Targeted Immunotherapy in the Treatment of Childhood and Adolescent Classic Hodgkin Lymphoma

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Abstract: Childhood and adolescent classic Hodgkin Lymphoma (cHL) has long been a model for how we balance improved outcomes with increased toxicities in pediatric cancer. The recognition that unacceptable short- and long-term toxicities come with increasing intensity of treatment has led to a decades-long attempt to better understand the patient-specific factors that dictate responses and outcomes. Targeted immunotherapy has emerged as a promising adjunct to cancer treatment; it has been shown to improve outcomes for poorly responding patients, to salvage relapsed disease, and more recently, to replace more toxic therapy modalities such as chemotherapy and radiation while maintaining excellent outcomes. Targeted antibody therapy for cHL—whether it be naked, conjugated, or bispecific—has been proven effective and well tolerated in the pediatric population. Targets include both Reed-Sternberg cells and the tumor microenvironment, and therapy can be directed against cell surface proteins or immune checkpoint blockade. Ongoing adult and pediatric cell therapy trials in which CD30-targeting chimeric antigen receptor T-cell therapy is used for patients with relapsed or refractory disease will determine the best approaches for these high-risk patients. As a result of innovations in tumor biology, the development of novel immunotherapy agents, and a better understanding of toxicities, targeted immunotherapy is now a component not only of the treatment of pediatric cHL but also of cancer treatment paradigms overall.

Introduction

The majority of children and adolescents (<19 years) with classic Hodgkin lymphoma (cHL) are cured with combined-modality chemotherapy and radiation therapy (RT).[1,2] Therapeutic success, however, is compromised by high rates of acute toxicity and by late morbidities, which are associated with an elevated mortality risk and a compromised quality of life for long-term survivors.[2] For instance, the Childhood Cancer Survivor Study (CCSS) reported substantial excess absolute risk of mortality due to cHL, secondary neoplasms, and cardiovascular disease. The increased risk of overall mortality among survivors was associated with the use of RT and exposure to alkylating or anthracycline agents.[1]

It is possible to reduce long-term morbidity and mortality in pediatric cancer survivors with modifications in cancer therapy and preventative measures.[2,3] A CCSS report found that among pediatric cHL survivors treated between 1990 and 1999, the 15-year cumulative incidence of at least one grade 3 to 5 chronic condition was 17.7% (95% CI, 15.0%-20.5%). This rate represents a significant decrease from the period from 1970 to 1979, during which the rate was 26.4% (95% CI, 23.8%-29.1%; $P<.001$).[3] In another CCSS report, survivors treated with contemporary regimens for low- to intermediate-risk pediatric HL had an estimated 40% reduction in the risk of a grade 3 to 5 condition in a comparison with survivors treated with chest radiation of at least 35 Gy in combination with an anthracycline or alkylator.[2] Still, the need to reduce the long-term toxicity of historically successful cHL therapy continues. The well-documented radiation-induced toxicity to the cardiovascular system and risk of second neoplasms are being reduced through manipulations of combined-modality therapy, a reduction in dose and field size in current radiation protocols, and an increase in the use of cardioprotective drugs, such dexrazoxane.[2,4-7] For instance, in analyzing 4 consecutive Children's Oncology Group (COG) pediatric HL clinical trials, it was demonstrated that for patients treated at the age of 15 years, the estimated 30-year cumulative incidence of fatal disease was 9.6% (95% CI, 4.2%-16.4%) in the AHOD0031 trial (enrolled 2002-2009), 8.6% (95% CI, 3.8%-14.9%) in the AHOD0831 trial (enrolled 2009-2012), 8.2% (95% CI, 3.6%-14.3%) in the AHOD1331 trial (enrolled 2015-2019), and 6.2% (95% CI, 2.7%-10.9%) in the S1826 trial (enrolled 2019-2022); the expected rate in an untreated population was 5% (95% CI, 2.1%-9.3%). These differences reflect a reduction in the use of mediastinal RT and increases in dexrazoxane use.[7] Current efforts in pediatric cHL clinical trials involve better risk stratification of patients. At present, most patients with early-stage or advanced-stage disease are cured with contemporary combined-modality therapy. The use of interim fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) as an early indicator of treatment failure provides a template for response-adapted therapy. Recently completed studies conducted by the COG, the German-Austrian Pediatric Hodgkin's Disease Study Group, and the United Kingdom group all provide support for investigating treatment de-escalation in the setting of responding disease, including elimination of RT in a proportion of patients.[8-10]

Another challenge in the current treatment of children, adolescents, and young adults (CAYAs; age <39 years) with cHL is to improve the outcomes of those who fail to attain a first remission or in whom a relapse or progression of disease develops. For instance, the COG A5962 study of re-induction chemotherapy in patients with lymphoma (age 12 months to 21 years) followed by myeloablative conditioning (MAC) and autologous hematopoietic stem cell transplant (autoHSCT) reported a 3-year event-free survival (EFS) rate of only 45% (95% CI, 29%-60%) and a significantly worse outcome in those who failed initial treatment within 12 months of diagnosis (3-year EFS rate, 25%).[11] Relapses following MAC-autoHSCT in CAYAs with poor-risk cHL remain a major limitation to improving progression-free survival (PFS).[12]

Advances in the field of oncology have led to the development and incorporation of different immunotherapy agents, such as CD30-targeted antibody-drug conjugates and immune checkpoint inhibitors (ICIs), in the treatment of a variety of lymphomas. The better understanding of cHL biology and the realization that cHL cells survive because of an aberrant, cancer-sustained immune system allow us to use targeted immunotherapies to manipulate and overcome mechanisms of tumor evasion. The proven safety and efficacy of the incorporation of targeted immunotherapy into upfront or relapsed/refractory (R/R) cHL treatment settings offer the possibility of developing clinical studies that rely less on conventional chemotherapy and RT while preserving outstanding survivorship rates. The present review summarizes the immunologic findings associated with cHL as well as the use of targeted immunotherapy agents in the treatment of pediatric cHL.

The Hodgkin-Reed-Sternberg Cell and Its Microenvironment

$CD4^+$ T-Cell Lymphocyte Subsets

Classic HL is a germinal center B-cell malignancy. The typically large tumor cells, known as Reed-Sternberg or Hodgkin-Reed-Sternberg (HRS) cells, have 2

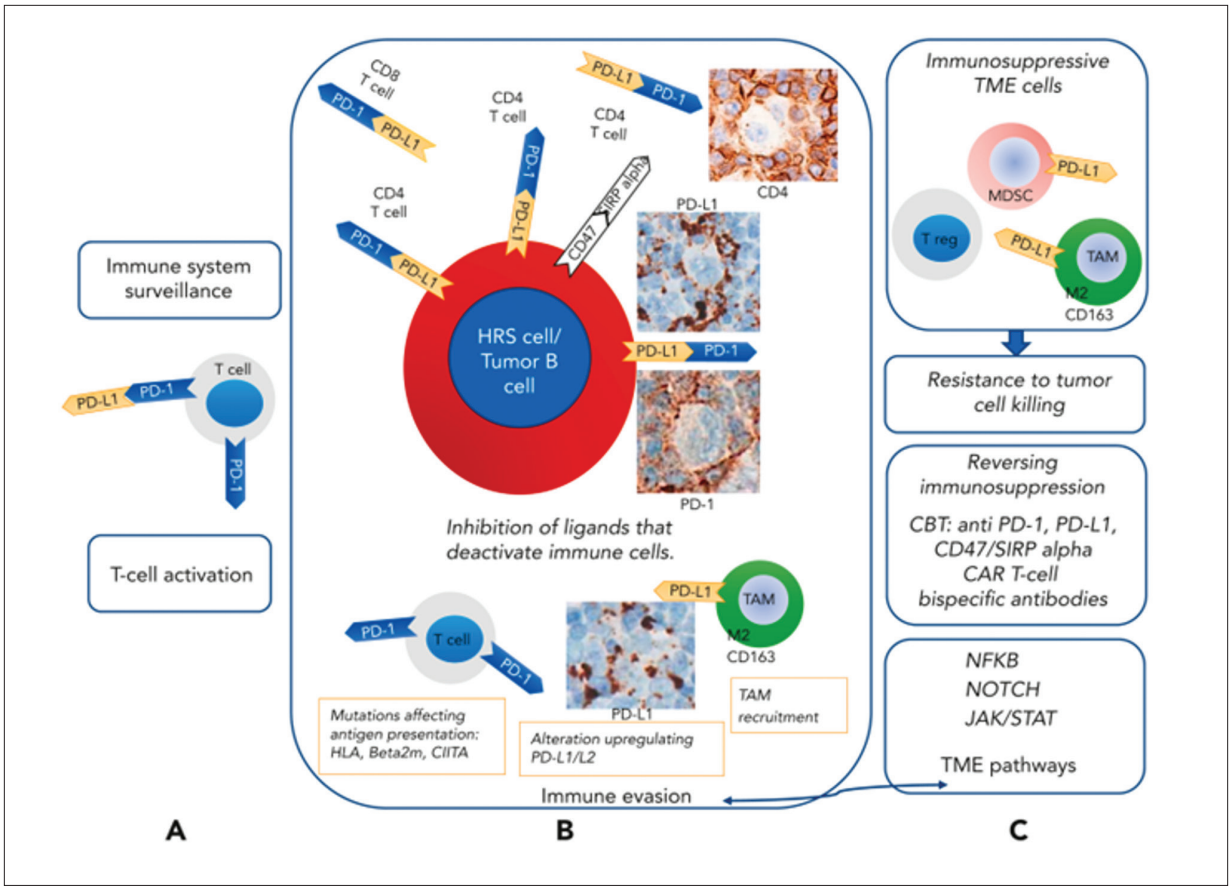

Figure 1. The tumor microenvironment in classic Hodgkin lymphoma leads to checkpoint blockade. Reprinted with permission from Carbone A et al. *Blood*. 2023;141(18):2187-2193.[20]
HRS, Hodgkin-Reed-Sternberg; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TME, tumor microenvironment.

prominent nuclei, each one with a large nucleolus and surrounded by a clear halo and abundant cytoplasm.[13] This pathologic feature reflects a remarkable mechanism of tumor survival.[14] During lymphomagenesis, HRS cells lose their B-cell phenotype, not expressing B-cell receptors (BCRs), B-cell surface markers (CD19, CD20, and CD79a/b, OBF-1, PU.1 negative; PAX5 expression is preserved), or immunoglobulin gene transcripts.[15] The lack of basic B-cell machinery would make the tumor vulnerable to apoptosis. Still, this is prevented by powerful anti-apoptotic mechanisms triggered by the lymphoma cell and maintained by its microenvironment.[15] The highly reactive background is classically characterized by small (different subsets of) CD4+ T-cell lymphocytes surrounding the HRS cells, forming rosettes (T-cell rosetting) and directly interacting and supporting individual HRS cells.[16] Intriguingly, HRS cells have a very poor ability to proliferate; the HRS compartment seems to be continually renewed by a small subset of clonotypic B cells.[17]

Type 2 T-helper CD4+ T-cell lymphocytes (Th2) are attracted by the HRS cells via chemokines such as TARC, CCL5, and CCL22. The TARC activation of CD4+ Th2 cells ultimately leads to constitutive activation of JAK/STAT and STAT6 signaling by the HRS cells. STAT6 activation promotes further increases in TARC production. Given the high level of expression of TARC by HRS cells and its detection in blood with immunohistochemistry, TARC serum levels are being used as a disease biomarker (Figure 1).[18-20]

Regulatory CD4+ T-cell lymphocytes are attracted by TARC, CCL5, CCL20, and CCL22. T-cell lymphocyte rosetting leads to the expression of cytokine interleukin 10 (IL-10), blocking CD8+ T cells and natural killer (NK) cells, with the consequent inhibition of programed death ligand 1 (PD-L1) or programed death ligand 2 (PD-L2). Importantly, *PD-L1/PD-L2* is localized to chromosome 9 (9p24). Molecular analyses of pediatric microdissected HRS cells have demonstrated amplifications and translocations involving *PD-L1*.[21,22] In fact, a genetic link has

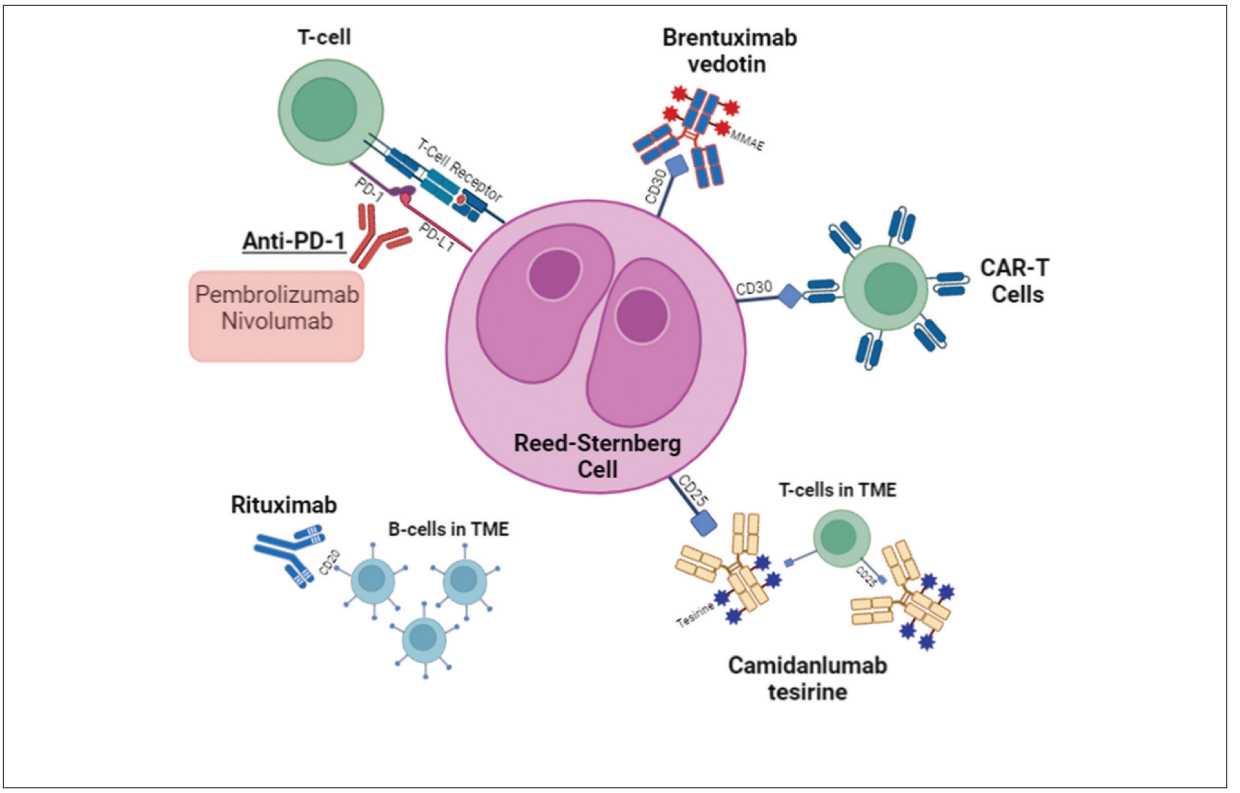

Figure 2. Targeting cell surface markers and/or the tumor microenvironment in classic Hodgkin lymphoma. Belsky JA et al. *Best Pract Res Clin Haematol*. 2023;36(1):101445.[37]
PD-1, programmed death 1; PD-L1, programmed death ligand 1; TME, tumor microenvironment.

been found between upregulation of *PD-L1/PD-L2* and *JAK2* (also localized to chromosome 9p24) and activation of the JAK/STAT pathway. STAT activation loops back to overexpress PD-L1/PD-L2.[23,24] Interestingly, LMP1 in Epstein-Barr virus–positive cHL leads to overexpression of PD-L1 via STAT activation.[25] Other cytokines/chemokines (eg, IL-9, tumor necrosis factor alpha [TNF-α], colony-stimulating factor 1 [CSF-1], galactin 1, exotoxin) are produced by the HRS cells for attraction, stimulation, or inhibition of eosinophils, mast cells, macrophages, NK cells, and fibroblasts.[18]

Furthermore, profiling studies of immune cells in the tumor microenvironment (TME) of cHL have uncovered a unique T cell–like subset that expresses lymphocyte activation gene 3 (LAG3$^+$ CD4$^+$ T cells). Interestingly, HRS cells surrounded by LAG3$^+$ CD4$^+$ T cells lack major histocompatibility class (MHC) II expression, as MHC II (the LAG3 ligand) downregulates LAG3 expression. FOXP3$^+$ CD4$^+$ T cells were found in lower numbers in the presence of LAG3$^+$ MHC-II$^-$ HRS cells.[26] LAG3$^+$ CD4$^+$ T cells promote an immunosuppressive environment and consequent immune escape.[26]

The complexity and differences in the TME composition may reflect differences in biology across age groups. For instance, gene signature profiles reflecting the TME composition differ between pediatric and adult cHL samples. Eosinophil, B-cell, and mast cell signatures were more prominent in younger patients with intermediate-risk cHL, whereas older patients' samples were characterized by macrophage and stromal signatures. A derived prognostic model based on TME composition gene expression generated a survival risk stratification model that is independent of commonly used stratification factors.[27]

CD30$^+$ (Ki-1, TNFRSF8) Hodgkin-Reed-Sternberg Cells

CD30 expression is noted in activated T cells and B cells. Normal CD30$^+$ B cells are found in small numbers in tonsils and lymph nodes, carry mutated *IgV*, are class-switched, and strongly express MYC.[28] CD30 is a cell membrane protein member of the TNF receptor superfamily (member 8) that interacts with other members of the same family (eg, TRAF2 and TRAF5), leading to regulated activation of the MAPK8/NF-κB, MYC, and JAK/STAT pathways. CD30 regulates apoptosis, limits the proliferation potential of CD8$^+$ T cells, and protects the body against autoimmunity.[29] The CD30 ligand

(CD30L, *TNFSF8*) is normally expressed in eosinophils and mast cells.[30,31]

Abnormal expression of CD30 is a typical immunophenotypic feature of cHL [PAX5$^+$ CD30$^+$ CD15$^+$ CD20$^-$ BCR$^-$]. It is believed that this allows HRS cells to escape apoptosis programs by acquiring features of normal CD30$^+$ B cells, leading to CD30L-independent NF-κB pathway activation.[32,33] In HRS cells, the NF-κB pathway is aberrant in multiple ways, which allows lymphoma cells to control the transcription of several target genes involved in apoptosis, B-cell expression loss, cell proliferation, and microenvironment crosstalk.[34] In cHL, the NF-κB pathway is also activated directly by interactions between the CD40 ligand (CD40L, *TNFSF5*) and its receptor (CD40, *TNFRSF5*) in nearby CD4$^+$ T cells or constitutively by the LMP1 protein in Epstein-Barr virus–driven cHL.[35,36] Mutation profiles performed on isolated HRS cells confirmed single-nucleotide variants, gains, or amplifications affecting mainly NF-κB (*NFKBIA*, *NFKBIE*, *TNFAIP3*, *REL*, *MAP3K14*, *BCL3*), JAK/STAT (*JAK2*, *SOCS1*, *STAT6*, *PTPN1*, *CSF2RB*), and PI3K/AKT (*ITPKB*, *GNA13*) pathways and those associated with immune evasion (*B2M*, *MHC2TA*, *PD-L1*, *PD-L2*), nuclear RNA and protein export (*XPO1*), chromatin remodeling (*ARID1A*), and epigenetic regulation (*JMJD2C*).[33]

The NF-κB pathway is essential for HRS-cell survival, PI3K/AKT activation maintains its BCR programming, and JAK/STAT signaling mediates cytokine/chemokine release and interference within the TME.[33] The unique biological makeup of the HRS cells within this complex TME creates the perfect rationale for targeted immunotherapy of both the malignant HRS cells as well the immunologic interactions supporting their growth (Figure 2).[37]

Overcoming Hodgkin-Reed-Sternberg Cell Antiapoptosis Mechanisms

CD30 as a Targeted Immunotherapy Approach

Anti-CD30 Targeted Antibodies. Brentuximab vedotin (BV; Adcetris, Seagen) is a construct that targets CD30. An antibody portion is conjugated to the antitubulin agent monomethyl auristatin E (MMAE). Once linked to the CD30 on the cell surface, the complex undergoes CD30 receptor–mediated endocytosis and interacts with lysosomal proteases, ultimately releasing MMAE.[38,39] Vinca alkaloids (ie, vinblastine, vincristine) are an essential component of contemporary treatment protocols for cHL. MMAE binds to the same tubulin site as vinblastine, but with increased potency (as a consequence of drug and antibody conjugation), leading to apoptosis via microtubule network disruption.[39] The efficacy of BV in adult cHL patients (≥18 years) was demonstrated in a pivotal study of BV monotherapy in the R/R setting, with an overall response rate (ORR) of 75%.[40] The combination of BV, doxorubicin, vinblastine, and dacarbazine vs the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was associated with a significantly improved 2-year modified PFS in adults with newly diagnosed advanced-stage cHL, leading to the US Food and Drug Administration (FDA) approval of this agent in upfront cHL therapy.[41] The main toxicity observed in adults treated with BV is neurotoxicity.[41,42]

In pediatric lymphoma, several studies have demonstrated the safety and efficacy of BV alone or in combination with other drugs (Table).[43,44] In the randomized phase 3 COG AHOD1331 trial, BV combined with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (BV-AVE-PC) was compared with ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) in pediatric patients with de novo high-risk cHL (stage IIB with bulky tumor, stage IIIB, stage IVA, or stage IVB). RT at 21 Gy was administered at the end of chemoimmunotherapy cycles to large mediastinal areas present at diagnosis only to patients with a partial response (slow-responding lesions) after interim FDG-PET. The 3-year overall survival (OS) was 99.3% (95% CI, 97.3%-99.8%) in the BV-AVE-PC arm vs 98.5% (95% CI, 96.0%-99.4%) in the ABVE-PC group, respectively. The 3-year EFS rate was 92.1% (95% CI, 88.4%-94.7%) in the BV-AVE-PC arm vs 82.5% (95% CI, 77.4%-86.5% in the ABVE-PC group, with a hazard ratio for event or death of 0.41 (95% CI, 0.25-0.67; P<.001) (Table). No differences were seen between the 2 arms in terms of RT use or toxicities.[45] The most common grade 3 or higher adverse events (AEs), occurring in more than 5% of the patients receiving BV-AVE-PC, were cytopenia, febrile neutropenia, stomatitis, and infection. Given the risk of infection and febrile neutropenia, support with granulocyte colony–stimulating factor (G-CSF) is recommended. No significant BV-induced neurotoxicity was observed in children treated with the protocol.[45] On the basis of results of the AHOD1331 study, the FDA approved the use of BV-AVE-PC for pediatric patients 2 years of age or older with previously untreated high-risk cHL. Similarly, BV was used to replace vincristine in a backbone of etoposide, prednisone, and doxorubicin plus cyclophosphamide, vincristine, prednisone, and dacarbazine (AEPA/CAPDAC) in a trial of pediatric advanced-stage cHL. This trial looked to reduce RT while maintaining overall good outcomes in these high-risk patients. The 3-year EFS rate was 97.4% (standard error [SE], 2.3%) and the OS rate was 98.7% (SE, 1.6%), with 35% of patients spared RT (Table).[46]

Table. Targeted Immunotherapy for De Novo or Relapsed/Refractory Pediatric, Adolescent, and Young Adult Classic Hodgkin Lymphoma

Regimen	Therapeutic Target	Phase	Risk Group	N	Age, median, y	Results, % (95% CI)†
BV monotherapy[43]	CD30	1/2	R/R	36	15	ORR: 46 (29-63); CRR: 34
BV+gemcitabine[44]	CD30	1/2	R/R	46	17.6	ORR: 74 (58-86); CRR: 67 (51-80)
(Arm 1) ABVE-PC vs (Arm 2) BV-AVE-PC[45]	CD30	3	De novo, HR	289 298	15.6	EFS: 83 (77-86)* EFS: 92 (88-95)*
AEPA/CAPDAC[46]	CD30	2	De novo, HR	77	16	EFS: 97 (SE 2.3%)* OS: 99 (SE 1.6%)*
BV+RTX+AVD[48]	CD30+CD20	2	De novo, IR, HR	30	15	CRR: 100** EFS: 100**
N+BV±BV+Benda[84]	CD30+PD-1	2	R/R	44	16	CRR: 94^
N+BV+I[85]	CD30+PD-1+CTLA-4	1/2	R/R	57	34	ORR: 88 CRR: 66.7 PFS/OS: NR
(Arm 1) BV+AVD vs (Arm 2) N+AVD[89]	CD30 PD-1	3	De novo, HR	487 489	26.8 27.6	PFS: 86# PFS: 94#

*3-y EFS or OS.
**5-y EFS or OS.
†Parentheses encompass 95% CI unless otherwise specified.
^CR at any time before consolidation.
#1-y PFS.
ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; AEPA, brentuximab vedotin, etoposide, prednisone, doxorubicin; AVD, doxorubicin, vinblastine, dacarbazine; Benda, bendamustine; BV, brentuximab vedotin; BV-AVE-PC, brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide; CAPDAC, cyclophosphamide, brentuximab vedotin, prednisone, dacarbazine; CRR, complete response rate; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; EFS, event-free survival; HR, high-risk; I, ipilimumab; IR, intermediate risk; N, nivolumab; NR, not reached; ORR, overall response rate; OS, overall survival; PD-1, programmed death 1; PFS, progression-free survival; R/R, relapsed/refractory; RTX, rituximab; SE, standard error; y, years.

In the R/R setting, BV was combined with bendamustine, gemcitabine, or an ICI (see below). The combination of BV and bendamustine (BVB) in pediatric (age <21 years, n=29) patients with R/R cHL was retrospectively evaluated in a multicenter study. Most patients achieved a complete metabolic response (66%; 95% CI, 46%-82%) and had an objective response (79%; 95% CI, 60%-92%). Most patients could be mobilized for the collection of stem cells, and the 3-year post-BVB EFS and OS rates were 65% (95% CI, 46%-85%) and 89% (95% CI, 74%-100%), respectively.[47] The COG AHOD1221 phase 1/2 trial combined gemcitabine with BV in patients younger than 30 years with high-risk R/R cHL (R/R <12 months after the initial diagnosis) and reported a complete response (CR) rate of 67% (95% CI, 51%-80%).[44]

Reducing cumulative doses of chemotherapy or exposure to RT while keeping outstanding outcomes is an important goal of the contemporary approach to treating pediatric cHL. This was recently successfully attempted by Hochberg and colleagues.[48] In this study, 30 CAYAs with intermediate- or high-risk de novo cHL were treated with 4 to 6 cycles of BV plus rituximab (RTX) in a (risk-adapted) chemotherapy backbone including vinblastine, doxorubicin, and dacarbazine. Involved-field RT was given only to high-risk patients with both bulky disease and a slow response and to those not in CR at the end of therapy. The group reported a CR in all patients and a 5-year EFS rate of 100% (median age, 15 years; range, 4-23). RT was not needed in 87% of the cohort (Table).[48] Four grade 3 or higher nonhematologic AEs (13%) occurred, including 2 cases of grade 3 neuropathy (6%), 1 case of a grade 3 allergic reaction to BV (3%), and 1 case of grade 3 mucositis (3%).[48] The currently accruing RADICAL study (NCT05253495) is investigating the safety and feasibility of adding the ICI nivolumab (Opdivo, Bristol Myers Squibb) to a similar backbone of BV plus RTX in combination with (risk-adapted) reduced-toxicity chemotherapy (including significantly reduced cumulative doses of anthracycline) to the treatment of CAYAs with newly diagnosed intermediate- or high-risk cHL.

Attaching bispecific monoclonal antibodies (mAbs) targeting CD30$^+$ in one arm while attaching CD3 or CD28 (leading to activation of resting T cells) or CD16 (leading to NK cell activation) in the other arm has been shown to cause cHL tumor lysis in vitro and in vivo.[49,50] Phase 1 studies of the use of CD30/CD16A mAbs in adult patients with cHL have shown promising results.[51,52] Other molecules involved in anti-HRS cell phagocytosis mechanisms, such as CD47 (binds to tumor-associated macrophages), have also been targeted in association with PD-L1 (anti–CD47/PD-L1 bispecific antibodies), with good responses in adult patients who have refractory cHL or other tumors.[53,54]

Anti-CD30 Targeted Cell Therapy. Adoptive immunotherapy with genetically engineered T cells expressing a chimeric antigen receptor (CAR T cell) specifically targeting an antigen on tumor cells has demonstrated high rates of efficacy and tolerability in clinical trials of acute lymphoblastic leukemia in children.[55,56] CD30-targeting CAR T cells have been used with promising results and acceptable safety in phase 1 and 2 clinical trials of adult patients with heavily treated R/R cHL, including treatment with BV.[57,58] Also, CD30-targeting CAR T-cell infusion as consolidation after MAC-autoHSCT has been shown to be safe with encouraging activity in high-risk patients with R/R cHL.[57] Currently, a phase 2 study open in the United States is evaluating a CD30-targeting CAR T-cell therapy in children older than 12 years with R/R cHL (NCT04268706). Studies of CD30-targeting CAR T cells that include only pediatric patients with poor-risk cHL following autoHSCT are currently under development.

Targeting Clonotypic B Cells and the Generation of HRS Cells: CD20 (MS4A1)

CD20 is a member of the membrane-spanning 4A (MS4A) gene family and encodes a B-cell surface molecule essential in the development and differentiation of B lymphocytes into plasma cells.[59] In cHL, the B lymphocyte–derived HRS cells lack (or nearly lack) CD20 expression, but that is not the case for small subsets of clonotypic B cells in the tumor with the same immunoglobulin gene rearrangements as lymph node–derived HRS cells. For instance, the HL cell line L-428 HL has been shown to contain small populations of CD19$^+$ CD20$^+$ B cells (clonotypic B cells) that generate and maintain the HRS cell compartment.[60] Clonotypic B cells were detected in the peripheral blood of patients with cHL, and the circulating levels of these cells correlated with stage of disease.[17]

CD20 as a Targeted Immunotherapy Approach: Anti-CD20 Monoclonal Antibodies

Anti-CD20 monoclonal antibodies are considered an essential component of mature B-cell malignancies and autoimmune disorders. Approved by the FDA in 1997, RTX is an anti-CD20 chimeric antibody with human immunoglobulin G1 (IgG1) constant regions and variable regions from an anti-CD20 murine antibody. It is thought that RTX binding triggers direct effects on CD20 and BCR signaling and on cell death through antibody-dependent cell-mediated cytotoxicity, complement-mediated cytotoxicity, and antibody-dependent phagocytosis.[61] Given the importance of B cells in the development of cHL and in maintenance of the HRS cell compartment, the use of RTX in cHL warrants further consideration. In fact, RTX monotherapy was tested in a group of adult patients (n=22) with relapsed cHL. They received 6 weekly doses of RTX to deplete infiltrating B cells in the TME. A partial or complete response that lasted a median of 7.8 months (range, 3.3-14.9) was achieved in 5 patients (22%).[62] In a phase 2 study of adults with newly diagnosed advanced-stage cHL treated with RTX weekly (6 doses) plus ABVD (6 cycles), the 5-year EFS and OS rates were 83% and 96%, respectively, with a median follow-up duration of 68 months (range, 26-110).[63] A second multicenter phase 2 study combining RTX with ABVD (R-ABVD) in adults with advanced-stage cHL looked at the behavior of circulating clonotypic B cells in addition to clinical outcomes. Only 8% of the patients had CD20$^+$ HRS cells. After 6 cycles, 81% of the patients were in CR. Only 8% required RT for residual disease. The actuarial 3-year EFS and OS rates were 83% and 98%, respectively.[64] Of particular interest, it was found that the persistence of detectable circulating clonotypic B cells was associated with a greater frequency of relapse (P<.05).[64] R-ABVD was tested in a multicenter, open-label, randomized phase 2 study of adult patients with advanced stage high-risk de novo cHL, with CD20 expression in HRS cells (not pre-HRS cells or protumoral B lymphocytes) taken into consideration. The authors observed that the 3-year EFS rate was higher (80%) in patients who had CD20$^+$ HRS cells (any degree) and were treated with R-ABVD than in the patients who had CD20$^-$ cells and were treated with the same regimen.[65] The German Hodgkin Study Group H18 trial added RTX to escalated bleomycin, cyclophosphamide, doxorubicin, etoposide, prednisone, procarbazine, and vincristine (BEACOPP) in adult patients with advanced-stage cHL who were in a partial metabolic response by FDG-PET (PET2). The study did not find differences in PFS with the addition of RTX; however, the PFS of the entire cohort was greatly superior to that in the previously reported study (H15), suggesting that PET2 cannot identify patients with an elevated risk of treatment failure.[66] As previously presented, RTX was added to BV in a risk-adapted chemotherapy backbone to treat intermediate- to high-risk cHL in CAYAs, with outstanding survival rates.[48] These

studies suggest that RTX in addition to chemotherapy and other immunotherapy agents may be an effective and safe adjuvant in the treatment of de novo or R/R cHL. The use of RTX in children treated for B-cell non-Hodgkin lymphomas has been associated with lymphopenia, prolonged hypogammaglobulinemia (≤1 year after the completion of chemoimmunotherapy), and the use of immunoglobulin replacement, but severe infections are rare.[67] Hypogammaglobulinemia has not been observed in pediatric patients with cHL treated with RTX.[48]

Overcoming HRS Immune Evasion Mechanisms: Programmed Death Axis

T-cell activation is triggered when an antigen is presented by the MHC of an antigen-presenting cell to the T-cell receptor, or when an antigen-independent mechanism delivers the antigen-presenting cell.[68] Resting naive T cells express CD28, which when activated by B7-1 and B7-2 ligands can lead to cell cycle progression, IL-2 production, and clonal expression.[69] Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) shares ligands with CD28, and its activation triggers co-inhibition of T cells via cell cycle arrest. The negative regulation role of CTLA-4 is key to avoiding fatal lymphoproliferation.[70] PD-L1/PD-L2 are other co-inhibitory molecules in T cells. PD-L1 and PD-L2 are independent of CD28 or CTLA-4, and they bind to PD-1 on the surface of T cells.[71,72]

Activated T cells can recognize and kill tumor cells. Inversely, tumor cells can activate co-inhibitory mechanisms via expression of PD-L1/PD-L2 or CTLA-4, preventing their recognition and destruction by the immune system. PD-L1/PD-L2 are overexpressed in a variety of lymphoid malignancies, especially those with an increased inflammatory background, such as cHL.[24,25,73] This is an important mechanism of cHL evasion, progression, and dissemination.[74-77]

CTLA-4 was the first immune checkpoint protein whose inhibition was shown to be effective in treating cancer.[66] Anti–PD-1 monoclonal antibodies are second-generation ICIs that have been safely used in cancer to produce a clinical response.[78-81] PD-1 is a negative regulator of T-cell activity; binding to one of its ligands, PD-L1 or PD-L2, leads to inhibition of T-cell function. CTLA-4 blockade with ipilimumab and blockade of PD-1 with nivolumab of pembrolizumab have been shown in a variety of adult cancers to lead to durable, long-term remissions.[82]

Nivolumab is the first human IgG4 anti–PD-1 mAb to be tested in adult patients with R/R lymphomas. The FDA granted Breakthrough Therapy Designation to nivolumab in 2014 for the treatment of refractory cHL after failure to respond to autoHSCT or BV. Nivolumab was initially tested in a phase 1 study conducted by the COG in CAYAs with R/R non–central nervous system tumors or lymphomas. The authors found no dose de-escalations or dose-limiting toxicities when a dose of 3 mg/kg was administered intravenously, and they found objective responses only in patients with PD-L1$^+$ lymphomas (30% of patients with cHL).[83] The subsequent phase 2 CheckMate 744 study, which treated CAYAs with R/R cHL, evaluated nivolumab plus BV followed by BV plus bendamustine in patients with a suboptimal response before consolidation. The complete metabolic response rates were 59% after nivolumab plus BV and 94% at any time before consolidation (Table). The 1-year PFS rate was excellent, at 91%. Overall, 18% of patients experienced a grade 3 or 4 treatment-related AE during induction with nivolumab plus BV. The most common AEs were hypersensitivity (20%), nausea (20%), and diarrhea (14%), all grade 1 or 2. Of the 11 patients who required intensification with BV plus bendamustine, 8 experienced an AE (grade 3/4 in 3 subjects [27%]). Treatment-related serious AEs occurred in 5 patients (11%) before consolidation (grade 3/4 in 3 patients). One AE led to discontinuation (grade 3 anaphylactic reaction). No treatment-related deaths occurred.[84]

The combination of BV with an ICI was tested in the E4412 study (NCT01896999). BV plus nivolumab in combination (or not) with the anti–CTLA-4 agent ipilimumab (BV/N vs BV/N/I) was tested in patients older than 12 years with R/R cHL. Efficacy did not differ between the 2 arms and disease control was excellent in both (Table), but the BV/N/I cohort experienced more grade 3 rash.[85] Recently published data from the SWOG S1826 trial compared 6 cycles of BV plus doxorubicin, vinblastine, and dacarbazine (AVD) vs N-AVD in patients with newly diagnosed advanced-stage cHL and found superior PFS in the N-AVD group, with a lower toxicity profile in both the adult and pediatric subgroups. The most frequently observed AE of any grade was neutropenia (56% in N-AVD vs 34% after BV-AVD). A total of 48% of the patients experienced grade 3 or higher neutropenia after N-AVD vs 26% after BV-AVD. Rates of febrile neutropenia, sepsis, and infection/infestation were similar in the study arms but higher in older patients, especially those treated with BV-AVD (12-17 years, 18%; 18-60 years, 20%; >60 years, 33%).[86] These data represent a new treatment paradigm in pediatric cHL, eliminating RT for the majority of patients while maintaining excellent outcomes. In the previously mentioned RADICAL study's (NCT05253495) preliminary safety report on 10 treated CAYAs with cHL (median age, 18 years [range, 10-23 years]; 4 intermediate-risk patients, 6 high-risk patients) showed that grade 4 myelosuppression developed in all patients, who were supported with

G-CSF. No grade 3 or higher fever, infection, and neurologic or immune-related AEs occurred. No unexpected grade 3/4 AEs secondary to nivolumab have occurred, and no dose-limiting toxicities.[87]

In the phase 1b KEYNOTE-013 study, adult patients with R/R cHL (including after BV) received a different ICI, pembrolizumab. The ORR was 65% (90% CI, 48%-79%), and the PFS rate was 69% at 24 weeks and 46% at 52 weeks.[88] In another study, of 15 adult patients with R/R cHL treated with pembrolizumab, the ORR was 60% (95% CI, 32.2%-83.7%).[89] Additional immune checkpoint regulators such as LAG3 and T-cell immunoglobulin and mucin-domain containing 3 (TIM3) have been shown to be represented in both the TME and on the surface of the HRS cell.[90] Furthermore, the expression of each varies among patients, which suggests a role for using these biomarkers to determine potential response to treatment. In a review of pediatric cHL samples for the COG repository, LAG3 expression was present in a large number of pediatric cases of cHL, and no correlation was found between LAG3 expression and outcomes.[81,91] These are novel potential targets for overcoming immune checkpoint blockade in cHL and further risk-stratifying patients.

Conclusions and Perspectives

Overall outcomes in pediatric and adolescent cHL have been excellent, but not without concerns regarding short- and long-term toxicities. The days of intensive multiagent regimens with post-treatment RT are unrealistic, given the emerging understanding of the biology of the malignant HRS cell and its vast and complex immune microenvironment. How we approach the interactions between the host immune system and the underlying genetic alterations seen in cHL is important. The identification of numerous genetic alterations in adult and pediatric cHL has led to the development of a myriad of targeted agents. Increasing evidence in children and adolescents with cHL indicates that immunotherapy offers an effective and potentially less toxic approach to cure. Targeted therapies directed against surface proteins on the HRS cell or disrupting the immune checkpoint blockade allow us to accomplish 2 important goals. First, how can we improve outcomes in high-risk patients with R/R disease who continue to do poorly despite intensified treatments such as higher doses of RT and MAC-autoHSCT? We have an obligation to focus on studies to improve response and survival in these patients. Even patients who can be salvaged with these standard approaches experience significant toxicities that should be considered unacceptable. Second, the current data demonstrate strong activity of and excellent outcomes with multiple immunotherapy approaches in de novo cHL. Therefore, focusing on studies designed with clear strategies to reduce cumulative doses of traditional chemotherapies and RT are required and should become the new standard of care. Pediatric cHL trials should be given equal access to novel immunotherapy agents with ongoing biologic correlatives that can determine optimal combination therapy based on patient-specific pathway alterations. Ultimately, targeted immunotherapy has the potential to change the landscape of the treatment of pediatric cHL so that we may strive toward a better cure.

Disclosures

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