the subgroups according to risk, the GAVS and DFSV for patients with low, intermediate and high risk were 100%, 37.5 % and 85.7% (p = 0.167); and of 100%, 90.9% and 53.1% (p=0.358) respectively.

Conclusion The GS and DFSV verified are similar to those reported in other studies. There were no differences between them and the patient's risk.

PW I-V-23 Pediatric lymphocyte-predominant Hodgkin lymphoma: Review of Spanish patients between November-2007 and October-2019

Chairs Carboné AI[1], Garcia M[2], Bárcena C[3], Guibelalde M[4], Vivanco JL[5], Garrido C[6], Echebarria A[7], Coronado M[8], Fernández-Teijeiro A[9] On behalf of Hodgkin Lymphoma researchers from Sociedad Española de Hematología y Oncología Pediátricas (SEHOP)
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DOI 10.1055/s-0040-1701861
Conflict of Interest: A Fernández-Teijeiro has had a consulting or advisory role for Amgen, Novartis, Takeda, SOBI and Bayer. She has has received honoraria from Takeda and Amgen for educational events and travel expenses from Servier, Shire and Gilead.

Introduction From 2007 SEHOP Hodgkin Lymphoma Working Group decided to recommend pediatric patients(p) diagnosed with lymphocyte-predominant Hodgkin lymphoma (LPHL) were treated according to Euronet-PHL-LP1 for stage IA and IIA and according to updated international strategies for advanced stages. From 2008 pathology central review was encouraged taking advantage of the Euronet-C1 trial pathology reviewers. Objective: Collect and review outcome of pediatric p withLPHL diagnosed in Spain 2007–2019.

Methods Questionnaire was sent to 36 Pediatric Onco-Hematology Units. Descriptive analysis was performed: sex distribution, mean age at diagnosis, pathology central review, PET, stage, treatment, median follow-up, outcome and relapse treatment.

Results 28 out of 36 Pediatric Onco-Hematology Units responded the questionnaire:52p from 26 hospitals with LPHL were collected. Gender distribution:34 male/18 female(1.88/1). Mean age at diagnosis: 10 years(yrs) and 6 months(m)(5-16yrs). Centralized pathological review was performed in 61,5%. PET was used for staging in 80,7%. Stage distribution: IA 18p,IIA 22p, IIB 1p,IIIA 6p,IV 5p. Most frequent location: Cervical.

Treatment:15/18p stage I underwent surgery alone;11/22p stage IIA received 3 CVP and 5/22 3 R-CVP,2/22 combination of CVP and R-CVP,4/22 received polichemotherapy. Advanced stages were treated according to Euronet-C1 or LH-2003 trials or with R-CHOP.

Outcome: Median follow up 49m(range 3m-132m).13/52p (25%) relapsed with median relapse time of 9m(5m-52m).Stage I:5/15p(33,3%) treated with surgery alone relapsed,median 7m(range 5-9m),IIA: 4,III: 2 and IV 2p. Treatment: stage I polychemotherapy (CVP,R-CVP) IIA-IV:IEP/ABVD/ICE +rituximab + radiotherapy: 1IV. 4p underwent TPH.All 52p p are alive: 38p in 1st complete remission(CR),12 in 2nd CR,1 in PR still on chemotherapy,1 in 3rd CR after R-CHOP and radiotherapy.

Conclusion In our series,Spanish p with LPHL have an excellent prognosis. Increasing centralized pathology review along last decade has been a major

achievement to improve the quality of pathology diagnosis. Surgery alone was effective treatment for 66% of stage I p. 79% of p treated with low intensity chemotherapy or polychemotherapy ± rituximab remain in 1st CR. Relapsed p can be safely rescued with low intensity chemotherapy and polychemotherapy ±rituximab ± radiotherapy. Unified international recommendations, participation in international multicenter trials and central pathology review will continue to be encouraged for Spanish pediatric p with LPHL along next years.

PW I-V-24 Clinical trial of Childhood, Adolescent and Young Adult Hodgkin Lymphoma in Japan

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DOI 10.1055/s-0040-1701862

Introduction Pediatric Hodgkin Lymphoma (HL) accounts for approximately 10-20% of lymphoma in pediatric patients, and the incidence of pediatric HL is lower in Japan than in Western countries. Here, we assess a multicenter, single-treatment trial (HL-14) that commenced in 2015 in Japan to determine the risk-adapted omission of radiation therapy for patients with negative fluorodeoxyglucose-positron emission tomography (FDG-PET) results, following an initial treatment response to combination chemotherapy.

Methods Patients with untreated HL aged <20 years at diagnosis are enrolled. The Japanese Pediatric Leukemia/Lymphoma Study Gropup, Japan Children's Cancer Groupe (JPLSG, JCCG) HL-14 sudy will examine the effects of omitting radiation therapy if the FDG-PET findings after two completed cycles of combination chemotherapy are negative. Low-risk patients (stage IA, IB, and IIA) receive two cycles of OEPA (vincristine, etoposide, prednisolone, and doxorubicin) (boys) or OPPA (vincristine, procarbazine, prednisolone, and doxorubicin) (girls). Intermediate-risk patients (stage IEA, IEB, IIEA, IIB, and IIIA) receive two cycles of OEPA (boys) or OPPA (girls) and two cycles of COPDAC (cyclophosphamide, vincristine, prednisolone, and dacarbazine) (boys) or COPP (cyclophosphamide, vincristine, procarbazine, and prednisolone) (girls). High-risk patients (stage IIEB, IIIEA, IIIEB, IIIB, IVA, and IVB) receive two cycles of OEPA (boys) or OPPA (girls) and four cycles of COPDAC (boys) or COPP (girls). If the PET2 results are negative, no radiation therapy will be administered. All patients with positive PET2 results will receive involved-field, involved-site, or node radiation therapy (20–36 Gy) following the completion of chemotherapy.

Results Our trial is now ongoing.

Conclusion This trial aimed to determine, within the confines of safety, whether assessing treatment response using PET (which is highly sensitive and specific) was effective for Japanese. In our next study, we plan to assess the safety and treatment response of brentuximab vedotin, which is used to treat cases of relapse in Japan, in early induction therapy using evaluation with PET2.

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PW I-V-25 Anemia: frequency and type in pediatric patients with Hodgkin's lymphoma

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Introduction [a] Pediatric Oncologist; [b] Resident Physician; [c] Pathologist. Determine the frequency and type of anemia, before and after treatment in children and adolescents patients with Hodgkin lymphoma (HL) treated at Hospital Nacional Edgardo Rebagliati Martins (HNERM) from January 2007 to December 2018.

Methods The presence of anemia was considered in male pediatric patients when hemoglobin was < 13 g/dL, and female pediatric patients when it was < 12 g/dL. Subsequently, to determine associations, the Chi-squared test was used. For the analysis, statistical analyses were done using percentage, anemia curves before and after the treatment and Student's't' test.

Results A total of 576 HL patients were included among children and adolescents. In which, 436 (76%) of them had solid tumors and 140 (24%) had lymphoma (non-Hodking lymphoma and Hodgkin lymphoma). Of which 33 (23.5%) cases corresponded to HL.

Afterwards, anemia was diagnosed in 22 (66%) patients with Hodgkin lymphoma. The type of anemia, both at the beginning and at the end of treatment, was microcytic anemia in the present study, most likely due to the fact that Hodgkin lymphoma is one of the pediatric cancer pathologies that tend to be chronic with time up to 12 months. Mild anemia was the most frequent according to the hemoglobin cut-off point to determine anemia.

Conclusion After the cases review, it was determined that microcytic anemia is common in pediatric patients with Hodgkin lymphoma at the beginning, and at the end of treatment.

PW I-V-26 Prognostic model for pediatric Hodgkin Lymphoma patients in developing country

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Conflict of Interest: The authors declare no conflict of interest.

Introduction Pediatric Hodgkin lymphoma (HL) is a disease with high cure rates, but with high treatment-related morbidity. This study aimed to identify prognostic factors for children and juvenile HL patients treated in a developing country given the lack of risk stratification targeting the populations of these countries.

Methods A retrospective cohort of patients diagnosed with HL and treated at the Instituto de Medicina Integral Professor Fernando Figueira - IMIP Hospital (Recife, Brazil) was constructed. The cohort comprised patients aged up to 18 years and treated between 1994 and 2017 using the HOD-94 or adapted HOD-08/99 protocols (replacement of mechlorethamine by cyclophosphamide). Demographic, clinical and laboratory data at diagnosis were evaluated by descriptive, univariate and multivariate analysis, associating these characteristics with unfavorable outcomes (death and relapse). Statistically significant variables in the multivariate analysis were considered for the construction of prognostic scores by latent class analysis. Statistical analyses were performed using the R software package and a 95% significance level.

Results Data were collected from medical records of 126 pediatric Hodgkin lymphoma patients. There was a predominance of male gender (72.0%), children up to 12 years (62.4%), and the histological subtype Nodular Sclerosis followed by Mixed Cellularity subtype. Patients with splenomegaly and high LDH levels presenting or not mediastinal bulk disease or lethargy were associated with a higher risk of relapse ($P < 0.0001$), and patients with lethargy or increased abdominal volume whether or not accompanied by nocturnal sweating had lower overall survival ($P = 0.015$).

Conclusion These prognostic scores were constructed for patients treated in developing countries and employ low-cost parameters at diagnosis, which may be relevant for a better management of the target population. However, prospective studies should be developed to validate this score in other developing countries with characteristics similar to Brazil.

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PW I-V-27 Is it Possible to Work together in Latin America? The Latin American Consortium (CLEHOP) experience with Hodgkin Lymphoma (HL)

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DOI 10.1055/s-0040-1701865
Conflict of Interest: We all declare no conflicts of interest.

Introduction The idea of working coordinately arose in Latin America in 2012 with the creation of CLEHOP. The Consortium is made up of regional and national groups and supported by SJCRH.

Aim Describe the outcome of patients treated according to the AHOPCA-GATLA-SOBOPE strategy (11-EHP-12) adopting OEPA/COPDAC for high Risk (HR) and ABVD for Intermediate (IR) and Low Risk (LR).

Methods 11-EHP-12: Risk assignment according to the Stanford/Danna-Farber/SJCRH consortium classification. LR: ABVD x 4 ± 20 Gy IFRT; IR: ABVD x 6 ± 20 Gy IFRT; HR: OEPA-COPDAC + 20/25 Gy IFRT. Response evaluation: LR after 4th cycle, IR and HR after the 2nd cycle. Complete Remission (CR): > 80% reduction and negative PET. Partial Remission (PR): >50% and <80% reduction and/or positive PET.

Results 465 patients were enrolled since 2012 in the 3 groups, 366 evaluable. In AHOPCA, GATLA and SOBOPE the epidemiological data are: Sex: M:78%, 64% and 67%. Median age: 8.6y, 13y and 12y (range 2.2-18 y). Histology: nodular sclerosis is the main subtype: 85%, 68% and 59,6%. While mixed cellularity 11%, 23% and 21%. Most patients were diagnosed in advance stages in all groups. Risk groups of treatment: AHOPCA: 53%HR, 37% IR, 10%LR. GATLA: 58%HR, 26% IR, 16%LR. SOBOPE: 46%HR, 32.6%IR, 21.4%LR.
The 2y-OS/2y-EFS achieved in SOBOPE is 100%/93,8%, while the 5y-OS/5y-EFS in AHOPCA and GATLA are 90%/86% and 94%/88% respectively.

Conclusion Thanks to this cooperation, Latin-America significantly improve outcome compared to the previous experience and reduce the number of patients who required radiotherapy while reproducing the EuroNet experience for HR patients in a different setting.

15 May 2020

S-V | Session V: Relapse treatments

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S-V-01 Introduction

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S-V-02 Novel agents beyond Immunotherapy

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S-V-03 Risk and Response adapted salvage treatments in R/R Classical HL in children and young people – European guidelines

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DOI 10.1055/s-0040-1701869

S-V-04 Interactive Case Presentations, Panel discussion, Scenarios

Chairs Panel members Leblanc T, Kelly K, Daw S, Dieckmann K
DOI 10.1055/s-0040-1701870

S-V-05 Response rates, long term outcomes and toxicity profile of Gemcitabine and Vinorelbine based outpatient chemotherapy regimen in primary progressive and relapsed pediatric Hodgkin Lymphoma

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DOI 10.1055/s-0040-1701871

Conflict of Interest: We have no conflict of interests

Introduction Depending on the time duration to relapse, relapsed Hodgkin Lymphoma can be divided into 3 groups. i.e. Primary Progressive disease defined as refractory disease/relapse within 3 months of the end of treatment, Early relapse as relapse within 3-12 months and late relapse as relapse after 12 months from the end of treatment. Various chemotherapy regimens are available to salvage these patients with almost similar outcomes and a superior chemotherapy-based regimen has not been determined [1, 2, 3]. The cost of treatment and ease of administration become the major factors in selecting a salvage regimen in this setting, especially in resource-limited countries. We use Gemcitabine/Vinorelbine (GV) based regimen for this subset of patients as it can be administered as outpatient chemotherapy leading to less burden on hospital resources. The aim of this review was to determine response rates, 3-year Overall Survival (OS), Event Free Survival (EFS) and acute toxicity of GV based salvage regimen.

Methods Data were retrospectively analyzed from the electronic record of patients from January 1, 2014, to December 31, 2018. The interim response was analyzed via FDG-PET CT. After remission, GV was followed by stem cells rescue in primary progressive/early relapse patients and radiotherapy in late relapse patients. Kaplan Meier method was used to determine 3-year OS and EFS and log-rank test to compare survival curves.

Results Total patients were 41 with a male: female ratio of 5.8:1 and mean age 8 years (range; 3-15). Overall response at interim assessment was 83% (n=34/41, complete response [CR] in 56%, partial response [PR] in 44%). Response rate for primary progressive (n=12), early (n=6) and late relapses (n=23) at interim was 75%, 83% and 87% respectively. The combined 3-year OS was 73% and EFS 71%. 3-year OS for primary progressive, early and late relapses was 65%, 80%, 89% (p-value: 0.07) respectively. 3-year EFS for primary progressive, early and late relapses was 47%, 62%, 86% (p-value: 0.01) respectively. 3-year OS for stage I/II (n=14) and stage III/IV at relapse was 100% and 78% respectively while 3-year EFS did not differ on the basis of the stage at relapse and was 66% for all stages. There were no toxic deaths. Febrile neutropenia was observed in 9.6% (n = 4) and lung toxicity in 2.4% (n =1).

Conclusion Gemcitabine and Vinorelbine is an efficacious and low toxicity outpatient salvage regimen for relapsed pediatric Hodgkin Lymphoma. Outcomes remain poor in primary progressive disease.

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S-V-06 Brentuximab vedotin plus bendamustine in relapsed and refractory classical Hodgkin lymphoma in children, adolescents and young adults: a single centre experience

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Conflict of Interest: None to declare.

Introduction The majority of children and young people with classical Hodgkin lymphoma (cHL) are cured with first line treatment, with treatment failure rates of 10 to 20% (early to advanced stage disease). [1] Cure may be achieved in the relapsed/refractory (R/R) setting but the optimal salvage treatment has not been defined. Conventional salvage chemotherapy yields complete response (CR) rates ranging from 20-60% [2]. Brentuximab vedotin (Bv) is a novel agent increasingly used in R/R cHL, with CR rates of 33% when used as monotherapy in the phase I/II paediatric trial [3]. A number of studies have reported that the combination of Bv plus bendamustine (Bv+B) achieves superior outcomes to either agent alone [2, 4]. Achievement of complete metabolic remission (CMR) prior to autologous stem cell tranplantation (ASCT) is highly predictive of long term progression free survival in R/R cHL [5].

Methods We present a series of nineteen consecutive patients treated with Bv+B as second line or later relapse therapy with R/R HL at our institution. Patients (age range 9-27 years) were treated from May 2015 to June 2019. Fifteen patients (79%) had primary refractory disease. Median number of prior treatment lines was 2, including ASCT in 4 patients. Patients received bendamustine (90mg/m^2) on days 1 and 2, and Bv (1.8mg/kg) on day 2 of a 21 day cycle, with responses assessed after 2 cycles.

Results Of nineteen patients, fourteen (74%) achieved a CMR, 1 achieved a partial response and 1 achieved stable disease. 3 patients (16%) did not complete 2 cycles of treatment due to grade 2 to 4 infusion related reactions (IRR) and so were not efficacy evaluable. CMR amongst the sixteen efficacy-evaluable patients was 88%. All 16 evaluable patients received consolidation therapy, 9 with ASCT and with allogeneic transplant in the remainder.

Due to frequency of IRRs, our treatment protocol was amended to include IV steroids as pre-medication prior to each cycle. Aside from IRRs, 4 of 19 patients (21%) had grade 3 or 4 adverse events comprising cytopenias or GI upset.

Conclusion This series indicates that Bv+B is a safe and highly active salvage regimen for children and young people, achieving a CMR in 74% of patients (88% in efficacy-evaluable patients). The CMR rate in this retrospective series is superior to reported outcomes of either drug as single agent. This combination can facilitate a bridge to HDCT/ASCT in a state of CMR in the majority of cases.

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S-V-07 A New Model for Stratification of Treatment Intensity in Relapsed Pediatric Hodgkin Lymphoma

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DOI 10.1055/s-0040-1701873

Introduction High-dose chemotherapy and autologous hematopoietic stem cell transplantation (AHSCT) are standard for most relapsed/refractory Hodgkin lymphoma (R/R HL). Although some do not require AHSCT for cure, there is no standard therapy or inclusion criteria for this group. The ongoing trial CheckMate CA209-744 (NCT02927769) tests a risk-stratified, response-based algorithm for patients aged 5-30 years with R/R HL. In it, LR patients who attain complete metabolic response to chemoimmunotherapy receive consolidative radiation but omit AHSCT. Low risk (LR) relapse is defined as relapse of stage IA, IIA 3-12 months from completing ≤3 cycles of chemotherapy or stage I, II, and IIIA relapsing >1 year from therapy completion. Standard risk (SR) relapse includes all other relapses and all patients with B symptoms or extranodal disease at relapse or relapse in a prior radiation field. To broaden the definition of LR R/R HL, we retrospectively investigated the overall survival (OS) of pediatric patients with R/R HL using two novel definitions of LR relapse.

Methods We proposed two new definitions of LR relapse (LR1, LR2) based on stage at diagnosis, initial treatment, time to relapse, and B symptoms and extranodal disease at relapse that are broader than used on CA209-744. LR1 included relapse of stage I, IIA, IIB, IIIA >3 months following ≤ 4 cycles of therapy, and relapse of stage IIB_E, $IIIA_E$, IIIB, IVA, IVB occurring >1 year off therapy. LR2 was identical except for the exclusion of relapse IIIB and IVB. We analyzed 261 R/R HL patients treated on pediatric clinical trials AHOD0431 (n=42, NCT00302003), AHOD0031 (n=192, NCT00025259), and AHOD0831 (n=27, NCT01026220). We compared survival of patients categorized as LR1, LR2 to SR and the change in proportion of patients who would be stratified as LR compared with CA209-744 stratification.

Results Using CA209-744 criteria, 38% and 62% patients were stratified as LR and SR, respectively. In the LR1 stratification 74% of patients would be LR (94% increase). Five-year OS in LR and SR patients based on the LR1 stratification was 74.2% (95%CI 62-83%) and 80% (95%CI 66-88%) respectively (p=0.72). Five-year OS rates for LR and SR patients based on the LR2 stratification are 81% (95% CI 67%-90%) and 74% (95% CI 63-83%) respectively (p=0.72).

Conclusion This analysis of outcomes of pediatric patients with R/R HL suggests that less intensive strategies beyond AHSCT may be considered for expanded subgroups of patients in future clinical trials.

S-V-08 Outcome of Pediatric Relapsed/Refractory Hodgkin Lymphoma Patients in 2 different Latin American Settings: AHOPCA (Asociación de Hemato-Oncología Pediátrica de Centro América) and GATLA (Grupo Argentino de Tratamiento de Leucemia Aguda)

Chairs Veron D[1], Streitenberger P[1], Castellanos M[2], Blanco J[2], de Alarcon P[3], Metzger M[3]On behalf of Members of AHOPCA and GATLA Cooperatives Groups
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DOI 10.1055/s-0040-1701874
Conflict of Interest: The authors declare no conflicts of interest

Introduction AHOPCA and GATLA have been cooperating on HL since 2012. Patients were treated with OEPA/COPDAC for high Risk (HR) and ABVD for Intermediate (IR) and Low Risk (LR) patients. This collaborative work significantly improved previous outcomes in Central America and Argentina and reduced radiotherapy as we reproduced the EuroNet experience for HR patients in a different setting. However, patients with refractory/relapsed (r/r) disease were salvaged according to the local resources of each setting. Aim: To describe the outcome of high-risk patients with r/r disease in AHOPCA and GATLA.

Methods HR patients with r/r disease were treated with ICE +/- RDT (AHOPCA) or with GV(Gemcitabine-Vinorelbin)/IV(Ifosfamide-Vinorelbin) +/- radiotherapy (RDT) + autologous stem cell transplant (ASCT) (GATLA) depending on patient's status performance.

Results In GATLA 7 out of 77 patients (9%) relapsed: Of 3 patients with early relapse/refractory disease one died of progressive disease, 2 were refractory to GV/IV strategy but are alive in CR after subsequent therapies. Four patients with late relapse were rescued with GV/IV +/- RT + ASCT and are alive in CR.
In AHOPCA 16 out of 123 (13%) relapsed: All 9 patients with early relapse/refractory disease died of progressive disease. Of the 7 late relapsed patients rescued by ICE+/-RDT, 3 were refractory and died and 4 remain alive and in CR.

Conclusion In an ethical randomization due to local resources, HR patients with early relapse or refractory disease after OEPA-COPDAC were difficult to salvage in both settings even with access to ASCT. Patients with late relapse after OEPA COPDAC appear to benefit from ASCT.

S-VI | Session VI: Cellular therapies

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DOI 10.1055/s-0040-1701875

S-VI-01 T cell therapies to overcome the tumor microenvironment in HL

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DOI 10.1055/s-0040-1701876

S-VI-02 CD30 CAR T for HL and ALCL

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DOI 10.1055/s-0040-1701877

S-VI-03 Study on primary immunodeficiencies & EBV- induced HL

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DOI 10.1055/s-0040-1701878

Content Since more than a century, numerous observations have confirmed the key role of the immune system in the defense against cancers. The Epstein Barr virus (EBV) is associated with the development of lymphoproliferative disorders including B-cell lymphomas such as Hodgkin's lymphoma (HL). Several pediatric forms of mendelian susceptibility to EBV infection leading to B-cell lymphomas have been recently identified. Studies of these primary immunodeficiencies allowed the discovery of factors and pathways involved the immune response against EBV, and more generally in the immune-surveillance of lymphomas. Our current hypothesis is that germinal mutations affecting the immune response could be responsible of pediatric forms of lymphoma. Until now 56 pediatric patients with B-cell lymphoproliferative disorders including 30 cases of HL have been recruited from pediatric clinical departments from French Hospitals. Patients and their relative were analyzed by whole exome sequencing (WES) to identify the genetic variations possibly contributing in the appearance of lymphoma in these patients. For patients diagnosed with Hodgkin lymphoma (HL), all were below 10 years old. Preliminary analyses of WES data identified relevant germinal genetic variations in 20% of cases. These mutations will be studied to understand their effect on the immune response and the lymphomagenesis. It is expected that this work will provide new insights into the pathophysiology of pediatric B lymphomas in particular Hodgkin's lymphoma, including tools for the molecular and genetic diagnosis of these conditions.

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S-VI-04 Interactive Case Presentation

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S-VI-05 Tumor associated antigen specific T cells for Hodgkin Lymphoma

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Conflict of Interest: Catherine M. Bollard Stock and Other Ownership Interests: Mana Therapeutics, NexImmune, Torque, Cabaletta Bio Consulting or Advisory Role: Torque, NexImmune, Cellectis, Cabaletta Bio Patents, Royalties, Other Intellectual Property: TAA-specific T cells and HIV-specific T cells

Patrick J. Hanley Stock and Other Ownership Interests: Mana Therapeutics Honoraria: Dava Oncology Consulting or Advisory Role: Mana Therapeutics, NexImmune Patents, Royalties, Other Intellectual Property: Mana Therapeutics has licensed technology of which I am listed as an inventor from Children's National, Health System Travel, Accommodations, Expenses: Terumo, Dava Oncology

Introduction Hodgkin Lymphoma (HL) Reed Sternberg cells express tumor associated antigens (TAA) that are potential targets for cellular therapies. We recently demonstrated that TAA specific T cells (TAA-T) targeting WT1, PRAME and Survivin were safe and associated with prolonged time to progression in solid tumors [1]. Hence, we evaluated whether TAA-T are safe and elicit anti-tumor effects in patients with relapsed/refractory (rel/ref) HL.

Methods TAA-T products were generated from patients or healthy donors on 2 trials (NCT02203903;NCT03843294). 7 patients (2 allogeneic; 5 autologous) received TAA-T for rel/ref HL or as consolidation after hematopoietic stem cell transplant (HSCT) at dose levels up to 2.0e7/m2 and were monitored for safety and response. Patients could receive Nivolumab as clinically indicated.

Results TAA-T products were predominantly CD3+ T cells (Median 84.9%; range 80.9-99.5%), with CD4+ T cells (Median 10.9%; range 1.74-20%) and CD8+ T cells (Median 69.8%; range 29.3-81.6%)] and NK cells (Median 0.92% (range 0.3-16.8%)). Products manufactured from patients with no PD1 inhibitor exposure (n=2) had significantly higher PD1 expression on CD4+ (p=0.001) and CD8+ T cells (p=0.02) compared to those who were exposed to PD1 inhibitors immediately prior to TAA-T generation (n=4). TAA-T products showed specificity to 1-3 TAAs. Median age of patients was 36 years (range 18-53) and median time to follow-up from TAA-T#1 was 8 months (range 2-32). 6 out of 7 patients completed the 45 days safety monitoring with no DLTs. One allogeneic HSCT recipient had measurable disease pre-infusion and progressed at 6 weeks. He then received Nivolumab off protocol and achieved complete remission (CR) but developed Grade 4 GVHD. The other allogeneic recipient was in CR prior to TAA-T and remained in CR for 2+ yrs. Of the 4 autologous recipients, one patient in CR pre TAA-T remains in CR at 2+ years. 3 with measurable disease pre TAA-T had stable disease at week 6 post TAA-T#1 (duration 1.5-9 months).To evaluate TAA-T persistence, unique T cell receptor clonotypes from a TAA-T cell product were detected in peripheral blood 4 weeks post infusion. Additional data is pending.

Conclusion TAA-T were safe in patients with rel/ref HL including after autologous or allogeneic HSCT. Prolonged continued CRs were observed when TAA-T were given post HSCT. TAA-T can be detected in vivo using TCR sequencing. We are now evaluating whether PD1 exposure plays a role in their long term persistence in vivo.

Study supported by:

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2. Safeway Foundation
3. American Society of Hematology

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S-VII | Session VII: Contemporary Radiotherapy across the PHL Working Groups

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DOI 10.1055/s-0040-1701881

S-VII-01 Panel Case Discussions (Low risk, Int risk, High risk)

DOI 10.1055/s-0040-1701882
Emphasis on field design
- David Hodgson (COG)
- Matthew Krasin (St. Jude/Stanford/Harvard)
- Maurizio Mascarin (EuroNet)

Cardiac/breast toxicity
- Louis (Sandy) Constine, USA

Radiation planning VMAT/Protons
- Brad Hoppe, USA

S-VII-02 Are event-free survival and freedom-from progression compromised by reduced radiation doses fields? Comparison between the results of the AIEOP (Italian Association of Pediatric Hematology and Oncology) LH-2004 & MH96 Protocols

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DOI 10.1055/s-0040-1701883
Introduction
Objective To compare the results of the LH2004 protocol with those of the previous MH96 study - already published - after a similar observation time, and to evaluate if reduced RT doses & fields compromise FFP and EFS rates.
Methods GR1: stages I-IIA w/out: M/T ≥0.33 or ≥4 nodal sites or hilar adenopathy; GR2: pts not included in G1 and GR3; GR3: stages IIIB-IV and pts with M/T≥0.33. MH96 therapy GR1: 3 ABVD+IFRT in pts with mediastinal mass and in PR pts after CT. GR2: 4 COPP/ABV+IFRT. GR3: 6 COPP/ABV+ IFRT. RT doses were: 20 Gy if CR or PR≥75%, 30 Gy if PR<75%. LH2004 therapy GR1: 3 ABVD+25,2 Gy only to PR after CT. GR2: 4 COPP/ABV+14,4 Gy if CR achieved; PR pts received 2 cycles of IEP (Ifosfamide, Etoposide and Prednisone) and RT (14,4 Gy if CR, 25,2 if PR). GR3: 4 COPP/ABV and 2 further COPP/ABV+RT if CR was achieved. PR pts: 2 IEP+14,4 Gy if CR was obtained; if not, pts received 2 additional COPP/ABV+RT according to the quality of response. Irradiation fields considered involved nodal regions. Response evaluation was after cycle 2 and 4 and after CT in GR3, by conventional imaging and with PET in pts with mediastinal mass.
Results From June 2004 to July 2017, 1300 pts were enrolled into the LH2004 protocol: 1201 evaluable for the analysis, with a median FUP time of 7,25 yrs. 181 pts were included in GR1, 274 in GR2 and 746 in GR3. The 10yr FFP rates registered in LH2004 GR1, GR2 and GR3 pts are 90.0%, 90.2% and 75.2% respectively and those of MH96 are 92.4%, 84.7% and 78.6%.
RT was spared in 70% of LH2004-GR1 pts, because of CR after CT; the 10yr EFS rates are 90.1% and 76.9% in noRT and irradiated pts respectively. In MH96-GR1 RT was avoided in 57% of pts; the 10yr EFS are 87.1% and 91.2% respectively for noRT and irradiated pts; no significant difference in both comparisons.
With regard to RT doses in the LH2004 study, 77% of GR2 pts received 14,4Gy; the 10yr FFP rate is 91.5% vs 89.5% of pts treated with higher dose because in PR. In GR3, 67% of pts received 14,4Gy; the 10yr FFP is 85.5% vs 66.1% of pts treated with higher dose (p=0.0000).
Conclusion In GR1 the removal of RT for all CR pts did not determine a significant difference with irradiated pts, who showed a lower EFS rate. In GR2 the reduction of RT doses & fields did not compromise the prognosis in pts in CR at the end of chemotherapy. In GR3 additional CT and RT dose did not succeed in overcome the gap between CR and PR patients. The long-term FFP rates of therapeutic groups in the two trials are superimposable.

S-VII-03 Reduction in Cardiac Radiation Dose Among Children Receiving Mediastinal RT: Comparison of Involved-Site vs Involved-Field RT Delivered in Three Children's Oncology Group Trials

Chairs Bergeron Gravel S[1], Khandwala M[2], Wolden SL[3], Castellino SM[4], Friedman DL[5], Kelly KM[6], Roberts KB[7], Constine LS[8], Schwartz CL[9], Fitzgerald TJ[10], Hoppe BS[11], Hodgson D[12]
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DOI 10.1055/s-0040-1701884
Introduction Delayed cardiac toxicity is a potential complication of treatment among survivors of pediatric Hodgkin Lymphoma (HL) treated with mediastinal radiation therapy (RT). The transition from involved-field RT (IFRT) to more conformal involved-site RT (ISRT) was intended to reduce normal tissue exposure among patients treated on Children's Oncology Group (COG) trials. We evaluated the cardiac dose received by patients treated on three COG trials to determine whether ISRT had achieved this goal.

Methods Cardiac radiation dose was determined for patients with available RT-DICOM data submitted to IROC for patients treated with mediastinal RT on COG trials AHOD 0031 [1] (treated with IFRT to all involved sites, N=87 with evaluable DICOM RT plans), AHOD 0831 [2] (IFRT to sites of bulk or slow response; N=121) and AHOD 1331 (treated with ISRT to large mediastinal adenopathy (LMA) or slow early response; N=227). For each patient we calculated the mean heart dose and percent volume of heart receiving ≥20Gy (V20), both of which have been shown previously to be correlated with delayed cardiotoxicity, and compared heart doses between AHOD 1331 (ISRT) and AHOD 0831 and AHOD 0031 (IFRT).

Results There was a significant decline in the percentage of patients who received protocol directed RT in more recent studies: 93.8%, 75.8% and 45.8% respectively in AHOD 0031 (standard arm), AHOD 0831 and AHOD 1331. The heart doses among patients getting mediastinal ISRT on AHOD 1331 were significantly lower (median of mean heart doses = 10.1Gy) compared to IFRT used on AHOD 0831 (13.8Gy) and AHOD 0031 (14.5Gy), $p<0.05$. Similarly, the cardiac V20 was also significantly lower with ISRT on AHOD 1331. Patients receiving mediastinal ISRT on AHOD 1331 for LMA had a lower mean heart doses (median value = 10.1Gy) than those with LMA on the older studies (15.2Gy on AHOD 0031 and 14.1Gy on AHOD 0831).

Conclusion The transition to ISRT on COG AHOD 1331 was associated with a significant decrease in cardiac heart dose compared to prior trials that used IFRT. Based on dose-risk data from the Childhood Cancer Survivor Study [3], these results suggest that compared to chemotherapy alone, mediastinal ISRT as used on AHOD 1331 could increase the 30-year cumulative incidence of heart disease by approximately 0.5-2% for all patients on the trial and 1-4% for those getting mediastinal RT.

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S-VII-04 Cost-effectiveness of proton therapy for young adults with mediastinal lymphoma: analysis of an institutional cohort

Chairs Mailhot Vega RB[1], Patel S[2], Bates JE[1], Lynch J[4], Bansal M[3], Slayton W[5], Parsons SK[6], Hoppe BS[7], Mendenhall NP[1]

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Conflict of Interest: In the last 36 months, RBMV received a travel grant from IBA.BSH is a scientific consultant for Merck & Co., and Bristol-Myers Squibb.

Introduction Proton beam therapy (PBT) decreases radiation doses to healthy tissues distal to the target when compared with intensity-modulated photon radiotherapy (IMRT). This physical property is particularly important for mediastinal lymphomas (ML), wherein tumors approximate the heart, since higher mean heart doses (MHDs) are associated with a higher incidence of coronary heart disease (CHD). Yet, PBT is more expensive than IMRT, and fewer centers offer PBT. In the absence of long-term clinical data, we pursued a cost-effectiveness analysis (CEAs) utilizing evidence-based modeling with known data to help guide decision-makers in allocating this limited resource.

Methods We evaluated the cost-effectiveness of PBT vs IMRT for treatment of ML to 30.6 Gy. We created a Markov cohort model for which patients age 30 years would possibly experience several health states for which CHD was modified by MHD between RT modalities: health, relapse, CHD, and death. Relapse risk was informed by HD14, and MHD-CHD probability was informed by van Nimwegen et al. CHD baseline risk used Framingham data and differed between men and women. Costs, calculated from a payer perspective, were in 2018 USD. Under an institutional IRB study, 40 patients with ML had RT treatments planned with both PBT and IMRT for which MHDs were calculated for both modalities. We used these 40 separate PBT-IMRT MHD pairs to evaluate the percentage of patients for whom PBT would be cost-effective. The model terminated at age 80 years, above which Framingham rates are not reported. The model results are reported using incremental cost-effectiveness ratios (ICERs) using willingness to pay (WTP) thresholds of $100K/QALY and $200K.

Results IMRT and PBT MHD averages were 13.9 (range, 1.6-26.2) and 10.2 (range, 2.0-19.8) Gy, respectively. Using these average MHDs, the respective ICERs for PBT use for men and women were $71K/QALY and $108K/QALY, respectively. On individual patient-level analyses of the 40 person ML cohort, using WTP=$100K/QALY, PBT was cost-effective for 50% of women and 60% of men. Using WTP=$200K/QALY, PBT was cost-effective for 60% of women and 73% of men.

Conclusion This CEA compared PBT and IMRT by differential risk of CHD without evaluating other toxicities like breast cancer, sarcoma, congestive heart failure, or lung disease. In this model, PBT was cost-effective for most patients although men were favored to benefit more than women given their higher baseline incidence of CHD.

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S-VII-05 Proton-Radiotherapy for treatment of Hodgkin's disease of minor or adolescent patients

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Introduction Radiotherapy (RT) is an integral part of the treatment of Hodgkin's disease. Especially for lymphoma located in the mediastinum adverse effects are of importance. In particular, secondary cancers, like in example

breast cancers or lung cancers, as well as cardiovascular side effects must be pointed out. These adverse effects depend either on the mean RT- dose or on the dose per volume. Proton-RT has compared to conventional Photon-RT unique features like a finite range and a maximum energy deposition in the region of the Bragg- peak. Therefore we choose to investigate and analyze the influence of Proton-RT for patients with Hodgkin's disease for lymphoma located in the mediastinum.

Methods In 10 adolescent and minor patients different photon- RT and proton-RT techniques have been compared regarding their dose to organs at risk located in the mediastinum. As important organs at risk the lungs, the heart with its substructures, the thyroid gland, the esophagus, the trachea, the breasts and the spinal cord has been selected. Dose volume histograms and mean doses as well as certain other dose parameters have been calculated for these organs at risk. With data derived from literature a risk assessment for late adverse effects has been conducted. A statistical evaluation was carried out by means of a non-parametric ANOVA with pairwise comparisons (Kruskal-Wallis).

Results Homogeneity indices, conformity indices and dose coverage were comparable for all different RT modalities.

Statistically significant reductions of the mean doses were achieved by proton irradiation for the mammary glands, the lungs, the spinal cord, the esophagus, the heart and the cardiac valves.

The calculated relative risk for lung cancers and breast cancers has been reduced by up to 2.2- fold and 2.7-fold. The calculated relative risk for cardiovascular adverse effects has been split half for proton-RT compared to photon-RT. [1]

Conclusion Proton-RT is suitable to reduce the dose to organs at risk in mediastinal lymphoma and might lead to a reduced rate of severe late onset adverse effects. Therefore, for suitable target volumes, Proton-RT for Hodgkin's disease should be taken into consideration.

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S-VIII | Session VIII: Survivorship and Aftercare

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S-VIII-01 Fertility preservation

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DOI 10.1055/s-0040-1701888

S-VIII-02 Late health outcomes

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DOI 10.1055/s-0040-1701889

S-VIII-03 Introduction

DOI 10.1055/s-0040-1701890

S-VIII-04 Interactive Case Presentation

DOI 10.1055/s-0040-1701891

S-VIII-05 Subsequent Malignant Neoplasms Among Children and Adolescents with Hodgkin Lymphoma Treated with Response-Adapted Therapy: A Report from the Children's Oncology Group Study AHOD0031

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DOI 10.1055/s-0040-1701892

Conflict of Interest: LGR has served on advisory boards for Cellege, Janssen, ADC Therapuetics.

Introduction Survivors of Hodgkin lymphoma (HL) have an increased risk of subsequent malignant neoplasms (SMNs). Response-adapted treatment may decrease this risk by reducing exposure to therapy associated with SMN risk. The Children's Oncology Group Study AHOD0031 evaluated response-adapted therapy for children and adolescents with intermediate-risk HL. We report the SMNs among 1,711 patients enrolled on AHOD0031.

Methods Patients were treated with four cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide with or without involved field radiation therapy (RT). Patients with a slow early response to initial chemotherapy were randomized to two additional cycles of dexamethasone, etoposide, cisplatin and cytarabine or no additional therapy. At a median follow up of 7.3 years, an analysis of SMNs was performed.

Results The 5-year cumulative incidence of SMN was 0.47%. SMNs included 3 patients with AML, 11 with solid tumors, and 3 with lymphoma. The standardized incidence ratio for SMN was 9.49 with an excess absolute risk of 1.23 per 1,000 person-years. The cumulative incidence of SMNs was higher among patients who received RT (p=0.037). In multivariate analysis, RT, B-symptoms, and race were associated with risk for SMNs.

Conclusion The incidence of SMNs in this cohort is low. Given the latency from exposure, we have likely captured all cases of secondary leukemia. Longer follow-up is needed to determine the risk of solid tumors. Avoidance of RT without sacrificing disease control should remain a goal for future therapeutic approaches. Patients treated according to this strategy are expected to be at lower risk of SMN.

S-VIII-06 Late effects after Hodgkin lymphoma in childhood and adolescence – results of the German Survivor Cohort after 22 years of follow-up

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Introduction Overall survival after Hodgkin lymphoma (HL) in childhood and adolescence is 94% after 10 years, but decreases to 88% after 30 years due to long term effects of cancer therapy. Treatment related late effects such as radiotherapy-induced malignant neoplasms, cardiovascular diseases, thyroid gland disorders, impaired male fertility, and pulmonary fibrosis have so far been identified.

Methods Starting in 1999, questionnaires were sent every 3 to 4 years to all long- term survivors of the first seven consecutive German-Austrian pediatric HL treatment studies to obtain information about their health status by the former chairpersons (G. Schellong and W. Doerffel) (1,2) In 2016, data of 1477/2187 survivors (68%) could be transferred to the current HL study center (chairperson D. Körholz) after obtaining

written informed consent. The late effect registry consecutively included survivors of the latest German-Austrian HL trial, GPOH-HD 2002 into the status questionnaire sent out in 2018.

Results Thestudy cohortnow consists of 1907 patientsthat were treated for HL at age < 18 years in 1978 to 2005. Median age at diagnosis was 13.9 years (2.5 – 23.3), 81% of all patients received radiotherapy. 1094 survivors (57%) (501 male/593 female) with a median age of 35.7 (18.1 – 55.2) years and a follow-up time of 21.7 (12.9 – 40.6) years responded to the questionnaire: 30% were smokers or former smokers and 58% reported physical exercise (38% > 150 min per week). 52.5% of all men and 30.1 % of all women reported overweight with BMI > 25. 29.5% of all men and 54.8% of all women had children.

Conclusion The current results require more detailed analysis and correlation to treatment factors. The long term follow-up of the German HL survivor cohort will be continued further and extended to more patients ≤ 10 years after treatment. Findings on treatment-related late effects may be used to design upcoming Pediatric Hodgkin Lymphoma trials. Results may translate into immediate improvements in long term follow-up care, e.g. breast cancer screening programs after chest irradiation. Long term follow-up of young HL survivors is essential for improving long term survival and follow-up care.

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S-VIII-07 Hyperlipoproteinemia, insulin resistance and metabolic syndrome in long-term survivors of Hodgkin lymphoma during childhood and adolescence

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Introduction Long-term survivors of Hodgkin lymphoma during childhood or adolescence (HL survivors) are at high risk of developing treatment-related late cardiovascular sequelae.

Methods In our study we evaluated the presence of modifiable cardiovascular risk factors (hypertension, hyperlipoproteinemia, hyperinsulinemia, obesity), endothelial and inflammatory markers (E-selectin, PAI-1, hs-CRP) and atherosclerotic changes in the common carotid arteries. Assessment was performed in 80 young adult Hodgkin lymphoma long-term survivors at more than 10 years after the potentially cardiovascular toxic anticancer treatment (median age at evaluation 34.7 years; range 24.1- 40.9 years). The HL survivors were compared with 83 age- and gender-matched healthy volunteers.

Results The HL survivors showedunfavorable lipid profiles compared to those of healthy controls: triglycerides (p=0.01); total cholesterol (p=0.0004), low density lipoprotein cholesterol (p=0.005). In HL survivors, we found a higher prevalence of hypertension (p=0.004), insulin resistance (p=0.0002), hyperglycemia (p=0.0002) and metabolic syndrome (p=0.01). Ultrasonographic examination of both common carotid arteries revealed a higher prevalence of atherosclerotic plaques (p=0.0009) and higher carotid intima-media thickness (p<0.0001) in HL survivors. Markers of oxidative stress (advanced oxidation protein products, oxidized low-density lipoprotein), inflammation (hs-CRP) and endothelial dysfunction (E-selectin, PAI-1) were also higher in HL survivors (p<0.0001, p=0.0002, p=0.0031, p=0.0087, p=0.004, respectively).

Conclusion Adult survivors of Hodgkin lymphoma during childhood and adolescence need follow-up with screening of metabolic syndrome components and unfavorable lifestyle factors and early management of these risk factors.

This study was supported by grant NV15-30494A from the Ministry of Health of the Czech Republic.

S-VIII-08 Chemotherapy-induced loss of protective antibody titers against commonest vaccine-preventable infections in patients with pediatric Hodgkin lymphoma

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Conflict of Interest: none

Introduction Loss of protective humoral immunity after cancer treatment has previously been recognized. Magnitude of this side effect depends on type of neoplasm, as well as the treatment strength and duration. The mechanism of loss is multifactorial; it involves depletion of memory B- and plasma cells, and their antibody production capacity [1]. It was demonstrated that after cessation of therapy for acute lymphoblastic leukemia (ALL), serum immunoglobulin (IgG) levels, which is a reflection of B cell function, will recover around 6 months off therapy, although it still may be suboptimal [2, 3]. Several studies have been published, testing only specific vaccine titers in isolated subsets of pediatric cancer patients, with somewhat inconclusive results about whether patients should be tested and revaccinated for preventable diseases[4, 5]. The pattern of loss of protective humoral immunity in pediatric Hodgkin lymphoma patients remains uncharacterized. We evaluated spectrum of loss of vaccination titers in pediatric HL patients, in order to determine if standardized evaluation and re-vaccination protocols should be instituted.

Methods Retrospective chart review of 156 HL and ALL patients treated at Cleveland Clinic Children's Hospital (CCCH), who were off therapy ≥ 6 months. Confirmation of vaccination per CDC schedule prior to diagnosis was made through EMR. Patients who had one or more serum antibody measurement against Hepatitis B, Measles, Mumps, Rubella, Varicella, Diphtheria or Tetanus, per CCCH laboratory reference standards were noted. Patients with pre-existing PID; treatment with IVIG; immunosuppressant therapy for another diagnosis; disease progression requiring ASCT, were excluded.

Results Thirty six HL patients were identified. Humoral immunity testing was performed in 16 patients (44%). The loss or equivocal titers for the following vaccines were noted; hepatitis B (13/16=81%), measles (7/16=44%), mumps (3/16=19%), rubella (2/16=13%), varicella (8/16=50%), diphtheria (5/16=31%), tetanus (2/16=13%). The most drastic changes were seen in HL patients treated on high-risk protocols. Results were similar to the ones seen in ALL patients.

Conclusion Results of this *pilot* project suggest that routine evaluation of antibody titers post-treatment in pediatric HL patients should be implemented uniformly as there are marked decline in protective IgG levels. Implementing a standardized re-vaccination schedule for all HL patients off-treatment will ensure seroprotection against common preventable diseases.

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PW VI-X | Guided Poster Walk

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PW VI-X-01 PW VI-X-01 Relapse-localization in pediatric patients with Hodgkin lymphoma

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Conflict of Interest: The authors report no conflicts of interest.

Introduction Radiotherapy (RT) is the single most effective modality to achieve local control of Hodgkin lymphoma (HL) [1]. However, large treatment fields of the past are associated with an increased morbidity and mortality in long-term survivors [2]. In the management of pediatric patients with HL (pHL), recent treatment protocols use a response-based approach to achieve omission of consolidating RT following combination chemotherapy due to the risk of late toxicity. Event-free survival rates decrease with up to 10% when RT is omitted, but salvage treatment is effective and overall survival rates are similar so far [3,4]. However, intensive salvage treatment is also associated with significant late effects. It is recognized that most relapses occur within the initially involved sites if RT is not used [5]. Here, we analyze the relapse-localization relative to the initially involved site, and if irradiated, to the irradiated site in pHL.

Methods The Danish Childhood Cancer Registry was used to identify children diagnosed with HL and those who relapsed from 1990–2018 at two institutions. Patient characteristics, treatment details (including RT plans), and diagnostic imaging were collected. We merged scans from the time of diagnosis and the time of relapse using the Eclipse treatment planning system (Varian Medical Systems) and visually assessed the relapse-localization relative to the initially involved site and, if irradiated, the irradiated site.

Results A total of 130 children were diagnosed with HL and 18 relapses were registered. Out of 18 patients 3 had refractory disease resulting in 15 relapses and a crude relapse-rate of 11.5%. The patients' median age at time of diagnosis was 13 years (range 5–17) and the median time to relapse was 6 months (range 2–59). Out of 15 patients 14 relapsed within the initially involved site. Six patients had received RT and 5 relapsed within both the initially involved and irradiated site (3 single site, 2 multiple sites). One patient relapsed outside of both the initially involved site and the irradiated site. Out of 5 patients with initially bulky disease, 2 relapsed within (no RT) and 3 relapsed outside (2 irradiated, 1 not) the site of bulky disease.

Conclusion It is reasonable to conclude that most relapses occur within the initially involved sites, and that RT improves local control. However, the number of relapses is small, and it is difficult to draw conclusions regarding the relapse pattern. Relapses-localization in pHL from all of Denmark will be analyzed.

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PW VI-X-02 BV-DHAP as salvage treatment for high risk adolescent Hodgkin lymphoma

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Introduction Hodgkin lymphoma (HL) is a highly curable lymphoid malignancy; however treatment of relapsed/refractory disease remains challenging. Early relapse, lung disease, stage IV at relapse, identify very high risk patients.

Brentuximab Vedotin (BV), an anti-CD30 antibody-drug conjugate, has shown clinical activity in relapsed/refractory classical HL as single agent or combined with various chemotherapeutic regimens, mostly in adulthood and in phase I-II studies in children and adolescent [1]. Recently the BV-DHAP (dexamethasone, cytarabin, cisplatin) combined regimen has been used with promising results in a phase II study in adults [2]. This regimen has not been reported in children or adolescents, so far. We present a case of relapse of classical HL with unfavorable prognosis, successfully treated with the combination BV-DHAP.

Methods Case report: the child, 15 years old, diagnosed with classical HL nodular sclerosis, stage IVB with lung involvement, received first line therapy according to international Euronet PHL-C2 protocol, TL3, random DECOPDAC + mediastinal irradiation. The CT scan performed at 3-month follow up showed a nodule in the left lung. The FDG PET/CT scan showed pathological uptake in the lung, mediastinum and subcutaneous nodular tissue. Unfortunately the subsequent biopsies of a subcutaneous nodule, mediastinal adenopathy and supraclavicular adenopathy failed to demonstrate the relapse. The imaging evaluation two months later revealed disseminated lung disease with ground glass infiltrates and enlarged parenchimal infiltrate with increased mediastinal adenopathy. A biopsy of the lung by VATS (video-assisted thoracoscopic surgery) confirmed the relapse of classical HL, showing massive infiltration of histiocytes CD68+, histological risk factor for poor prognosis, as recently reported [3].

Results A combination therapy consisting of BV and classical lymphoma salvage regimen DHAP was administered. Following 3 treatment cycles in 21-day intervals, the evaluation of the disease showed complete metabolic response (FDG-PET/CT Deauville Score 2). He went on with a further cycle BV-DHAP, achieving pretransplant complete radiological and metabolic response (negative FDG-PET/CT).

The treatment was well tolerated, hematological toxicity (grade 3 CTCAE) was reported. The boy performed autoSCT and BV post-transplant consolidation.

Conclusion The regimen BV-DHAP, not previously reported in children or adolescent, in our experience was highly effective with manageable toxicity.

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PW VI-X-03 Brentuximab vedotin (BV) in recurrent and refractory Hodgkin Lymphoma (HL) in children. Experience of Polish Pediatric Leukemia/Lymphoma Study Group

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Introduction Brentuximab Vedotin treatment gives a chance of cure in patients who suffer from relapsing or refractory HL. In Poland BV started to be used in 2012, Initially as monotherapy and later, since 2014 as a combination treatment with chemotherapy.

Methods To estimate BV use in pediatric HL in Poland a questionnaire survey was performed. Questionnaires were sent to 17 pediatric oncology departments in Poland. Status of disease before BV treatment, prior treatment, BV treatment type, treatment response and patient's care after BV therapy were addressed.

Results BV treatment has been in use since 2012 in 9 polish pediatric oncology centers. It was introduced in 17 patients 7,3-22,3 (median: 15,9) years old with relapsing/refractory HL. Three patients developed disease progression before completion of first-line treatment, 14 patients completed first-line treatment of which 6 were treated without radiotherapy.
BV therapy was administered as second-line, third-line and fourth-line treatment in 12, 3 and 2 patients respectively.
BV monotherapy was used in earlier period (2012-2015), in 5 patients, who received 3-8 (median:5) BV cycles. In three cases further disease progression was observed and in 2 cases disease stabilization occurred. Two patients died of disease progression and one of allo-SCT complication. Two patients are alive after auto-SCT.
BV in combination with chemotherapy was used in 12 patients since 2014. In 2 cases BV-AVD was introduced, in 5 cases BV+Bendamustin and 5 patients received BV in combination with other chemotherapy protocols. In 9 cases BV combination therapy was used as a part of second line treatment, in 3 was used in second and further disease progressions. Death from progressive disease occurred in 2 cases and death from allo-SCT complications occurred in another 2 cases.

Conclusion BV treatment was used in monotherapy initially and as a combination treatment in later period, initially as a salvage therapy after second and further disease progressions. As more data on combination treatment are available BV+chemotherapy is currently used as a part of second line treatment in patients not responding adequately to initial salvage chemotherapy. More efforts to increase availability of BV therapy in Poland are required as initially this therapy was lacking sufficient financing of public health system in Poland.

PW VI-X-04 Cardiac substructures dose sparing in pediatric Hodgkin's lymphoma

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Conflict of Interest: Authors declare no conflict of interest

Introduction Pediatric Hodgkin's Lymphoma (PHL) survivors represent a group of patients (pt) at high risk for clinical and subclinical cardiovascular (CV) disease. The incidence of CV events increases over time from the diagnosis. Both chemotherapy and radiotherapy (RT) are responsible for cardiotoxicity. Often RT target is located near critical cardiac substructures (CS) such as origin of coronary arteries and cardiac valves. Thus, became important to assess the risk of long-term CV complications after therapy. In this study, we analyzed the dose received by different CS using intensity-modulated radiation therapy (IMRT) "butterfly" technique (BT)

Methods Four PHL pt (mean age 13±4) with stage II-IV and mediastinal bulky disease were treated with involved-site radiotherapy (IS-RT). Treatment plans were performed with TPS Pinnacle, planning a total dose range from: 14,4Gy in 8 fractions (fr) for pt enrolled in AIEOP LH 2004 protocol, and 28.8Gy in 16 fr for pt enrolled in Euronet PHL C2 protocol. We use Contrast CT (cCT) for segmentation of CS, than we performed deformable image registration (DIR) in MIM Software to adapt organs at risk between cCT and Simulation CT. The following CS were contoured: right and left atrium, right and left ventricle, aortic, pulmonary, mitral and tricuspid valves, left main, left anterior descending, left circumflex and right coronary arteries. IMRT plans were generated using 5 co-planar beams (3 anterior 330°- 0°- 30° and 2 posterior 160°-210°) BT. We analyzed PTV coverage (V95% -percentage volume receiving 95% of prescription dose-), and doses to CS (Dmax, Dmean). Furthermore, we performed a CS dosimetry comparison between IMRT and 3DCRT plan

Results Dose sparing of CS, especially origin of coronary arteries and cardiac valves, is achievable with IMRT BT. In in case of overlap with target, priority is assigned to target coverage. We met IMRT PTV coverage V95% =97% vs 81,09% 3DCRT (pvalue 0.04). Whole heart Dmean and Dmax were respectively 5,18Gy (±3,37) and 19,62Gy (±5,47) with IMRT vs 4,04Gy (±2,25) and 19,67Gy (±4,85) with 3DCRT plan. The lowest Dmean was achieved for aortic

and pulmonic valves and for left main, left circumflex and right coronary artery with IMRT BT plan

Conclusion Mediastinal radiation dose is the most important risk factor for the appearance of late CV disease in PHL. Lower radiation doses for current protocols and IMRT BT treatment planning increase dose sparing for CS so that further reduction of cardiac late effects may be expected

PW VI-X-05 Dosimetric comparison of active scanning Proton Therapy and Helical Tomotherapy in pediatric and adolescent Hodgkin's lymphoma treated with tomotherapy.

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Introduction The aim of this study is to compare radiotherapy plans using helical tomotherapy (HT) and active scanning proton technique (PT) for a group of pediatric-adolescent Hodgkin Lymphoma (HL) patients treated with HT.

Methods Five HL patients (pts), age 13-24 years (mean 16.5), (4 female IIB, IIIB, IVA an IVB, and 1 male stage IIIA), were enrolled in the AIEOP LH 2004 trial. Tumor sites were in the neck- mediastinum (n=1), mediastinum only (n=2), neck-mediastinum-abdomen (n=2). The pts were treated with 4 or 6 COPP-ABV plus involved fields HT, delivered at dose of 14.4Gy/8fr (2 pts in CR) or 25.2Gy/14fr (3 pts in PR). HT plan generated by the Hi-Art TomoPlan with a field of 2.5 cm, mean pitch of 0,215 and mean modulation factor of 1,75. All pts were re-planned with either proton multifield optimization dose (MFO) or single field optimization dose (SFO) active scanning proton technique. The median number of beams used for PT re-planning were 3 (2-5). The quality of target coverage (D2, D98), homogeneity (HI D2-D98), conformity (CI95) and the exposure of normal tissues for selected organs at risk (OARs) and the efficiency of radiation delivery were analyzed.

Results All HT patients are in CR after a median follow-up of 8 years (range 7,5-11). No chronic toxicity, nor second malignancy occurred. All HT plans as well as the PT plans feature excellent PTV coverage, high conformity and homogeneity (CI mean for PT 0.8, for HT 0.8; HI mean for PT 0.9, for HT 0.8). For all OARs, PT showed dose reductions compared with HT, especially in the lower and intermediate dose region of the DVHs, with the main advantages resulting in: heart, breast, lungs, thyroid gland. The dose to the OAR, expressed as average dose reduction (ADR) with PT compared with HT, is lowered as follow: heart ADR of D_{mean} by 4.9 Gy reduction in all pts; breast tissue ADR in D_{mean} of 3,3 Gy; lungs ADR in D_{mean} of about 2 Gy; thyroid ADR of D_{mean} of 4.5 Gy; esophagus no-differences. Spinal cord maximun dose, average reduction of 1,4 Gy. Noteworthy that one patient with extensive neck/axillary/supra/infradiaphragmatic disease could not be treated with PT because of the time required for the delivery of the treatment.

Conclusion Both techniques achieve high target coverage, homogeneity and conformal treatment plan; all parameter are slightly superior for PT plan. PT features superior dose-sparing of OARs. Dosimetric advantages may have the potential to translate into a reduction of long-term radiation-induced toxicity.

PW VI-X-06 Access to proton beam therapy (PBT) for patients with large mediastinal adenopathy (LMA)

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Introduction Highly conformal radiation (RT) techniques that reduce normal tissue exposure can maximize the therapeutic ratio for pediatric patients with classical Hodgkin Lymphoma (cHL). PBT has equivalent disease control with reduced dose to healthy tissues among patients with LMA in cHL. However, this treatment is costly and generally restricted to patients in urban areas in North America. We evaluated patient and disease factors associated with PBT delivery to see if disparities existed.

Methods We examined individual-level data from patients enrolled on Children's Oncology Group (COG) study AHOD1331 (NCT02166463), a phase III trial for patients 2-21 years of age with high-risk cHL who received RT due to LMA. We conducted univariate testing by chi-square test for receipt of PBT with stage, age (< or ≥12), B symptoms, race/ethnicity, payment method (private vs. non private), and neighborhood socioeconomic status (SES), based on a binary definition of poverty level (< or ≥20%).

Results Among 265 patients with LMA who received RT, 200 (75%) received photon RT and 76 (25%) received PBT. Among those receiving PBT vs photon RT respectively, 13.8% vs 12.0% were Black, 24.6% vs 19.5% were Latinx, and 13.8% vs 10.0% were of low SES. While there was no significant difference in RT modality in univariate analysis by age, sex, race, ethnicity, or SES, there were statistically significant differences by stage (p=0.01) and B symptoms (p=0.01), with fewer children with B symptoms receiving PBT. A significantly higher proportion of patients receiving PBT were privately insured (67.7% private with PBT vs 50.5% photon RT, p=0.02).

Conclusion Understanding disparities in treatment of pediatric cHL is important. Future studies will apply multivariate analysis to understand drivers of disparate access to PBT beyond payment method. Analysis of geographic access to PBT will provide additional information for patients who live in remote areas.

PW VI-X-07 Long term effects of consolidative radiotherapy in Hodgkin's Lymphoma patients at Single institution

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Conflict of Interest: None

Introduction Radiotherapy (XRT) has historically played an important role in cure of patient with Hodgkin's Lymphoma (HL). However, the occurrence of

late adverse treatment effects effect the life expectancy and quality of life in HL survivors. Common late effects include second and subsequent malignant neoplasms (SMNs), several cardiovascular diseases (CVDs), thyroid dysfunction, sub-fertility, premature menopause, and fatigue. The aim of our study is to determine the long-term side effects of consolidative radiotherapy (XRT) in Paediatric Hodgkin lymphoma patients

Methods Medical records from January 2009 to December 2014 retrospectively reviewed after IRB approval. Data collected for patients diagnosed with Hodgkin's lymphoma at Shaukat Khanum Cancer Hospital, who had received consolidative radiotherapy as part of their treatment and looked at their the long-term side effects till January 2019.

Results Out of 749 patient, 117 (15.6%) were included who had radiotherapy as part of treatment. Low stage disease in 30 patients (26%) and 87 (74%) had advance stage. 36 patients (31%) treated with OEPA/COPP chemotherapy, 10 (8.5%) with CHLVPP/ABVD, 50 (43%) with COPDac/ABVD and 21 (18%) treated on other chemotherapy protocols. Mid-assessment scans showed 65% in partial remission, 33% in complete remission and 2% had disease progression. The most common site of XRT was neck and chest in 68 (58%) of patients followed by abdomen in 34 (29%) and skeletal in 15 (13%). 64 patients (55%) received less than 15 Gy radiations, 38 patients (32.5%) received 15-20 Gy radiations and 15 patients (13%) received more than 20 Gy radiations. Outcomes at end of consolidative XRT was complete remission in 99 patients (85%), 13 (11%) relapsed and in 5 patients disease progressed. Most common long-term side effect was hypothyroidism in 11 patients (9%) followed by hypogonadism in 2 patients likely due to Procarbazine. One patient had mild cardiotoxicity with Doxorubicin and recovered his cardiac functions with anti-failure meds. All 14 patients with late effects are alive and in remission until last follow up.

Conclusion Our analysis showed less long terms effects in patients as outcomes have improved with chemotherapy alone. However, those who develop them needs to be monitored closely. Patients who had complete remission at mid-assessment do not need to have radiotherapy

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PW VI-X-08 Hyperthyroidism as late adverse effect of treatment for Hodgkin lymphoma

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Introduction Recently, survival rate of Hodgkin lymphoma in childhood and adolescence is over 90%. However, late effects are important problem in this disease. Hyperthyroidism is reported as late effect in long surviving patients with Hodgkin lymphoma, especially in irradiated patients. As Hodgkin lymphoma is relatively rare disease in Asia compared with US and Europe, the report about this complication from Asia is rare.

Methods Herein, we report 2 cases of hyperthyroidism as late adverse effect of treatment for Hodgkin lymphoma.

Results Case 1 is 12-year-old boy. He complained left cervical swelling, fever and body weight loss. Biopsy of cervical lymph node revealed classical Hodgkin lymphoma, nodular sclerosis. His clinical stage was IIB. He was treated with 4 courses of ABVD regimen. However, additional 2 courses of BEACOPP regimen and irradiation therapy (cervical and mediastinal lesion: 21Gy, additional tumor bed: 12Gy) were performed because of positive image of PET. After 2 years and 8 months from the end of treatment, he was diagnosed as hyperthyroidism by blood examination (fT3 8.4pg/ml, fT4 2.2ng/dl, TSH <0.1mIU/ml). In addition, his family (mother, grandfather and aunt) had a past medical history of hyperthyroidism. He was treated with thiamazole.

Case 2 is 12-year-old girl. She complained cough and dyspnea. The chest X-ray revealed giant mass of thymus. She was diagnosed as classical Hodgkin lymphoma, nodular sclerosis by biopsy of thymic mass. Her clinical stage was IIBX. She received 2 courses of OPPA regimen and achieved complete remission. Moreover, she received additional 2 courses of COPP regimen and did not receive irradiation therapy. After 2 years and 6 months from the end of treatment, she complained palpitation, excessive sweating and body weight loss. Blood examination revealed hyperthyroidism (fT3 10.79pg/ml, fT4 2.78ng/dl, TSH <0.1mIU/ml). She was treated with thiamazole.

Hyperthyroidism as late effect of treatment for Hodgkin lymphoma is well known. Many manuscripts showed that irradiation therapy was the risk factor for hyperthyroidism as late effect. In case 1, he received irradiation therapy and had family history. In case 2, however, she never received irradiation therapy and never have family history of hyperthyroidism.

Conclusion Hyperthyroidism is notable late adverse effect in all treated patients with Hodgkin lymphoma.

16 May 2020

S-IX | Session IX: Staging Evaluation and Response Criteria Harmonization (SEARCH) for CAYAHL

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DOI 10.1055/s-0040-1701931

S-IX-01 E-lesions with an emphasis on bone involvement

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DOI 10.1055/s-0040-1701932

S-IX-02 Nodular sclerosis lymphoma - the new radiology sign

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Content

Objective To define a new radiological sign, the central hypo-attenuated lymph node in nodular sclerosis in Hodgkin's lymphoma in computed tomography (CT).

Materials and methods Throughout the last year, all patients diagnosed with lymphoma were CT - scanned with intravenous non-ionic contrast. CT scans were evaluated by an expert pediatric radiologist and were later pathology- proven to be nodular sclerosis type.

Results 7 newly-diagnosed cases of nodular sclerosis Hodgkin's lymphoma presented with the central hypo-attenuation of the compromised lymph

nodes in the CT-scans. All of them were pathology-proven diagnosed with nodular sclerosis Hodgkin's lymphoma.

Discussion We propose that the central hypo-attenuated lymph node sign is because of the accumulated lymph inside the compromised lymph node. This finding has been proven with pathology by the presence of collagen bands in the lymph node periphery. There's still work to be done, a systematic retrospective study on all Hodgkin's lymphoma at the moment of the diagnosis will determine the sensitivity, specificity, positive predictive value, and negative predictive values for this new radiologic sign.

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S-IX-03 Creating an International Hodgkin Lymphoma Data Commons

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S-IX-04 Methodological comparison of volumetric analysis on FDG PET in pediatric Hodgkin Lymphoma assessed at different timing

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Introduction Assessment of response to therapy in pediatric Hodgkin lymphoma (HL) patients by 18F-fluorodeoxyglucose PET/CT (FDG PET) has become a powerful tool for the discrimination of responders from non-responders. The addition of volumetric analyses can be regarded as a valuable help for disease prognostication and biological characterization. Given the multitude of methods available for volumetric analysis in HL, the AIEOP Hodgkin Lymphoma Study Group has designed a prospective evaluation of the Italian cohort of patients enrolled in the EuroNet-PHL-C2 trial.

Methods The primary objective of the study was to compare the different methods of volumetric assessment in the same HL patients at baseline and during the course of therapy. Overall, 50 patients with 150 scans were investigated for the current study. A dedicated software was used to delineate, semi-automatically, contours of the lesions using different threshold methods. More specifically, four threshold methods were applied: 1) Fixed 41% threshold of the SUVmax within the respective lymphoma site (V41%), 2) Fixed absolute SUV threshold of 2.5 (V2.5); 3) SUVmax(lesion)/SUVmean liver >1.5 (Vliver); 4) Adaptative method (AM). All parameters obtained from the different methods were compared and analyzed with respect to response.

Results Among the different methods investigated, the strongest correlation was observed between AM and Vliver (rho>0.9; p<0.001 for SUVmean, MTV and TLG at all scan timing), as well as V2.5 and AM or Vliver (rho 0.98, p<0.001 for TLG at baseline; rho>0.9; p<0.001 for SUVmean, MTV and TLG at interim and end-treatment response). Logistic regression demonstrated that MTV and TLG computation according to V2.5 and Vliver significantly correlated to response to treatment (p=0.01 and 0.04 for MTV and 0.03 and 0.04 for TLG, respectively).

Conclusion The best correlation for volumetric analysis is obtained for AM and Vliver, followed by V2.5. The volumetric analysis obtained from V2.5 and Vliver significantly correlated to response to therapy.

S-IX-05 The impact of the Point-spread-function (PSF) reconstruction on the response assessment in the Interim-PET (iPET) in Hodgkin lymphoma (HL)

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Conflict of Interest: Nothing to declare

Introduction Within the EuroNet-PHL-C2 study the iPET result has an impact on the further treatment. The iPET assessment is done quantitatively by the qPET method (mean SUV of the hottest connected voxel inside the tumor divided by mean SUV of the liver). A qPET-value < 1.30 corresponds to a Deauville score ≤ 3 and implies omission of radiotherapy (RTx). The aim of this study was to investigate the impact of the PSF reconstruction on the further treatment decision in comparison to a pure Ordered-subset-expectation-maximization reconstruction without PSF (OSEM) (current standard).

Methods The iPET datasets from 106 EuroNet-PHL-C2 patients were investigated. All datasets were available as PSF- as well as pure OSEM-reconstructions. The qPET-values were measured in both reconstruction forms. Based on these results, the influence of PSF concerning the treatment decision (RTx yes/no) was investigated.

Results 98/106 HL patients showed tumor residuals in iPET. The PSF-qPET-values were 13.3% (± 17.1%) higher than the OSEM-values. These results would have induced a change of treatment in 16/106 patients. The main reason seemed to be the Time-of-Flight (TOF) reconstruction which was applied more often with PSF (84x) than with OSEM (18x). If OSEM and PSF were both reconstructed with or without TOF, the PSF-qPET-values were 4.1% (± 13.7%) higher and a change of treatment would have occurred in 2/36 patients. If only PSF was reconstructed with TOF, the PSF-qPET-values were 19.3% (± 15.9%) higher and the treatment would have changed in 13/61 patients.

Conclusion The PSF-qPET-values in iPET were higher than the OSEM-qPET-values, especially if PSF was reconstructed with TOF and OSEM without. In these cases, PSF would have induced a radiotherapy in addionally 21% of the patients.

S-IX-06 Staging of Waldeyer's ring in Pediatric and Adolescent Patients with Hodgkin's lymphoma – Importance of multimodality imaging

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Conflict of Interest: No conflicts of interest!

Introduction Compared to pediatric Non-Hodgkin's lymphoma, involvement of Waldeyer's ring (IOWR) is rare in pediatric Hodgkin's lymphoma (HL). The decision on IOWR is based on ENT inspection. This method was included into the staging algorithm more than 30 years ago when modern cross-sectional imaging techniques were not as sophisticated as they are nowadays. ENT inspection can only evaluate the mucosal surface and is prone to interobserver variability. We hypothesize that combined morphologic and metabolic image reading results in a more accurate staging of the Waldeyer's ring (WR).

Methods The EuroNet-PHL-C1 trial recruited 2102 patients. 14 of them were diagnosed to have an IOWR and fulfilled the three inclusion criteria 1) central review was performed, 2) sufficiently evaluable imaging data (18F-FDG-PET, CT or MR) were available and 3) IOWR was diagnosed with ENT examination. The WR of these 14 patients was re-evaluated by applying an image-based algorithm consisting of 18F-FDG-PET and CT or MR (F18-FDG-PET worked as gate keeper by detecting asymmetric glucose metabolism in the WR region; then CT/MR evaluated the underlying reason for the asymmetric glucose metabolism). This algorithm was also applied to 100 consecutive patients who fulfilled the above mentioned criteria 1) and 2), but whose WR was inconspicuous on ENT examination.

Results The image-based algorithm confirmed only four of the 14 patients with IOWR on ENT examination. Of the remaining 10 patients, four had involvement of a retropharyngeal lymph node by HL but an inconspicuous WR and six had a completely inconspicuous WR on imaging. Applied to 100 consecutive patients with inconspicuous WR on ENT examination, the image-based algorithm confirmed non-involvement in 99 patients. Suspicion of IOWR was raised in one patient.

Conclusion The application of an image-based algorithm is feasible and easily applicable. It may subsitute ENT investigation in future study protocols and may also have an influence on the number or/and on the extension of irradiation fields of the upper neck in HL patients.

S-IX-07 Impact of central review of imaging in an FDG-PET response adapted Pediatric Hodgkin lymphoma protocol

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Introduction Response adapted treatment approaches are utilized in pediatric Hodgkin lymphoma (PHL) trials. Early response on FDG-PET can identify patients that may do well with less intensive therapy or may benefit from escalation in chemotherapy or involved site radiotherapy (ISRT). Central review of imaging ensures uniform response grading and subsequent treatment adaptation. As FDG-PET and visual Deauville scoring (D5S) has been adopted in PHL we investigated the correlation of institutional and central review of interim PET scans.

Methods AHOD 1331 is a randomized clinical trial for patients 2-21 years of age with newly diagnosed Stage IIB with bulk, III B or IV A/B classical HL (NCT02166463); accrual was complete in August 2019. Patients were randomized between two different systemic therapies and underwent response assessment after 2 cycles of chemotherapy (PET 2) in order to identify slow responding lesions (SRL) by D5S of 4,5, which would require ISRT at completion of treatment. Institutions reported a D5S of target lesions on PET2 and submitted it with the images to for central review.[1] Review consisted of two COG radiology reviewers for each case, with an additional reviewer adjudicating any discordance between the initial 2 central reviews. Levels of agreement were measured between institutional and central review, using nonweighted kappa (k) statistics. k values between 0.81 and 1.00 indicate very good agreement, 0.61 and 0.80 indicate good agreement, 0.41 and 0.60 indicate moderate agreement, and 0.21 to 0.4 indicate fair agreement.

[1] The study was supported in part with a grant from the National Cancer Institute (NCI), U10 CA180886, U10CA180899; and St. Baldrick's Foundation; IROC- RI NCI CA180803

Results Among 454 scans reviewed to date, PET2 agreement between central and institutional review was good with a k of 0.72 (95% CI 0.64-0.80). Overall, 16% (14/87) of all cases with SRL and 7% (27/367) rapid responding lesions (RRL) would have been misclassified as RRL or SRL respectively. Overall, 3.1% (14/454) would have been under treated and 6% (27/454) would have been incorrectly assigned to ISRT in the absence of central review.

Conclusion Central review of imaging remains essential for response adapted treatment protocols, by providing consistent response determination, and in 9% of cases in AHOD 1331, resulted in change in therapy. Further analysis is needed to identify factors associated with discordant institutional reporting of response assessment.

S-IX-08 Comparison of interim PET response to relapse vs. first-line treatment in children with classical Hodgkin lymphoma (HL) – contribution to the development of response criteria for relapsed HL

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Introduction Criteria for standardized interpretation of PET response to treatment in HL have been established in large patient cohorts at first-line treatment using the Deauville scale or quantitative parameters like qPET (1). There is no systematic data yet, if the same criteria can be adopted also at relapse.

Methods Between 2007 and 2013, 2131 children and adolescents with classical HL have been included in the EuroNet-PHL-C1-trial. From this cohort, interim PET datasets after two cycles of first-line treatment (iPET-FL) were available on the central server from 177 patients who subsequently developed relapse. From 101 of these patients interim PET datasets after two cycles of relapse treatment (iPET-rel) were available. SUVpeak in the most FDG-avid tumor residual, SUVmean in the liver and qPET values were determined.

Results SUVpeak- and qPET-values of iPET-FL and iPET-rel were not systematically different (p=0.28 and 0.47). In 33/177 iPET-FL and 27/101 iPET-rel no quantification could be performed due to already completely normalised FDG-uptake. The median SUVpeak in the remaining iPET was 1.9 at FL and 2.2 at relapse, the median qPET 1.8 at iPET-FL and 1.7 at iPET-rel. The mean liver uptake increased slightly but systematically from 1.7±0.5 at iPET-FL to 2.0±0.6 at iPET-rel, p<0.001.

Conclusion qPET-values of iPET of patients during first-line and relapse treatment are nearly identical. This supports the current approach to use the established first-line response criteria also in the relapse treatment.

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S-IX-09 CT-morphologic vs. metabolic tumor volume in pediatric Hodgkin-Lymphoma - A comparison of 19 different semiautomatic delineation methods

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Introduction The aim of this study was to evaluate the performance of automated tumour delineation methods for 18F-FDG PET (PET) and compare the metabolic tumour volume with the CT volume, to investigate factors potentially affecting the segmentation result and to deduce recommendations for the use of certain delineation methods.

Methods 19 different PET delineation methods were applied to assess the primary metabolic tumour volume (MTV) of the mediastinal tumour mass of 63 paediatric patients with untreated Hodgkin lymphoma. 13 segmentations based on region growing with varying SUV-thresholds (Hermes Hybrid 3D). Additionally, 6 based on two different iterative threshold algorithms (3 voxel- and 3 lesion-specific thresholds) (ABX-Rover).

The results were compared with manual CT morphologic delineations (GTV) and visual optimal metabolic volume (vMTV) to determine the volume error (VE). Additionally, potential influence factors like the SUV_{max}, the coefficient of variance (COV and the size of the lesion were investigated. A detailed analysis of the origin of deviations was also accomplished.

Results 18 of 19 delineation methods and the vMTV (median and range: 75,60ml; 4.10ml-389,70ml) were systematically smaller than the GTV (Med.: 141,80ml; 4,80ml-520,8ml) therefore, GTV is not a suitable reference standard for MTV in HL.

Mean VE with vMTV was lowest for an iterative voxel-specific-threshold (0,74%; SD: 27,44%), the best region growing algorithms work less exact and satisfactory (3SUV: 6,68%, SD: 63,59%; -41%SUV_{peak}: -4,95%, SD: 41,42%).

Conclusion GTV and MTV are different parameters in HL and GTV is not a suitable reference standard. Iterative segmentation methods, especially voxel-specific thresholds, measure the MTV more satisfactory, reproducible and less varying than region growing algorithms.

S-X | Session X: AYA Session

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S-X-01 HL biology in adolescents and young adults

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S-X-02 Navigating Survivorship for AYAs with Hodgkin Lymphoma

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S-X-03 Simulation modelling to delineate long term patient outcome in AYA HL

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S-X-04 Outcomes by age in pediatric and adolescent patients treated for de novo Hodgkin lymphoma on contemporary Children's Oncology Group trials

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Introduction Population-level studies suggest that adolescent/young adults (AYAs, defined by the National Cancer Institute as 15 – 39 years) with Hodgkin lymphoma (HL) have worse outcomes than younger patients. Recent guidelines from the American Society of Clinical Oncology and Friends of Cancer Research call for including patients ≥12 years of age on late phase trials spanning children and adults. We examined whether, in pediatric and adolescent patients receiving risk-based, response-adapted therapy for HL on contemporary Children's Oncology Group (COG) trials, age ≥12 years (vs. younger) would define a group with inferior outcomes.

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

Results Median follow-up was 6.9 years. A total of 1,733 patients were included in the study cohort. Mean age was 14.6 years (± 3.5) with 55% of patients ≥15 years (N= 956) and 82% ≥ 12 years (N= 1,417). Five-year cumulative incidence of relapse was higher in patients ≥12 years vs. <12 years (18% vs. 11%, p=0.008) as well as in those ≥15 years, vs. < 15 years (19% vs. 13%, p=0.003). In unadjusted analyses age ≥12 years vs. younger was associated with significantly worse EFS (87% vs. 80%, p= 0.01), as was age ≥15 years vs. younger (87% vs. 80%, p= 0.008). Multivariable modeling revealed that age was an independent risk factor for EFS using thresholds of both 12 and 15 years. Age ≥ 15 years was also an independent risk factor for all-cause mortality (hazard ratio: 2.6, 95% confidence interval: 1.2, 5.4).

Conclusion In patients treated for HL with response-based therapy on contemporary COG trials, age ≥12 years (vs. younger) was associated with inferior EFS and age ≥15 years was significantly associated with higher hazard of death. These findings provide rationale for including patients ≥ 12 years in clinical trials evaluating novel agents in the up-front setting for HL. Analyses examining early response to therapy, treatment-related toxicities, treatment delays and post-relapse survival by age are ongoing.

Chair Index

Author Index

Keyword Index