A decision tree analysis of pros and cons of upfront checkpoint inhibition in newly-diagnosed Hodgkin lymphoma

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Background: Standard treatment of Hodgkin lymphoma (HL) in children and adolescents includes chemotherapy often followed with radiotherapy (RT) and can result in a number of complications. For example, 5-25-year follow-up determines that the incidence of such complications as thyroid dysfunction, and cardiopulmonary and cardiovascular was 4-79% and 2-23%, respectively. With a follow-up of 10 and 30 years second cancers were 10.6 and 20.6%, respectively. Thus, precise and effective management strategies are essential in order to achieve the best outcomes for patients diagnosed with HL. The utilization of checkpoint inhibitors as a first-line treatment has exhibited significant potential in recent times, demonstrating enhanced survival rates, reduced toxicity and treatment-related morbidity.

Methods: A literature review of upfront checkpoint inhibition in newly-diagnosed HL was conducted.

Results: Study records on the subject are insufficient.

One of the trials suggested nivolumab and ADV in early-stage unfavorable classical Hodgkin lymphoma (NIVAHL) as a first-line treatment. The target group was 18-60 y/o. The efficacy of two strategies was examined: concomitant therapy comprised of 4 cycles of nivolumab and doxorubicin, vinblastine, and dacarbazine (N-AVD); and sequential treatment with 4 doses of nivolumab, 2 cycles of N-AVD, and 2 cycles of AVD at standard doses, followed by 30-Gy involved-site RT. The results of a median 13-month follow-up period were good. These strategies showed higher 12-month progression-free survival achieving 100 and 98% for concomitant and sequential treatments, respectively.

The CheckMate 205 trial analysed patients with advanced stage cHL who were treated with nivolumab monotherapy followed by nivolumab plus doxorubicin, vinblastine, and dacarbazine (N-AVD) for newly diagnosed cHL. With a minimum follow-up of 9.4 months, the 9-month modified progression-free survival was 92%.
According to the Keynote 667 study pembrolizumab combined with multiagent chemotherapy is preferable to treat pediatric and young adult patients with high-risk cHL and SER to frontline chemotherapy.

The combination with brentuximab vedotin studied in the AHD1331 trial also exhibits a higher efficacy and safety in the treatment of pediatric population with high-risk cHL.
These trials showed no differences in adverse effects compared with standard chemotherapy regimens. Rates of late toxicity have not been determined.

Conclusions: Recent studies have shown increased survival rates and lower incidences of relapse/progression, mortality, adverse effects and late toxicity, using front-line checkpoint inhibitor-based combination therapy. New studies are needed to confirm the relevance of checkpoint inhibitors for early-stage disease, especially for patients who would not need radiation therapy when treated with conventional approaches.

A rare form of Post-Transplantation Lymphoproliferative Disorder in a pediatric patient

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Objective : To report a case of Post-transplant Lymphoproliferative Disorder (PTLD) in iris.

Case report:
Eight-year-old male patient, who underwent kidney transplantation in January 2016, at the age of four due to chronic kidney disease secondary to bilateral renal hypodysplasia, who developed PTLD in iris, diagnosed through biopsy of the iris lesion of the left eye four years after kidney transplantation.
The mother noticed a “little ball” in the left eye. The ophthalmologist identified two cysts in the iris, performed diagnostic iridocyclectomy of the left eye. The anatomopathological diagnosis was compatible with Polymorphic PTLD with EBV positive , detected by in situ hybridization.
Staging was performed with CT scan of the chest, neck, and abdomen and Whole-body magnetic resonance imaging (WB-MRI), which revealed parietal thickening and contrasting areas in bowel loops, with the presence of retroperitoneal lymphadenomegaly.
The patient received four cycles of COP and MADIT. Biomicroscopy performed by the ophthalmologist in the left eye showed the presence of two nasal nylon sutures and sector iridectomy. Whole body MR imaging showed normal bowel.
One year after the end of treatment, the patient started having fever daily and four months after that, hardened cervical lymphadenomegaly appeared. Whole body MR revealed lymph nodes in the left cervical region and retroperitoneal para-aortic nodes, with diffusion restriction, compatible with relapse. Cervical lymph node biopsy was performed, Hodgkin-like PTLD was diagnosed. Bone marrow biopsy revealed the presence of CHL infiltration. Chemotherapy treatment for HL was applied, the patient was then reassessed with a bone marrow biopsy, which revealed absence of neoplasm. Whole body MR showed the disappearance of cervical and retroperitoneal lymphomegalies.
After receiving two cycles of chemotherapy, the patient was reassessed with imaging examinations, and remained in radiological remission as a kidney post-transplantation patient, with complete remission after two cycles of chemotherapy.
Four months after the end of treatment, the patient achieved clinical and radiological remission.
Ocular involvement is a rare finding in PTLD; we have identified only four cases of intraocular involvement in medical literature. Brodsky et al reported a case of a seven-year-old girl, who underwent liver transplantation and was immunosuppressed with cyclosporine. She developed bilateral iris nodules. Robinson et al reported the case of a two-year-old girl, who received cyclosporine after liver transplantation and developed multiple pigmented nodules in the iris. Clark et al reported a case of intraocular PTLD in a two-year-old boy, who developed a unilateral iris tumor. This patient was immunosuppressed with cyclosporine and prednisolone after undergoing liver transplantation. Demols et al reported the case of a 59-year-old man with PTLD after lung transplantation, who developed a unilateral iris nodule.

ADAPTED RESOURCE AND IMPLEMENTATION APPLICATION (ARIA) ADAPTED MANAGEMENT GUIDELINE (AMG): AN APPROACH TO BETA TESTING FOR HODGKIN LYMPHOMA

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Background: Resource-adapted clinical guidelines such as the ARIA (Adapted Resource and Implementation Application) Adapted Management Guideline (AMG) have the potential to improve global pediatric cancer care and close the cancer survival gap. User feedback is a critical preimplementation strategy to overcome guideline-specific barriers and improve utilization and dissemination. We hypothesized that the systematic involvement of end-users would lead to superior usability of the ARIA Hodgkin lymphoma (HL) AMG.

Methods: A global representative panel of content and context experts was assembled to participate in the final review of the ARIA HL AMG and beta-testing of integration on the ARIA Guide portal – a web-based platform. This multidisciplinary panel included pediatric oncologists, radiation oncologists, surgeons, nurses, and pharmacists. Based on prior beta testing of the ARIA Guide portal, a 51-question digital survey was developed to evaluate usability, functionality, platform navigation, and intention to use. Responses included a combination of 5-point Likert-type scale and open-ended questions. Themes were identified from open-ended responses.

Results: The ARIA HL global representative panel included 36 collaborators. Twenty-five respondents completed the survey (69% response rate) with diverse geographic representation (12% Africa, 12% Central America, 16% South America, 8% Europe, 16% Eastern Mediterranean, 20% North America, 16% Southeast Asia). All participants (n=13) who accessed the platform on a mobile device agreed it was easy to use and navigate. Users agreed the platform was easy to follow, the content came from a legitimate source, and believed oncology providers could quickly learn how to use it. Users reported the material from the ARIA HL AMG was well integrated into the platform and the ARIA HL AMG would increase awareness of the importance of guidelines and knowledge of how to manage cancer in children and adolescents. Ninety-two percent (n=23) reported they were confident using and navigating the platform, and 96% would recommend the portal to other providers. However, when asked if they would use the guideline at their institution, 60% agreed or strongly agreed, 32% were neutral, and 8% disagreed. Utilization was supported by the fact the ARIA HL AMG was adapted, comprehensive, and would decrease errors. A potential barrier to use was administrative acceptance of a guideline.

Conclusions: This survey identified possible opportunities to improve platform function and inform the future investigation of personal and institutional factors that impact guideline uptake. As the first disease-specific ARIA AMG to reach completion, the results from this beta testing will inform future testing of each ARIA disease-specific guideline. Beta-testing is an important consideration for clinical guideline development to tailor the design, increase utilization, and ultimately increase the impact of these tools on a global scale.

AHOD2131: A Randomized Phase 3 Interim Response-Adapted Trial Comparing Standard Therapy with Immuno-oncology Therapy for Children and Adults with Newly Diagnosed Stage I and II Classic Hodgkin Lymphoma, An Intergroup NCTN Phase 3 Study

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Background: Chemotherapy in combination with radiotherapy (RT) has long-been the standard for early-stage (ES) Hodgkin lymphoma (cHL). Despite current cure rates, there is room to improve short and long-term outcomes for children and adults with ES disease. Incorporation of immunotherapy (IO) into frontline treatment in ES cHL is an opportunity to both improve progression-free survival (PFS) ad maintain overall survival (OS), while minimizing long-term morbidity and treatment-related mortality by reducing exposure to RT and high-dose chemotherapy.

Methods: HL leaders representing all of the NCTN groups, expert HL researchers and physicians, and representatives from the Cancer Therapy Evaluation Program (CTEP) initiated a working group in April 2020 with the goals of harmonizing treatment approaches for ES cHL across pediatric and adults patients and reaching consensus regarding the optimal study design for incorporating IO therapy into frontline treatment. Study champions identified from each of the North American cooperative groups [Children's Oncology Group (COG), SWOG, ECOG-ACRIN, Alliance, NRG] and experts in imaging, radiation oncology, lymphoma biology, and patient-reported outcomes (PROs) were included in the study team. The resulting clinical trial - AHOD2131 - led by COG, represents the largest ES cHL trial in the history of North American cooperative groups and the first to enroll young children as well as older adults.

AHOD2131 (NCT 05675410; Figure) is a randomized, phase 3 trial enrolling patients ages 5 to 60 years with newly diagnosed stage I and II cHL and will investigate the addition of the CD30-antibody drug conjugate Brentuximab-vedotin (Bv) with PD-1 blockade (nivolumab) compared to standard chemotherapy +/- RT.

The primary objective is to compare the 3-year PFS of patients with ES cHL through a response-adapted, superiority design with either standard therapy or with an IO approach (Bv + nivolumab). Patients will be randomized to standard chemotherapy vs. IO therapy following initial response assessment by PET/CT (via central review) after 2 cycles of ABVD. All will be stratified as favorable or unfavorable based on disease risk features. Those who are PET2 positive (defined as 5 Point 4 or 5, ~15% of patients) will receive involved site RT (ISRT). In addition to the primary outcomes of PFS, the study will examine the effect of therapy on acute and long-term adverse effects including health-related quality of life (HRQoL) and overall survival for up to 12 years.

Results: AHOD 2131 activated in April 2023. 89 sites have opened the trial and 16 patients have enrolled. Target enrollment is 1875 patients over 5 years of accrual, for an estimated 1782 evaluable patients (RER n=1514; SER n=268).

Conclusions: AHOD2131 strengthens the effort between the North American cooperative groups to conduct collaborative clinical trials and aims to establish the standard of care for ES cHL across the age continuum.

Altered biodistribution of FDG in Pediatric Hodgkin Lymphoma after completion of high dose steroid therapy: A case series with important clinical implications

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INTRODUCTION: Altered fluorodeoxyglucose (FDG) biodistribution and accumulation in white fat has been reported in pediatric lymphoblastic lymphoma patients receiving high dose corticosteroid therapy and undergoing PET/CT scanning immediately following induction therapy. PET/CT plays an important role in assessing response to therapy in patients undergoing treatment for Hodgkin's lymphoma (HL). A negative PET/CT following completion of chemotherapy has a high negative predictive value (>95%) for disease progression, relapse, or recurrence, and interim PET scan after 2 cycles of treatment is frequently used to adapt subsequent therapy. Thus, obtaining accurate PET/CT results is of the utmost importance.

RESULTS: High doses of corticosteroids are used in many pediatric HL treatment regimens. Reports in the literature have suggested high steroid doses being given around the time of PET/CT can be associated with altered FDG distribution and accumulation in white fat, thus limiting the interpretability of the PET/CT.

We present a series of 10 pediatric HL patients in whom this altered pattern of FDG distribution was observed on PET/CT examinations. 2 patients were receiving high dose steroid treatment at the time of imaging. In 8 patients PET/CT was performed after the patients had completed their HL therapy course and were no longer receiving high dose corticosteroids. In 3 of these 8 patients the altered FDG distribution resulted in uninterpretable images. In the remaining 5 patients images were interpretable but the altered biodistribution of FDG limited quantitative assessments. PET/CT examinations performed several days later revealed normalization of FDG distribution.

To contextualize our findings, we present results from an additional patient with methylmalonic acidemia (MMA), in whom the same altered FDG uptake distribution was observed. Taken together, these results demonstrate that the "Cushingoid" pattern of altered FDG uptake in subcutaneous white fat can occur even when patients are not actively receiving high treatment doses of steroid, and the homology between the FDG distribution seen in these HL patients to the pattern seen in a patient with MMA suggest altered gluconeogenesis as a possible mechanistic explanation for the altered FDG uptake pattern.

CONCLUSION: The results presented here extend the previous observations on imaging among patients with lymphoblastic lymphoma treated with glucocorticoids and show that this altered pattern of FDG distribution can also occur even after patients are no longer actively receiving corticosteroids. We posit that altered gluconeogenesis may be an underlying mechanism. These results underscore the importance of optimizing timing of interim PET/CT examinations in HL to minimize the residual steroid effects on glucose metabolism and enhance the negative predictive value of interim PET/CT examinations.

An expert consensus on the definition of independent lymph node regions in pediatric Hodgkin lymphoma by the International Collaboration on Staging Evaluation and Response Criteria Harmonization (SEARCH) for Children, Adolescent, and Young Adult Hodgkin Lymphoma (CAYAHL)

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Background/Purpose

Historically the staging of pediatric Hodgkin lymphoma (pHL) is based on the Ann Arbor classification and on the current Lugano criteria. The pattern of involvement, together with other individual risk factors, determines the treatment strategy.

To reflect the greater anatomical detail provided by modern imaging modalities and to enable precise communication with physicians a consistent lexicon for lymph node level definitions is needed.

Methods

An expert consensus of leaders of the Children’s Oncology Group (COG), the European Network for Pediatric HL (EuroNet-PHL) and the Pediatric Hodgkin Consortium (PHC) defined typically involved lymph node regions in pHL based on other published consensus guidelines for the delineation of lymph node levels. Anatomical landmarks visible on modern staging CT and MRI were used to delineate the originally described lymph node levels from each other. The definitions were tested in the central review process of the ongoing C2-trial.

Results

12 regions and additional 7 subregions were defined with their cranial, caudal, medial, lateral, ventral and dorsal border. The regions were then delineated on a typical neck and torso CT scan of an adolescent male patient in complete remission without significant anatomic variants or residual tumor volume.

Also recurring situations are discussed that typically lead to queries from investigation sites.

Conclusions

The presented atlas provides criteria for nodal involvement and can serve as a standardized guide to the anatomical location of lymph node involvement in pHL.

Association of health insurance continuity with cancer stage and survival among US children, adolescents, and young adults newly diagnosed with Hodgkin lymphoma

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Background: Many previously uninsured patients do not receive Medicaid (a public insurance program) coverage until the point of, or after, cancer diagnosis. This may delay access to care and increase late-stage diagnoses, leading to poor survival. We examine whether the timing of gaining Medicaid coverage and the continuity of coverage is associated with disease stage at diagnosis and mortality in children and adolescents/young adults (AYAs) with Hodgkin lymphoma (HL).
Methods: Using the linked SEER cancer registry-Medicaid enrollment data, we identified 7,079 children and AYAs (aged 0-39 years) newly diagnosed with HL in 2006-2013. To measure insurance coverage continuity, we categorized patients who had: (1) continuous Medicaid (enrolled for ≥12 months prior to and through diagnosis), (2) newly gained Medicaid at/after diagnosis (enrollment only at or ≤12 months after diagnosis), (3) other patterns of noncontinuous Medicaid, (4) private insurance, (5) other insurance, or (6) uninsured/unknown insurance. The last three groups contain patients in SEER not linked to Medicaid data; however, these patients' insurance status at diagnosis was available in SEER registry. Cox proportional hazard model estimated the association between insurance continuity and 5-year overall survival. Logistic regression estimated the association of insurance continuity with stage IV disease at diagnosis, based on Ann-Arbor stage. Models also controlled for sex, race/ethnicity, age at diagnosis, diagnosis year, rurality, and neighborhood socioeconomic status.
Results: Of our sample, 50% had private insurance, followed by Medicaid insurance (27%), other insurance types (10%), and no insurance (5%) or unknown insurance (8%). Among Medicaid-insured patients, 33% had continuous Medicaid, 40% gained Medicaid at or after diagnosis, and 27% experienced other patterns of noncontinuous Medicaid. When examining 5-year survival, patients with newly gained Medicaid at or after diagnosis had a hazard ratio for death of 3.35 (95% CI=2.50-4.50), whereas patients with continuous Medicaid and those with other patterns of noncontinuous Medicaid had hazard ratios of 2.87 (95% CI=2.41-3.43) and 2.97 (95% CI=2.16-4.08), respectively, compared to privately insured patients. When examining lymphoma stage at diagnosis, compared with privately insured patients, the adjusted percentage of stage IV diagnoses was 12.7 percentage points (ppt; 95% CI=10.2-15.2), 6.2 ppt (95% CI=1.3-11.1), and 4.2 ppt (95% CI=0.5-7.9) higher in patients with newly gained Medicaid, other patterns of noncontinuous Medicaid, and continuous Medicaid, respectively.
Conclusion: Less than half of Medicaid-insured children and AYAs with HL had continuous insurance coverage prior to cancer diagnosis. Lacking continuous Medicaid coverage was associated with advanced-stage lymphoma at diagnosis and inferior survival. This work informs needed policy changes for low-income children and AYA in the U.S. public insurance system.

Brazilian Results of a Latin American Guide to Treat Children and Adolescents with Classical Hodgkin Lymphoma: An Effort to Harmonize Nationwide Care

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Background/purpose: Hodgkin Lymphoma has excellent cure rates in children and adolescents even in LMIC. However, there is no standard of care in these countries. Herein, we analyze the partial results in Brazil of the first Latin American effort to provide unified management.

Methods: This guide was based on previous experience in Central America/AHOPCA, with 3 risk groups: low risk/LR (stage IA and IIA, no bulky and less than 4 nodal regions), High risk/HR (stage IIB, IIIB, and IV), and Intermediate risk/IR (all other patients). Recommendations for LR: 4xABVD and 20 Gy IFRT to those with partial response at the end; IR: 6xABVD and 20 Gy IFRT to those with partial response after 2 cycles and HR: 2xOEPA and 4xCOPDac and 20 Gy IFRT to those with complete response after 2xOEPA and 25 Gy IFRT to those with partial response. After a shortage of Bleomycin in Brazil, centers had an amendment to change chemotherapy blocks, for LR: 2xOEPA and IR: 2xOEPA and 2xCOPDac.

Results: Between Mar/2016 and Mar/2021, 166 patients younger than 21 years were included across eleven centers. Median age was 13,7 years (2-21,29); 92/164 (56%) had B symptoms; 21/165 (12,7%) were allocated as LR, 49/165 (29,7%) as IR and 95/165 (57,6%) as HR. Regarding response evaluation, 80/146(54.8%) had a complete response, 65/146 (44,5%) had a partial response and 1/146 (0.7%) had no response; the OS was 96,3%, 100%, 100%, and 94,6% for all patients, LR, IR, and HR respectively and EFS was 84,7%, 83,1%, 93,8% and 81,4%, for all patients, LR, IR and HR respectively, with a median follow-up of 32,8 months (0,95-80,59). There were no treatment-related deaths.

Conclusion: Establishing a harmonized guide for diagnosis, treatment, and registry of these population in the context of LMIC is needed and demands the development of a network for mutual cooperation.

Brentuximab Vedotin in combination with bendamustine in paediatric patients or young adults with relapsed or refractory Hodgkin Lymphoma: a real-world experience

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Background:
Children and young adults with Hodgkin's lymphoma (HL) usually have a favorable prognosis; however, patients with primary refractory disease and some subsets of relapsed patients still have a dismal outcome. In light of these observations, novel therapies are needed. Brentuximab vedotin (BV) in combination with bendamustine may represent a suitable salvage therapy for pediatric patients/young adults with relapsed/refractory (R/R) HL. Retrospective data on 32 patients with R/R HL, aged less than 25 years and treated in 2 Italian centers, were published in 2022 (Pediatr Blood Cancer. 2022), showing a 3-year overall response rate of 78,1% and a progression-free survival of 67%.
We here report the updated results of an enlarged retrospective cohort of patients with R/R HL.

Methods:
Patients with R/R HL identified through individual sites querying local databases were aged 20 years or less at time of diagnosis and 25 years or less at time of treatment. Treatment cycle included 1.8 mg/kg BV on day 1 and 120 mg/m2 bendamustine on days 2 and 3 (90 mg/m2/day in the heavily pretreated group), administered every 3-4 weeks. We assessed the objective response through high-resolution computed tomography (CT) and 18 fluorodeoxyglucose-positron emission tomography (FDG-PET) scans performed at diagnosis, after the first 2 cycles and at the end of treatment, as per institutional practice. All patients were evaluated for treatment response according to the Cheson's Criteria.

Results:
Between December 2013 and May 2023, 41 pediatric patients/young adults with pathologically confirmed CD30-positive R/R HL were treated with BV in combination with bendamustine in 2 Italian sites.
Median age at the time of treatment was 16 years (range, 7-25); 18 patients were females (44%) and 23 males (56%). Patients received up to 6 cycles of treatment of BV-bendamustine, administered every 3-4 weeks. The most common treatment-related adverse event was grade >2 hematological toxicity. After the first 2 cycles, complete response (CR) was recorded in 18 out of 34 evaluated patients (53%), while it was not assessed in 7. At the end of treatment, the overall response rate (ORR) was 83%: 29 patients obtained CR, 5 patients obtained a partial response (PR). Twenty-nine patients were consolidated with hematopoietic stem cell transplantation (HSCT), 25 patients receiving autologous and 4 patients receiving allogeneic HSCT. Thirty-three patients (80% of the whole initial population) are actually alive (29 CR, 2 PR and 2 relapses).

Conclusions:
Our data confirm that, in the pediatric R/R HL setting, the combination of BV and bendamustine has an acceptable safety profile and it is associated with a good efficacy.

Case report: Rare combination of Hodgkin Lymphoma and Hypoplastic Left Heart Syndrome- tailoring treatment to medical comorbidities to achieve excellent response while minimising unwanted toxicities.

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Background: 14yo male presenting with a large left sided neck mass, diagnosed with stage IIIB Hodgkin Lymphoma, on a background of completion of a fenestrated Fontan at age 4 for Hypoplastic Left Heart Syndrome. Additional co-morbidities at presentation included morbid obesity (BMI 44); impaired glucose tolerance with metabolic syndrome/ insulin resistance; obesity related sleep disordered breathing; plastic bronchitis; mild restrictive lung disease; acanthosis nigrans; learning difficulties; fear of medical services. He was already on Enalapril anti-hypertensive and aspirin for VTE prophylaxis.
Given his significant medical co-morbidities, our standard of care, EURONET PHL C2 was felt not suitable largely due to the high corticosteroid dosages.

Methods: Literature review and consulting with local and international colleagues to determine the best treatment options as well as intensive collaboration with his other medical treating teams was required.

Results: Only a couple of articles of similar cases was found, which were of some use. Treatment was tailored to his individual situation, co-morbidities and particular attention to medical supportive care was required in view of his single ventricle physiology. Fortunately there was no large mediastinal mass, but there were non specific lung nodules, felt to be infective. Six cycles of A-AVD- dose adjusted for weight (Brentuximab, Doxorubicin with Dexrazoxane cardio protection, Vinblastine and Dacarbazine) were used with great effect- he achieved a complete metabolic response (CMR) at his first response assessment after 3 cycles (only 2 with Brentuximab due to time lag with obtaining hospital permission to use though special drug access scheme). Even arranging PET-CT took extra time as it needed to be done at an adult centre as the machine at the Children's Hospital he was treated at was not suitable for his size. Gcsf was used prophylactically. A shorter single lumen port was placed with tip sitting in the left innominate vein; under guidance by his cardiologist and with extra attention to anaesthetic safety. Anti-coagulation for thrombus prevention was changed to rivaroxaban, and later to low molecular weight heparin due to potential drug interactions, and he required a higher red cell transfusion threshold of haemoglobin > 120 g/L to maintain relative polycythaemia for his single ventricle physiology and to maintain adequate pulmonary pressures. BAL suggested fungal lung disease so he also required treatment anti-fungal therapy. Treatment was relatively well tolerated with minimal inpatient admissions required. Psychosocial support was essential for the patient and family.

Conclusion: Developing a patient specific plan is possible with extensive background work and collaboration. A-AVD was an excellent alternative treatment regimen for this young person with Hodgkin Lymphoma on a background of structural congenital heart disease with significant co-morbidities.

CD70 immunohistochemical expression in classic Hodgkin lymphoma (CHL): An argument for the use of targeted anti-CD70 therapy in pediatric CHL; A single institutional experience

Background: Classic Hodgkin lymphoma (CHL) is the most common subtype in children and young adults. The primary tumor cell in CHL is the Hodgkin Reed-Sternberg (HRS) cell. CHL's tumor microenvironment (TME) outnumbers the HRS cells and contains inflammatory/ immune cells. HRS cells survive through cross-talk with TME cells with different pathways and escape immunosurveillance through a mechanism that regulates cell-mediated immune responses. Immunotherapy with monoclonal antibodies that interfere with adaptive immune checkpoints has revolutionized the treatment of numerous human cancers with less toxicity compared to conventional chemotherapy. CD70 is a transmembrane protein member of the tumor necrosis factor superfamily (TNFSF) and stimulates cells that express CD27. The constitutive expression of CD27 and CD70 has been described in various tumors, and therapeutic approaches targeting CD70 have been under investigation in different hematologic malignancies. Although CD70 positivity of the tumor cells is a prerequisite to enter solid and hematologic tumor clinical trials using anti-CD70 immunotherapy, there is currently no uniform immunohistochemistry (IHC) assay for evaluating CD70 expression in CHL. In this study, we assessed the degree of CD70 expression across cases of CHL using one standardized and validated IHC assay.

Methods: IHC for CD70 expression was validated for Abcam clone BU69 using control tonsils and cell lines expressing progressive levels of CD70 expression. The CD70 expression was further evaluated in the HRS and TME cells of 12 FFPE tissue specimens of CHL, representing a mixture of EBV-positive and -negative CHL. CD70 expression was scored by assessing the percentages of expressing cells and staining intensity (negative, +1, +2, and + 3). An H-score (HS) {HS = [(%positive cells intensity 1+) x 1] + [(%positive cells intensity 2+) x 2] + [(%positive cells intensity 3+) x 3]} was used to provide a final score.

Results: CD70 expression was observed in both TME and HRS cells. Positivity for CD70 was detected in the cytoplasmic membrane, cytoplasm only, or membrane only; no nuclear expression was observed. CD70 was detected at different levels of expression in 92% of the HRS cells in CHLs (n = 11/12) with a median percentage of expression and HS of 93.5% (0–100%) and 151.5 (0–288), respectively, in HRS cells. CD70 expression in TME was observed at 100% of background inflammatory cells. Differences between EBV positive and negative HL cases were not appreciated.

Conclusions: CD70 is widely expressed in most CHLs, with various degrees of positivity in HRS cells and TME. IHC is a useful methodology to determine CD70 expression in emerging clinical trials targeting CD70 in other hematopoietic and nonhematopoietic malignancies. Further studies are needed in larger pediatric and adult CHL cohorts to confirm our findings. However, our data support the use of anti-CD70 monoclonal antibodies in CHL.

Figure legend:

Figure 1: Examples of CD70 expression in classic Hodgkin lymphoma: A: A case of classic Hodgkin lymphoma with many large Hodgkin Reed-Sternberg (HRS) cells (Hematoxylin and eosin, x400).
B: HRS tumor cells (some highlighted by red arrow) are positive for CD30 (x200). B: Uniform and strong expression (positivity in 100% of HRS cells, intensity 3+) of CD70 in HRS cells (some highlighted by red arrow) and many small background lymphocytes. Note that CD70 expression is detected in the Golgi region as well as in the cytoplasmic membrane

Checkpoint inhibitor immunotherapy for relapsed Hodgkin's lymphoma in children and adolescents in Armenia

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Background:

Most children and adolescents with Hodgkin lymphoma (HL) have a good prognosis when using modern treatment methods. In general, 5-year survival rate in the early stages of the disease exceeds 90%, regardless of the chosen treatment regimen. Even with high-risk diseases, modern methods of treatment provide durability at the level of 85% or more. Nevertheless, there are a small percentage of patients who relapse after treatment, but in many cases additional therapy allows to achieve a stable second remission. There are many treatment options for children and adolescents with recurrent HL. These include immunotherapy recovery with autologous stem cell transplantation, high-dose chemotherapy with autologous stem cell transplantation, allogeneic stem cell transplantation or another new approach, and radiation therapy, as part of a combined approach, plays an important role.

Methods:

Retrospective analysis of medical histories of children and adolescents with HL aged 0-18 y/o between the period of 2019 and June 1, 2023 was performed in the Pediatric Cancer and Blood Disorders Center of Armenia created in 2019 as a result of the union of three medical units. This is the first report devoted to HL relapse in pediatric population of Armenia.

Results:

Between 2019 and June 1, 2023 HL was diagnosed in 31 patients. Of 31 cases of HL 3 cases of relapse, and 1 case of disease progression in Covid-19 infection were discovered. Relapse or disease progression was confirmed by biopsy with further histological and IHC analysis. Relapse and progression were observed in males whose median age was 13.5. The patients who experienced a relapse initially had stages IIA, IIIB, and IVA of HL. The patient with IIIB, IVA received 2 cycles of OEPA and 4 cycles of COPDAC, the patient with IIA stage revived 2 cycles of OEPA and 2 cycles of DECOPDAC. None of them received RT.

The patient with HL progression received the 5 cycles of chemotherapy (2 OEPA / 3 COPDAC) when tested positive for COVID-19. 10 days later persistent fever up to 39^{o}C, pericardial effusion, diarrhea, rash and lymphadenopathy were developed. CT scan and biopsy of cervical lymph nodes revealed disease progression.

The patients with relapse of HL were cured with immunotherapy representing the combination of Bendamustine with Brentuximab vedotin or Nivolumab with further autologous stem cell transplantation (ACST) and RT. The patient with disease progression received 2 cycle of ABVD and IEP regimen then ASCT and RT.

All the therapies resulted in remission for the patients. They are all currently under follow-up.

Conclusion:

This study has shown that immunotherapy allows achieving complete remission in children and adolescents with HL and therefore can be considered a very promising approach to the treatment of HL relapse and progression. Due to a short-term follow-up further investigation should be conducted to confirm the efficacy of the mentioned treatment option.

Circulating cell-free DNA in classical Hodgkin lymphoma in children adolescents and young adults. Preliminary results from the HOLY study. A French ancillary study of EuroNet PHL-C2 protocol.

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Context : Circulating cell free tumor DNA (ctDNA), has shown great promise in genotyping, stratification, and response assessment in adult classical Hodgkin lymphoma (cHL). However, its applicability in pediatric and adolescent cHL is not yet defined. This prospective national study aimed to define the potential role of ctDNA in pediatric and adolescent with cHL.

Methods :
This prospective trial was conducted in France between December 2019 and January 2023 and recruited pediatric and adolescent patients (≤ 25 years old) with newly diagnosis cHL Patients were treated according to Euronet PHL C2 trial (EudraCT: 2012-004053-88). To explore ctDNA role in pediatric cHL, a 18-genes amplicon-based NGS (Next Generation Sequencing) targeted panel encompassing the most frequently mutated genes in cHL was design. ctDNA evaluations were performed at diagnosis and after 2 cycles of chemotherapy (C2).

Results :
At the time of analysis 284 patients were included. Samples were collected at diagnosis and after C2 (n = 241). Median age at diagnosis was 15 years (2 – 22), sex ratio (M/F) = 1.15, 48% of the patients were treated as advanced stages (TL-3).
A total of 2299 variants were detected in 242/284 patients (85%). Median variant number per patient was 9 (range 1–54) with median variant allele frequency (VAF) per patient of 2.8% (0.13 – 22%). The most frequently mutated genes were SOCS1 (67%), IGLL5 (43%), B2M (42%) and CIITA (42%) with a median VAF of 3.7% (range 1.9–6.1%) per gene. B-symptoms, high erythrocyte sedimentation rate, and advanced stages were significantly associated to higher amounts of ctDNA at diagnosis.
Survival/event analyses were conducted in a subset of 141 patients with documented follow-up (FU): median FU=11 months (4–21 months). Patient with undetectable ctDNA at diagnosis were associated with excellent outcome independently of ERA (PFS 100%, n = 21). At C2 ctDNA became undetectable in 93% of the cases. Detectable ctDNA (n=11) at C2 was strongly associated with inadequate response (IR) at ERA (n=9/11) . Patients combining IR and detectable ctDNA at C2 had inferior outcome compared to patients with IR and undetectable ctDNA at C2: 12-months PFS; 89%, 95%CI(80%-100%) vs 71%, 95%CI(45%-100%), p = 0.04.

Conclusion : Using a 18-genes NGS panel we were able to detect at least one mutation in 85% of diagnosis samples. Variant detection in ctDNA is suitable to explore the genetic landscape of pediatric and adolescent cHL at diagnosis and could contribute to improve the therapeutic stratification in association with (18F-FDG) PET/FDG.

Data Collaborations Accelerate Pediatric Hodgkin Lymphoma Research Through NODAL

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Background: Data collaborations accelerate research through rapid access to data via robust technical infrastructure. The Pediatric Cancer Data Commons (PCDC; flagship project of Data for the Common Good, University of Chicago, established in 2015) enables access to federated data that facilitates research initiatives for rare diseases, such as pediatric Hodgkin lymphoma (HL). Through such initiatives as the PCDC, data from clinical trials can safely be shared without loss of agency by each contributor. NODAL is the HodgkiN lymphOma DatA coLlaboration through the PCDC that builds on an existing partnerships between pediatric HL consortia to help advance the field.

Methods: NODAL was founded in 2018 with a goal to accelerate research for pediatric HL with initial collaboration agreements from the Children’s Oncology Group (COG) and the Pediatric Hodgkin Consortium (PHC). An executive committee with four members (including a biostatistician) from each research group and a comprehensive governance structure were solidified. NODAL members worked from 2019- 2020 in subgroups (Dose Modification, Outcomes, Staging and Response, and Toxicity Grading) to formulate a harmonized data dictionary for data elements obtained on case report forms from previous clinical trials. In preparation for data transfer a memorandum of understanding to establish the consortium and data contributor agreements were signed by each group. Data were harmonized according to the data dictionary and the COG and PHC transferred data for collaborative research questions.

Results: To-date, data from 1,789 participants in the COG phase 3 intermediate risk trial AHOD0031 (n=1712) and the PHC phase 2 high risk trial HLHR13 (n=77) are currently in the PCDC data portal. More data are expected in the coming months. Two projects to utilize the data have been approved by the NODAL Executive Committee. One for nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) patients to be used in an NLPHL retrospective review to assess clinical and pathologic features and identify prognostic factors to define clinically relevant risk groups. Another will be led by radiation oncologists to evaluate the therapy related risk factors associated with the development of subsequent cancers among children with HL in the context of contemporary therapy.

Conclusion: Large data initiatives such as NODAL provide rapid access to facilitate research and overcome barriers through utilization of technology today. NODAL will allow the field to answer meaningful research questions on smaller, important, subsets of patients across clinical trials. NODAL looks forward to building on the data contributions from international cooperative groups, COG and PHC trials and to expanding access for invested researchers.

oral abstract

Distinct Hodgkin lymphoma subtypes identified by noninvasive genomic profiling

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Introduction: The scarcity of malignant Reed-Sternberg cells has hampered comprehensive genomic profiling of classic Hodgkin lymphoma (cHL) as might inform personalized therapeutic strategies. Since profiling of circulating tumor DNA (ctDNA) has shown utility in non-Hodgkin lymphoma genotyping and risk stratification, we employed a noninvasive approach in cHL to overcome challenges imposed by low tumor fractions.

Methods: We profiled baseline plasma samples from 366 patients diagnosed with cHL, 99% of whom were enrolled prior to anti-lymphoma therapy. Median age was 32 (range 4-88), 48% had advanced stage (III/IV) disease, and among the subset with early stage (I/II) disease (52%), 91% had unfavorable GHSG risk. We applied CAPP-Seq and Whole Exome Sequencing (WES) to explore noninvasive genotypes. Whole exome genotypes were generated using a novel gradient boosting model from mutation and cfDNA fragmentomic features. Distinct cHL genetic subtypes were identified by lexical clustering through Latent Dirichlet Allocation.

Results: We first profiled all pretreatment samples using a 576-kb capture panel targeting genes recurrently mutated in cHL and other B-cell lymphomas. 293 patients (80% of cases) were evaluable for noninvasive genotyping and clustering analyses. We separately used WES to additionally profile a subset of patients (n=119; 41%) enriched for samples with higher plasma allelic fractions. We then integrated somatic copy-number aberrations (SCNAs) with non-silent somatic mutation calls as weighted features to discover 2 dominant genetic subtypes. Cluster H1 comprised ~68% of cases and was dominated by somatic mutations in genes canonically involved in NFkB, JAK/STAT, and PI3K signaling. Conversely, cluster H2 (~32% of cases) was primarily characterized by a variety of SCNA events as well as mutations in TP53, KMT2D, and BCL2 (Fig.A). H1 tumors had a significantly higher somatic mutational burden, while H2 tumors had a larger fraction of their genome affected by SCNAs (both $P<0.001$, Fig.B-C). Patients with H2 subtype demonstrated the known bimodal age distribution of cHL with an early peak in the 20s and a second peak at >60 years. In contrast, H1 tumors predominantly occurred in younger patients ($P=0.02$, Fig.D). Patients with an H2 genotype were predominantly male ($P=0.007$), enriched for EBV positive tumors ($P<0.0001$, Fig.E) and mixed cellularity subtype ($P=0.01$, Fig.F). Importantly, patients with the H2 subtype had inferior clinical outcomes ($P<0.01$, Fig.G) independent of high ctDNA levels (Hazard ratio 2.0, $P<0.05$). Further exploration of a pediatric extension cohort, transcriptional differences between genetic subtypes, and correlation between MRD by ctDNA and iPET is underway and will be presented at the meeting.

Conclusions: With our novel non-invasive approach, we overcome known challenges in cHL profiling and delineate molecularly distinct cHL subtypes with clinical and prognostic correlates.

Dose-dense chemotherapy for low-risk pediatric Hodgkin lymphoma enables de-escalation of radiotherapy: a report from the Pediatric Hodgkin Consortium

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BACKGROUND

Disease-free survival in classical Hodgkin lymphoma (cHL) in children and adolescents treated with combined modality therapy is outstanding, making it imperative to minimize the late effects of treatment to optimize long-term survival and quality of life. Our Pediatric Hodgkin Consortium (PHC) has conducted sequential clinical trials over several decades, with recent trials focused on eliminating radiation therapy when possible, given its attendant risks of second malignancy, impaired musculoskeletal growth, and cardiopulmonary toxicity.

METHODS

Between 2009 and 2018, we conducted HOD08, an IRB-approved single arm trial of eight weeks of Stanford V chemotherapy in low-risk pediatric classical Hodgkin lymphoma (cHL). Patients up to 21 years of age with newly diagnosed cHL were offered enrollment, with low-risk defined as stage IA or IIA disease, mediastinal mass less than one-third of the transthoracic diameter, no extranodal extension, and fewer than three nodal sites.

After chemotherapy, treatment response was assessed using PET scan and anatomic imaging, either CT or MRI. Adequate response (AR) was defined as negative PET (uptake less than or equal to the mediastinal blood pool) with at least 75% reduction in the product of two perpendicular diameters of each site by anatomic imaging. For radiation, sites with an inadequate response (IR) received 25.5 Gy following chemotherapy using a modified tailored field. The primary objective was to increase the proportion of patients treated with chemotherapy alone by at least 20% (to 64% or above) relative to a historical comparison group of low-risk patients treated with VAMP chemotherapy on our predecessor trial, HOD99.

RESULTS

Forty-five patients were evaluable for the primary outcome. Median follow up time from diagnosis was 6.9 years (IQR 5.1-8.5 years). Thirty-five of 45 patients (77.8%) were followed for at least five years. Thirty-four patients (75.6%) achieved an AR at all sites and did not receive radiation, while the remaining eleven patients (24.4%) had an IR, nine of whom received radiation, while two declined. The 5-year EFS and OS rates for all patients were 93.0% (95% CI 85.6%-100%) and 100%, respectively. Among those with IR who received RT, the 5-year EFS and OS rates were 88.9% (95% CI 70.6%-100%) and 100%, respectively.

Four patients experienced treatment failure, one with progressive disease after radiation, and three with relapses more than 12 months after completing treatment, none of whom had received radiation therapy. There have been no secondary malignancies or deaths.

CONCLUSIONS

A dose-dense modified Stanford V regimen reduced the proportion of low-risk pediatric cHL patients who required RT compared to a historical sample of similar patients treated with VAMP chemotherapy. Our current trial uses a similar approach with the substitution of bendamustine for mechlorethamine, which is no longer available.

Dosimetric benefits of MR-guided radiotherapy in pediatric mediastinal Hodgkin Lymphoma: A case report

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Child, adolescent, and young adult (CAYA) Hodgkin Lymphoma (HL) survivors face heightened risks of radiation treatment (RT)-associated long-term sequelae such as cardiovascular and pulmonary disease and second malignancies, especially after receiving RT for mediastinal disease involvement. New RT techniques may improve the RT safety profile. Magnetic resonance-guided RT (MRgRT) combines magnetic resonance imaging (MRI) with an RT linear accelerator (LINAC), allowing real-time MRI cine target tracking and gating during RT delivery. There is a dearth of data on MRgRT use in the CAYA population.

We present an 11-year-old female with Stage IIB Classic HL with mediastinal bulk (mass 42% of thoracic diameter on upright chest radiograph) treated as per the high-risk arm of the cHOD17 study (NCT03755804) with 2 cycles of brentuximab vedotin, etoposide, prednisone, and doxorubicin (AEPA) and 4 cycles of cyclophosphamide, brentuximab vedotin, prednisone, and dacarbazine (CAPDac). 18FDG-avid positron emission tomography after 2 cycles of AEPA (PET2) demonstrated slow early response (SER) with residual metabolically active (Deauville 4) anterior mediastinal nodal disease. Accordingly, we recommended post-chemotherapy involved-nodal RT 25.5Gy/17 fractions to the PET2 Deauville 4 lymph nodes. The patient underwent 2 simulation sessions, CT and MRI, both with deep inspiratory breath hold, to guide the choice between conventional LINAC and MR-LINAC.

Two independent radiation plans were made for comparison by 2 radiation oncologists and the same dosimetrist to mitigate inter- and intra-observer variability, respectively. We designated the same plan objectives, target metrics, and organs at risk (OARs) constraints for both treatment modalities.

Upon comparative plans evaluation, a lower integral dose to most OARs favored the MR-LINAC plan over the conventional one (Table 1). Static intensity-modulated RT was delivered using the MRIdian linear accelerator system (ViewRay, Inc).

0.35T MRI of the patient was acquired and aligned to the planning image of the original plan for every fraction. The target was tracked in real-time during treatment with cine imaging. Radiation beam stoppage was triggered if 5% or more of the target was outside of the 3-mm gating boundary at any time. MRgRT eliminates excess on-treatment ionizing radiation exposure associated with the conventional cone beam computed tomography-guided workflow.

MRgRT to an anterior mediastinal target in this patient with pediatric HL results in dosimetric improvements in target and organ-at-risk dosimetry. Potential toxicity reduction and clinical benefits that may result from intrafraction motion management, planning target volume (PTV) reductions, and on-treatment multi-parametric MRI warrant further investigation. Cooperative groups can facilitate access to novel technologies by incorporating MRgRT-permissive language and instructions in RT guidelines of future study protocols.

Evaluating CHIPS Validation in Pediatric High Risk Hodgkin Lymphoma Treated on AHOD1331

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Background: CHIPS (Childhood Hodgkin International Prognostic Score) is a predictive model for Event-Free-Survival (EFS), originally developed in patients with intermediate risk Hodgkin lymphoma (HL). Prospective validation of CHIPS in high-risk HL was a pre-specified aim of AHOD1331, a trial comparing the efficacy of Brentuximab, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (Bv-AVE-PC) to standard ABVE-PC. Response-adapted radiation therapy was included. For this analysis, we examined CHIPS scoring components by study arm.

Methods: AHOD1331 (NCT02166463) was a multicenter randomized phase 3 study. Patients were ages 2-21 with untreated stages IIB+bulk, IIIB, IV HL. CHIPS was determined by assigning 1 point each for: Stage 4 disease, large mediastinal mass (LMA), albumin (<3.5), fever. Events included disease relapse/progression, second malignancy, and death. Multivariable Cox Regression was used to examine the unique CHIPS components.

Results: The distribution of CHIPS among 587 high risk patients eligible for AHOD1331 did not differ by study treatment arm (p=0.2405). 3-yr EFS differed overall by CHIPS score in this high-risk cohort (p=0.0135). The trend for CHIPS predictive potential was similar by treatment arm, and the comparison EFS for CHIPS 0,1 vs CHIPS 2,3,4 was statistically significant for each treatment arm (Bv-AVE-PC, p= 0.0333; ABVE-PC p= 0.0402). In multivariate model including treatment arm, CHIPS was an independent predictor of EFS (p=0.0203). On multivariate analyses of individual CHIPS components, stage IV (p=0.0289) and fever (p=0.0149) were predictive of adverse EFS. Low albumin and LMA were not predictive of EFS. Stage IV disease and fever were predictive (p=.007 and 0.02) in the experimental arm; in the standard arm only, fever was borderline as a predictor (p=0.09)

Conclusion: The CHIPS score is predictive of outcome in patients with high-risk HL treated on both the experimental (+ brentuximab) and control arm (ABVE-PC). Multivariate analysis of individual components confirm the relevance of fever and stage IV disease but neither albumin nor large mediastinal adenopathy (LMA) contributed to the predictive value of CHIPS in this high-risk cohort, likely because of their overall frequency in high-risk disease. Based on clinical factors known at the time of diagnosis, CHIPS components may aid in the allocation of patients to risk-based treatment algorithms.

FDG PET/CT in pediatric Hodgkin Lymphoma: initial results of an Italian prospective study

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AIM: [18F]fluorodeoxyglucose PET/CT (FDG PET) semi-quantitative and volumetric analyses might be used as a valuable tool to better discriminate disease prognostication and response in pediatric Hodgkin Lymphoma. To validate this assumption, the AIEOP Study Group has designed a parallel study of the Italian cohort of patients enrolled in the EuroNet-PHL-C2 trial. Herein, we present the initial results of the prospective data obtained from our cohort of patients.

METHODS: We analyzed data derived from the first 200 patients (94 male, 106 female; median age 15 years) with HL and enrolled in 24 different Italian centers from January 2017 to December 2020, all treated within the same EuroNet-PHL-C2 protocol. The cohort was classified based on treatment level into: TL1 (31 patients), TL2 (90 patients) and TL3 (79 patients), of whom 71 presented with bulky masses. Response to therapy was based on Deauville score (DS) and classified into adequate response (AR) and inadequate response (IR) as per protocol definitions. The primary objective of the study was to define the predictive role of volumetric and semiquantitative analyses, i.e., SUVmax, SUVmean, MTV and total lesion glycolysis (TLG), as well as lymphoma dissemination (Dmax), in patients scanned with FDG PET at baseline and during the course of therapy. In particular, treatment response was assessed at early (ERA) and late evaluation (LRA). A dedicated software was used to delineate the lesions by using as reference a fixed absolute SUV threshold of 2.5. All parameters and their variations (Δ) were analyzed with respect to response.

RESULTS: At baseline evaluation, our cohort presented a median SUVmax of 12.5 (95%CI: 12.1-13.1), median SUVmean 4.3 (95%CI: 4.2-4.5), median MTV 223 (95%CI: 183-264), median TLG 1009 (95%CI: 868-1213) and median Dmax of 18 (95%CI: 14.7-21.7). There was a statistically significant difference of median values for baseline SUVmax (P = 0,002), MTV (P = 0,022), TLG (P = 0,005) and Dmax (P = 0,003) and treatment evaluation with early response at ERA PET. Median variations from baseline resulted respectively: 81% for SUVmax, 59% for SUVmean, 92% for MTV, 97% for TLG and 40% for Dmax, with ΔSUVmax and ΔSUVmean showing a significant correlation to LRA (P = 0,027 and 0,020, respectively). There was a significant correlation of semi-quantitative and volumetric parameters at baseline also at logistic regression for SUVmax (p=0.0025), MTV (p=0.0272), TLG (p=0.0078) and Dmax (p=0.0045). While pooled together with other clinical data (i.e. stage, TL, and bulky masses), multiple regression defined as independent predictive factors TL (treatment level) and bulky masses (p=0,0071 and 0,0078, respectively).

CONCLUSIONS: Semi-quantitative and volumetric parameters correlate to ERA PET results and their variations show a statistically significant correlation to LRA for SUVmax and SUVmean. Baseline Dmax seems to have a potential role as predictor of response also in pediatric HL patients.

Health-related Quality of Life Trajectories among Patients with High Risk Pediatric Hodgkin Lymphoma treated on the Children's Oncology Group (COG) AHOD 1331 Study

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Background: Brentuximab vendotin (BV) with AVE-PC (Adriamycin, Vincristine, Etoposide, Prednisone, Cyclophosphamide) demonstrated superior efficacy to ABVE-PC (Adriamycin, Bleomycin, Vincristine, Etoposide, Prednisone, Cyclophosphamide) for pediatric patients with high-risk HL in the COG-led AHOD 1331 trial. However, data are limited regarding the impact on health-related quality of life (HRQoL) when incorporating the novel agent, BV, into treatment. Additionally, mean trajectories of HRQoL may not capture heterogeneity among individual participants. Therefore, we aimed to identify and describe subgroups of participants with similar HRQoL trajectories over time from study entry to end of therapy in the AHOD 1331 trial.

Methods: Eligibility for AHOD 1331 included previously untreated pediatric HL with stage IIB + bulk, IIIB, IVA, or IVB. Participants were randomly assigned to either BV-AVE-PC or ABVE-PC. Among the first 309 participants enrolled in a prespecified longitudinal patient-reported outcomes sub study, 268 age 11+ completed the seven-item Child Health Ratings Inventories (CHRIs)–Global scale (HRQoL) at least once. HRQoL was assessed prior to treatment (T1), after cycle 2 (T2), after cycle 5 (T3), and at the end of treatment (T4). We utilized group-based trajectory models to identify latent clusters of individuals with similar HRQoL patterns over time. The number of groups was selected based on model fit statistics, clinical interpretability, and group size. Ordinal logistic regression identified characteristics associated with membership in those trajectory-based sub-groups.

Results: Participant and disease characteristics were balanced by treatment arm; mean age at enrollment was 15.6 years (SD=1.9), 52% were female, and 58% were stage IV. At T1 mean HRQoL scores did not differ by arm (p=0.692). Three groups were identified in group trajectory-based analyses (Figure 1A): consistently favorable HRQoL (n=79), moderate and improving HRQoL (n=119), and consistently unfavorable HRQoL (n=70). Participants in the ABVE-PC arm were more likely to be in the consistently unfavorable HRQoL group (Figure 1B; 30.7% vs 21.4%, OR=1.98 95%CI 1.03, 3.82; p=0.040) compared to the BV arm. Similarly, participants in the ABVE-PC arm were less likely to in the consistently favorable HRQoL group (Figure 1B; 24.8% vs. 34.4%, OR 0.50 95%CI 0.26, 0.97; p=0.040) compared to the BV arm. Older age and female sex were associated with an increased odds of membership in the consistently unfavorable group (age OR=1.21 95%CI 1.02, 1.45; p=0.029; female OR=2.47 95%CI 1.27, 4.77; p=0.007).

Conclusions: Patients with high-risk pediatric HL treated with BV-AVE-PC experienced better HRQoL trajectories during treatment. These data highlight the impact of novel therapies on the HRQoL of patients. Additional research is needed to understand the biologic drivers of these differences.

HLA and chemokines influencing relapse risk in EBV-related Hodgkin's lymphoma in young patients treated with EuroNet-PHL-C2 protocol - AIEOP Group

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Background/Purpose: Epstein-Barr virus [EBV] infection and host genetic HLA background contribute to the pathogenesis of classical Hodgkin lymphoma [cHL]. The present study aims to characterise EBV+cHL according to genetic and tissue HLA mRNA expression to assess whether EBV and HLA may influence response or resistance in patients treated with the same response-adapted therapeutic EuroNet-PHL-C2 protocol.

Methods:Forty-six patients with newly diagnosed cHL, younger than 25 years, treated with the PHL-C2 protocol were included in the study. 17.4% were EBV+cHL. Demographic, laboratory and clinical data were collected. EBV positivity, histological subtypes and tumour-associated macrophage phenotypes were assessed by immunohistochemistry. Comprehensive immune gene profiling and HLA typing were performed using NanoString nCounter analysis and DNA sequencing, respectively. EBV/HLA pairing data were then correlated with histological and clinical information. The results were used to characterise patients based on EBV+/HLA pairing and then correlated with the prognostic effect on event-free survival [EFS] at a median follow-up of 3 years.

Results: The HLA-A2 genotype, in linkage disequilibrium with the HLA-G UTR1 haplotype and the HLA-F rs9269081 G allele, was associated with EBV-cHL and the nodular histological sclerosis histotype. Conversely, HLA-A01/HLA-G-UTR2 was associated with EBV+cHL and showed a reduction in heterozygosity. The EBV+cHL transcriptome showed downregulation of many HLA genes and chemokine receptor 3 (CXCR3), upregulation of the chemokine CCL4 and CCR4 receptor, and enrichment of M2 CD163+ macrophages associated with increased PD-L1 mRNA, which together conferred an increased risk of tumour recurrence. Enrichment of the linear regression score including these risk factors was associated with some negative clinicopathological features such as the presence of CD15- tumour cells, an increase in the CD68+/CD163+ phenotypic ratio of macrophages associated with a decrease in blood haemoglobin level, higher tumour histology, necrosis, higher therapeutic grade and the presence of bulky disease. It was also associated with a significant difference in gene expression of IL17RB, ITGB2, S100A2 and TREM2.

Conclusions: We concluded that a specific combination of HLA-A-F-G genes was associated with the MC subtype EBV+cHL. Expression of the HLA, CXCR3, CCL4, CCR4, CD163+/PDL1+ genes that associated with this cHL subtype proved useful in classifying young patients treated with the PHC2 protocol as being at risk of tumour recurrence and requiring closer monitoring. Although only <5% of patients showed disease recurrence or progression, these genes were associated with increased risk, mainly because together with IL17RB, ITGB2, TREM2 and S100A2 they create an immunosuppressive tumour microenvironment that could promote tumour recurrence.

Hypertension and Related-Disorders are Prevalent in Hodgkin Lymphoma Patients Identified from the EPIC Cosmos System

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Background

Advances in Hodgkin lymphoma (HL) have resulted in dramatic improvement in disease-free survival however the long-term comorbidities and rates of non-oncologic mortality in survivorship are higher compared to peers. Survivorship studies have been limited by the length of time needed for comorbidities to develop, patient loss to follow up, variable disease-specific treatments, and differences across age groups of survivors. Cosmos provides a validated population-based informatic approach to generate observational relationships between therapy and longitudinal non-oncologic outcomes which may be translated into improvements in clinical care.

Methods

Cosmos is a data science tool created from a HIPAA-defined limited centralized data set from participating health systems using Epic Electronic Medical Record (EMR) system. The data set, as of this submission, consists of 152,450,619 patients across a number of US health care systems throughout the country. A query population of 89,963 patients with a diagnosis of HL and more than one face-to-face encounter in any two-year period of the query interval was created and validated associated ICD-10 diagnoses were assessed within the Cosmos system.

Results

At the time of the query, HL patients had a median age of 56, a male predominance (51.8%), and 35% were diagnosed between ages 15-39. Staging information was available in only 10% of patients. The most common comorbid diagnoses defined by ICD-10 were essential hypertension (45.4%), hyperlipidemia (36.1%), anemia (32.1%), GERD (32.1%), shortness of breath (31.4%), fatigue (30.1%), non-HL (30%), cough (26.3%), anxiety (25.6%). Further assessment of hypertension and associated disorders was queried using Epic grouper terms in comparison to the general Cosmos population. The HL population had higher prevalence of hypertension (46.1 vs. 24.5%), chronic kidney disease (14.9 vs. 5%), hypertensive renal disease (10.1% vs. 3.1%), hyperlipidemia (44 vs. 21.1%), coronary artery disease (20.7% vs. 6.2%), ischemic or unspecified stroke (4.4 vs. 1.6%), and myocardial infarction (9.6 vs. 2.8%). Of note, the HL population had 12.5% death dates documented (3% in the general Cosmos population) with few available cause of death (0.028%).

Conclusions

EMR informatics provides a powerful tool to rapidly generate real time observational data that can inform dedicated studies and interventions. This may be important to inform trends in treatment-related morbidity and mortality in diseases like HL that can affect future health in survivorship. This study suggests hypertension and related disorders may be more prevalent in the HL population compared to the general Cosmos population and warrant further directed study and future validation.

Title: Inferior Outcomes for Young Adults Treated on Advanced Stage Clinical Trials: Report from the HoLISTIC Consortium

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Background: Inferior outcomes have been reported for adolescents and young adults (AYAs) across several cancer types, as compared to younger pediatric or older patients (pts). While lack of access to clinical trials has been implicated, we described inferior outcomes for AYAs treated on a large US Hodgkin Lymphoma (HL) adult study (Henderson, 2018). Earlier this year, in an analysis of three US phase 3 pediatric HL trials, worse outcomes were reported for pts >15 years (yrs) compared with younger pts (Kahn, 2022). Little is known about the impact of age on outcomes from recent adult clinical trials.

Methods: Individual patient data from eight advanced stage clinical trials (ECOG2496, SWOG0816, HD2000, HD9601, HD0607, HD0801, UK Stanford V, and RATHL), conducted from 1996-2012, were harmonized as part of the HoLISTIC Consortium. Pts with classic HL, stage IIb, III or IV disease, ages 14-65 yrs, and treated at adult centers were included. Outcomes were 5-yr progression-free survival (PFS) and 5-yr overall survival (OS), which were estimated in univariable and multivariable models. Age at diagnosis and 10 other clinical factors, were examined with multivariable adjusted plots and piecewise linear splines to identify functional forms of the relationship with PFS or OS. Multiple imputation was used for missing data.

Results: Data on 3893 HL patients were included. Across all studies, 5-year PFS was 76.5% (95% CI=75.1%, 77.9%); 5-year OS was 91.6% (95% CI=90.7%, 92.6%). Median age was 32 yrs and 41% of patients were <30 yrs at diagnosis. Associations between age (analyzed as a continuous variable) and PFS displayed a distinct piecewise linear relationship with an inflection point at age 30 (Figure A). In multivariable analyses, PFS improved from ages 14 to 30, and then declined after age 30 (Figure B). The association between age and OS was not significant <30 yrs, advancing age >30 yrs was associated with worse OS. These patterns were seen broadly across studies and not dominated by one trial.

Conclusion: The association between age and HL survival in the modern era appears to be more nuanced than the dichotomous variable of age at 45 yrs, as used in previous models. While patients under 30 yrs have worse short-term disease outcomes than age 30 yrs, 5-yr OS results suggest that younger patients may be amenable to successful salvage. Further research is needed to understand these differences to optimize outcomes.

INVESTIGATING DIAGNOSIS AND MANAGEMENT OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY: CURRENT PRACTICE PATTERNS OF PEDIATRIC AND MEDICAL ONCOLOGISTS

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) affects up to 78% of oncology patients receiving chemotherapy and results in detrimental side effects. CIPN is characterized by symptoms including pain, weakness, gait disturbances, and constipation. There is a lack of standardized approach to diagnosis, though patient reported outcomes have recently demonstrated a high sensitivity of CIPN detection. Further, there is a lack of standardized approaches to CIPN treatment. Due to this lack of standardization to diagnose and manage CIPN in children and adolescent young adults (CAYA) with cancer, practice patterns of oncologists remain unknown. We sought to evaluate practice patterns of oncologists regarding their diagnosis and management of CIPN in the CAYA cancer population.

Methods: A case-based survey was developed by pediatric oncologists and pharmacists. Survey included an 18-year-old receiving vincristine (VCR) with mild neuropathy (Case 1) and severe neuropathy (Case 2). The survey included several questions regarding how respondents would diagnose and manage each case. Survey was IRB approved and distributed to oncologists via email from June 2023-July 2023 utilizing REDCap. Data were aggregated and reported using descriptive statistics.

Results: To date, a total of 103 responses were submitted by 84 (82%) pediatric and 15 (15%) medical oncologists, with 5 (3%) working with both populations. Half of participants, 51 (49.5%) primarily treat CAYAs with lymphoma. Participants were female (56%), with a wide variety of years in practice (range <5 to >30 years). Majority (n=64, 62.1%) of respondents for Case 1 (mild neuropathy) would refer the patient to physical therapy (PT), while 46 (44.7%) would prescribe a pharmacologic agent, 23 (22.3%) would dose reduce or omit chemotherapy, and 18 (17.5%) would not intervene. VCR dose reduction included 16 participants (69.6%) choosing a 50% dose reduction, 6 (26.1%) a 25% dose reduction, and 1 (4.3%) a 75% dose reduction. Medications prescribed included 43 (95.6%) gabapentin, 6 (13.3%) pregabalin, and 3 (6.7%) topical treatments. Majority (82, 79.6%) of respondents for Case 2 (severe neuropathy) would dose reduce or omit VCR, 75 (72.8%) would refer for PT, 55 (53.4%) would start a pharmacologic agent, and 3 (3%) would continue to monitor. VCR dose reduction included 52 participants (63.4%) choosing to dose reduce by 100%, 23 (28%) dose reduce by 50%, and 7 (8.5%) dose reduce by 25%. Majority of respondents (n=94, 91.2%) reported they were comfortable diagnosing CIPN, and (n=88, 85%) were comfortable managing CIPN.

Conclusion: Our survey demonstrated a wide range of clinical practices regarding diagnosis and management of CIPN in CAYAs with cancer. The wide range of responses in VCR dose reductions, interventions, and diagnostic tools, demonstrates a critical need for more robust research to provide evidence-based strategies to inform a standard of care for CAYA with cancer suffering from CIPN.

ONECUT2 and endogenous retrovirus expression in Hodgkin lymphoma cells

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Background

By analysing a cDNA library from the Hodgkin Lymphoma (HL) cell line L-1236, we identified a transcript variant of the transcription factor ONECUT2. Members of the ONECUT family of transcription factors are characterized by the presence of a single CUT (cut wings) domain together with a homeodomain. The new variant (ONECUT2s) lacks the homeodomain. The human genome contains a large number of endogenous retroviruses (HERV) and other members of the long terminal repeat (LTR) class of repetitive elements. Activation of such elements in HL cells has been described. We studied the impact of ONECUT2 and ONECUT2s on gene expression with a focus on repetitive elements.

Methods

Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was used for quantification of ONECUT2 and ONECUT2s in cell lines and tissue samples. In addition, publicly available microarray data sets were analyzed. Knock-down of OC2 and OC2s was performed by RNA interference. The two variants were clones into a doxycycline-inducible vector and transfected into different cell lines. Over-expression was studied by qRT-PCR and Westernblot. Microarray analysis and RNA-seq were performed for assessing the influence of the variants on expression of genes and repetitive elements.

Results

High expression of OC2 and OC2s was detected in HL cell lines. Public available microarray data also indicated high expression of ONECUT2 in HL cell lines and a subset of HL biopsies. Microarray and RNA-seq analysis indicated that ONECUT2 has a stronger impact on gene expression than ONECUT2s. ONECUT2 protein could be detected not only in the nucleus but also in the cytoplasm of transgenic cells. Interestingly, we observed a strong correlation between ONECUT2 expression and the expression of an endogenous retrovirus of the HERV-H/F family. However, ONECUT2 transgenic cells showed no direct induction of this HERV, suggesting that both genes might be co-regulated by other factors.

Conclusions

ONECUT2 influences gene expression in HL cells and correlates with the expression of endogenous retroviruses. The low impact of ONECUT2s on gene expression suggests that this variant lacks transcription factor activity. HL specific repetitive elements might represent new diagnostic and therapeutic target structures.

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Patterns of presentation and outcomes in Stage IV Hodgkin lymphoma: A report from the Children's Oncology Group (COG) AHOD1331 trial

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Background: Outcomes for high-risk pediatric and adolescent and young adult classic Hodgkin lymphoma (cHL) improved substantially with the addition of brentuximab vedotin (Bv) to AVEPC (adriamycin, vincristine, etoposide, prednisone, cyclophosphamide) chemotherapy. As patients with stage IV disease have poor outcomes, we evaluated the prognostic implications of sites contributing to stage IV disease.

Methods: On AHOD1331 (NCT02166463), patients age 2-21 years with high-risk cHL (stage IIB with bulk, IIIB, IVA, and IVB) were randomized to 5 cycles of AB (bleomycin)VE-PC versus Bv-AVE-PC, and consolidative radiotherapy based on interim response and large mediastinal adenopathy (LMA) determined by chest radiograph at diagnosis. Patients with stage IV disease, as determined by protocol defined and centrally reviewed contrast CT and PET-CT, were identified. Stage IV was defined as disseminated involvement of ≥1 extralymphatic organ or tissues (with or without lymph node involvement) or isolated extralymphatic organ involvement with distant nodal involvement. E-lesions were distinguished from sites of stage IV involvement in the lung, but any liver and/or bone marrow involvement, regardless of contiguity, was considered stage IV. Central review was performed to confirm institutional classification of stage, upstaging 33 patients to stage IV and downstaging 17 among the 353 enrolled and stratified as Stage IV by the institution. Baseline characteristics and progression-free survival (PFS) were compared by pattern of metastatic involvement (lung, bone, bone marrow, interim PET positive and LMA).

Results: 369 patients (median age 15 years, range 3-22) with stage IV disease treated on AHOD1331 were included, of which 183 (50%) were treated with ABVE-PC and 186 (50%) with Bv-AVE-PC. Patterns of disease included any involvement of lung (241; 65%); bone (106; 29%); bone marrow (78; 21%); or liver (15; 4%). Bv-AVE-PC significantly improved PFS among all stage IV patients compared to ABVE-PC (3-year PFS 90.2% vs 81.5%, p=0.01). Among patients with lung involvement, PFS was improved with Bv (3-year PFS 91.5% vs 83.3%, p=0.05). Patients with bone involvement experienced significantly improved PFS with Bv (3-year PFS 93.8% vs 77.7%, p=0.03). PFS was also superior with Bv among stage IV patients with a positive interim PET (3-year PFS 88.0% vs 64.9%, p=0.056) and those with LMA (3-year PFS 92.9% vs 78.4%, p=0.004). However, among patients with bone marrow involvement, there was no difference in PFS with Bv (3-year PFS 85.8% vs 82.9%, p=0.71).

Conclusions:
Among children and adolescents with stage IV cHL, PFS was notably improved with Bv-AVE-PC in patients with most patterns of metastatic disease, with the exception being those with bone marrow involvement. These results will help guide future efforts to understand strategies to improve outcomes among children with stage IV disease.

PD-1 expression in children and adolescents with Classical Hodgkin Lymphoma

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Introduction:

Hodgkin Lymphoma (HL) affects mainly adolescents and young adults. In Brazil, the estimated population of children and adolescents under 19 is almost 59 million. Therefore, the number of new cases of Hodgkin Lymphoma expected for this age group is 491 new cases every year (INCA 2023)

HL have high cure rates, after treatment with chemotherapy alone or combined with radiotherapy. However, survivors may develop late side effects such as a secondary neoplasm, hypothyroidism, lung fibrosis and cardiovascular diseases. Over the past 30 years, the main pediatric study groups have made adaptations to treatment based on the therapeutic response, reducing or eliminating RT in order to reduce toxicity (Mauz-Körholz et al, 2015)

Once survival rates of HL patients is so high, developing protocols that minimize treatment late effects has become a challenge (Flerlage et al.,2018). The recent finding of PDL-1 and PDL-2 expressions in RS cells and in reactive cells of the tumor microenvironment, and the concomitant PD-1 positive regulation on the surface of intratumoral T-cells have opened the way for immune PD-1/PD-L1 checkpoint inhibitors in the treatment of relapsed HL (Calabretta et al, 2019)

The immunotherapy medications Pembrolizumab and Nivolumab have an acceptable toxicity profile, with a reduction of side effects related to immunosuppression. In a study with 30 adults with HL with poor prognosis factors, the use of PDL1-PD1 inhibitor after transplant increased the survival rates from 60 to 80% over a period of 18 months (Ansell, 2020). In 15 children and adolescents with relapsed or refractory HL, 60% had objective responses with Pembrolizumab (Geoerger et al, 2020)

In the future, it is likely that the use of monoclonal antibodies and immune checkpoint inhibitors will be important tools for treating HL, to be used as first line drugs and in relapsed diseases. For this reason, it is important to identify the profile of PD-1 expression in children and adolescents with HL, so that they can benefit from new therapies.

Objectives

To assess PD-1 expression in tumor samples of children and adolescents with Classical Hodgkin Lymphoma and correlate it with clinical and prognostic parameters.

Materials and Methods

This is a retrospective study of 76 patients with CHL by means of the immunohistochemical analysis of slides, stored at the Pathology Department of EPM/UNIFESP, with the aim of determining the pattern of PD-1 expression through an imaging technique. The quantitative assessment of this expression was performed using Image J software and correlated with clinical data, overall survival and event-free survival. The study was approved by UNIFESP Research Ethics Committee.

Conclusion

All tumor samples showed PD-1 expression. There was no correlation between PD-1 expression and any other clinical parameter, overall survival and event-free survival.

Pembrolizumab in children and young adults with classical Hodgkin lymphoma with slow early response to front-line chemotherapy: phase 2 KEYNOTE-667

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Background: Patients with classical Hodgkin lymphoma (cHL) with a slow early response (SER) to initial chemotherapy (chemo) are at high risk of relapse, and management strategies such as dose intensification and radiotherapy (RT) can cause long-term toxicity. KEYNOTE-667 (NCT03407144) is an open-label, phase 2 study designed to evaluate pembrolizumab (pembro) + chemo in pts with cHL and SER to front-line chemo. Results of an interim analysis in pts with high-risk cHL (group 2) and SER are presented.

Methods: Eligible pts were 3-17 (children) or 18-25 y (young adults) old with newly diagnosed stage IIEB, IIIEA, IIIEB, IIIB, IVA, or IVB cHL. Pts received induction with 2 cycles of vincristine, etoposide, prednisone/prednisolone, and doxorubicin (OEPA). Early response was then assessed by PET/MRI/CT. Pts with rapid early response received nonstudy therapy. Pts with SER received consolidation with 4 cycles of cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine (COPDAC-28) + pembro 2 mg/kg up to 200 mg IV Q3W (aged 3-17 y) or 200 mg IV Q3W (aged 18-25 y). Pts with PET positivity (Deauville score 4-5) after consolidation (late response assessment [LRA]), received involved-site RT (28.8 Gy) to late PET-positive residua; pts with PET negativity at LRA continued pembro without RT. All pts with SER received maintenance pembro Q3W for up to 17 doses. The primary end point was ORR by blinded independent central review (BICR) per Cheson 2007 International Working Group criteria in pts with SER. PET negativity after consolidation and safety were secondary end points.

Results: 49 pts with high-risk cHL and SER to front-line OEPA were included. Median follow-up at the data cutoff (Sept 2, 2022) was 15.3 mo (range, 3.2-30.5). Median age was 15 y (range, 6-22), 24 pts (49%) had bulky disease, and 31 (63%) had Ann Arbor stage IV disease. Of 49 pts, 22 (45%) had completed treatment and 24 (49%) were ongoing on consolidation/maintenance treatment. The median time on pembro was 10.4 mo (range, 0.5-11.8). 42 of 49 pts (86%) had a LRA, of whom 27 (64%) were PET negative by BICR (30 [71%] were PET negative by investigator review). All-cause adverse events (AEs) occurred in 42 pts (86%); grade ≥3 in 13 pts (27%). No pts died because of an AE. 7 pts (14%) had a serious AE. Treatment-related AEs occurred in 30 pts (61%); grade ≥3 in 6 pts (12%). 4 pts (8%) had immune-mediated AEs (2 grade 1 hypothyroidism; 2 grade 2 hypothyroidism).

Conclusions: Pembro + COPDAC-28 consolidation had manageable safety in pediatric pts with high-risk cHL with SER to front-line OEPA, and resulted in 64% of pts having a PET-negative response at end of chemo and being spared RT. These results suggest adding pembro to COPDAC-28 consolidation may augment response in this population.

Positron Emission Tomography Response and Outcome in Low-Risk Nodular Lymphocyte Predominant Hodgkin Lymphoma

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Background: Although Positron Emission Tomography (PET) plays an important role in staging and response assessment for classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma, there is little published about use of PET to guide treatment in nodular lymphocyte predominant Hodgkin lymphoma (nLPHL). nLPHL has different histology, clinical presentation, and outcomes than cHL. A better understanding of the clinical significance of PET response in nLPHL is critical for incorporating PET into prospective trials.

Methods: Children's Oncology Group study AHOD03P1 (NCT00107198) enrolled patients with low-risk nLPHL < 22 years of age. Patients with stage IA and more than one lymph node or stage IIA nLPHL were treated with 3 cycles of doxorubicin, vincristine, prednisone, and cyclophosphamide (AV-PC) chemotherapy, given every 21 days. Patients with complete response (CR) based on anatomic response and qualitative reading of negative PET on central review did not receive radiation therapy while patients with < CR received 21-Gy involved-field radiation therapy (IFRT). All PET scans from this study available in the Imaging and Radiation Oncology Core (IROC) were retrospectively reviewed and assigned Deauville scores. Patients without evaluable imaging due to inaccessible scans on CD-ROM or poor quality were excluded from this analysis. Event-free survival (EFS) across end of therapy Deauville score was analyzed using the Kaplan Meier method.

Results: A total of 183 eligible patients enrolled on study and 135 received 3 cycles of chemotherapy. PET imaging was available for review from diagnosis in 99 patients and after 3 cycles of chemotherapy in 106 patients. Median age 12.7 years (range 4.2-20.7), 85% male, 34% Stage IA, and 66% Stage IIA. Deauville score at diagnosis D1 n=1, D2 n=3, D3 n=0, D4 n=5, D5 n=90, no Deauville assigned n=84. After 3 cycles of chemotherapy D1 n=50, D2 n=35, D3 n=11, D4 n=7, and D5 n=3. Three-year EFS for patients with post-cycle 3 score of D1 was 89.9% (95% CI 77-96%), D2 was 97.1% (95% CI 81-99.6%), D3 was 90.9% (95% CI 51-99%), D4 was 28.6% (95% CI 1-71%), D5 was 66.7% (95% CI 5-95%) p=0.0081 (Figure 1A). When divided into PET negative (D1-D3) and PET positive (D4-D5), 3-year EFS was 92.6% (95% CI 85-96%) for PET negative and 45.0% (95% CI 11-75%) for PET positive patients, p=0.0036 (Figure 1B). Including D3 as PET positive, as has been used in some circumstances for patients with nLPHL, showed 3-year EFS of 92.9% (95% CI 85-97%) for D1-D2 and 69.8% (95% CI 41-86%) for D3-D5, p=0.083. Of the 7 patients considered PET positive on study, on review D5 n=3, D4 n=3, D3 n=1. No patient with a negative PET scan at the end of chemotherapy but < CR due to anatomic response experienced a relapse.

Conclusion: At diagnosis, low-risk nLPHL lesions were almost always PET avid with Deauville score 5. PET response following 3 cycles of AV-PC chemotherapy is highly predictive of outcome in pediatric patients with low-risk nLPHL.

Prognostic Significance of PD1, PD-L1 Expression, Pathological Subtypes and Metabolic Activity on 18F-FDG PET/CT in Refractory/Relapsing Pediatric Hodgkin Lymphoma

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Background: Hodgkin Lymphoma (HL) is a unique disease entity both in its pathology and the young patient population that it primarily affects. Several meta-analyses have demonstrated that high PD-L1 expression levels are correlated with adverse clinical and pathologic features. Objectives: The aim of this study is to evaluate the correlation between the expression of PD-L1 and clinicopathological features, as well as the prognostic significance of PD-L1 expression with regard to interim PET response in relapsing / refractory pediatric HL.

Methods: We measured the expression of PD-1/PD-L1 in the baseline diagnostic samples of children with relapsing/ refractory classical HL. The results were correlated with the pathological subtypes as well as the clinical outcome.

Results: Of the 88 included patients, 77% had advanced stage HL. PD-1 expression was detected in 50% of cases, whereas PD-L1 (membranous) was expressed by tumor cells in 60% of the cases, and strongly expressed in 16% of cases. Notably, PD-L1 (cytoplasmic) was detected in 55% of the cases. There was a significant differences in the expression levels of PDL-1 between the different pathological subtypes ($p = 0.006$). OS of patients with PD-L1 expression (Cytoplasmic) was 83% vs 91% in patients with absent expression ($P=0.001$). There was no prognostic significance of PD-L1 expression with regard to PET response ($p=0.31$).

Conclusion: Although PD-L1 expressions did not show statistical significance with well-established prognostic factors, our preliminary data indicate that pathological subtypes and cytoplasmic expression of PD-L1 may have a prognostic implication on survival in pediatric HL.

Radiotherapy utilization and outcomes on a contemporary trial for pediatric high-risk Hodgkin lymphoma study

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Purpose: We investigated the outcomes of proton therapy (PT) and photon therapy (XRT) with 3D conformal radiotherapy (3D) and intensity modulated radiotherapy (IMRT) among patients with pediatric hodgkin lymphoma(HL) on the Children's Oncology Group (COG) trial AHOD1331 (NCT021664643).

Methods: This multicenter randomized, phase 3 study enrolled patients 2-21 years (yrs) with untreated HL: stages IIB bulk, IIIB, IVA, IVB. Patients were randomized to 5 cycles of ABVE-PC or the brentuximab vedotin (Bv) containing regimen Bv-AVE-PC given every 21 days. ISRT to 21 Gy was given to bulky mediastinal adenopathy and slow responding lesions defined by 5-point score 4 or 5 on PET-CT after 2 cycles. RT plans were normalized to 21 Gy and doses to the thyroid, breast, and heart were evaluated for the modalities.

Results: Among 587 eligible patients, 317 (54.0%) received protocol RT of which 28.7% received 3D, 44.8% received IMRT, and 26.5% received PT. PT utilization increased over the study from 21.5% in the first half to 31.5% in the second half (p= 0.045).

Radiation plans were available with doses to the OARs in 82, 126, and 74 patients for 3D, IMRT, and PT, respectively. The average mean heart dose was 9.9Gy, 10.5Gy, and 7.4Gy with 3D, IMRT, and PT, where PT was significantly lower than IMRT and 3D (P<0.001). The average mean breast dose was 2.9Gy, 5.5Gy, and 2.2Gy, where PT was significantly lower than IMRT (p=0.00001) and 3D (p=0.032), while IMRT was significantly higher than 3D (p=0.00001). The average mean thyroid dose was 11.6Gy, 11.5Gy, and 13.8Gy with 3D, IMRT, and PT, where PT was statistically significantly higher than IMRT (p=0.017) and 3D (p=0.0377).

The 3-yr progression-free survival rates overall by RT were comparable: PT (88.0%, 90% CI 80.6% – 92.7%%); XRT (87.1%, 90% CI 82.9%-90.4%) (p=0.85). No difference in PFS was observed between 3D versus IMRT (p= 0.65). No differences were observed in severe acute toxicities (8.33% vs. 8.15%, p=0.96) between PT and XRT.

Conclusions: Selective use of RT results in excellent outcomes for pediatric patients with high-risk HL and combination chemotherapy, including the novel agent Bv. Patients treated with PT had significantly lower doses to the heart and breast compared with 3D and IMRT with similar disease control and acute toxicity. Long term follow-up (>10 years) is needed to evaluate for secondary malignancies and cardiac toxicity among the different RT modalities.

TITLE: RESOURCE-ADAPTED GLOBAL RADIATION THERAPY RECOMMENDATIONS THROUGH THE ADAPTED RESOURCE AND IMPLEMENTATION APPLICATION (ARIA) ADAPTED MANAGEMENT GUIDELINE (AMG) FOR HODGKIN LYMPHOMA (HL)

Background/Purpose:
An international working group of pediatric radiation oncologists with expertise in the treatment of pediatric Hodgkin lymphoma (HL)—including representation from North America, Europe and Low- and Middle-Income Countries (LMIC)—developed radiotherapy (RT) guidelines designed to align with the chemotherapy in each stratum where radiotherapy is available for the ARIA (Adapted Resource and Implementation Application) Adapted Management Guideline (AMG).

Methods:
The radiotherapy approach integrates the Children's Oncology Group (COG) and Euronet strategy for resource and risk-stratified guidance on both the dose and volumes. Members of the ARIA HL AMG radiation oncology international working group were tasked with development of the guideline and a separate ARIA HL global representative panel provided additional review of the guideline.

Results:
The RT guidance within the ARIA HL AMG provide details on the indications for radiotherapy, treatment planning, volumes and field based on the available imaging, dose prescription, with attention to critical organ radiotherapy doses, treatment delivery, on-treatment imaging, acute and long-term toxicities. The RT guidance integrates early response based-assessment on computed tomography (CT) alone with modern RT concepts. For strata B and C, where radiotherapy is available, details of staging and response assessment using CT only for centers that do not have fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans were provided. The radiotherapy simulation and treatment for centers that have only 2D technology were provided in addition to the guideline for centers with advanced technology including Intensity Modulated Radiation Therapy (IMRT) and volumetric modulated arc therapy (VMAT). As part of the guideline development, a series of Delphi questions were used to assist in arriving at consensus of experts for specific and controversial RT issues with pediatric HL treatment.

Conclusions:
The goal was to provide clear, detailed and reasonable global RT guidance that is adapted for any resource setting, including images that would be able to be used by a qualified radiation oncologists who may not have considerable expertise in the treatment of pediatric Hodgkin lymphoma. There remain areas which require further studies like extent of treatment volumes with limited resources.

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Response-adapted therapy (tx) with nivolumab plus brentuximab vedotin (nivo + BV) without autologous hematopoietic cell transplantation (auto-HCT) in children, adolescents, and young adults (CAYA) with low-risk relapsed/refractory (R/R) classic Hodgkin lymphoma (cHL): CheckMate 744.

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Background

Outcomes are poor for patients (pts) with cHL who develop R/R disease after first-line (1L) chemotherapy +/- radiotherapy (RT). Salvage tx that attain high event-free survival (EFS) rates and minimize late toxicity by omitting high-dose chemotherapy (HDCT)/auto-HCT are needed. CheckMate 744 (NCT02927769) was conducted in collaboration with the Children's Oncology Group and the EuroNet PHL consortium and is the first multicenter phase 2 study evaluating a risk-stratified, response-adapted salvage tx with nivo + BV in CAYA with R/R cHL. In the standard-risk cohort, complete metabolic response (CMR) rate before consolidation with HDCT/auto-HCT was 94% (Harker-Murray et al. *Blood* 2022). With highly active salvage tx, pts in low-risk cohort could achieve high EFS without HDCT/auto-HCT; we report data from this cohort.

Methods

Pts were aged 5–30 y and had ≤ 3 cycles (C) of 1L anthracycline-based systemic tx. Risk stratification was described in Harker-Murray et al. Pts received 4C of nivo + BV induction. Pts with CMR received additional 2C nivo + BV before involved-site radiation therapy (ISRT) consolidation (dose, 30-30.6 Gy). Pts with suboptimal response received 2C BV + bendamustine intensification; pts with CMR proceeded to ISRT consolidation. Primary endpoints: CMR rate (Lugano 2014) any time before ISRT and 3-y EFS rate, both per blinded independent central review (BICR). For CMR and overall response rate (ORR), a 90% confidence interval (CI) was used per statistical plan.

Results

Among 28 pts treated with nivo + BV, median (range) age was 17 (6–27) y; 64% of pts were aged < 18 y. Most (64%) pts had stage II disease at relapse; 82% had relapse ≥ 12 mo after 1L tx, 2 pts had prior RT. Median (range) follow-up was 31.9 (2.2–55.3) mo. CMR, ORR, 3-y EFS and PFS rates are shown in **Table**. Median duration of response was not reached; 87% of pts had sustained response at 36 mo' follow-up. Efficacy outcomes were comparable in the pediatric population (CMR per BICR before ISRT, 88.9%; 3-y EFS rate, 78.3%).

During induction, 22 (78.6%) pts had treatment-related adverse events (TRAEs; grade 3/4, 25.0% pts; hematologic, < 10% pts; immune-mediated, 21.4%). Serious AEs leading to discontinuation included rash, pyrexia, and acute kidney injury (1 pt each).

Conclusions

The findings demonstrate that most CAYA with low-risk R/R cHL can be salvaged with chemoimmunotherapy with a favorable toxicity profile, and do not require HDCT/auto-HCT.

Table. CMR and ORR per BICR and investigator (INV) in low-risk cohort

	BICR	INV
Any time before ISRT		
CMR, n (%) [90% CI]	26 (92.9) [79.2-98.7]	25 (89.3) [74.6-97.0]
ORR, n (%)	28 (100.0)	28 (100.0)
After 4C nivo + BV		
CMR, n (%)	23 (82.1)	24 (85.7)
ORR, n (%) [90% CI]	27 (96.4) [84.1-99.8]	28 (100.0) [89.9-100.0]
3-y EFS, % [90% CI]	86.9 [69.5–94.7]	88.0 [71.8-95.2]
3-y PFS, % [90% CI]	95.0 [76.7–99.0]	95.7 [79.4-99.1]

Skeletal Muscle Index and Early Response in Pediatric Hodgkin Lymphoma (HL): A Children's Oncology Group (COG) Study AHOD0031 and AHOD0831 Report

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Introduction: Low skeletal muscle index (SMI, a computed tomography [CT] image-derived measure of skeletal muscle mass) is associated with worse disease-free survival among adults with cancer, an association hypothesized to be either due to altered chemotherapy biodistribution or inflammatory changes associated with cancer cachexia; its role in children with cancer remains understudied. We examined the association between baseline SMI and early response (ER: slow [SER]; rapid [RER], a key predictor of survival among those receiving conventional chemotherapy) in children with newly diagnosed intermediate-risk (COG-AHOD0031) or high-risk (COG-AHOD0831) HL.

Methods: Patients enrolled on AHOD0031 or AHOD0831 with baseline digital abdominal CT images and ER assessment after two cycles of chemotherapy were included. Two consecutive slices per patient at third lumbar vertebra were identified and skeletal muscle area (SMA, in cm2) and total adipose tissue area (TAT, in cm2) was calculated using sliceOmatic software (Canada). Height at diagnosis was used to calculate SMI (SMA averaged across 2 slices/ [height in m]2) and TAT index (TATI=TAT averaged across 2 slices/ [height in m]2). SMI and TATI were divided into quintiles (Q1 [lowest] to Q5 [highest]). Demographic (age at HL diagnosis, sex, race/ethnicity) and disease characteristics (stage, histology, bulk disease, 'B' symptoms) and ER status were obtained from COG Statistics and Data Center. The association between SMI and SER was examined using logistic regression after adjusting for demographic and disease characteristics, TATI, and study. Analyses stratified by 'B' symptoms were also performed.

Results: Overall, 1,321 patients met eligibility (Table); 301 (22.8%) had SER (AHOD0031=223 [19.1%]; AHOD0831= 78 [50%]). Patients with SER were more likely to be older (P=0.02), have stage IV disease (P<0.001), nodular sclerosing histology (P<0.001), bulk disease (P<0.001) and 'B' symptoms (P<0.001). Higher SMI was associated with lower odds of SER (SMI Q5: adjusted Odds Ratio [aOR]=0.53, 95% confidence interval [CI]= 0.32-0.89, P=0.02; SMI Q2-Q4: aOR=0.70, 95%CI=0.49-1.00, P=0.05; ref=SMI Q1). While the association between SMI and SER was significant among patients without 'B' symptoms (SMI Q5: aOR=0.46, 95%CI=0.24-0.88, P=0.02; SMI Q2-4: aOR=0.61, 95%CI=0.39-0.96, P=0.03), the association was mitigated among patients with 'B' symptoms (SMI Q5: aOR=0.62, 95%CI=0.27-1.43, P=0.3; SMI Q2-4: aOR=0.78, 95%CI=0.44-1.39, P=0.4).

Conclusions: Lower skeletal muscle mass at cancer diagnosis is associated with worse early response in children with HL, especially in patients without 'B' symptoms. SMI may be a novel image-derived marker that is independently associated with poor early response in children with HL.

THE ROLE OF PROTOCOL-STIPULATED DOSE MODIFICATION IN THE CHILDREN'S ONCOLOGY GROUP AHOD1331 STUDY TO MANAGE CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

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Background/Purpose: Incorporation of Brentuximab Vedotin (BV) into upfront multiagent chemotherapy regimens has improved outcomes for high-risk classic Hodgkin lymphoma (HL). The shared mechanism of action of BV and vinca alkaloids creates a unique challenge for managing chemotherapy- induced peripheral neuropathy (CIPN), a potentially treatment limiting toxicity. Echelon-1 reported rates of CIPN among adults with advanced stage HL of 67% in the BV arm as compared to 43% in the control arm (Connors, 2018) with dose modifications at the discretion of the treating physician of 66% for BV and 57% for vinblastine (VBL). We examined use of protocol-stipulated dose modification in the Children's Oncology Group (COG) AHOD1331, a Phase 3 randomized comparison of standard multi-agent chemotherapy (ABVE-PC vs. BV-AVE-PC) among children and adolescents with high-risk HL (NCT02166463).

Methods: COG AHOD1331 required clinician grading of CIPN with each cycle using Balis Peripheral Neuropathy Scale and required reporting of ≥Grade 2. In the experimental arm, protocol stipulated dose modifications of vincristine (VCR) preceded modification of BV in cases of CIPN ≥ grade 2 based on both time and grade of neuropathy. Rates of PN were calculated by treatment cycle by study arm. Dose modifications were summarized for each drug by treatment cycle. Median time to first dose modification was estimated by treatment arm. A Cox model estimated hazard ratios (HR) and 95% confidence intervals (CI) for dose modifications by treatment arm and patient clinical characteristics. Progression-free survival (PFS) was compared with Log-rank test by study arms and within arm by presence or absence of PN.

Results: Incidence of clinician reported CIPN did not differ by study arm (19%, p=0.86). Dose modifications of BV, VCR, or both occurred more frequently in the experimental arm (16.8% vs. 4.2%, p<0.001). Dose modification occurred earlier in patients on the experimental arm (40.75 days [95%CI 31.5-73.5, p = 0.004 vs. 75.5 days [95%CI 59.00-94.75], p = 0.004). Three-year PFS with CIPN in the experimental arm remained unchanged compared to patients without CIPN (93.2% vs. 92.3%) and was superior in the experimental arm when compared to the standard arm (p=0.0030).

Conclusions: At a cumulative BV dose of 9 mg/kg, overall rates of CIPN were substantially lower than previously reported in adults treated with BV. CIPN occurred earlier in the experimental arm and was responsive to the dose modification strategy. No differences in rates of CIPN were observed between arms. Despite higher rates of CIPN-related dose modification of VCR and BV in the experimental arm, PFS remained superior in the experimental arm. Protocol stipulated dose modifications of BV prevented potential excess toxicity, while preserving the efficacy of the successful experimental agent.

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The spatially resolved tumor microenvironment predicts treatment outcome in relapsed/refractory Hodgkin lymphoma

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INTRODUCTION:
Despite recent treatment advances, about a third of relapsed or refractory classic Hodgkin lymphoma (r/r CHL) patients succumb to their disease after high dose chemotherapy followed by autologous stem cell transplantation (HDC/ASCT). Here, we aimed to determine spatially resolved tumor-microenvironment ecosystems to establish novel biomarkers associated with treatment failure in r/r CHL.

METHODS:
We performed imaging mass cytometry (IMC) on 169 paired primary diagnostic and relapse biopsies using a marker panel specific for CHL biology. For each cell type in the TME, we calculated a 'spatial score' measuring the distance of nearest neighbor cells to the malignant Hodgkin Reed Sternberg cells within close interaction range (Fig. A),

RESULTS:
We obtained highly multiplexed images for a total of 7,146,042 cells. Overall, CHL biopsies from early relapse demonstrated shared TME patterns between diagnostic and relapse samples, and were characterized by lower abundance of CD8+ cells ($P < 0.01$) as well as enrichment of a CD163+ myeloid cell population ($P < 0.05$). In contrast, late relapse samples often demonstrated significant TME changes between diagnostic and relapse biopsies ($P < 0.01$). Integrative analysis of single cell RNA sequencing and imaging data further identified a unique spatial architecture defined by CXCR5+ HRS cells and their strong interactions with CXCL13+ macrophage in a subset of cases (Fig. B).
Next, we sought to develop a prognostic assay using spatially resolved parameters. Using LASSO- based outcome analysis, CXCR5+ HRS cells (Hazard Ratio [HR]: 2.86), PD1+ CD4+ T cells (HR: 2.80), macrophages (HR: 1.99), and CXCR5+ B cells (HR: 0.19) were identified as factors that were significantly associated with post-autologous stem cell transplantation (ASCT) failure-free survival (FFS). Using these 4 variables, we developed a spatial score-based prognostic model (RHL-4S) and compared performance with a classical protein%-based model. The RHL-4S produced a high-risk group of patients with significantly inferior post-ASCT FFS compared with a low-risk group (5-year post-ASCT FFS: high risk, 41% vs low risk, 81%; $P < 0.00021$, Fig. C). We further translated the findings from IMC into a more simplified multi-color immunofluorescence (MC-IF) assay, which can be applicable in routine clinical practice. When applying the MC-IF assay to an independent validation cohort, high-risk patients defined by RHL4S displayed unfavorable post-ASCT FSS compared with low-risk patients (5-year post-ASCT FFS: high risk, 41% v low risk, 83%; $P = .027$; Fig. D).

CONCLUSION:
We identified the interaction of CXCR5+ HRS cells with ligand-expressing CXCL13+ macrophages as a prominent crosstalk axis in relapsed CHL. Harnessing this TME biology, we developed a novel prognostic model applicable to r/r CHL biopsies, RHL-4S, opening new avenues for spatial biomarker development.

Towards Incorporation of Pediatric Specific Criteria in the Revised Lugano Classification of Hodgkin Lymphoma (HL) Staging and Response: Report from the ICML Pediatric Subcommittee

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Purpose

The Lugano Classification is the benchmark for evaluation of nodal lymphomas (Cheson, J Clin Oncol 2014) yet pediatric (ped) specific recommendations have not been included limiting its application to children. Differences exist in ped specific lymphomas impacting biomarker selection, developmental changes (eg size thresholds for bulk), and others. With increasing collaboration for adolescent and young adult lymphomas clinical trials, inclusion of ped criteria is essential to allow for use of the Lugano Classification to all patients. With planned major updates to the 2014 classification, an opportunity to consider ped specific issues was identified.

Methods

6 representatives from North America & Europe, HL & NHL, pediatric & radiation oncology & nuclear medicine were convened to develop ped recommended revisions to the 2014 Lugano Classification. Ped-specific biomarker expertise was obtained

Results

The Ped Subcommittee (11 meetings 9/2022-4/2023) recommended:

Initial Evaluation: Systematic assessment of cancer predisposition risk and referral to genetic counseling; Consider risk for underlying immunodeficiency in selected patients.

Staging Criteria–Imaging: Limit lifetime exposures to radiation, sedation, anesthesia; Use measures (warming, pharmacologic suppression) to reduce brown fat activation to minimize FDG-PET false-positive results; FDG-avid reactive nodes <2 cm due to infection/inflammation are more common in children; Specific size criteria used in adults may underestimate bulk or organomegaly in children.

Staging Criteria–Biomarkers: Few validated for HL clinical practice; TME by nanostring, image mass cytometry; molecular tumor burden, ctDNA, TARC, MTV are of clinical trial interest.

Prognostic Groups & Treatment Allocation: Risk stratification criteria vary from adult HL and across ped HL regimens. Most utilize low, intermediate and high-risk groups: E-lesions, bulk, & ESR/CRP elevations are used for treatment allocation regardless of stage; Age, leukocyte count, hematocrit, lymphocyte count, albumin, & number of nodal sites are not routinely used.

Assessment of Response During Treatment: New PET avid nodes should not be considered a new site of disease if original sites had adequate response, especially if history or other findings suggest infection/inflammation.

Follow Up Evaluations: False-positive findings may be related to thymic rebound or small nodal areas related to inflammation/infection; Ongoing imaging in the absence of clinical symptoms >2 years after treatment is not recommended; MRI or ultrasound are prioritized to limit lifetime radiation exposure; Lifelong follow up to monitor for late toxicities associated with treatment is highly encouraged.

Conclusions

Inclusion of ped specific criteria for lymphoma staging & response criteria into the Lugano Classification is essential and will expedite advances in ped & adult lymphoma. Next steps involve formalizing ped recommendations in working groups.

Validation of Childhood Hodgkin International Prognostic Score (CHIPS) for Predicting Event-Free Survival in Intermediate and High-risk Hodgkin Lymphoma

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Background: Improving risk stratification of patients with Hodgkin lymphoma (HL) allows for optimization of treatment allocation and minimization of late effects. The Childhood Hodgkin International Prognostic Score (CHIPS) was developed as a predictive model for event-free survival (EFS) using clinical data at diagnosis from patients with intermediate-risk HL treated on Children's Oncology Group protocol AHOD0031 with doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC) chemotherapy and response-adapted radiation therapy (RT). Stage IV, large mediastinal mass, albumin <3.5 g/deciliter, and fever were identified as independent predictors of EFS and assigned one point each. CHIPS was highly predictive of EFS in this patient cohort, but has not been validated in high-risk patients or with other therapeutic regimens. We aim to validate the CHIPS as a risk stratification tool for patients with intermediate or high-risk HL treated with Stanford V chemotherapy by the Pediatric Hodgkin Consortium (PHC).

Methods: PHC trial HOD99 enrolled patients on the high-risk arm with stage IIB, IIIB, or IV disease <22 years (n=123). HOD05 enrolled patients with intermediate-risk HL with stage IB, IA or IIA with "E" lesions, ≥3 nodal sites, or bulky mediastinal adenopathy, or IIIA disease <22 years (n=49). All patients received 12 weeks of Stanford V chemotherapy with doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone followed by low-dose, response-adapted RT. Patients missing documentation of any elements of CHIPS were excluded from the analysis.

Results: Our final analysis included a total of 164 patients, 116 with high-risk HL from HOD99 and 48 with intermediate-risk HL from HOD05. One patient was excluded for missing fever data and 7 were excluded due to missing albumin. Patients were classified into 2 groups based on CHIPS: CHIPS 0-1 (n=88, 53.7%) and CHIPS 2-4 (n=76, 46.3%). EFS for patients in the CHIPS 0-1 and CHIPS 2-4 groups was analyzed using Kaplan-Meier curves (Figure 1A). The 2-year EFS for patients with CHIPS 0-1 and CHIPS 2-4 was 95.5% (95% confidence interval (CI) 91.2%-99.9%) and 80.3% (95% CI 71.8%-89.7%), respectively, p=0.003. Similarly, the 4-year EFS for patients with CHIPS 0-1 and CHIPS 2-4 was 93.2% (95% CI 88.0%-98.6%) and 77.6% (95% CI 68.7%-87.6%), respectively, p=0.004. The reduced EFS in patients with higher CHIPS is consistent across different stages and early response assessments (Figure 1B).

Conclusions: CHIPS is highly predictive of EFS in pediatric and adolescent patients with intermediate and high-risk HL treated with Stanford V chemotherapy, as it identifies a subset (CHIPS 2-4) with significantly lower EFS. Assessment of CHIPS alongside novel approaches such as circulating tumor DNA and total metabolic tumor volume should be analyzed across trials to allow for further enhancements to risk stratification.

VALIDATION OF A GENE SIGNATURE BASED ON THE COMPOSITION OF THE TUMOR MICROENVIRONMENT FOR RISK STRATIFICATION OF PEDIATRIC PATIENTS WITH CLASSIC HODGKIN'S LYMPHOMA

Background. Classical Hodgkin lymphoma (cHL) is a cancer that affects children and requires treatment with potential long-term toxicity. The presence of Reed-Sternberg cells dispersed in a reactive microenvironment is a peculiar feature of cHL. The aim of this study is to evaluate, on tissue specimens of pediatric LHc at diagnosis, a newly tested gene transcript profile with prognostic value reflecting the composition of the tumor microenvironment.

Methods. 31 paraffin-embedded tissue specimens from patients with cHL at diagnosis (age 5-17 years, mean 13.3 years), processed according to AIEOP-LH-2004 protocol, were subjected to RNA extraction and profiling by nCounter platform (NanoString Technology) for digital measurement of 111 transcripts related to 9 cytotypes (CD8+ T lymphocytes, Th1 lymphocytes, Th2 lymphocytes, Treg, mast cells, myeloid suppressor cells, follicular dendritic cells, B lymphocytes, Reed Sternberg cells). 5-year event-free survival was used as the primary endpoint.

Results: The 31 cases included: 11 patients at stage 2A, 6 at stage 2B, 2 at stage 3A, 5 at stage 3B, 3 at stage 4A and 4 at stage 4B. The composition of the microenvironment was related to the 3 treatment groups (GT) 1, 2, 3 by comparing the average expression of genes associated with each cytotype. We observed significant high expression of normal B-cell-associated genes in GT1, compared with GT2-GT3 (Kruskal-Wallis test= 0.04), evidence confirmed by *gene set enrichment analysis* (significant enrichment of B-cell genes in GT1 vs GT2-GT3 patients, NES=2, FDR< 10-3). Correlation analyses between gene expression and EFS, seem to demonstrate the prognostic validity of the molecular signature.

Conclusions: Our results highlight a different composition of the microenvironment in different GTs, which should be validate in a larger case series. Correlation analyses between gene expression and outcome data are still ongoing. The results of this project would provide independent validation of an innovative molecular prognostic tool and strengthen its clinical applicability. The study could represent a methodological model applicable in the future for stratifying subgroups of pediatric patients undergoing new therapeutic regimens.

References

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