Best Practice & Research Clinical Haematology 36 (2023) 101445

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/issn/15216926

Diagnosis and management of Hodgkin lymphoma in children, adolescents, and young adults

Jennifer A. Belsky [a,*], Jessica Hochberg [b,1], Lisa Giulino-Roth [c,1]

[a] Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA
[b] Pediatrics, New York Medical College, Valhalla, NY, USA
[c] Division of Pediatric Hematology/Oncology, Department of Pediatrics, Weill Cornell Medical College, New York, NY, USA

ARTICLE INFO

Keywords:
Hodgkin lymphoma
Pediatrics
Novel therapeutics

ABSTRACT

Advances in the management of Hodgkin lymphoma in children, adolescents and young adult have resulted in survival outcomes exceeding 90%. The risk of late toxicity, however, remains a significant concern for survivors of HL and the focus of modern trials have been to advance cure rates while reducing long term toxicity. This has been accomplished through response-adapted treatment approaches and the incorporation of novel agents, many of which target the unique interaction between the Hodgkin and Reed Sternberg cells and the tumor microenvironment. In addition, an improved understanding of prognostic markers, risk stratification, and the biology of this entity in children and AYAs may allow us to further tailor therapy. This review focuses on the current management of HL in the upfront and relapsed settings, recent advances in novel agents that target HL and the tumor microenvironment, and promising prognostic markers that may help guide the future management of HL.

1. Introduction

Classic Hodgkin lymphoma (HL) is the most common cancer in adolescent young adult (AYA) patients between ages 15 and 19, and accounts for 18% of cancer diagnoses annually in children and AYAs in the United States [1]. Outcomes in HL are extremely favorable with overall survival rates exceeding 90%. These excellent outcomes, however come at the cost of increased risk for long term toxicity due to chemotherapy and/or radiation. This risk may be improved as novel therapies are introduced that may successfully cure patients with the potential to reduce acute and long-term toxicity. Here, we will review the current state of the field in pediatric HL including the use chemotherapy and immunotherapy agents in upfront and relapsed disease, risk stratification, the evolving role for radiation, and recent research into the biology of HL in children and AYAs.

2. Epidemiology and risk factors

HL occurs in a bimodal distribution, peaking between ages 15–30 years and again in patients >55 years. The incidence of HL is 2.6 per 100,000 persons across all age groups and 3.4 per 100,000 in AYA patients aged 15–39 years [2]. HL is uncommon in children <5 years of age.

* Corresponding author. 705 Riley Hospital Dr, Indianapolis, IN, 46202, USA.
E-mail address: jbelsky@iu.edu (J.A. Belsky).
[1] Authors contributed equally.

https://doi.org/10.1016/j.beha.2023.101445
Received 1 February 2023; Accepted 1 February 2023
Available online 3 February 2023

Over the past several decades, researchers have discovered several risk factors associated with HL. Living in a western country, higher socioeconomic status, male sex, smaller family size, and >15 years of age have all been associated with increased risk of HL [3,4]. There also is strong emerging evidence of a familial predisposition to HL in a subset of cases. In a recent genomic characterization of 36 pedigrees of families with 2 or more first degree relatives with HL the top 4 recurrent risk variants identified include: a coding variant in KDR (rs56302315), a 5′UTR variant in KLHDC8B (rs387906223), a noncoding variant in an intron of PAX5 (rs147081110), and another noncoding variant in an intron of GATA3 (rs3824666), suggesting a genetic risk in cases of familial HL [5].

3. Hodgkin lymphoma biology

Hodgkin lymphoma includes two distinct disease entities: classic HL and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). These diagnoses differ in histology, epidemiology, immunophenotype, and treatment approaches. Histologically, classic HL is characterized by large neoplastic Hodgkin and Reed-Sternberg (HRS) cells with abundant reactive bystander cells and a rich tumor microenvironment. HRS cells characteristically express CD15, CD30 and PAX5. A subset (30–40%) will also express CD20 [6].

Classic HL can be further classified into four histologic subtypes: nodular sclerosing, mixed cellularity, lymphocyte rich, and lymphocyte depleted. Nodular sclerosing HL comprises 80% of HL in the AYA population and 45% and 62% of HL in the pediatric and adult populations, respectively [7]. Epstein- Barr virus (EBV) is associated with Hodgkin lymphoma in up to 40% of cases [8]. The EBV-encoded latent gene products latent membrane protein 1 and 2 A (LMP1 and LMP2A) play important roles in lymphomagenesis. The rates of EBV-associated disease vary by histological subtype, with EBV association in up to 96% of cases of mixed cellularity subtype, and only 10% of NLPHL [8].

In contrast to classic HL, NLPHL is a rare, slow growing, B-cell malignancy characterized by CD20 expression, and the absence of Reed-Sternberg cells. As the classification of HL continues to evolve NLPHL has recently been suggested to fit more as a subtype of NHL than HL [9]. This review will focus on classic HL.

Classic HL has several distinct characteristics that distinguish it from other B-cell lymphomas. In a HL tumor, the HRS cells comprise only a minor population, with the majority of the cellular composition being a dense and complex tumor microenvironment which supports tumor persistence and growth. HRS cells are suspected to be derived from germinal center B-cells but have lost many B-cell markers including the B-cell receptor [10]. They frequently harbor copy number gains in 9p24.1 which results in upregulation of programmed death ligand 1 and 2 (PD-L1 and PD-L2) as well as JAK2 [11,12]. This, along with other molecular alterations, contribute to the ability of the HRS cells to evade the immune response. The rarity of the HRS cell in a tumor biopsy has made genomic characterization challenging and our understanding of HL genomics lags far behind other malignancies. With recent advances in the ability to isolate HRS cells and sequence with low input as well as the identification of circulating tumor DNA (ctDNA) in patients with HL, the genomic landscape of HL has become better understood. Common alterations in HL include B2M, which supports immune evasion through loss of MHCI; SOCS1 which results in dysregulation of JAK/STAT signaling; and TNFAIP3 (A20) leading to altered NF-KB signaling [13–15]. Little is known about potential genomic differences between HL in pediatric and adult populations however recent whole genome sequencing of HL revealed a significantly higher burden of molecular alterations in pediatric and AYA cases when compared to older adults, suggesting that the biology of the disease may differ in these distinct age groups [16].

4. Disease presentation and diagnostic work up

The clinical presentation of HL most commonly starts as a painless mass, most frequently found in the cervical or supraclavicular (50–60%) or axillary (30%) lymph nodes. Involved nodes are characteristically matted and firm. Patients often report them as slow growing over weeks to months [17]. Approximately 25% of patients will develop B symptoms, which include fevers, unintentional weight loss of 10% over a 6 month time period, and drenching night sweats [18]. HL can also present as large, bulky disease in the mediastinum which can result in respiratory impairment secondary to airway obstruction and/or superior vena cava syndrome [19]. This presentation of HL is an oncologic emergency, making an excisional biopsy potentially challenging in these cases.

Children and AYAs presenting with concerning lymphadenopathy with suspicion for HL should undergo an excisional lymph node biopsy for histologic diagnosis. An interventional radiology-guided core biopsy is sometimes required in cases where anesthesia is not feasible due to airway compromise. Fine need aspiration samples are insufficient, as they do not provide the adequate tissue needed to

Table 1
Ann Arbor Classification staging system for Hodgkin lymphoma, including Cotswolds modifications.

Stage	Disease Involvement
I	Single lymph node region (I) or one extralymphatic site (IE)
II	Two or more lymph node regions, on the same side of the diaphragm (II) or local extralymphatic extension plus one or more lymph node regions on the same side of the diaphragm (IIE)
III	Lymph node regions on both sides of the diaphragm (III), which may be accompanied by local extralymphatic extension (IIIE)
IV	Diffuse involvement of one or more extralymphatic organs or sites
A	No B symptoms
B	Presence of at least one of: unexplained weight loss >10% baseline during 6 months prior to staging; recurrent unexplained fever >38 °C; recurrent night sweats
X	Bulky tumor: either a single mass exceeding 10 cm in largest diameter or a mediastinal mass exceeding one third of the maximum transverse transthoracic diameter measured on a standard posterior-anterior chest radiograph

visualize the Reed-Sternberg cells, which are relatively rare (0.1–5%) within the background of the reactive tumor microenvironment [20].

Once the diagnosis of HL is confirmed, clinical staging should include: 1) a thorough physical exam with documentation of abnormal lymphadenopathy and the presence/absence of B symptoms, 2) chest radiograph to assess for bulky mediastinal adenopathy, which is defined as a mass >1/3 the thoracic chest diameter, and 3) and a fluorodeoxyglucose positron emission tomography (FDG-PET) scan. Staging is based on the Ann Arbor classification (Table 1). Bilateral bone marrow biopsies have been traditionally required, however recent literature in adults has suggested that bone marrow biopsies are less sensitive than FDG-PET and may not be necessary in the setting of FDG-PET [21]. Central nervous system involvement is an exceedingly rare at the initial presentation of HL, and unless a strong clinical suspicion arises, lumbar puncture for cerebrospinal fluid is not routinely performed. Baseline laboratory studies should include a complete blood count, comprehensive metabolic profiling, erythrocyte sedimentation rate and lactate dehydrogenase. Common laboratory abnormalities in HL include elevated erythrocyte sedimentation rate, ferritin, and lactate dehydrogenase reflective of acute inflammation [22]. HL is occasionally associated with a normocytic anemia of chronic inflammation and elevated platelets as an acute phase reactant.

5. Approach to treatment

5.1. Risk stratification

Pediatric patients with HL have historically been classified to low, intermediate, and high risk groups based on stage, B-symptoms, and disease bulk (Table 2). Specific definitions for each risk cohort vary by cooperative group and have evolved over time as data emerges on outcomes in successive clinical trials. Across all risk groups, pediatric HL treatment regimens historically have utilized a combination of conventional chemotherapeutic agents including alkylators and anthracyclines with or without radiation therapy with increased intensity in higher risk populations. As these approaches are associated with treatment related mortality including secondary malignancy, cardiotoxicity, and infertility, clinical trials have sought to improve outcomes while reducing the risk for long term toxicity.

5.2. Low risk HL

There are multiple treatment approaches that have been successfully used in low risk pediatric HL with no single standard of care (Table 3). Outcomes are excellent with 5-year event-free survival (EFS) ranging from 85 to 92% [23–26]. Chemotherapy backbones that have been used in this group include OEPA (vincristine, etoposide, prednisone, and doxorubicin) for boys, OPPA (vincristine, procarbazine, prednisone, and doxorubicin) for girls, VAMP (vinblastine, doxorubicin, methotrexate, and prednisone), AV-PC (doxorubicin, vincristine, prednisone, cyclophosphamide), and ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) [27,28]. Several clinical trials using these backbones have focused on optimizing conventional chemotherapy and omitting radiation for patients who achieve a complete response (CR) on interim imaging. In the prospective GPOH95 trial, radiation therapy (RT) was omitted in patients in CR after 2 cycles of OEPA or OPPA chemotherapy, as defined by CT or MRI; patients not in a CR were treated with involved field RT at a dose of 20Gy with a 10–15Gy boost to larger residual disease. Among low risk patients treated with this approach with 10 year EFS was 96% [29]. Similar excellent outcomes have been demonstrated using the VAMP chemotherapy backbone which eliminates alkylator agents, bleomycin, and epipodophyllotoxins. In a single arm phase II trial patients were treated with four cycles of VAMP and RT was omitted in those who achieved a CR after cycle 2. The 2- year EFS of the entire cohort was excellent at 91% [24]. The combination of doxorubicin, vincristine, prednisone, and cyclophosphamide (AV-PC) was studied in the Children's Oncology Group (COG) AHOD0431 trial. In this study patients with stage IA and IIA disease were treated with 3 cycles of therapy, and those not in a CR at the completion of therapy received 21Gy involved field RT. The 4-year EFS for the entire cohort was less than that observed in other trials at 80%, however outcomes for patients with MC histology were excellent (4- year EFS 95%). This approach should therefore be restricted to patients with MC histology [30]. Lastly, the adult regimen ABVD has been studied in limited pediatric patient cohorts, but may be a reasonable approach in patients with low risk disease. In a single center series of 28 pediatric patients with HL of all risk groups treated with ABVD for 4–6 cycles with RT restricted those not in a CR at the completion of therapy, the 5-year EFS was 91% [31,32]. Larger studies will be needed to evaluate the ABVD chemotherapy regimen in children (see Table 4).

Table 2
Pediatric clinical risk group stratifications and associated clinical trials.

Clinical Trial	Low Risk	Intermediate Risk	High Risk
POG 9226, POG 9426[72]	I, IIA, IIIA1		
AHOD0431[30]	IA, IIA, no bulk		
POG 9425[73]		IB, IIA/IIIA$_1$ with bulk, IIIA$_2$	IIB, IIIB, IV
AHOD0031[74]		IB, IAE, IIB, IIIA, IVA, IA with bulk, IIA with bulk	
CCG-59704[75]			IIB with bulk, IIIB with bulk, IV
AHOD0831[76]			IIIB, IVB
AHOD1331[38]			IIB with bulk, IIB, IV
EuroNet-PHL[7]	I, IIA	IEA/B, IIEA, IIB, IIIA	IIEB, IIIEA/B, IV

Table 3
Treatment approaches in low risk HL.

Group	Trial Type/Trial name	Risk Group	n	Chemotherapy Backbone	RT Dose (Gy)	% RT	EFS (yr)
German Society of Pediatric Oncology[23]	Prospective GPOH2002	LR	195	OPPA/OEPA	19.8–30	68.2	92% (5yr)
Stanford, Dana Farber, St. Jude[24]	Prospective	LR	88	VAMP	25.5	46.5	91% (2yrs)
COG[30]	Prospective AHOD0431	LR	287	AV-PC	21	51	80% (4yrs) *MC histology 95%
COG[74]	Prospective AHOD0031	IR	1712	ABVE-PC	21	77.2	85% (4yrs)
UCSF[77]	Retrospective	all	28	ABVD	+	11.1	91% (5yrs)

COG= Children's Oncology Group, LR = Low Risk, IR= Intermediate Risk, RT = radiation therapy, EFS = event free survival, Gy = Gray +not reported.

Table 4
Treatment approaches in intermediate and high risk HL.

Trial	Risk	N	Agents	RT dose (Gy)	% RT	Event Free Survival
AHOD0031[74]	Intermediate Risk	1712	ABVE-PC	21	68	85% (4 y)
AHOD0831[76]	High Risk	164	ABVE-PC ± IV	21	76	79.1% (5 y)
AHOD1331[38]	High Risk	587	Bv-AVE-PC	21	53 BV arm 57 standard of care	92.1% (3 y)
GPOH 2002[23]	High Risk	195	OPPA/OEPA + COPP	19.8	100	87% (5 y)
EuroNet-PHL-C1[78]	Intermediate/Advanced	2102	OEPA, COPP vs COPDac	19.8	51 intermediate 65 advanced	84–90% (5 y)
HLHR13 St Jude[36]	Intermediate/Advanced	77	AEPA, CAPDac	25.5	65	97.4% (3 y)
Hochberg et, al[37]	Intermediate/Advanced	30	BV + rituximab, + AVD	21	13	100%

5.3. Intermediate risk HL

Reduction of therapy in good responding patients and therapy augmentation in poor responders has been investigated in children and AYAs with intermediate-risk disease HL. The COG clinical trial AHOD0031 investigated a response-based therapy approach in patients with intermediate-risk HL defined as IB, IAE, IIB, IIIA, IVA, IA with bulk, and IIA with bulk. The study examined 1712 patients who received two cycles of doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone (ABVE-PC) followed by response evaluation. Patients were divided into 2 cohorts of rapid early responders (RERs) and slow early responders (SERs). RER patients received an additional two cycles of ABVE-PC followed by end of therapy evaluation. RERs in CR were randomized to receive involved-field radiotherapy (IFRT) or no additional therapy, while all other patients received IFRT. SERs were randomized to receive standard of care with 2 additional cycles of ABVE-PC + RT vs. standard of care plus two cycles of DECA (dexamethasone, etoposide, cisplatin, cytarabine). RERs and SERs had a 4 year EFS of 86.9%, and 77.4% respectively. There was no difference in EFS among the RER/CR patients randomized to RT vs. no further therapy, suggesting that RT can be safely omitted in this favorable group. DECA augmentation was not associated with an improved outcome among the SER patients suggesting other agents are needed in this higher risk group [26].

EuroNet-PHL-C1 was a recent randomized controlled trial conducted in 16 European countries who enrolled 2102 children aged <18 years with newly diagnosed intermediate and advanced stage HL defined as stages IIAE, IIB, IIBE, IIIA, IIIAE, IIIB, IIIBE, and all stages IV. Patients were treated with 2 cycles of OEPA, and then randomized to receive 2 or 4 cycles of COPP (cyclophosphamide, vincristine, prednisone, and procarbazine) vs. 2 or 4 cycles of COPDac (where dacarbazine replaced procarbazine). Radiation at a dose of 19.8 Gy to involved sites was restricted to patients with an inadequate response to OEPA (60% of all patients). The 5 year EFS of patients with an adequate response to OEPA and no RT was 90.1%, demonstrating that radiotherapy can be safely omitted in this group. Among all patients' outcomes were slightly better in those treated with COPP vs. COPDAC with a 5-year EFS of 89.9% and 86.1% respectively, however gonadotoxicity was greater among those treated with COPP [33].

5.4. High risk HL

Children and AYAs with high risk HL have historically been treated with combined modality therapy utilizing higher intensity and/or additional cycles of chemotherapy to address the increased risk of relapse in this group. More recent studies have also investigated the role for brentuximab vedotin (BV) in initial therapy. BV is an antibody-drug conjugate composed of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to monomethyl auristatin E, a microtubule-disrupting agent (Fig. 1) [34,35]. The addition of BV to upfront therapy was first studied in the adult population with advanced stage disease in the ECHELON-1 trial where the addition of BV to the AVD backbone resulted in a superior PFS compared to ABVD (82.1% vs. 77.2% respectively, HR 0.77; p =

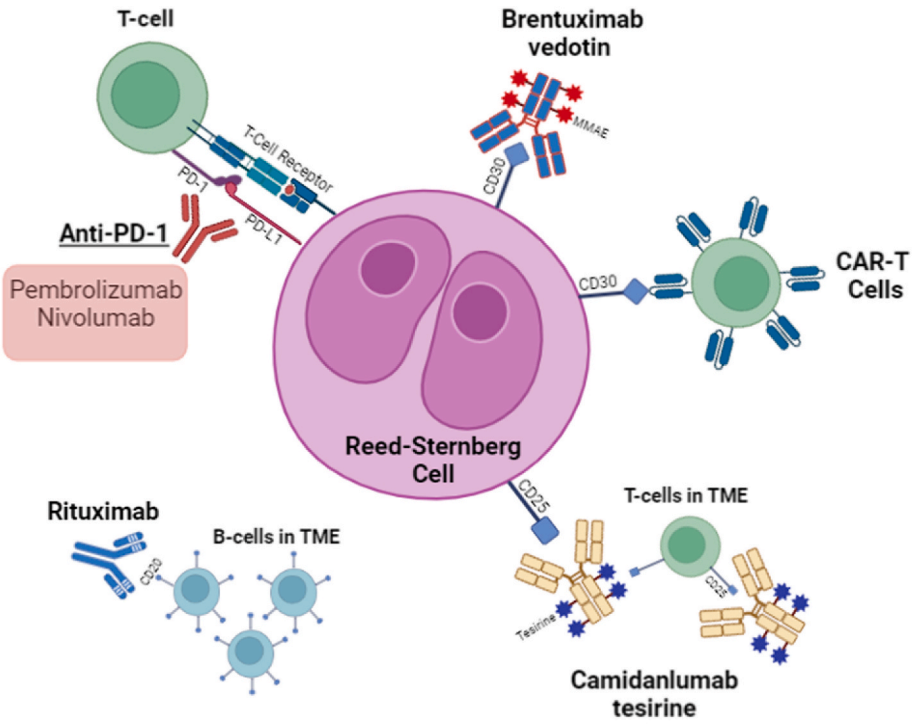

Fig. 1. Novel therapies in HL targeting cell surface markers and/or the tumor microenvironment.

0.04) [34].

In 2021, Metzger et al. published the results of a single-arm, multicenter trial investigating BV in combination with chemotherapy for patients aged ≤18 years with high risk HL defined as stage IIB, IIIB or IV. In this trial BV replaced vincristine in the OEPA/COPDac chemotherapy backbone and patients were treated with a total of 6 cycles of chemotherapy [36]. Patients who were not in CR following 2 cycles of treatment (62%) received radiotherapy. Among the 77 patients enrolled on this trial, the 3-year EFS and OS were 97.4% and 98.7% respectively. EFS was superior to a historic control with standard chemotherapy where 3 year EFS was 80.8% (SE 3.3%; $p = 0.0008$), suggesting that BV may improve EFS in the upfront setting.

Hochberg et al. recently published the results of a phase II results evaluating the combination of both BV and the anti-CD20 monoclonal antibody rituximab to target B-cells in the tumor microenvironment with an AVD chemotherapy backbone in newly diagnosed patients aged 1–30 years old with intermediate- and high-risk classic HL. Radiation was limited to high-risk patients with slow early response and bulky disease only. Among the 30 patients enrolled, the 5- year event-free and overall survival rates were 100%, with a median follow-up of >60 months. Radiation was limited to 13% of patients [37].

The Children's Oncology Group recently reported results from a randomized phase III trial investigating the addition of BV to the chemotherapy backbone of ABVE-PC for children and AYAs with previously untreated high risk HL [38]. In this trial patients were randomly assigned to receive 5 cycles of ABVE-PC or 5 cycles of BV-AVE-PC. Involved site radiation at a dose of 21Gy was restricted to lesions that remained PET avid (Deauville score 4 or 5) after 2 cycles of chemotherapy or those with large mediastinal adenopathy at diagnosis. The study enrolled 600 patients from March 2015–August 2019. The 3-year EFS was 92.1% in the BV arm compared to 82.5% in the traditional chemotherapy arm (HR, 0.41; 95% CI, 0.25 to 0.67; $P < 0.001$). Toxicity was similar between the two arms. Based on the successful results from this trial, BV is now FDA approved in combination with AVE-PC in patients age 2 years and older with previously untreated high risk HL [39].

5.5. Ongoing trials evaluating immune checkpoint blockade in the initial treatment of HL in children are underway

Immune checkpoint inhibitors, including nivolumab and pembrolizumab, are humanized IgG4 monoclonal antibodies that interrupt PD-1 receptor-ligand interactions and restore T-cell meditated immunity and antitumor responses (Fig. 1) [40]. These agents have demonstrated activity in adult and pediatric populations with relapsed HL and are now being evaluated in upfront treatment [41,42]. The S1826 trial is a National Cancer Institute funded, randomized phase III trial comparing BV-AVD to nivolumab + AVD in adult and pediatric patients age ≥12 years with advanced stage HL (NCT03907488). This trial has recently completed accrual and we are awaiting final results.

Other smaller trials are also evaluating checkpoint inhibition in the upfront treatment of HL in children and AYAs. At the recent 7th International Symposium on Childhood Adolescent and Young Adult Non-Hodgkin Lymphoma, two ongoing trials investigating checkpoint inhibitors in upfront HL therapy were presented. In the phase II KEYNOTE-667 trial, children, and AYAs age 3–25 years with HL with a slow early response to standard chemotherapy are treated with standard therapy plus pembrolizumab [43]. Among the 30 patients enrolled to date, the combination of therapy has been well tolerated. The RADICAL study presented by Hochberg et al. is evaluating the combination of BV-AVD, rituximab and nivolumab in children with intermediate and high risk HL. In this trial, the total anthracycline dose is reduced, and radiation is limited to patients who do not achieve a CR at the end of therapy. To date, 5 patients have been enrolled with no dose limiting toxicity [44]. These trials will provide early data on the role for checkpoint inhibition in the upfront management of children and AYAs with HL.

6. Approach to refractory/relapsed Hodgkin lymphoma

Relapse from HL typically occurs early, within the first 3 years from diagnosis, though late relapse has been reported [45]. There are no clear predictors of relapse, but historically poor prognostic features include advanced stage, bulky or extra lymphatic disease, presence of B symptoms and poor initial early response. The standard of care for relapsed HL is salvage chemotherapy followed by autologous stem cell transplantation (SCT) [7]. Hodgkin lymphoma often remains chemo sensitive at relapse. There are a number of second line chemotherapy and immunotherapy options for relapsed disease with no single standard of care (Table 5, Fig. 1). BV has shown significant activity as a single agent in relapsed/refractory HL in adults and children [46,47]. Similarly, phase I trials of nivolumab and pembrolizumab have also shown significant single agent activity in children and adults with refractory HL [48,49]. Phase II clinical trials suggest that combining brentuximab with PD-1 checkpoint blockade will be highly effective against relapsed lymphomas and well tolerated [50]. Furthermore, the addition of brentuximab vedotin or checkpoint inhibitors to standard reinduction combinations of gemcitabine, vinorelbine or bendamustine have shown promising results with overall response rates around 70–80% in both adult and pediatric trials [41,51,52].

While some patients with relapsed HL patients can experience durable remission with chemotherapy ± radiation alone, most patients who relapse or progress, particularly those within 12 months from diagnosis, are candidates for myeloablative chemotherapy and autologous SCT with or without radiation once in a second CR [53]. Retrospective studies have demonstrated decreases in relapse in patients with HL following allogeneic vs. autologous SCT indicating a strong graft-vs-lymphoma effect. Although earlier studies showed no improvement in overall survival due high transplantation-related mortality, reduced-intensity conditioning or non-myeloablative regimens were successful at reducing regimen-related morbidity and mortality associated with myeloablative allogeneic SCT and mitigates this concern [54].

There is growing evidence for post SCT maintenance therapy with BV. In a randomized trial among adult patients with relapsed HL at high risk for recurrence, maintenance therapy with BV improved PFS compared to placebo (hazard ratio [HR] 0·57, 95% CI 0·40–0·81; p = 0·0013) [55]. In a retrospective review of maintenance BV in the pediatric population, outcomes were excellent (3 year EFS 92%) and BV was well tolerated suggesting that this may be an appropriate therapy in children [56].

For more multiply refractory cases, cytotoxic T-cell therapy has shown some promise. Both EBV-specific cytotoxic T-lymphocytes as well anti-CD30 CAR-T cells have been reported to have high rates of durable responses in relapsed/refractory HL [57,58]. Combinations of checkpoint inhibitors with the JAK/STAT inhibitor ruxolitinib or the histone deacetylase inhibitor vorinostat are also showing early signs of activity in adults with highly refractory disease [50,59].

The novel CD25-targeted antibody-drug conjugate camidanlumab tesirine (Cami) consists of an anti-CD25 antibody conjugated to a

Table 5
Novel agents studied in relapsed HL in children and AYAs.

Regimen	Trial Type	N	ORR/CR
BV, gemcitabine, vinorelbine (AHOD1221)[41]	Prospective phase I/II	46	70%/57%
BV, bendamustine[79]	Retrospective, single center	29	83%/79%
Nivolumab/BV followed by BV/bendamustine (Checkmate 744/AHOD1721)[42]	Prospective	32	80%/64%
BV, nivolumab, ipilumumab (E4412)	Prospective phase I - ongoing	–	ongoing

BV= Brentuximab vedotin, ORR= Overall response rate, CR= Complete Response.
Table Abbreviations: ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide, Bv-AVE-PC, Brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide, OPPA/OEPA + COPP, vincristine, procarbazine, prednisone, and doxorubicin/ Vincristine, etoposide, prednisone, and doxorubicin + cyclophosphamide, vincristine, procarbazine, and prednisone, COPDac, cyclophosphamide, vincristine, prednisone, and dacarbazine, CAPDac, cyclophosphamide, brentuximab vedotin, prednisone, and dacarbazine, AVD, doxorubicin, vincristine, dacarabazine, AEPA, brentuximab, etoposide, prednisone, and doxorubicin, IV, vinorelbine, ifosfamide.

the cytotoxin tesirine. This agent has demonstrated promising results in Phase I and II trials in patients with multiply relapsed and refractory HL having previously received BV and/or checkpoint inhibitor therapy. In these very high risk, heavily pretreated patients, Cami has been well tolerated with manageable toxicities and has shown an ORR of 70.2% with a 33.3% CR rate. Median response duration was just over 1 year and about 10% of patients were able to proceed to HSCT. A Phase III trial is planned to better determine efficacy, but the continued success of multiple immunotherapy agents against HL represents a promising paradigm shift in otherwise poor risk patients [60].

7. Radiation therapy in HL

As HL is exquisitely radio-sensitive, radiation therapy (RT) has historically been an essential component of HL therapy [61]. RT is also associated with adverse long term toxicities to normal tissue including risk of cardiac and pulmonary toxicity and subsequent neoplasms, particularly breast and thyroid cancer [62]. Recognition of these late effects has resulted in the tailored use of RT in children, with a focus on minimizing exposure to normal tissues by decreasing radiation dose and modifying radiation fields [63,64]. In addition, trials have sought to identify lower risk populations for whom the omission of radiation does not compromise outcome.

Contemporary trials in pediatric HL restrict the use of radiation to specific populations at higher risk of relapse such as those with bulky disease and those with a slow early response to therapy. This has resulted in reduced percentages of pediatric patients with HL receiving RT however the question remains if RT can be safely reduced even further. In the phase III AHOD1331 trial, involved site radiotherapy (ISRT) was delivered only to those patients with slow responding lesions or initial bulk disease. Using these criteria approximately half of patients received RT (53% in the BV arm and 57% in the standard arm). Similarly, the EuroNet-PHL-C1 trial restricted RT among intermediate and high risk patients to those with an inadequate response to two cycles of OEPA, which eliminated RT in 40% of patients. However, in the recently completed study by Hochberg et al. excellent outcomes were achieved with 13% of patients receiving RT, indicating a potential role for omitting radiation in this age of immunotherapy combinations. In the recent SWOG S1826 trial for AYA patients with advanced stage HL, RT was only administered at physician discretion to patients with residual PET avid disease at the completion of therapy [65]. We do not yet know the outcome of this trial to determine if this approach to RT is sufficient in children and AYAs.

8. Identifying prognostic markers in Hodgkin lymphoma

The key to advancing outcomes in HL will likely be identifying patients at low risk for relapse for whom reduced therapy is appropriate and those at high risk for whom therapy augmentation is needed. This is being investigated through multiple approaches including clinical factors, biomarkers, and advanced radiomics.

The Childhood Hodgkin International Prognostic Score (CHIPS) was developed as a prognostic marker among children and AYAs with intermediate risk disease [66,67]. CHIPS assigns one point to each of the following risk factors: stage 4 disease, large mediastinal mass, albumin (<3.5), and fever at diagnosis. Among 1103 patients with intermediate-risk HL enrolled on AHOD0031 those with CHIPS score of 0, 1, 2, and 3 had a four-year EFS of 93.1%, 88.5%, 77.6%, and 69.2% respectively [66]. More recently, CHIPS criteria was applied prospectively to 587 high risk patients on AHOD1331 and was predictive of interim ^{18}FDG-PET/CT (PET) response and EFS [68], suggesting that this may be used to risk stratify pediatric patients in future studies.

A promising biomarker to predict response in HL is circulating tumor DNA (ctDNA). Despite the rare nature of the Hodgkin and Reed Sternberg cells, ctDNA can be identified in the majority of patients with HL [15]. This has allowed for non-invasive genomic profiling and early studies to determine if ctDNA burden can predict outcome. In a recently presented large adult series among 244 patients ctDNA level prior to the start of therapy was predictive of PFS as both a continuous and dichotomous variable (HR 2.1, $P = 0.02$ and HR 3.3, $P = 0.003$ respectively) [69]. Prospective trials in children and adults with HL are collecting ctDNA to determine how best to utilize this biomarker.

Baseline metabolic tumor volume (MTV) on FDG-PET is also being evaluated a predictive marker in HL. MTV is quantified as the total volume of disease with FDG uptake that exceeds a particular threshold. When retrospectively applied to pre-treatment PET scans, a significant association with EFS was noted, suggesting that MTV could improve risk stratification in both pediatric and adult patients with HL [70,71].

9. Future directions

As the survival rates for children and AYAs with HL continue to improve, the focus of current and future research is to maximize cure while minimizing acute and long-term toxicities in survivors. This will likely be made possible through the use of novel agents in careful and selected groups that may be identified using emerging prognostic markers. The promising use of ctDNA in liquid biopsy, improved radiomics, enhanced risk stratification and personalized therapy makes for an exciting time in the field of HL. By building on prior studies, pediatric trials continue the march toward highly efficacious, biology-driven, approaches that minimize toxicity. Collaboration with adult oncologists has allowed for accelerated answers to key questions in HL and will continue to be an essential component of the blueprint for pediatric HL moving forward.

Disclosures

The authors have nothing to disclose.

Practice points

- Children and adolescent young adults with classic Hodgkin lymphoma have excellent event free survival however are at risk for long term toxicity due to chemotherapy and radiation
- Risk-adapted and response based therapies as well as novel agents have allowed for improved outcomes and reduced risk for long term toxicities
- Improved understanding of the tumor and the microenvironment in Hodgkin lymphoma will aid in the ongoing discovery of novel therapeutic targets

Research agenda

Current research priorities in HL include: 1) the integration of targeted agents into frontline treatment to reduce reliance on conventional chemotherapy and radiation; 2) improving our understanding of the interaction between Hodgkin and Reed Sternberg cells and the tumor microenvironment to develop therapies targeting this interaction, 3) to develop prognostic markers to help guide risk-based treatments that minimize toxicity while optimizing survival.

Table 3. Pediatric and adolescent young adult low and intermediate stage Hodgkin lymphoma clinical trial backbones and outcomes.

Conflicts of interest

The authors have no conflicts of interests.

References

[1] Surveillance, epidemiology, and end results (SEER) program. Bethesda, MD: National Cancer Institute; 2019. cited 2019 October 25].
[2] Institute NC. Surveillance, epidemiology, and end results program. 2019 [August 30, 2022]. Available from: https://seer.cancer.gov/statistics-network/explorer/application.html?site=83&data_type=1&graph_type=10&compareBy=age_range&chk_age_range_1=1&chk_age_range_16=16&chk_age_range_62=62&series=9&sex=1&race=1&stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=1.
[3] Kharazmi E, Fallah M, Pukkala E, Olsen JH, Tryggvadottir L, Sundquist K, et al. Risk of familial classical Hodgkin lymphoma by relationship, histology, age, and sex: a joint study from five Nordic countries. Blood 2015;126(17):1990–5. https://doi.org/10.1182/blood-2015-04-639781.
[4] Caporaso NE, Goldin LR, Anderson WF, Landgren O. Current insight on trends, causes, and mechanisms of Hodgkin's lymphoma. Cancer J 2009;15(2):117–23. https://doi.org/10.1097/PPO.0b013e3181a39585. PubMed PMID: 19390306.
[5] Flerlage JE, Myers JR, Maciaszek JL, Oak N, Rashkin SR, Hui Y, et al. Discovery of novel predisposing coding and noncoding variants in familial Hodgkin lymphoma. Epub 20220817 Blood 2022. https://doi.org/10.1182/blood.2022016056. PubMed PMID: 35977101.
[6] Ranuhardy D, Suzanna E, Sari RM, Hadisantoso DW, Andalucia R, Abdillah A. CD30, CD15, CD50, and PAX5 expressions as diagnostic markers for hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL). Acta Med Indones 2018;50(2):104–9. PubMed PMID: 29950528.
[7] Daw S, Hasenclever D, Mascarin M, Fernández-Teijeiro A, Balwierz W, Beishuizen A, et al. Risk and response adapted treatment guidelines for managing first relapsed and refractory classical hodgkin lymphoma in children and young people. Recommendations from the EuroNet pediatric hodgkin lymphoma group. Epub 20200110 Hemasphere 2020;4(1):e329. https://doi.org/10.1097/hs9.0000000000000329. PubMed PMID: 32072145; PubMed Central PMCID: PMC7000476.
[8] Pallesen G, Hamilton-Dutoit SJ, Rowe M, Young LS. Expression of Epstein-Barr virus latent gene products in tumour cells of Hodgkin's disease. Lancet 1991;337(8737):320–2. https://doi.org/10.1016/0140-6736(91)90943-j. PubMed PMID: 1671232.
[9] Jiang M, Bennani NN, Feldman AL. Lymphoma classification update: T-cell lymphomas, Hodgkin lymphomas, and histiocytic/dendritic cell neoplasms. Epub 20170129 Expet Rev Hematol 2017;10(3):239–49. https://doi.org/10.1080/17474086.2017.1281122. PubMed PMID: 28133975; PubMed Central PMCID: PMC5514564.
[10] Schwering I, Bräuninger A, Klein U, Jungnickel B, Tinguely M, Diehl V, et al. Loss of the B-lineage–specific gene expression program in Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma. Blood 2003;101(4):1505–12. https://doi.org/10.1182/blood-2002-03-0839.
[11] Green MR, Monti S, Rodig SJ, Juszczynski P, Currie T, O'Donnell E, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Epub 20100713 Blood 2010;116(17):3268–77. https://doi.org/10.1182/blood-2010-05-282780. PubMed PMID: 20628145; PubMed Central PMCID: PMC2995356.
[12] Roemer MG, Advani RH, Ligon AH, Natkunam Y, Redd RA, Homer H, et al. PD-L1 and PD-L2 genetic alterations define classical hodgkin lymphoma and predict outcome. Epub 20160411 J Clin Oncol 2016;34(23):2690–7. https://doi.org/10.1200/jco.2016.66.4482. PubMed PMID: 27069084; PubMed Central PMCID: PMC5019753.
[13] Reichel J, Chadburn A, Rubinstein PG, Giulino-Roth L, Tam W, Liu Y, et al. Flow sorting and exome sequencing reveal the oncogenome of primary Hodgkin and Reed-Sternberg cells. Epub 20141208 Blood 2015;125(7):1061–72. https://doi.org/10.1182/blood-2014-11-610436. PubMed PMID: 25488972.
[14] Wienand K, Chapuy B, Stewart C, Dunford AJ, Wu D, Kim J, et al. Genomic analyses of flow-sorted Hodgkin Reed-Sternberg cells reveal complementary mechanisms of immune evasion. Blood Adv 2019;3(23):4065–80. https://doi.org/10.1182/bloodadvances.2019001012. PubMed PMID: 31816062; PubMed Central PMCID: PMC6963251.
[15] Spina V, Bruscaggin A, Cuccaro A, Martini M, Di Trani M, Forestieri G, et al. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. Epub 20180215 Blood 2018;131(22):2413–25. https://doi.org/10.1182/blood-2017-11-812073. PubMed PMID: 29449275.
[16] F M. Molecular evolution of classic Hodgkin lymphoma revealed through whole genome sequencing of Hodgkin and Reed Sternberg cells. Blood Cancer Discovery; 2023. Epub In press.
[17] Jamil A, Mukkamalla SKR. Lymphoma. StatPearls. Treasure Island (FL; 2022.
[18] Khanna P, Malluru N, Pyada R, Gupta M, Akkihal K, Varkey TC. Fever of unknown origin: the workup and diagnosis of pel-ebstein fever. Epub 20220206 Cureus 2022;14(2):e21959. https://doi.org/10.7759/cureus.21959. PubMed PMID: 35282507; PubMed Central PMCID: PMC8903813.
[19] Oyake M, Suenobu S, Miyawaki M, Ohchi Y, Ihara K. Airway emergencies due to anterior mediastinal T-lymphoblastic lymphoma managed with planned extracorporeal membrane oxygenation and endotracheal stent: a case report and literature review. Epub 20220201 Cureus 2022;14(2):e21799. https://doi.org/10.7759/cureus.21799. PubMed PMID: 35261827; PubMed Central PMCID: PMC8892228.
[20] Aggarwal P, Limaiem F. Reed Sternberg cells. StatPearls. Treasure island (FL). StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.
[21] Cortés-Romera M, Sabaté-Llobera A, Mercadal-Vilchez S, Climent-Esteller F, Serrano-Maestro A, Gámez-Cenzano C, et al. Bone marrow evaluation in initial staging of lymphoma: 18F-FDG PET/CT versus bone marrow biopsy. Clin Nucl Med 2014;39(1):e46–52. https://doi.org/10.1097/RLU.0b013e31828e9504. PubMed PMID: 23640215.

[22] Lynch RC, Sundaram V, Desai M, Henry S, Wood D, Daadi S, et al. Utility of routine surveillance laboratory testing in detecting relapse in patients with classic hodgkin lymphoma in first remission: results from a large single-institution study. Epub 20200505 JCO Oncol Pract 2020;16(9):e902–11. https://doi.org/10.1200/jop.19.00733. PubMed PMID: 32369413; PubMed Central PMCID: PMC7489479.
[23] Mauz-Körholz C, Hasenclever D, Dörffel W, Ruschke K, Pelz T, Voigt A, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. Epub 20100712 J Clin Oncol 2010;28(23):3680–6. https://doi.org/10.1200/jco.2009.26.9381. PubMed PMID: 20625128.
[24] Metzger ML, Weinstein HJ, Hudson MM, Billett AL, Larsen EC, Friedmann A, et al. Association between radiotherapy vs no radiotherapy based on early response to VAMP chemotherapy and survival among children with favorable-risk Hodgkin lymphoma. JAMA 2012;307(24):2609–16. https://doi.org/10.1001/jama.2012.5847. PubMed PMID: 22735430; PubMed Central PMCID: PMC3526806.
[25] Keller FG, Castellino SM, Chen L, Pei Q, Voss SD, McCarten KM, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: a report from the Children's Oncology Group. Epub 2018/05/09 Cancer 2018;124(15):3210–9. https://doi.org/10.1002/cncr.31519. PubMed PMID: 29738613; PubMed Central PMCID: PMC6097921.
[26] Friedman DL, Chen L, Wolden S, Buxton A, McCarten K, FitzGerald TJ, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. Epub 2014/10/15 J Clin Oncol 2014;32(32):3651–8. https://doi.org/10.1200/jco.2013.52.5410. PubMed PMID: 25311218; PubMed Central PMCID: PMC4220044 are found at the end of this article.
[27] Nagpal P, Akl MR, Ayoub NM, Tomiyama T, Cousins T, Tai B, et al. Pediatric Hodgkin lymphoma: biomarkers, drugs, and clinical trials for translational science and medicine. Oncotarget 2016;7(41):67551–73. https://doi.org/10.18632/oncotarget.11509. PubMed PMID: 27563824; PubMed Central PMCID: PMC5341896.
[28] Giulino-Roth L, Keller FG, Hodgson DC, Kelly KM. Current approaches in the management of low risk Hodgkin lymphoma in children and adolescents. Epub 20150330 Br J Haematol 2015;169(5):647–60. https://doi.org/10.1111/bjh.13372. PubMed PMID: 25824371.
[29] Dörffel W, Rühl U, Lüders H, Claviez A, Albrecht M, Bökkerink J, et al. Treatment of children and adolescents with Hodgkin lymphoma without radiotherapy for patients in complete remission after chemotherapy: final results of the multinational trial GPOH-HD95. J Clin Oncol : official journal of the American Society of Clinical Oncology 2013;31(12):1562–8. https://doi.org/10.1200/jco.2012.45.3266. PubMed PMID: 23509321.
[30] Keller FG, Nachman J, Constine L, Thomson J, McCarten KM, Chen L, et al. A phase III study for the treatment of children and adolescents with newly diagnosed low risk hodgkin lymphoma (HL). Blood 2010;116(21):767. https://doi.org/10.1182/blood.V116.21.767.767.
[31] Spinner MA, Advani RH. Risk-adapted therapy for advanced-stage Hodgkin lymphoma. Hematology 2018;2018(1):200–6. https://doi.org/10.1182/asheducation-2018.1.200.
[32] Stieglitz E, Dinh T, Phelps AS, Pampaloni MH, Olshen AB, Robbins E. ABVD without radiation for newly diagnosed pediatric and young adult patients with hodgkin lymphoma: a single center retrospective analysis of 28 consecutive patients. J Pediatr Hematol Oncol 2018;40(4):290–4. https://doi.org/10.1097/mph.0000000000001094. PubMed PMID: 00043426-201805000-00005.
[33] Mauz-Körholz C, Landman-Parker J, Balwierz W, Ammann RA, Anderson RA, Attarbaschi A, et al. Response-adapted omission of radiotherapy and comparison of consolidation chemotherapy in children and adolescents with intermediate-stage and advanced-stage classical Hodgkin lymphoma (EuroNet-PHL-C1): a titration study with an open-label, embedded, multinational, non-inferiority, randomised controlled trial. Epub 20211209 Lancet Oncol 2022;23(1):125–37. https://doi.org/10.1016/s1470-2045(21)00470-8. PubMed PMID: 34895479; PubMed Central PMCID: PMC8716340.
[34] Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab vedotin with chemotherapy for stage III or IV hodgkin's lymphoma. N Engl J Med 2017;378(4):331–44. https://doi.org/10.1056/NEJMoa1708984. PubMed PMID: 29224502.
[35] Brentuximab Adcetris. Vedotin 2022. Available from: https://www.adcetrispro.com/?&utm_source=GOOGLE&utm_medium=cpc&utm_campaign=GS_Branded_PTCL_Subtype_2.0&utm_content=Branded+-+PTCL_Subtype_PH&utm_term=adcetris+chp&gclsrc=ds&gclid=Cj0KCQiA_bieBhDSARIsADU4zLcU4skQ7KE0grCA1ywVB1bELwMfdOmYS8IQHX3Nkdivlr54TVjd1q0aAjwMEALw_wcB&gclsrc=aw.ds.
[36] Metzger ML, Link MP, Billett AL, Flerlage J, Jr JTL, Mandrell BN, et al. Excellent outcome for pediatric patients with high-risk hodgkin lymphoma treated with brentuximab vedotin and risk-adapted residual node radiation. J Clin Oncol 2021;39(20):2276–83. https://doi.org/10.1200/jco.20.03286. PubMed PMID: 33826362.
[37] Hochberg J, Basso J, Shi Q, Klejmont L, Flower A, Bortfeld K, et al. Risk-adapted chemoimmunotherapy using brentuximab vedotin and rituximab in children, adolescents, and young adults with newly diagnosed Hodgkin's lymphoma: a phase II, non-randomized controlled trial. J Immunother Cancer 2022;10(5). https://doi.org/10.1136/jitc-2021-004445. PubMed PMID: 35584865; PubMed Central PMCID: PMC9119160.
[38] Sharon M, Castellino QP, Parsons Susan K, Hodgson David C, McCarten Kathleen, Punnett Angela, Terzah M, Horton Hema, Dave Kishore, Cho Steve Y, Wu Yue, Henderson Tara O, Hoppe Bradford, Keller Frank G, Kelly Kara. Brentuximab vedotin and association with event-free survival (EFS) in children with newly diagnosed high-risk Hodgkin lymphoma (HL): a report from the Children's Oncology Group phase 3 study AHOD1331. J Clin Oncol 2022:40.
[39] FDA approves brentuximab vedotin in combination with chemotherapy for pediatric patients with classical Hodgkin lymphoma [Internet]. November 2022;10:2022.
[40] Hu B, Jacobs R, Ghosh N. Checkpoint inhibitors hodgkin lymphoma and non-hodgkin lymphoma. Curr Hematol Malig Rep 2018;13(6):543–54. https://doi.org/10.1007/s11899-018-0484-4. PubMed PMID: 30338457.
[41] Cole PD, McCarten KM, Pei Q, Spira M, Metzger ML, Drachtman RA, et al. Brentuximab vedotin with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin's lymphoma (AHOD1221): a Children's Oncology Group, multicentre single-arm, phase 1-2 trial. Epub 20180816 Lancet Oncol 2018;19(9):1229–38. https://doi.org/10.1016/S1470-2045(18)30426-1. PubMed PMID: 30122620; PubMed Central PMCID: PMC6487196.
[42] Harker-Murray P, Leblanc T, Mascarin M, Mauz-Körholz C, Michel G, Cooper S, et al. Response-adapted therapy with nivolumab and brentuximab vedotin (BV), followed by BV and bendamustine for suboptimal response, in children, adolescents, and young adults with standard-risk relapsed/refractory classical hodgkin lymphoma. Blood 2018;132(Supplement 1):927. https://doi.org/10.1182/blood-2018-99-111279.
[43] Mauz-Korholz C, Kelly KM, Keller FG, Giulino-Roth L, Nahar A, Balakumaran A. KEYNOTE-667: phase 2, open-label study of pembrolizumab in children and young adults with newly diagnosed classical Hodgkin lymphoma (cHL) with slow early response (SER) to frontline chemotherapy. J Clin Oncol 2018;36(15_suppl). https://doi.org/10.1200/JCO.2018.36.15_suppl.TPS7583. TPS7583-TPS.
[44] Hochberg J, Xavier A, Audino A, Barth M, Miles R, Kahwash S, et al. 015 - reducing the burden of oncology chemoradiotherapy and radiation exposure from diagnostic imaging by utilizing targeted immunotherapy in children, adolescents and young adults with lymphoma (RADICAL, hodgkin lymphoma cohort. Leuk Res 2022;121:S11–2. https://doi.org/10.1016/S0145-2126(22)00209-0.
[45] Bröckelmann PJ, Goergen H, Kohnhorst C, Bv Tresckow, Moccia A, Markova J, et al. Late relapse of classical hodgkin lymphoma: an analysis of the German hodgkin study group HD7 to HD12 trials. J Clin Oncol 2017;35(13):1444–50. https://doi.org/10.1200/jco.2016.71.3289. PubMed PMID: 28240973.
[46] Locatelli F, Mauz-Koerholz C, Neville K, Llort A, Beishuizen A, Daw S, et al. Brentuximab vedotin for paediatric relapsed or refractory Hodgkin's lymphoma and anaplastic large-cell lymphoma: a multicentre, open-label, phase 1/2 study. Lancet Haematol 2018;5(10):e450–61. https://doi.org/10.1016/s2352-3026(18)30153-4. PubMed PMID: 30290902.
[47] Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. Epub 20120326 J Clin Oncol 2012;30(18):2183–9. https://doi.org/10.1200/jco.2011.38.0410. PubMed PMID: 22454421; PubMed Central PMCID: PMC3646316.
[48] Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory hodgkin's lymphoma. N Engl J Med 2014;372(4):311–9. https://doi.org/10.1056/NEJMoa1411087. PubMed PMID: 25482239.
[49] Davis KL, Fox E, Merchant MS, Reid JM, Kudgus RA, Liu X, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1-2 trial. Epub 20200317 Lancet Oncol 2020;21(4):541–50. https://doi.org/10.1016/s1470-2045(20)30023-1. PubMed PMID: 32192573; PubMed Central PMCID: PMC7255545.

[50] Advani RH, Moskowitz AJ, Bartlett NL, Vose JM, Ramchandren R, Feldman TA, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. Blood 2021;138(6):427–38. https://doi.org/10.1182/blood.2020009178.
[51] Forlenza CJ, Gulati N, Mauguen A, Absalon MJ, Castellino SM, Franklin A, et al. Combination brentuximab vedotin and bendamustine for pediatric patients with relapsed/refractory Hodgkin lymphoma. Blood Adv 2021;5(24):5519–24. https://doi.org/10.1182/bloodadvances.2021005268. PubMed PMID: 34559223; PubMed Central PMCID: PMC8714712.
[52] Cole PD, Mauz-Körholz C, Mascarin M, Michel G, Cooper S, Beishuizen A, et al. Nivolumab and brentuximab vedotin (BV)-based, response-adapted treatment in children, adolescents, and young adults (CAYA) with standard-risk relapsed/refractory classical Hodgkin lymphoma (R/R cHL): primary analysis. J Clin Oncol 2020;38(15_suppl):8013. https://doi.org/10.1200/JCO.2020.38.15_suppl.8013.
[53] Bollard CM, Rocha V. The 2013 educational supplement on hematopoietic cell transplantation. Epub 20121017 Biol Blood Marrow Transplant 2013;19(1 Suppl):S1. https://doi.org/10.1016/j.bbmt.2012.10.022. PubMed PMID: 23085600.
[54] Satwani P, Jin Z, Martin PL, Bhatia M, Garvin JH, George D, et al. Sequential myeloablative autologous stem cell transplantation and reduced intensity allogeneic hematopoietic cell transplantation is safe and feasible in children, adolescents and young adults with poor-risk refractory or recurrent Hodgkin and non-Hodgkin lymphoma. Epub 20140618 Leukemia 2015;29(2):448–55. https://doi.org/10.1038/leu.2014.194. PubMed PMID: 24938649.
[55] Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Epub 20150319 Lancet 2015;385(9980):1853–62. https://doi.org/10.1016/s0140-6736(15)60165-9. PubMed PMID: 25796459.
[56] Forlenza CJ, Rosenzweig J, Mauguen A, Buhtoiarov I, Cuglievan B, Dave H, et al. Brentuximab vedotin as consolidation therapy following autologous stem cell transplantation in children and adolescents with relapsed/refractory hodgkin lymphoma: a multi-center retrospective analysis. Blood 2021;138:2465. https://doi.org/10.1182/blood-2021-151808.
[57] Bollard CM, Aguilar L, Straathof KC, Gahn B, Huls MH, Rousseau A, et al. Cytotoxic T lymphocyte therapy for Epstein-Barr virus+ Hodgkin's disease. J Exp Med 2004;200(12):1623–33. https://doi.org/10.1084/jem.20040890. PubMed PMID: 15611290; PubMed Central PMCID: PMC2211993.
[58] Ramos CA, Grover NS, Beaven AW, Lulla PD, Wu MF, Ivanova A, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory hodgkin lymphoma. Epub 20200723 J Clin Oncol 2020;38(32):3794–804. https://doi.org/10.1200/jco.20.01342. PubMed PMID: 32701411; PubMed Central PMCID: PMC7655020.
[59] Bachanova V, Ghobadi A, Patel K, Park JH, Flinn IW, Shah P, et al. Safety and efficacy of FT596, a first-in-class, multi-antigen targeted, off-the-shelf, iPSC-derived CD19 CAR NK cell therapy in relapsed/refractory B-cell lymphoma. Blood 2021;138(Supplement 1):823. https://doi.org/10.1182/blood-2021-151185.
[60] Zinzani PL, Carlo-Stella C, Hamadani M, Herrera AF, Ansell SM, Radford J, et al. Camidanlumab tesirine efficacy and safety in an open-label, multicenter, phase 2 study of patients (pts) with relapsed or refractory classical hodgkin lymphoma (R/R chl). Hematol Oncol 2021;39(S2). https://doi.org/10.1002/hon.75_2879.
[61] Hall MD, Terezakis SA, Lucas JT, Gallop-Evans E, Dieckmann K, Constine LS, et al. Radiation therapy across pediatric hodgkin lymphoma research group protocols: a report from the staging, evaluation, and response criteria harmonization (SEARCH) for childhood, adolescent, and young adult hodgkin lymphoma (CAYAHL) group. Epub 20210812 Int J Radiat Oncol Biol Phys 2022;112(2):317–34. https://doi.org/10.1016/j.ijrobp.2021.07.1716. PubMed PMID: 34390770; PubMed Central PMCID: PMC8802654.
[62] Palmer JD, Tsang DS, Tinkle CL, Olch AJ, Kremer LCM, Ronckers CM, et al. Late effects of radiation therapy in pediatric patients and survivorship. Pediatr Blood Cancer 2021;68(S2):e28349. https://doi.org/10.1002/pbc.28349.
[63] Breneman JC, Donaldson SS, Constine L, Merchant T, Marcus K, Paulino AC, et al. The children's Oncology group radiation Oncology discipline: 15 Years of contributions to the treatment of childhood cancer. Epub 2018/07/07 Int J Radiat Oncol Biol Phys 2018;101(4):860–74. https://doi.org/10.1016/j.ijrobp.2018.03.002. PubMed PMID: 29976498; PubMed Central PMCID: PMC6548440.
[64] Terezakis SA, Kasamon YL. Tailored strategies for radiation therapy in classical Hodgkin's lymphoma. Epub 20120329 Crit Rev Oncol Hematol 2012;84(1):71–84. https://doi.org/10.1016/j.critrevonc.2012.02.006. PubMed PMID: 22463873; PubMed Central PMCID: PMC4251770.
[65] Castellino SM, LeBlanc ML, Herrera AF, Parsons SK, Punnett A, Hodgson DC, et al. An intergroup collaboration for advanced stage classical Hodgkin lymphoma (cHL) in adolescents and young adults (AYA): SWOG S1826. J Clin Oncol 2020;38(15_suppl). https://doi.org/10.1200/JCO.2020.38.15_suppl.TPS8067. TPS8067-TPS.
[66] Schwartz CL, Chen L, McCarten K, Wolden S, Constine LS, Hutchison RE, et al. Childhood hodgkin international prognostic score (CHIPS) predicts event-free survival in hodgkin lymphoma: a report from the children's Oncology group. Epub 20161027 Pediatr Blood Cancer 2017;64(4). https://doi.org/10.1002/pbc.26278. PubMed PMID: 27786406; PubMed Central PMCID: PMC5702912.
[67] Schwartz C, Chen L, Constine L, Wolden S, Keller FG, Kelly KM, et al. The childhood hodgkin international prognostic score (CHIPS) for predicting event free survival in pediatric and adolescent hodgkin lymphoma. Blood 2011;118(21):3649. https://doi.org/10.1182/blood.V118.21.3649.3649.
[68] Schwartz CL, Pei Q, Keller FG, Cho SY, Hodgson DC, McCarten KM, et al. Evaluating CHIPS in pediatric high risk hodgkin lymphoma treated on AHOD1331. Blood 2022;140(Supplement 1):6565–6. https://doi.org/10.1182/blood-2022-167188.
[69] Alig SK, Shahrokh Esfahani M, Li MY, Adams RM, Garofalo A, Jin MC, et al. Distinct molecular subtypes of classic hodgkin lymphoma identified by comprehensive noninvasive profiling. Blood 2022;140(Supplement 1):1295–6. https://doi.org/10.1182/blood-2022-164744.
[70] Milgrom SA, Kim J, Chirindel A, Kim J, Pei Q, Chen L, et al. Prognostic value of baseline metabolic tumor volume in children and adolescents with intermediate-risk Hodgkin lymphoma treated with chemo-radiation therapy: FDG-PET parameter analysis in a subgroup from COG AHOD0031. Epub 20210710 Pediatr Blood Cancer 2021;68(9):e29212. https://doi.org/10.1002/pbc.29212. PubMed PMID: 34245210; PubMed Central PMCID: PMC8809108.
[71] van Heek L, Stuka C, Kaul H, Müller H, Mettler J, Hitz F, et al. Predictive value of baseline metabolic tumor volume in early-stage favorable Hodgkin Lymphoma - data from the prospective, multicenter phase III HD16 trial. Epub 20220618 BMC Cancer 2022;22(1):672. https://doi.org/10.1186/s12885-022-09758-z. PubMed PMID: 35717166; PubMed Central PMCID: PMC9206242.