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EDITED BY

Shyamala Maheswaran,
Massachusetts General Hospital and
Harvard Medical School, United States

REVIEWED BY

Maulik Vyas,
Massachusetts General Hospital and
Harvard Medical School, United States
Yu Zhao,
Xuanwu Hospital, Capital Medical
University, China

*CORRESPONDENCE

Valli De Re,
vdere@cro.it
Maurizio Mascarin,
mascarin@cro.it

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Promising drugs and treatment options for pediatric and adolescent patients with Hodgkin lymphoma

Valli De Re^{1*}, Ombretta Repetto¹, Lara Mussolin²,
Giulia Brisotto¹, Caterina Elia³, Egesta Lopci⁴,
Emanuele S. G. d'Amore⁵, Roberta Burnelli⁶ and
Maurizio Mascarin^{3*}

¹Immunopatologia e Biomarcatori Oncologici, Dipartimento di Ricerca e Diagnostica Avanzata dei Tumori, CRO Aviano, National Cancer Institute, Istituto di Ricovero e Cura a Carattere Scientifico, IRCCS, Aviano, Italy, ²Pediatric Hemato-Oncology Unit, Department of Women's and Children's Health, University of Padua, Padua, Italy, ³AYA Oncology and Pediatric Radiotherapy Unit, Centro di Riferimento Oncologico IRCCS, Aviano, Italy, ⁴Nuclear Medicine, IRCCS—Humanitas Research Hospital, Rozzano, MI, Italy, ⁵Department of Pathology, San Bortolo Hospital, Vicenza, Italy, ⁶Pediatric Hematology-Oncology Unit, Azienda Ospedaliera Universitaria, Ospedale Sant'Anna, Ferrara, Italy

Currently-available therapies for newly-diagnosed pediatric and adolescent patients with Hodgkin lymphoma result in >95% survival at 5 years. Long-term survivors may suffer from long-term treatment-related side effects, however, so the past 20 years have seen clinical trials for children and adolescents with HL gradually abandon the regimens used in adults in an effort to improve this situation. Narrower-field radiotherapy can reduce long-term toxicity while maintaining good tumor control. Various risk-adapted chemo-radiotherapy strategies have been used. Early assessment of tumor response with interim positron emission tomography and/or measuring metabolic tumor volume has been used both to limit RT in patients with favorable characteristics and to adopt more aggressive therapies in patients with a poor response. Most classical Hodgkin's lymphoma relapses occur within 3 years of initial treatment, while relapses occurring 5 years or more after diagnosis are rare. As the outcome for patients with relapsed/refractory classical Hodgkin lymphoma remains unsatisfactory, new drugs have been proposed for its prevention or treatment. This review summarizes the important advances made in recent years in the management of pediatric and adolescent with classical Hodgkin lymphoma, and the novel targeted treatments for relapsed and refractory classical Hodgkin lymphoma.

KEYWORDS

Hodgkin lymphoma, Epstein-Barr virus, chemotherapy, radiation, tumor target, adolescent

Introduction: A model of Hodgkin lymphoma biology and biomarkers

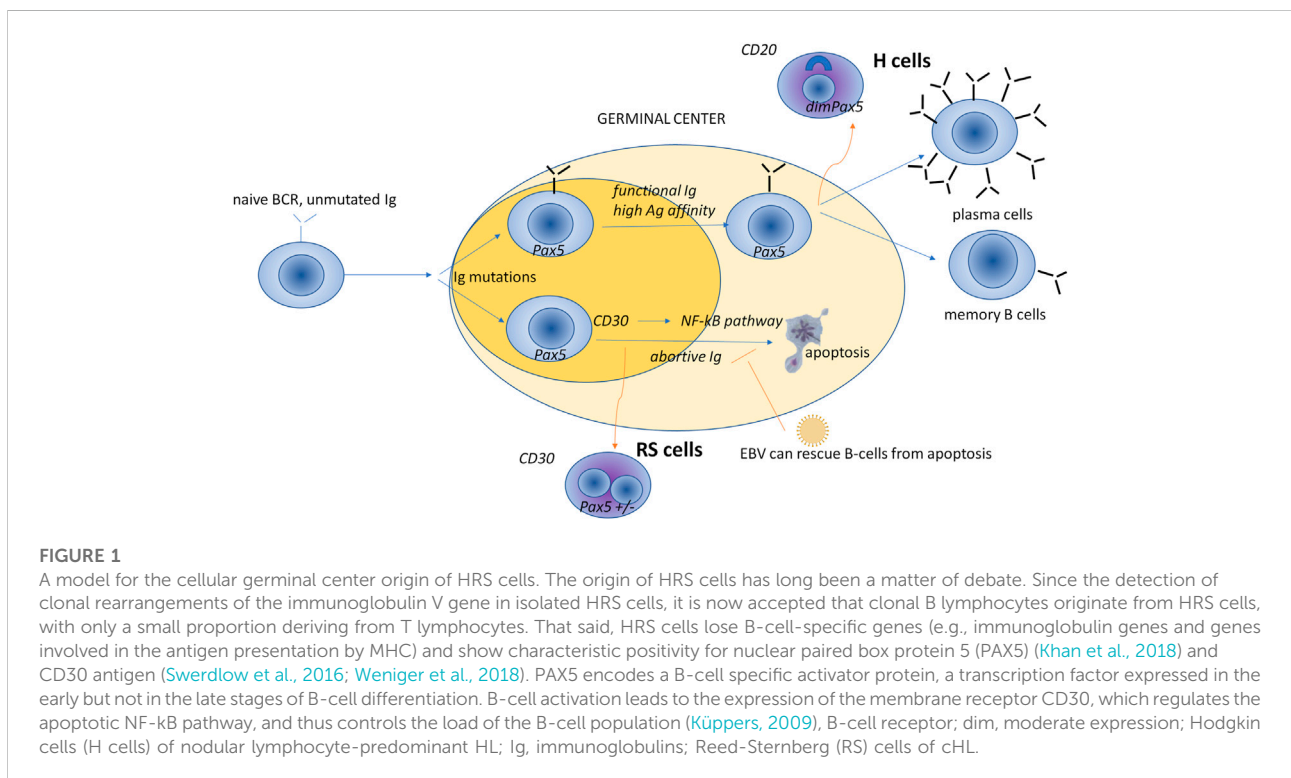
Classical Hodgkin lymphoma (cHL) accounts for approximately 6%–7% of all pediatric cancers, with a peak incidence in adolescence and young adulthood. Reported incidence rates are: 29/myr in 15- to 19-year-olds; approximately 10/myr in 10- to 14-year-olds; 3.5/myr in children 5–9 years old; and 1/myr in infants up to 4 years old. Among Italian adolescents aged 15–19 years the incidence rate is 23.6/myr, which is twice the rate reported for the same age group in the United States and the rest of Europe (AIRTUM Working Group and CCM, 2013). HL is also associated with congenital immunodeficiency: it is estimated that 4.5% of HL cases are familial (McAulay and Jarrett, 2015).

There are four subtypes of cHL: nodular sclerosis (NSHL); mixed cell (MCHL); lymphocyte-rich (LRHL); and lymphocyte-depleted (LDHL) (Connors et al., 2020). NSHL is the most common of these subtypes. Patients with nodular lymphocyte-predominant HL (NLPHL) are classified as cases of non-cHL. Epstein-Barr virus (EBV) plays a role in the etiology of HL in approximately 30% of cases. The frequency of EBV positivity ranges from ~75% in MCHL and LDHL to <20% in NSHL and LRHL (Massini et al., 2009).

Malignant cells are large and multinucleated, and derive from B lymphocytes. They are known as Hodgkin and Reed-Sternberg (HRS) cells. Figure 1 illustrates the model that the HRS cells

originate from the postgerminal center. HRS cells are typically CD30⁺ and embedded in a tumor-promoting microenvironment (TME) rich in immune cells, where exhausted T cells, Th1 and Th2 T-helper (Th) cells, polarized regulatory T (T_{reg}) cells, PD1+ T follicular helper (T_{FH}) cells, lymphocyte-activating 3 (LAG3, CD223)-positive T cells, and various subpopulations of macrophages play a key role in tumor support (for more details, see the next section). Patients with NLPHL have scattered, large neoplastic B cells with multilobate nuclei (lymphocyte-predominant or popcorn cells) expressing a broad panel of B-related markers (CD19, CD20, CD79a, PAX5, OCT2, BOB1) within nodules dominated by mantle zone B cells and follicular dendritic cells (FDCs) (Connors et al., 2020).

HL is diagnosed on histological examination of an excisional biopsy of a suspect lymph node. Though not specific for HRS cells when considered separately, the relevant immunohistochemical markers include the expression of CD15⁺ (Lewis X antigen), CD30⁺ (TNFRSF8), PAX5⁺ (B-cell transcription factor) with a typical loss of B-cell antigens (e.g., CD19, CD20, CD79a), surface membrane immunoglobulin (Ig), and some B-cell transcription factors (Oct2 and Bob1). In contrast, tumor cells in NLPHL retain a complete B-cell program (CD19⁺, CD20⁺, and all transcription factors), but are CD30⁻ and CD15⁻ negative. In cases of cHL associated with EBV infection, tumor cells express a type II latency pattern associated with EBV-encoded RNA (EBER), latent membrane proteins (LMP) 1 and 2a, EBV nuclear antigen 1



(EBNA 1), and BamHI-A right frame 1 (BARF1) (De Re et al., 2020).

The overexpression of novel markers in cHL has been investigated both for diagnostic purposes and for novel targeted therapies (for more details, see the following sections). These include: integrin-associated protein (IAP) CD47 (Lopez-Pereira et al., 2020); transcription factor GATA3 activated by the NF- κ B pathway; signal transducer and activator of transcription (STAT) 6; cluster of differentiation (CD) 83; transcription factor FOXO3A; Wilms tumor gene-1 (WT1); preferentially expressed antigen in melanoma (PRAME); and survivin (Dave et al., 2022).

Extracellular vesicles (EVs) formed inside endosomal compartments (i.e., exosomes), and carrying RNA, DNA, and proteins, are actively released from HRS cells and function as intercellular messengers. In HL, serum EV levels increase considerably. The EVs are rich in CD30 antigen (Hansen et al., 2014), also known as tumor necrosis factor receptor 8 (TNFR8), and exhibit functional protumoral effects. Hansen et al. (2014) showed that CD30-rich EVs stimulate the secretion of the tumorigenic chemokine interleukin-8 (IL-8) by eosinophil-like cells and primary granulocytes. CD30-rich EVs also facilitate the crosstalk between HRS cells and immune cells in the microenvironment, thus playing a part in the recruitment of distant immune cells with a key role in tumor growth. A recently-developed diagnostic analytic technique involves an aurum nanoparticle (AuNPs) with peroxidase activity capable of binding and ascertaining the concentration of CD30 antigen in circulating EVs for the purpose of monitoring cHL activity (Slyusarenko et al., 2022).

EVs released by HL cells also carry high levels of the metalloproteinase ADAM10 (Tosetti et al., 2018). Using the ADAM10 inhibitors LT4 and CAM29 to counteract ADAM10 shedding from HRS cells was found to restore the expression on the HRS cell surface of the major histocompatibility complex (MHC) Class I chain-related protein A (MICA) (Tosetti et al., 2018), a ligand for the activating receptor NKG2D present on NK and cytotoxic CD8⁺ T cells; and this resulted in the activation of cytotoxic T cells. ADAM10 also targets CD30, leading to the release of soluble CD30, which could interfere with anti-CD30 treatments.

EVs were also found involved in the crosstalk between the HRS and fibroblasts, leading to the production of highly-activated cancer fibroblasts that contribute to the tumor-promoting microenvironment (TME) (Dörsam et al., 2018). Plasma EVs encode proteins such as fibrinogen γ chain, complement C4B (an isotype of C4 protein), and transthyretin, which are more abundant in pediatric relapsed HL (Repetto et al., 2021).

Many miRNAs, such as miR21-5p, miR127-3p, let7a-5p, miR24-3p, and miR155-5p, are strongly enriched in the EVs of patients with cHL. In addition, miR-155-5p is related to disease progression, and miR155 responds to chemotherapy

(van Eijndhoven et al., 2016). In an *in vivo* model of EBV-positive cHL, HRS cells were shown to release the EBV-encoded miRNA BamHI fragment A rightward transcript (BART), which induces the expression of immunosuppressive IL-10, TNF- α , and arginase-1 in macrophages, further supporting the development of HL (Higuchi et al., 2018). HRS cells may also transfer cell membrane fragments—including important proteins such as PD-L1, CD38, CD137, and CD30—to non-cancerous cells, a phenomenon known as trogocytosis and indicated as another mechanism contributing to the establishment of a TME (Zeng and Schwarz, 2020).

Genetic alterations in Hodgkin lymphoma

Patients have genetic alterations in their HRS cells (Table 1) that may also be present in their circulating mononuclear B cells, possibly due to telomere dysfunction (Buedts et al., 2021; Oki et al., 2015; M'kacher et al., 2018). The genetic basis for immune evasion and the anti-apoptotic signaling mediated by NF- κ B and PI3K/AKT/mTOR pathways play a key role in cHL survival, while JAK/STAT signaling is known to sustain tumor growth. A reduced MHC Class I and/or Class II antigen expression and a reduced antigenic peptide/MHC complex presentation (Figure 2), which often correlates with worse prognosis, is reportedly common in HL, affecting from 40% to 70% of cases (Diepstra et al., 2007; Reichel et al., 2015).

Clinical studies for the treatment of young patients with Hodgkin lymphoma

The standard of care for adults with relapsed cHL involves high-dose chemotherapy combined with autologous stem cell transplantation after conventional chemotherapy. At the end of 2019, the EuroNet Group published guidelines for pediatric and adolescent patients with recurrent or refractory cHL based on risk stratification, response-adapted therapy, and a limited use of transplantation (Daw et al., 2020). It recommended initially stratifying patients in one of two risk groups (low- and standard-risk). At tumor relapse, the two groups were differentiated in terms of: 1) time to relapse; 2) tumor stage before first-line treatment; and 3) tumor stage and tumor burden at relapse. A third (high-risk) group included non-responders when positron emission tomography (PET) was positive (i.e., Deauville score 4, 5) after two cycles of salvage chemotherapy.

Patients in the low-risk group were treated with conventional-dose salvage therapy and RT. The standard-risk group received conventional-dose salvage chemotherapy plus consolidation with high-dose chemotherapy followed by

TABLE 1 Known genetic aberrations in HRS cells.

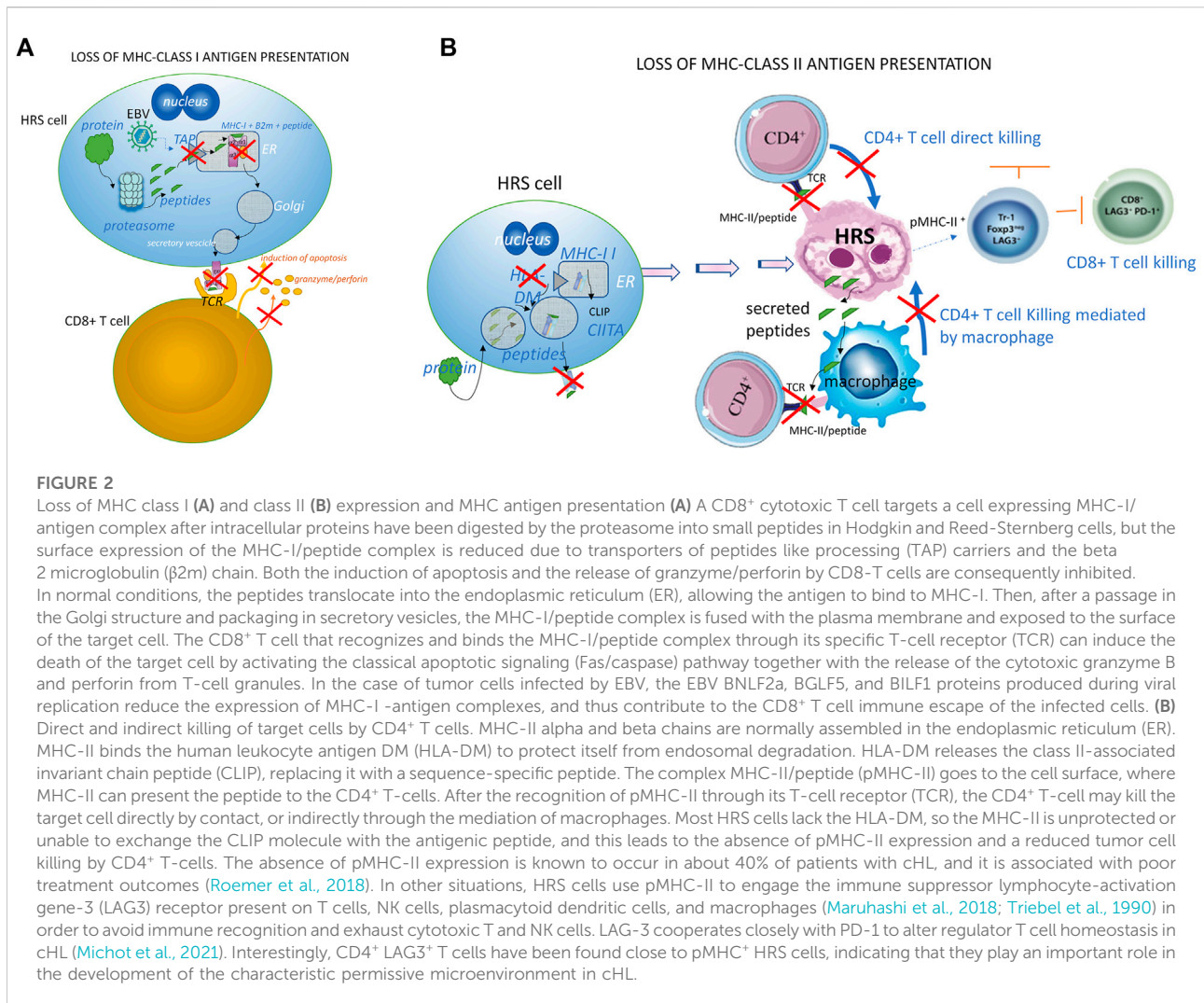
Mechanism	Gene	Locus	Alteration	Function
Immune evasion	PDL1/2	Chr9p	Genomic amplification and rearrangements leading to overexpression	T-cell PDL1/PDL immune checkpoint inhibition Roemer et al. (2016)
	B2M	Chr15q	Inactivating mutations	Limiting MHC Class I protein expression and associated antigen presentation to CD8 T cells Reichel et al. (2015) and Wienand et al. (2019)
	CIITA	Chr16p	Gene fusion	Limiting MHC Class II transcription and inducing immunosuppressive CD4 ⁺ LAG3 ⁺ (CD223) T cells Maruhashi et al. (2018)
	CD58	Chr1p	Truncating mutation/deletion	A ligand of the CD2 protein on T and NK cells, important for adhesion and activation of cytotoxic T and NK cells Schneider et al. (2015) and Veldman et al. (2020)
	CD47 (IAP)	Chr3q	Overexpression	CD47 interacts with SIRP α on macrophages, inhibiting phagocytic signals Lopez-Pereira et al. (2020)
Aberration related to pathway	JAK/STAT	JAK2, PDL, KDM4C, NOTCH1, Chr9p STAT3, STAT6, Chr12q SOCS1, Chr16p, PTPN-1, Chr20q Tiacci et al. (2018)	Copy number gains Deletion/mutation	Kinases that transport JAK/STAT signals are mainly produced by interleukin (IL) 4 and 13 from membrane receptors into the nucleus, where they activate genes of cell growth and induce PDL expression. KDM4C is a lysine demethylase, and a pro-oncogenic chromatin remodeler Shi et al. (2006) and Rui et al. (2010) . It has also been reported that NOTCH activation can trigger NF- κ B signaling, promoting the survival of cHL cells in cooperation with the EBV Schwarzer and Jundt (2011) .
	NF- κ B	JUNB (AP-1), Chr19p REL, exportin 1 (XPO1/CRM1), Chr2p Schwarzer and Jundt (2011) , TNFAIP3, Chr6q Camus et al. (2016) and Desch et al. (2020)	Immunoglobulin gene translocation, copy number gains, mutation	They are positive regulators of NF- κ B leading to B-cell survival and proliferation Gilmore et al. (2004) and Kober-Hasslacher and Schmidt-Supprian (2019) . NF- κ B controls JUNB Mathas et al. (2002) .
	PI3K/Akt/mTOR	mTOR Chr1p	Constitutive high mTOR cell cycle activity	Key role in regulating cell functions such as survival, proliferation, cell death, and metabolic activities Feng et al. (2020) and Spina et al. (2018) .
Family history	KLHDC8B	Chr3p	Loss of heterozygosity for actin-binding midbody protein expressed during cytokinesis	Promotion of the formation of the signature binucleated RS cells Salipante et al. (2009) . Other genes are also found associated with altered cytokinesis in cHL Rengstl et al. (2013) and Webermatthiesen et al. (1995) , (e.g., GNA13 and CDH1).
DNA methylation	Numerous B-cell transcription factors are downregulated, and transcriptional antagonists are upregulated		Several specific DNA methylation changes Wang et al. (2019b) and Ben Dhiab et al. (2015)	Methylated phenotype increases immune evasion
EBV infection	Latency II pattern generating intracellular EBNA1, viral-encoded RNAs EBER1/2, BART miRNAs, and the latent membrane proteins LMP1/2 (6) De Re et al. (2020)		Prevalence of EBV infection in less-developed nations, in immunodeficient and pediatric cases, and mixed cellularity and lymphocyte-depleted subtypes Dolcetti et al. (1995) , Boiocchi et al. (1993) , and Frisan et al. (1995)	Recovery of B cells from apoptosis

AP-1, activator protein-1; CD, cluster of differentiation; DNAm, DNA methylation; IAP, integrin-associated protein; Jak/STAT, Janus kinase/signal transducers and activators of transcription; mTOR, mechanistic target of rapamycin kinase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PDL1(CD274), programmed cell death 1 ligand; PI3K/Akt, key regulator pathway of survival during cellular stress.

autologous stem cell transplantation. Patients in the high-risk group were candidates for autologous or allogeneic transplantation, or experimental therapies. There is currently no gold standard for choosing the best first-line and rescue therapies. Clinical trials conducted in the 2000s using different

combinations of conventional chemotherapy, alone or followed by RT, in children and adolescents with low-risk, intermediate/high-risk, or relapsed HL are listed in [Tables 2–4](#), respectively.

Consolidation RT improves progression-free survival in HL, but large irradiation fields are associated with an increased risk of



secondary cancers and infertility, as well as heart and lung toxicities. Among these treatment-related complications, fertility issues have been paid particular attention in the setting of pediatric cancer care (given the patients' young age), and fertility preservation is included in the discussion on the choice of treatment. In 2006, the American Society of Clinical Oncology (ASCO) published recommendations for fertility preservation in cancer patients. This document, and the update published in 2013, underscores the importance of discussing the risk of infertility associated with cancer therapies, and the options available for fertility preservation with patients as soon as possible. There are currently no effective ways to preserve fertility in prepubertal males with cancer, but most other patients can produce enough seminal fluid for cryopreservation before starting cancer therapy (Brannigan, 2014). Treatments may also adversely affect female reproductive organ function. In collaboration with the International Late Effects of Childhood Cancer Guideline

Harmonization Group, the PanCareLIFE Consortium recently developed a practice guideline containing recommendations for fertility preservation in females with cancer up to 25 years of age (Mulder et al., 2021).

Fortunately, the use of smaller target volumes, combined with technological advances in treatment techniques, has led to the sparing of organs at risk without altering the efficient control of the tumor mass. Specifically, proton therapy has been proposed for treating mediastinal HL to significantly reduce the dose to organs at risk, such as cardiac substructures, and late toxicity (Loap et al., 2021). How to identify patients who may benefit from proton therapy is still being debated, however, as the slowness and complexity of technical aspects of the pretreatment setup and the cost of the instrument limit its routine use in clinical practice.

New target-specific biological drugs for cHL have been available since 2010, and have been used in combination with chemotherapy. Among them, brentuximab vedotin (Bv,

TABLE 2 Main clinical trials in pediatric patients with low-risk HL.

Study groups	Period	Clinical studies	Pts (n)	Chemotherapy	Radiotherapy	ETS% (y)	OS (y)	
GPOH-HD95	1995–2001	CS IA/IB/IIA	328	2 O(P/E)PA	RC: no RT RP: 20–35Gy IF	PFS 93.2 (10)	98.8 (10)	Dörffel et al. (2013)
AIEOP MH96	1996–2004	CS IA, IIA no FPN*	159	3 ABVD	RC e PR >75%: 20Gy IF RP < 75%: 36Gy IF	92.8 (10)		Burnelli et al. (2018)
POG9426	1996–2000	CS I, IIA, and IIIA	294	DBVE x2-4 based on response after cycle 2	IF 25.5Gy IF	86.2 (8)	97.4 (8)	Tebbi et al. (2012)
GPOH-HD2002	2002–2005	CS IA/IB/IIA	195	F 2 OPPA M 2 OEPA	RC: no RT RP: 19.8Gy IF ± boost	93.2 (5) 91.7 (5)	100 (5) 100 (5)	Mauz-Körholz et al. (2010)
AIEOP MH2004	2004–2016	CS IA, IIA no FPN*	56	3 ABVD	RC no RT RP 25. 2Gy	95.8 (3)		Burnelli et al. (2020)
AHOD0431	2006–2012	CS IA and IIA HL without bulk	287	AVPC x3	CR after cycle 3: none RT; PR 21 RT IF	84 (10)	100 (2)	Keller et al. (2010)
EuroNet-PHL-C1	2007–2013	CS TG1: I A/B and II A without bulk ≥200 ml and without ESR ≥30 mm/h	714	OEPA x2	AR no RT IR RT 20Gy	90.6 (5)		Landman-Parker et al. (2016)

ABV, doxorubicin, bleomycin and vinblastine; ABVD, doxorubicin, bleomycin, vincristine, dacarbazine; ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; AIEOP, Associazione Italiana di Ematologia ed Oncologia Pediatrica; AVPC, doxorubicin, vincristine, prednisone, cyclophosphamide; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; CS, clinical study; AR, adequate response; CR, complete remission; DFS, disease-free survival; DBVE, doxorubicin, bleomycin, vincristine, and etoposide; EFS, event-free survival; FPN, negative prognostic factors; FFP, freedom from progression; GPOH, German Pediatric Oncology Hematology; IF, involved-field radiotherapy. MOPP, mechlorethamine, vincristine, procarbazine, prednisone; IR, inadequate response; OPPA, vincristine, procarbazine, prednisone, doxorubicin; O(P/E)PA, vincristine (procarbazine or etoposide), prednisone, doxorubicin; OS, overall survival; PFS, progression-free survival; POG, Pediatric Oncology Group; RP, partial response; VAMP, vinblastine, doxorubicin (adriamycin), methotrexate, prednisone; VBVP, vinblastine, bleomycin, etoposide, prednisone.

SGN35), an anti-CD30 drug-conjugate antibody, and nivolumab, a monoclonal antibody (mAb) programmed cell death protein 1 (PD-1) inhibitor, were the first to be used in cases of relapsed/refractory cHL (Table 5). Clinical research on the specific clinical indications for their use, their association with traditional chemotherapy, and their potential long-term side effects is ongoing.

Bv conjugated with the antimetabolic agent monomethylastatin E (MMAE), a cell cycle blocker that leads to tumor cell apoptosis, targets the tumor necrosis factor CD30⁺ in RS cells. A Phase I/II trial conducted in Europe and the United States showed a good safety profile and clinical benefits in 36 children with relapsed/refractory cHL (Locatelli et al., 2018). This therapy can also bridge to curative autologous and/or allogeneic stem cell transplantation in patients initially considered transplant-ineligible. Reported adverse events include: neutropenia (11%); fever (6%); increased gamma-glutamyl transferase levels (6%); and peripheral neuropathy (33%). The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved Bv for use in adult patients with cHL if stem cell transplantation fails, or in patients not candidates for transplantation after ≥2 cycles of chemotherapy. Current therapies, including high-dose

chemotherapy and stem cell transplantation, cure approximately 50% of children and young people with relapsed/refractory chronic HL. The Center for International Blood and Marrow Transplant Research (CIBMTR) reported a progression-free survival rate of 56%, and an overall survival of 73% in 671 patients (age ≤30 years).

A combination of Bv and the chemotherapy drug bendamustine showed a promising activity in a Phase II study conducted on adults with relapsed/recurrent HL (O'Connor et al., 2018). When administered before autologous stem cell transplantation, the overall response rate was 93%, with a 74% complete response and a favorable safety profile. Authorization is needed for its use in children, however. More recently, brentuximab was used in combination with various chemotherapeutic agents, with or without RT, in pediatric and young adults with newly-diagnosed, advanced-stage HL (NCT02979522, NCT02166463, and NCT01920932); the results are under evaluation.

In 2016, the EMA approved the use of nivolumab, a PD-1/PD-L1 immune checkpoint inhibitor that regulates T lymphocyte function in the TME, for the treatment of adults with relapsed/refractory cHL after autologous stem cell transplantation and Bv consolidation. CheckMate 744 (NCT02927769) was the first Phase II trial involving nivolumab, Bv, and bendamustine

TABLE 3 Main clinical trials on pediatric patients with intermediate- and high-risk HL.

Study groups	Period	Clinical stage	Pts (n)	Chemotherapy	Radiotherapy	ETS% (y)	DFS% (y)	OS% (y)	Reference
GPOH-HD95	1995–2001	CS IIB, IIIA, I/IIA _E CS, IIIB, IV, IIB _E , IIIA/B _E	256 341	2 OP (E) PA + 2COPP 2 OP (E) PA + 4COPP	RC: no RT RP: 20–35Gy IF RC: no RT RP: 20–35Gy IF		PFS 86.7 (10) PFS 84.5	97.3 (10) 93.2 (10)	Dörffel et al. (2013)
AIEOP MH96	1996–2004	CS IA, IIA con FPN*/IB, IIB, IIIA pts with M/T > 0.33, IIIB, IV	85 310	4 COPP/ABV 6 COPP/ABV	RC e RP >75% 20Gy IF RP <75%: 36Gy IF	80 (10) 75 (10)			Burnelli et al. (2018)
POG 9425	1997–2001	CS IB, IIA/IIIA ₁ , M/T>0.33, IIIA ₂ /IIB/IIIB/IV	216	RER: 3 ABVE-PC SER: 5 ABVE-PC	21Gy IF 21Gy IF	86 (5) 83 (5)		95 (5) 95 (5)	Schwartz et al. (2009)
CCSG-59704	1999–2002	CS IIB/IIB w/bulk; IV	99	RER: BEACOPP +4 COPP/ABV (F) or 2 ABVD (M) SER: 8 BEACOPP	RER F: none RER M: 21–35Gy IF SER: 21–35Gy	94 (5)		97 (5)	Kelly et al. (2011)
GPOH-HD-2002	2002–2005	I _F A/B, II _F A, IIB, IIIA II _F B, III _F A/B, IIIB, IV	139 239	F 2 OPPA+2COPP M 2 OEPA+2COPDAC F 2 OPPA+4COPP M 2 OEPA+4COPDAC	19.8Gy IF	88.3 (5) 86.9 (5)	PFS 93.4 (5) 87.4 (5)	98.5 (5) 94.9 (5)	Mauz-Körholz et al. (2010)
AHOD0031	2002–2009	IB, IA/IIA with bulk, IIB, IIIA, IVA	1734	2ABVE-PC + RER:2ABVE-PC SER: 2ABVE-PC ± 2DECA	RER, CR: None RER, CR: 21 IF SER: 21 IF	83.5 (5)		97.3 (5)	Marks et al. (2018)
AIEOP LH2004	2004–2016	CS (G2) IA, IIA FPN*/IB, IIB, IIIA, (G3) pts with M/T > 0.33, IIIB, IV	48 152	4 COPP/ABV ± 2 IEP 6 COPP/ABV ± IEP	RC 14.4Gy RP 25.2Gy	82.8 (3) 78.7 (3)			Burnelli et al. (2020)
EuroNet-PHL-C1	2007–2013	CS: TG-2 (IAE, IBE, IIAE, II B or III A) and TG-3 (IIBE, IIIAE, IIIBE, III B or IV A and IVB)	1388	OEPA x2 + 2/4 COPP or 2/4 COPDAC	AR at ERA: no RT IR 20Gy + 10Gy boost if slow responder or residual volume >100 ml	TG2 93 (5) TG3 88 (5)			Mauz-Körholz et al. (2022)

ABV, doxorubicin, bleomycin, vinblastine; ABVD, doxorubicin (adriamycin), bleomycin, vincristine, dacarbazine; ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide; AIEOP, Italian Association of Hematology and Pediatric Oncology; AR, adequate response; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CCSG, Children's Cancer Study Group; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; COP, cyclophosphamide, vincristine, procarbazine; COPDAC, cyclophosphamide, vincristine, prednisone, dacarbazine; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; CS, clinical stage; DFS, disease-free survival; EF, extended fields radiotherapy; EFS, event-free survival; ERA, slow response to therapy; FFP, freedom from progression; IEP, isocyanide, etoposide, prednisone; IF, involved fields radiotherapy; GPOH, German Pediatric Oncology Hematology; IR, inadequate response; OEPA, vincristine, etoposide, prednisone, doxorubicin; O(P/E)PA, vincristine (procarbazine or etoposide), prednisone, doxorubicin; OPPA, vincristine, procarbazine, prednisone, doxorubicin; OS, overall survival; PFS, progression-free survival; PS, pathological stage (by exploratory laparotomy); pts, patients; POG, Pediatric Oncology Group; RC, complete remission; RER, rapid response to therapy; RP, partial response; VAMP, vinblastine, doxorubicin (adriamycin), methotrexate, prednisone; y, years. *FPN = negative prognostic factors.

TABLE 4 Response rate after standard chemotherapy in patients with relapsed HL.

Regime	Drugs	Patients (n)	ORR (%)	CR rate (%)	References
DHAP	Dexamethasone, high-dose Ara-C-cytarabine, cisplatin	102	88	21	Moskowitz et al. (2001)
IGEV	Ifosfamide, gemcitabine, vinorelbine, prednisolone	91	81	54	Baetz et al. (2003)
IIEP-ABVD	Ifosfamide, etoposide, prednisolone, Adriamycin, bleomycin, vinblastine, dacarbazine	176	85	Not reported	Schellong et al. (2005)
ICE	Ifosfamide, carboplatin, etoposide	65	88	26	Santoro et al. (2007)
BeGEV	Bendamustine, gemcitabine, vinorelbine	59	83	73	Bartlett et al. (2007)
IVE	Ifosfamide, etoposide, epirubicin	51	84	60	Santoro et al. (2016)
GDP	Gemcitabine, dexamethasone, cisplatin	23	70	17	Younes et al. (2016)
GVD	Gemcitabine, vinorelbine, liposomal doxorubicin	91	70	19	Borchmann et al. (2017)

with response-adapted therapy for children, adolescents, and young adults at low or standard risk of relapse. Preliminary results for the standard-risk cohort were presented by the American Society of Clinical Oncology (ASCO) in 2020 (Cole et al., 2020). Of the 44 patients enrolled in the study, 31 were children, and 17 of them had refractory disease while 14 had recurrent cHL. The treatment was well tolerated and resulted in a complete metabolic response rate of 88%, making it an effective rescue therapy for relapsed/refractory cHL before stem cell transplantation.

Combination treatments with Bv plus PD/PD-L1 inhibitors have reportedly been tried in an effort to avoid RT, but they can induce immune-related adverse events. Bv is associated with peripheral neuropathy or severe pulmonary toxicity when combined with bleomycin, and PD/PD-L1 inhibitors may cause autoimmune toxicities. Further investigations in randomized trials are needed to assess the benefits and best uses of these agents as frontline treatments. The results of the ongoing Phase III trial (NCT03907488) comparing Nivo-AVD with Bv-AVD are awaited with particular interest (Castellino et al., 2020), though their use in pediatric patients has yet to be formally authorized.

The safety and efficacy of pembrolizumab, another PD-1 inhibitor, are under evaluation in the MK-3475/KEYNOTE-667 trial involving children and young adults with newly-diagnosed cHL and an inadequate response to chemotherapy. The results will be compared with the findings of the standard EuroNet-PHL-C2 study. The widespread use of immunotherapy has made it difficult to assess patients using this new therapeutic modality accurately, however. As PET often fails to differentiate pseudoprogression from true tumor progression in patients treated with immune complex inhibitors (ICIs) (Cheson et al., 2016; Aide et al., 2019), new criteria are needed to help clinicians assess response to ICIs, such as the iRECIST guidelines (Persigehl et al., 2020). A small number of patients also continue to show resistance to these new treatments, and the results are unsatisfactory, so it remains important to explore new strategies and targets for treating cHL.

Novel target drugs and treatment options in young patients with relapsed classic Hodgkin lymphoma

Table 5 gives a list of promising new targeted drugs. Alternative ICIs targeting PD-1/PD-L1 and other immune complexes that sustain an immunosuppressive TME have been discovered.

Sintilimab, camrelizumab, and tislelizumab all target PD-1. Ipilimumab targets the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) ligands CD80 (B7-1) and CD86 (B7-2), regulating the crosstalk between T cells and antigen-presenting cells (APC). Notably, CTLA-4+ cells, CD4+ Th1 polarized T cells, and T-reg (the main T-cell subsets in HL) are in close proximity to the CD68+ macrophages around HRS cells, and they are PD-1 negative (Patel et al., 2019). A Phase II trial is ongoing to verify the efficacy of dual PD-1 and CTLA-4 blockade with Bv (NCT01896999).

Relatlimab targets lymphocyte activation gene-3 (LAG-3; CD223 antigen). LAG-3 inhibits the function and expansion of both CD4 and CD8 T cells, serving as a marker of exhausted T cells during chronic antigen stimulation. LAG-3 is strongly expressed in T cells around the HRS cells, particularly in those lacking MHC-II expression (Gandhi et al., 2006), and in relapsed HL compared with cases in remission. The mechanism of T-cell inhibition is still poorly understood (Workman et al., 2002). The specific functional ligands of LAG-3 are still uncertain too, but it is now recognized that LAG-3, with its structural homology to the CD4 antigen (Triebel et al., 1990), preferentially recognizes specific MHC-II peptide complexes and consequently suppresses the function of specific CD4+ T cells (Maruhashi et al., 2022). Several other ligands for LAG-3 have been found, such as lymph node sinusoidal endothelial cell C-type lectin (LSEctin), galectin-3, and fibrinogen-like protein 1 (FGL1/FREP1), and their role in LAG3+ immune cell interactions is still under investigation (Chocarro et al., 2021; Wang et al., 2019).

SRF231 and TTI-621 block the interaction between CD47 (a “do not eat me” signal) and its ligand, the regulatory protein α (SIRP α), primarily expressed on phagocytic cells. Cases of cHL with a strong CD47 expression in HRS cells are associated

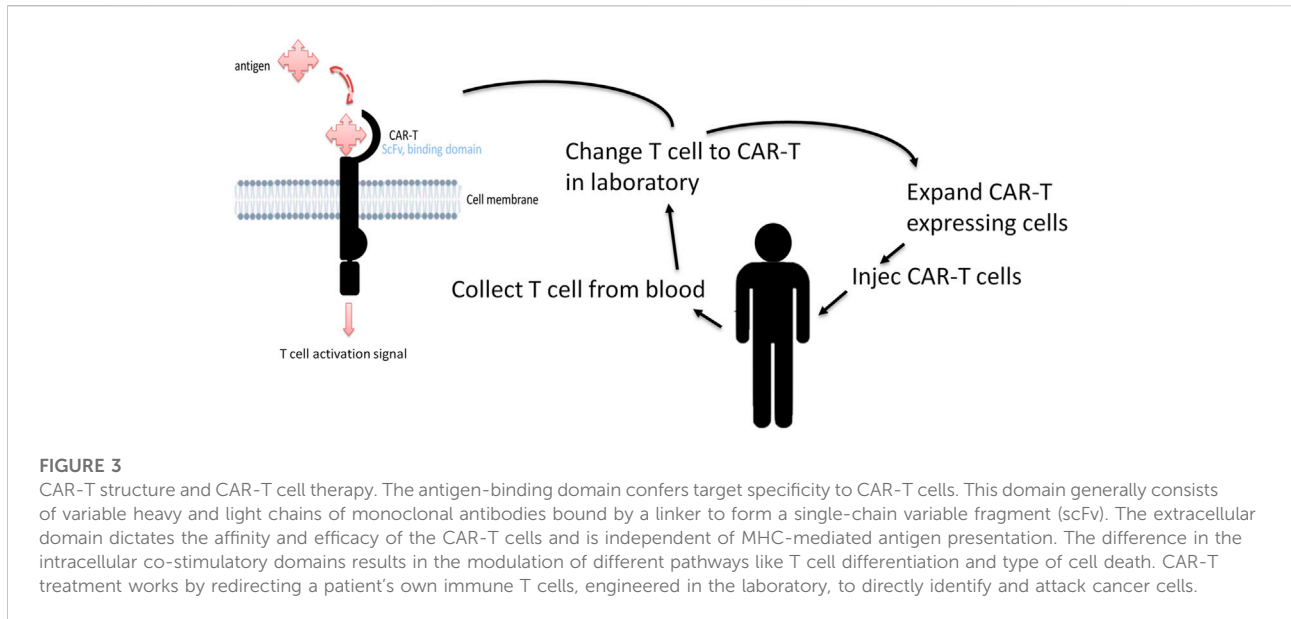
TABLE 5 New drugs and targeted treatments for children and young adults with cHL.

Drug	Class	Function	
Brentuximab vedotin (Bv, SGN35)	anti-CD30 drug-conjugate antibody	Antibody conjugated with the anti-mitotic agent monomethylastatin E (MMAE); it blocks the cell cycle and triggers apoptosis of HRS. Based on the promising results of a clinical trial Connors et al. (2018) , the FDA approved Bv combined with chemotherapy for stage III-IV disease.	Cole et al. (2018) , Traila et al. (2018) , Castellino et al. (2019) , and Wolska-Washer and Robak (2019)
Nivolumab Pembrolizumab	anti-programmed cell death protein 1 (PD-1) inhibitor	Inhibitor of PD-1/PD-L1 immune checkpoint	Cole et al. (2020) , Davis et al. (2020) , Kuruvilla et al. (2021) , Sheikh et al. (2022) , and Goerger et al. (2020)
Promising new candidates			
Sintilimab, camrelizumab, tislelisumab	PD-1 inhibitor	Inhibitor of PD-1/PD-L1 immune checkpoint	Kaplon and Reichert (2019) and Song et al. (2021)
Ipilimumab	CTLA-4	Inhibitor of CTLA-4/CD80 and CD86 immune checkpoint	Diefenbach et al. (2020)
Anti-LAG-3	LAG-3 inhibitor	It reduces T-cell activation and mediates the immunosuppressive functions of regulatory cells	Nagasaki et al. (2020) and Tobin et al. (2021)
SRF231 TTI-621	anti-CD47 antibody	Inhibition of signal regulatory protein α (SIRP α)/CD47 interaction needed for macrophages and dendritic phagocytic activity	Peluso et al. (2020) and Ansell et al. (2021)
Anti-TIM-3	TIM-3 inhibitor	It inhibits cytotoxic T cells and Th1 responses, modulates T regulatory cell function, decreases monocyte/macrophage activation, and promotes expansion of myeloid-derived suppressor cells	El Halabi et al. (2021)
Car-T	T- cell based therapy	Chimeric antigen receptor modified T (Car-T) cell based therapy gives T lymphocytes the ability to combine both antigen recognition and T cell activation functions into a single receptor.	Bollard et al. (2014) , Ramos et al. (2017) , Ruella et al. (2017) , Wang et al. (2017) , Ramos et al. (2020) , Gholiha et al. (2022) , Meier et al. (2022) , and Ho et al. (2021) .
Trabectedin	CD30/CD37	A bispecific antibody targeting CD30 and CD37, both members of the tumor necrosis factor receptor family overexpressed on HRS cells: it increases HRS cell killing.	Casagrande et al. (2022)
90Y-daclizumab camidanlumab	anti-CD25 antibody	Human anti-CD25 antibody-radiolabeled or conjugated through a cathepsin-cleavable valine-alanine linker to a pyrrolbenzodiazepine (PBD) dimer toxin, SG3199.	Hamadani et al. (2021) and Janik et al. (2015)
Ruxolitinib Fedratinib Itacitinib	JAK inhibitors	Inhibitors of Janus kinases (JAK), selective for JAK1 and JAK2. A Phase I/II study (NCT03697408) of itacitinib in combination with everolimus in relapsed or refractory HL is ongoing.	Van den Neste et al. (2018)
Everolimus Idelalisib	mTOR inhibitor	Everolimus developed as an analog of rapamycin, an inhibitor of the serine protein kinase mTOR. Idelalisib, a PI3K inhibitor, reduces activation of the PI3K/Akt/mTOR pathway.	Johnston et al. (2018) and Gopal et al. (2017)
Selinexor	XPO1 inhibitor	Selective inhibitor of nuclear exportin 1 (XPO1) protein simultaneously inhibiting several active tumorigenic processes and also synergizing with other targeted drugs and chemotherapy Fisher et al. (2021) . Hot spot mutations in HL Balasubramanian et al. (2022) .	Galinski et al. (2021)
Vorinostat	HDAC inhibitors	Histone deacetylase (HDAC) inhibitors. Histones regulate gene expression and chromosome packaging during cell division.	Janku et al. (2021)
Decitabine	DNMT inhibitors	DNA methyltransferase (DNMT) inhibitors. In particular, EBV infection is associated with an altered expression of specific DNMTs Pei and Robertson (2020) . A decreased expression of 5hmc in HRS is a common epigenetic marker Siref et al. (2020) .	Falchi et al. (2016) , Nie et al. (2019) , and Wang et al. (2021)

with a shorter event-free survival ([Ding et al., 2021](#); [Gholiha et al., 2022](#)).

More studies are needed on other immune checkpoint receptors that can downregulate immune cell function, such

as T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), T-cell immunoglobulin and ITIM domain (TIGIT), and V-domain Ig suppressor of T-cell activation (VISTA).



In recent years, there has been increased interest in immunotherapies that use chimeric antigen receptor (CAR) T cells (Bollard et al., 2014; Ramos et al., 2017; Ruella et al., 2017; Wang et al., 2017; Ramos et al., 2020; Ho et al., 2021; Ghohliha et al., 2022; Meier et al., 2022). Unlike conventional immunotherapies, CAR-T cells use engineered receptors that modulate the structure and function of human T-cell receptors (TCRs). CAR-T cells consist of an extracellular antigen-binding domain allowing antigen specificity, a transmembrane domain, and one or more intracellular signaling domains (Figure 3). CAR-T cells packaged in a viral vector are then transported onto T cells to transduce CAR-T cells on the cell membrane surface. The T cells can thus recognize and kill the cells that express the target antigen. The power advantage of CAR-T cells over conventional immunotherapies lies in that they do not depend on antigenic peptide/MHC complex presentation for their activation, and in their long-term persistence and efficacy in the organism. Epitope location and antigen density on the surface of cancer cells may influence CAR-T cell efficiency. In addition, research into functional intracellular signaling domains has gained importance in the scientific community because intracellular co-stimulatory domains modulate several important cellular pathways, such as cell differentiation and cell death, which may increase CAR-T efficacy. Early studies demonstrating the advantage of CAR-T cell therapy in relapsed HL involved CAR-T cells directed against HRS cells expressing the EBV LMP-1 antigen (Bollard et al., 2014). Then CAR-T cells were used for all types of refractory/relapsed HL, regardless of their EBV status, by targeting HRS-specific surface markers such as CD30 molecules (Wang et al., 2017; Ramos et al., 2020). Several preclinical and clinical studies are now ongoing to upgrade the potential efficacy of CAR-T cell treatments using several approaches. The focus is mainly on targeting several antigens associated with HRS or immunosuppressive cell interactions in the

TME, or on prolonging and increasing the immune response by increasing the living CAR-T cell levels and/or modulating the T-cell death pathway as recently reviewed in (Meier et al., 2022).

Other targetable drug strategies, in mono- or combined therapies, include targeting HRS cell markers using antibody-toxin conjugates such as camidanlumab, or specific molecular pathways that are altered in HL, such as JAK (i.e., ruxolitinib, fedratinib, itacinib), or using mTOR inhibitors (i.e., everolimus) (Table 5). Alternatively, CD30⁺ CD15⁻ peripheral B cells may be the progenitors of the CD30⁺ HRS cells (Jones et al., 2009), and thus B cells might be potential targets of therapy.

Another approach to treating HL involves potentiating the effects of conventional chemotherapies with the aid of nuclear export (XPO1) inhibitors (i.e., Selinexor), epigenetic histone deacetylases (HDACs), and DNA methyltransferases (DNMTs), for instance (Table 5). One promising strategy is based on the use of hypomethylating agents in combination with ICIs. The rationale behind this approach stems from the discovery that MHC gene silencing can be reversed using hypomethylating drugs, resulting in a greater efficacy of cytotoxic T cells according to several studies (Falchi et al., 2016; Nie et al., 2019; Wang et al., 2021). Since EBV latency is partly controlled by DNA methylation, however, the use of hypomethylating agents has only been proposed for the EBV-negative cHL subtype. The combination of HDAC and ICIs has also shown efficacy and adequate tolerability.

Conclusion

Current research has led to the development of various strategies aimed at striking the best balance between

supporting survival and reducing the long-term risk of toxicities related to therapies, including RT. The therapeutic strategies adopted for pediatric and young adults are consequently now quite different from those applied to adults and elderly patients with HL. It will be important to: 1) develop further studies on risk classification based not only on the classical parameters, but also using metabolic PET imaging; 2) identify patients eligible for proton therapy; and 3) discover new targeted drugs to include in more efficient combination treatment strategies. Studies on HRS cell biology and its close interaction with a multitude of cell subtypes in the TME could be useful for clarifying the molecular mechanisms that sustain the disease, and thereby reveal the best targets of treatment with a view to further reducing the risk of recurrence and long-term toxicity.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

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Glossary

HL Hodgkin lymphoma

cHL classic Hodgkin lymphoma

RT radiotherapy

PET positron emission tomography

HRS Hodgkin and Reed-Sternberg

LAG-3 lymphocyte activation gene 3

NLPHL nodular lymphocyte-predominant HL

NSHL nodular sclerosis Hodgkin lymphoma

MCHL mixed cell Hodgkin lymphoma

LRHL lymphocyte-rich Hodgkin lymphoma

LDHL lymphocyte-depleted Hodgkin lymphoma

EBV Epstein-Barr virus

EBER EBV-encoded RNA

LMP latent membrane protein

BCR B-cell receptor

PAX5 nuclear-paired box protein 5

Ig immunoglobulin

CD cluster of differentiation

TNF tumor necrosis factor

MHC major histocompatibility complex

miRNA microRNA

AP-1 activator protein-1

Jak/STAT Janus kinase/signal transducers, and activators of transcription

mTOR mechanistic target of rapamycin kinase

NF- κ B nuclear factor kappa-light-chain-enhancer of activated B cells

PDL programmed cell death ligand

TCR T-cell receptor

mAb monoclonal antibody

MMAE anti-mitotic agent monomethylastatin E

Bv Brentuximab vedotin

ICI immune complex inhibitor

EMA European Medicines Agency

SIRP α signal regulatory protein α

TIM-3 T-cell immunoglobulin and mucin domain-containing protein 3

TIGIT T-cell immunoglobulin and ITIM domain

VISTA V-domain Ig suppressor of T-cell activation

HDAC histone deacetylase

DNMT DNA methyltransferase