Blood and Lymphatic Cancer: Targets and Therapy

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REVIEW

Advances in the pathophysiology and treatment of relapsed/refractory Hodgkin's lymphoma with an emphasis on targeted therapies and transplantation strategies

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Abstract: Hodgkin's lymphoma (HL) is highly curable with first-line therapy. However, a minority of patients present with refractory disease or experience relapse after completion of frontline treatment. These patients are treated with salvage chemotherapy followed by autologous stem cell transplantation (ASCT), which remains the standard of care with curative potential for refractory or relapsed HL. Nevertheless, a significant percentage of such patients will progress after ASCT, and allogeneic hematopoietic stem cell transplantation remains the only curative approach in that setting. Recent advances in the pathophysiology of refractory or relapsed HL have provided the rationale for the development of novel targeted therapies with potent anti-HL activity and favorable toxicity profile, in contrast to cytotoxic chemotherapy. Brentuximab vedotin and programmed cell death-1-based immunotherapy have proven efficacy in the management of refractory or relapsed HL, whereas several other agents have shown promise in early clinical trials. Several of these agents are being incorporated with transplantation strategies in order to improve the outcomes of refractory or relapsed HL. In this review we summarize the current knowledge regarding the mechanisms responsible for the development of refractory/relapsed HL and the outcomes with current treatment strategies, with an emphasis on targeted therapies and hematopoietic stem cell transplantation.

Keywords: relapsed/refractory Hodgkin's lymphoma, pathophysiology, novel agents, immunotherapy, hematopoietic stem cell transplantation

Introduction

Hodgkin's lymphoma (HL) is the most common malignancy in adolescents and young adults.[1] HL is divided into classical HL (cHL) accounting for 95% of cases and nodular lymphocyte-predominant HL, which is less common. The cHL subtype is defined by the presence of neoplastic cells of B-cell origin expressing CD30 and CD45, including mononucleated Hodgkin cells and multinucleated Reed–Sternberg (RS) cells, which are in direct interaction with an inflammatory microenvironment consisting of granulocytes, mast cells, T and B lymphocytes, plasma cells and fibroblasts.[2] The cross talk between cancer cells and microenvironment is critical for the pathogenesis and progression of HL.[3,4]

First-line chemotherapy and/or radiation for cHL in patients with advanced disease is associated with cure rates between 70% and 75%.[5,6] However, 25%–30% of patients either have primary refractory disease or will relapse following first-line therapy.[7] Salvage chemotherapy followed by autologous stem cell transplantation (ASCT) is

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the standard of care for these patient groups. However, only a subset of patients with primary refractory or relapsed HL achieves long-term progression-free survival (PFS) with this approach, and the prognosis is influenced by the presence or absence of certain risk factors.[8,9] Patients who progress or relapse after ASCT have poor prognosis with a median survival of 12–29 months.[10,11] Thus, development of novel therapeutic approaches is critical for the treatment of relapsed or refractory HL. The antibody–drug immunoconjugate targeting CD30, named brentuximab vedotin, and immunotherapies targeting programmed cell death-1 (PD-1) receptor represent the most promising new therapies,[12,13] while several promising agents are in development or in early clinical trials. However, to date, allogeneic hematopoietic stem cell transplantation (alloHCT) remains the only potentially curative approach for relapsed or recurred disease.[14]

The purpose of this review is to summarize recent data regarding the molecular mechanisms implicated in the development of refractory or relapsed HL and novel therapeutic approaches for the management of patients failing frontline therapy.

Mechanisms involved in the development of refractory and relapsed HL

The role of microenvironment

In contrast to most other neoplastic diseases, the non-neoplastic cells of the tumor microenvironment outnumber the neoplastic cells in HL, and the distribution of these cells may contribute to the emergence of resistance to conventional therapy.[15,16]

Macrophages

Infiltration of the cHL microenvironment by $CD68^+$ macrophages is considered a negative predictor of PFS for cHL after induction with doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) treatment with or without radiotherapy, independent of the International Prognostic Score.[17] High numbers of $CD68^+$ and $CD163^+$ macrophages in cHL are associated with worse overall survival (OS), but they also correlate with the presence of Epstein–Barr virus (EBV) in the neoplastic cells[18] which, in turn, has been associated with worse outcomes mainly in older individuals.[19,20] The exact mechanism underlying the negative impact of macrophages on the above-described outcomes has not been fully elucidated, but it is believed that these cells have an immunosuppressive role and, therefore, may hamper the antitumor immune responses (Figure 1). In support of this hypothesis, macrophages in the tumor microenvironment can inhibit the response of T cells by releasing various immunosuppressive cytokines, such as IL-10 and TGF-β.[21] Moreover, TNF-α and IL-10 secretion from monocytes induces the expression of PD-L1 by the same cells in an autocrine manner, leading to decreased T-cell activity and proliferation.[22] Tumor-associated macrophages are also known to secrete CCL22, which promotes the trafficking of regulatory T (Treg) cells in the tumor microenvironments through the activation of CCL22/CCR4 axis.[23] In turn, Treg cells inhibit antitumor T-cell responses, further supporting the immunosuppressive role of macrophages in the microenvironment of cHL.

T cells

The presence of Treg and $CD4^+$ T cells, especially with Th2 phenotype, in the tumor microenvironment has been associated with worse prognosis likely through immune escape.[24] Higher density of Treg cells and decreased density of cytotoxic T cells correlate with poorer PFS and OS in patients with cHL.[25] Moreover, higher CD4/CD8 ratio in the tumor microenvironment is an independent factor for ABVD treatment failure in patients with HL.[26]

Interactions between HL and cells of the microenvironment

The interactions between the neoplastic cells and the cells of the microenvironment play a critical role in the development of refractory or relapsed HL. RS cells produce various Th2 and Treg cell chemoattractive cytokines such as IL-4, IL-5 and IL-10[27,28]; CCL22 and CCL5[29] and also cytokines with macrophage chemotactic activity, such as IL-5 and IL-8.[30] The recruitment of these cells is reinforced by the reactive cells themselves and particularly macrophages secreting CCL-3, CCL-4 and CCL-8.[31,32] Similarly, the neoplastic cells secrete TNF-α and TGF-β promoting the activation of fibroblasts.[33,34] In turn, collagen IV produced by fibroblasts in the tumor microenvironment is recognized by the DDR1 receptor in RS cells,[35] which is a tyrosine kinase promoting the survival and proliferation of these cells.[36] These mechanisms generate a vicious cycle between the neoplastic cells and particular components of the microenvironment, promoting resistance to treatment and disease progression. The inflammatory cells of the tumor microenvironment express surface antigens that act as survival signals for the neoplastic cells. These include CD40L expressed on T cells and CD30L expressed on masts cells, and bind the CD40 and CD30 receptors, respectively, which are expressed on RS and Hodgkin cells (Figure 1).[30,37] CD40L:CD40 signaling leads to increased survival

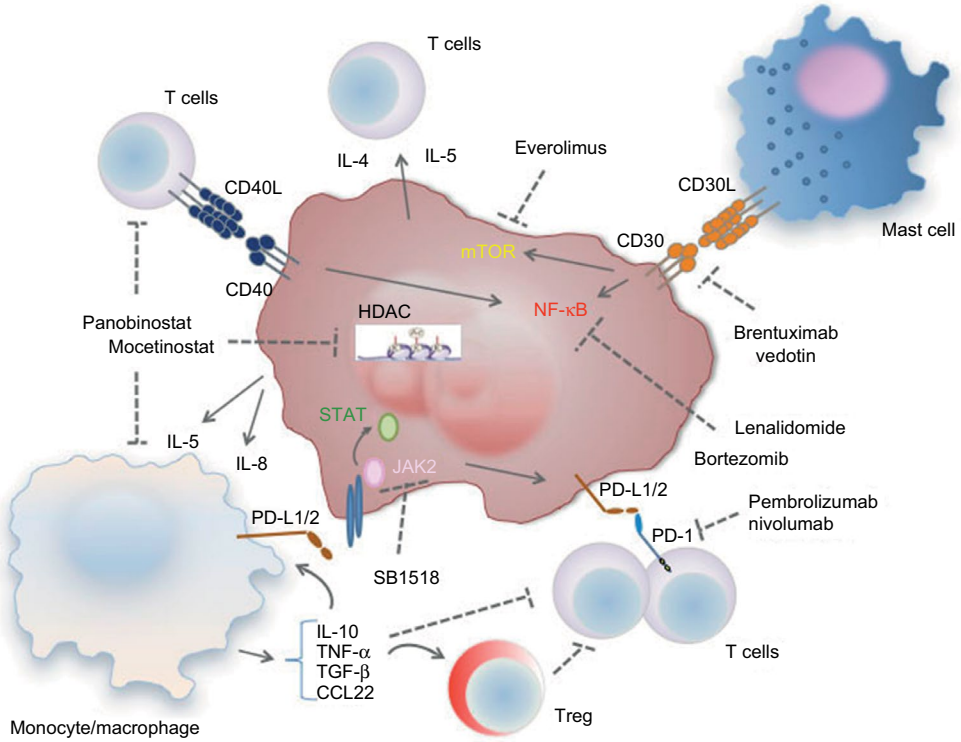

Figure 1 Dysregulation of the TME involved in the development of refractory/relapsed HL and targets of novel compounds targeting the TME or the malignant cells.
Notes: In HL, macrophages release TNF-α and IL-10 that induce the expression of PD-L1/2 by monocytes and malignant cells in an autocrine manner leading to decreased T-cell activity and antitumor function. PD-L1/2 are also increased in neoplastic cells through gene amplification with simultaneous increase of JAK2 and activation of JAK–STAT signaling. Tumor-associated macrophages also produce T-cell immunosuppressive cytokines IL-10 and TGF-β, as well as CCL22, which promote the recruitment of Treg cells in the tumor microenvironment through the activation of CCL22/CCR4 axis, thereby further inhibiting anti-tumor T-cell responses. Novel therapies target signaling pathways that promote the expression of inhibitory receptors, recruit Treg cells and suppress T-cell immune function. CD30 expressed on malignant cells is a novel therapeutic target.
Abbreviations: HL, Hodgkin's lymphoma; Treg, regulatory T; PD-L1/2, programmed cell death-L1/2; mTOR, mammalian target of rapamycin; TME, tumor microenvironment; HDAC, histone deacetylases.

of Hodgkin cells and disease progression.[38] CD40 ligation inhibits Fas-mediated apoptosis of Hodgkin cells potentially promoting the development of resistant disease.[39] CD40 also promotes the upregulation of IRF4/MUM1 expression through the activation of NF-κB.[40,41] Addition of sCD40L in cultures of Hodgkin cells protects them from the apoptotic effect of bortezomib by downregulating IRF4,[42] which acts as a survival factor. CD40-mediated activation can promote the survival and growth of Hodgkin and RS cells via ERK phosphorylation and might be involved in the contact and interaction of the malignant cells with activated cytokine-producing $CD4^+$ T cells in the tumor microenvironment creating a positive feedback loop that leads to Hodgkin and RS cell expansion.[43,44] Similarly, CD30L expressed on mast cells of the tumor microenvironment interacts with CD30 on the surface of RS cells and leads to activation of NF-κB signaling, resulting in increased cell survival, proliferation[45] and secretion of cytokines including IL-6 and TNF-α.[46]

These signaling events and secreted factors have a significant effect in the cellular composition of the tumor microenvironment and the development of refractory and relapsed HL.

Aberrant activation of signaling pathways in HL cells

Several oncogenic pathways have been implicated in the development of disease resistance and progression. As mentioned earlier, aberrant activation of NF-κB is a hallmark of HL cell lines[47] as well as primary RS and Hodgkin cells.[48] Activation of IKK via upregulation of TRAF is one of the main mechanisms implicated in the activation of NF-κB in HL.[49] Oligomerization of CD30 molecules recruits TRAFs leading to IKK activation and subsequent NF-κB upregulation.[50] Gain-of-function mutations in positive regulators of NF-κB such as BCL3 and inactivating mutations of its negative regulators such as *TNFAIP* and *NFKBIA* have been identified with high frequency in HL.[24] Activation of NF-κB in HL promotes cell cycle progression by upregulation of cyclins D1 and D2,[51] c-*myc*[52] and c-*myb*,[53] and inhibits apoptosis by induction of antiapoptotic molecules such as BCL-X_L[54] and c-FLIP.[55] NF-κB also promotes secretion of various cytokines such as CCL5, CCL7 and IL-6 by Hodgkin cells, which not only act as autocrine promoters of cancer cell proliferation but also alter the tumor microenvironment by regulating the trafficking of macrophages.[24]

PI3K pathway signaling alterations have been identified in HL, and the efficacy of PI3K, Akt and mTOR inhibitors in HL is currently under evaluation. INPP5, a PI3K inhibitor, is silenced in HL cells,[56] PI3K activation has been implicated in the development of resistance to brentuximab vedotin, while inhibition of PI3K by TGR-1202 increases the efficacy of the drug by promoting mitotic arrest.[57] STAT proteins are activated in RS and Hodgkin cells.[58] and are essential for their survival and proliferation.[59,60] Moreover, JAK2 rearrangements leading to constitutive JAK2 activation and STAT signaling are recurrent in cHL,[61] while inhibitors of this pathway, such as lestaurtinib, induce apoptosis in HL cell lines.[62] Nonsense, missense and frameshift mutations of PTPN1, a negative regulator of JAK–STAT signaling, are observed in a high percentage of HL cell lines and HL cases,[63] while HSP90 is critical for the activation of JAK–STAT signaling in HL cells.[64] Importantly, selective amplification of the 9p24.1 chromosome region is associated with simultaneous amplification of PD-L1 and JAK2. As a consequence, the enhanced JAK–STAT signaling further promotes the expression of PD-L1 and PD-L2 in Hodgkin cells,[65] thereby inhibiting T-cell activation and antitumor immunity. Coexpression of PD-L1 and PD-1 in the HL microenvironment serves as an independent poor prognostic factor,[66] while a subgroup analysis demonstrated that the prognostic value of PD-1 is significant for patients with limited-stage cHL.[67]

EBV infection

Monoclonal EBV infection occurs in 40% of cHL and up to 90% of HIV-related HLs suggesting that EBV may be implicated in oncogenic signaling. Indeed, EBV-infected HL cells overexpress LMP1, which leads to constitutive activation of TNF-α receptor, NF-κB signaling and protection from apoptosis.[68] The absence of mutations of IκBα, a suppressor of NF-κB activation, in EBV-positive HL cells suggests that EBV activates an alternate (non-IκBα-dependent) mechanism of NF-κB activation.[69] EBV-infected HL cells overexpress LMP2 which induces the upregulation of E2F, EBF and Pax-5, promoting cell survival and proliferation.[70] Despite the confirmed overexpression of oncogenes encoded in the EBV genome in Hodgkin and RS cells, studies regarding the impact of EBV infection on prognosis and response to treatment are inconclusive.

Novel therapeutic approaches for primary refractory and early relapsed HL

Advancements in the understanding of HL pathophysiology have led to the development of novel therapeutic approaches for the management of relapsed or refractory disease. Compounds that have been evaluated in clinical trials for this purpose include agents targeting the oncogenic signaling in the neoplastic cells or the tumor microenvironment (Table 1).

Targeting the malignant cells

Multiple oncogenic pathways are upregulated in HL cells, including CD30 downstream signaling pathways, JAK–STAT and PI3K–Akt–mTOR. Compounds individually targeting these signaling pathways as single agents or as part of

Table 1 Novel agents for relapsed/refractory HL

Agent	Target	Line of therapy	Results	Reference
Brentuximab vedotin	CD30	Refractory/relapsed HL	OR 50% with a median duration of 10 months	12
		Relapsed/refractory HL after ASCT	ORR 75%, CR 35%	72
		Relapsed/refractory HL after ASCT or unable to do ASCT	Brentuximab vedotin before AlloSCT improved PFS	73
		Relapsed/refractory HL after ASCT	OR 50%, CR 38%, median PFS 7.8 months	77
Nivolumab	PD-1	Relapsed/refractory HL	OR 87%, CR 17%, PR 70%	13
		Relapsed/refractory HL after ASCT	OR 66.3%	90
Pembrolizumab	PD-1	Relapsed/refractory HL after ASCT	PR 48%, OR 65%	91
Mocetinostat	HDAC	Relapsed/refractory HL	Disease control rate 35%	95
Panobinostat	HDAC	Relapsed/refractory HL after ASCT	OR 27%, PR 23%, CR 4%	96
Bortezomib	NF-κB	Relapsed/refractory HL	No response	84
Lenalidomide	NF-κB	Relapsed/refractory HL (87% with prior ASCT)	PR 16%, stable disease 14%	88
		Relapsed/refractory HL after ASCT in combination with cyclophosphamide	ORR 38%, clinical benefit 62%	89
SB1518	JAK2	Relapsed/refractory HL	CR 12%, PR 44%	78
Everolimus	mTOR	Relapsed/refractory HL (84% with prior ASCT)	ORR 47%, PR 42%, CR 5%	79

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; HL, Hodgkin's lymphoma; OR, overall response; ORR, overall response rate; PFS, progression-free survival; PR, partial response.

combinational approaches have generated promising results, especially in patients with refractory or relapsed disease.

Brentuximab vedotin, an antibody–drug immunoconjugate targeting CD30, has demonstrated high efficacy in cHL.[71] In a Phase I trial including 45 patients with refractory or relapsed HL, the objective response at the maximum tolerated dose was 50% with a median duration of 10 months, whereas 86% of evaluable patients had some disease regression.[12] In a subsequent Phase II clinical trial in patients with relapsed and refractory HL after ASCT, the objective response rate was 75%. Approximately one-third of patients achieved complete response (CR) with a median duration of 20.5 months.[72] Moreover, brentuximab vedotin has been used, as a single agent or in combination, as salvage chemotherapy prior to ASCT with low toxicity and promising efficacy.[73–75] Similarly, the administration of brentuximab vedotin before alloHCT has been associated with improved 2-year PFS and OS and decreased relapsed rate.[76] This is particularly critical for the improvement of outcomes in patients who progress after ASCT and proceed to alloHCT. Administration of brentuximab vedotin after failure of alloHCT was associated with an overall response (OR) rate of 50% and a CR rate of 38% without any differences in the rates of graft versus host disease (GVHD) and cytomegalovirus (CMV) reactivation.[77] Together, these data strongly suggest that brentuximab vedotin is a promising therapeutic modality for patients with relapsed and refractory HL before or after failure of ASCT. Moreover, administration of brentuximab vedotin before alloHCT may improve transplant outcomes.

The efficacy of a novel JAK2 inhibitor, SB1518, was evaluated in 34 patients with relapsed or refractory HL or non-HL demonstrating CR in 4 patients and partial response (PR) in 15 patients.[78] The mTOR inhibitor everolimus as single agent is associated with an OR rate of 47% and PR in 42% of patients.[79] These clinical outcomes strongly support the conclusion that therapeutic targeting of oncogenic pathways in HL cells represents a promising treatment approach in patients with relapsed or refractory disease. Moreover, the combination of such targeted therapies with chemotherapy during early stages of disease warrants further investigation.

It should be noted that not all molecular/immunological aberrations of HL neoplastic cells are amenable to targeted therapies. Although some RS cells – as well as infiltrating lymphocytes – express CD20, the use of the anti-CD20 monoclonal antibody rituximab in combination with chemotherapy has not provided clinical benefit for the treatment of cHL.[80,81] Similarly, CD80, which is expressed on RS cells and immune cells in the tumor microenvironment, has also been used as a therapeutic target, but the anti-CD80 monoclonal antibody galiximab did not provide a significant benefit.[82]

Targeting cellular components of the tumor microenvironment

Given the critical role of the cross talk between the neoplastic cells and the cellular components of the tumor microenvironment, compounds targeting these interactions have shown significant efficacy in HL (Figure 1).

The efficacy of bortezomib and lenalidomide has been evaluated in patients with advanced HL with a goal to target NF-κB, which is activated by the interactions of cancer cells with components of the tumor microenvironment, as previously discussed. Bortezomib as single agent, or in combination with dexamethasone or gemcitabine, has not shown any significant activity in patients with relapsed or refractory disease,[83–85] whereas addition of bortezomib to ifosfamide-based combination regimens led to more encouraging results.[86,87] In a Phase II clinical trial, lenalidomide as single agent led to an OR of 19% and a cytostatic OR rate of 33% in heavily pretreated patients with cHL.[88] In another study including 46 patients with refractory or relapsed HL after ASCT, lenalidomide in combination with metronomic low-dose cyclophosphamide was associated with an OR rate of 38%, whereas 62% of the patients achieved clinical benefit.[89] These conclusions support a beneficial role of lenalidomide potentially in combination with chemotherapy in patients with refractory or relapsed HL. It should be noted, however, that the mechanisms accounting for the antilymphoma effect of lenalidomide in HL have not been fully elucidated and may extend beyond the interference with the NF-κB pathway.

Various clinical studies provide compelling evidence that targeting the PD-1/PD-L1 pathway is a promising approach for patients with relapsed or refractory HL. Specifically, a recent Phase I clinical trial demonstrated that the PD-1 blocking antibody, nivolumab, has a good toxicity profile. Adverse events of any grade and those of grade 3 occured in 78% and 22% of patients, respectively.[13] In this study, objective responses were observed in 20 of 23 patients (87%), although CR was not common (17%).[13] Subsequently, a single-arm Phase II clinical trial evaluating the efficacy of nivolumab in patients with HL after failure of ASCT and brentuximab vedotin reported OR in 66.3% of patients.[90] Pembrolizumab, a different PD-1 blocking antibody, was recently shown to induce PR in 48% of patients with HL relapsing after ASCT with objective responses in the order of 65%.[91] Pembrolizumab was also associated with objective responses in 80% of patients with relapsed/refractory HL who failed previous

treatment with brentuximab vedotin. Thus, targeting PD-1/PD-L1 interaction in the tumor microenvironment is a promising therapeutic approach for patients with relapsed and refractory HL.

HDACs are commonly overexpressed or overactivated in neoplastic diseases, and targeting of HDACs has been employed as a novel therapeutic approach in various malignancies including lymphomas.[92] In HL, activation of HDACs has been associated with downregulation of B-cell-specific antigens and p21, upregulation of STAT signaling and suppression of caspase pathways.[93] In addition, tumor-infiltrating lymphocytes in cHL express high levels of HDACs,[94] suggesting that HDAC inhibitors might target not only neoplastic cells but also immune cells of the tumor microenvironment. Recent Phase II clinical trials have demonstrated significant efficacy of HDAC inhibitors in patients with relapsed[95] and recurrent HL following ASCT.[96] The HDAC inhibitor panobinostat alters the secretion of cytokines including TNF-α and IFN-γ, thus modulating the activity of lymphocytes in the tumor microenvironment and promoting cancer cell autophagy and death.[97] These panobinostat-mediated cytokine modulations have been recently associated with alterations in PD-1 expression in T cells,[98] suggesting that the combination of HDAC inhibitors and PD-1/PD-L1 inhibitors might be a promising therapeutic approach in HL. Other studies have focused on the combination of HDAC inhibitors with molecules targeting oncogenic signaling in HL including mTOR inhibitors, such as everolimus and sirolimus,[99,100] or angiogenesis inhibitors, such as sorafenib.[101]

Transplantation strategies for refractory or relapsed HL

Outcomes of refractory or relapsed HL treated with conventional dose salvage chemotherapy were historically characterized by transient responses and low probability for long-term remission or cure.[102] Although the development of novel targeted therapies with potent activity against HL is promising, long-term outcomes with these agents are not well established. The role of ASCT in refractory and relapsed HL is well established and ASCT remains the standard of care for patients who are candidates for curative therapy. AlloHCT is typically reserved for carefully selected patients who relapse after ASCT. Moreover, several transplantation strategies in the autologous or allogeneic setting have been developed with the goal to further improve outcomes, albeit with variable success (Table 2).

Table 2 Transplantation strategies for relapsed/refractory HL

Transplantation strategies	References
ASCT following high-dose chemotherapy is associated with PFS advantage over nontransplant strategies and is considered the standard of care in patients with relapsed or refractory HL who are responding to salvage therapy.	8,103–108,135–138
A variety of pre-ASCT salvage regimens can be considered and are associated with ORR in approximately two-thirds of patients and CR in approximately one-third of patients. Common regimens include ICE, ESHAP, DHAP, GV, GDV, and more recently BV in sequence or in combination with cytotoxic chemotherapy or PD-1 inhibitors. There is not enough evidence that one regimen is superior to others.	8,13,73–75,111–120
A variety of myeloablative conditioning regimens are considered acceptable for patients with relapsed or refractory HL undergoing ASCT, most commonly BEAM, CBV, busulfan-based or TBI-based regimens. BEAM may be superior to other conditioning regimens for HL based on retrospective registry data.	8,106,107,113, 121–134
Pre-ASCT FDG-PET is a major determinant of post-ASCT relapse risk and may be used for risk-adapted treatment design.	74,113,141,148–152
Frontline ASCT as consolidation for high-risk HL is not associated with a survival benefit.	154–156
SHDCT is associated with increased toxicity and no survival benefit in patients with relapsed ASCT.	163
Tandem ASCT may be of some benefit to chemoresistant patients with relapsed or refractory HL, but routine use has not been adopted due to lack of randomized data.	164–168
BV maintenance post-ASCT is associated with PFS benefit in patients with relapsed or refractory HL undergoing HL with one or more high-risk factors.	142
Second ASCT may be considered in patients with long remission duration after first ASCT, but data are limited.	172
alloHCT should be offered to patients who relapse post-ASCT, who are not considered curable with standard chemotherapy, and is associated with long-term disease control in a minority of patients.	173,174,177–182, 187, 191–199
RIC alloHCT is associated with less TRM and is considered the standard of care, although there is no consensus regarding the optimal conditioning regimen and intensity.	175–177,180, 184,199
Alternative graft sources (UCBT, haploidentical) are acceptable in patients who lack suitable HLA-matched related or unrelated donors.	191–198

Abbreviations: alloHCT, allogeneic hematopoietic stem cell transplantation; ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; BEAM, carmustine (BCNU), etoposide, cytarabine (Ara-C) and melphalan; CBV, cyclophosphamide, carmustine and etoposide; CR, complete response; DHAP, dexamethasone, cisplatin and cytarabine; ESHAP, etoposide, methylprednisolone, cytarabine and cisplatin; GV, gemcitabine and vinorelbine; GVD, GV with doxorubicin; HL, Hodgkin's lymphoma; ICE, ifosfamide, carboplatin and etoposide; ORR, overall response rate; PFS, progression-free survival; RIC, reduced intensity conditioning; SHDCT, sequential high-dose chemotherapy; TRM, treatment-related mortality; UCBT, umbilical cord blood transplantation.

Autologous transplantation (ASCT)

Early experience with the use of high-dose chemotherapy requiring autologous stem cell support for the treatment of relapsed or refractory HL showed promising results.[103–105] The British National Lymphoma Investigation compared in a randomized fashion the outcomes of patients with HL relapsing after first-line chemotherapy who were treated either with non-myeloablative doses of carmustine (BCNU), etoposide, cytarabine (Ara-C) and melphalan (mini-BEAM) administered without stem cell support, or with high-dose BEAM conditioning followed by ASCT.[106] Event-free survival (EFS) and PFS were significantly improved in the arm treated with BEAM plus ASCT. Similarly, in a study by the German Hodgkin Study Group, 161 patients with relapsed HL were treated with two cycles of non-myeloablative doses of dexamethasone and BEAM (Dexa-BEAM), and the responders were subsequently randomized to two more cycles of either Dexa-BEAM or BEAM followed by ASCT.[107] Freedom from treatment failure (FFTF) at 3 years was significantly improved in chemosensitive patients who underwent ASCT compared to those who received conventional chemotherapy, although no significant OS benefit was shown. In both studies, radiotherapy was allowed for patients with residual sites of disease. A systematic review and meta-analysis of these two randomized studies again demonstrated that ASCT was associated with improved PFS (hazard ratio [HR] = 0.55; 95% confidence interval [CI]: 0.35–0.86; $p = 0.009$), but only a trend toward improved OS (HR = 0.67; 95% CI: 0.41–1.07; $p = 0.10$),[108] most likely due to lack of statistical power. Based on the results of these two randomized controlled trials, high-dose chemotherapy followed by ASCT has been established as the standard of care for patients with relapsed or refractory HL.

Although the indication of ASCT for patients with relapsed disease is supported by randomized trials, there are no randomized data with regard to the optimal salvage therapy and conditioning regimens. A concern with the use of melphalan-containing salvage regimens, such as mini-BEAM or Dexa-BEAM which were used in the two randomized ASCT trials, is the relatively high treatment-related mortality (TRM) and bone marrow toxicity, which may compromise adequate stem cell collection in preparation for ASCT.[109–111] Therefore, alternative chemotherapy regimens incorporating non-cross-resistant agents have been extensively studied as salvage treatment for cytoreduction before ASCT. The combination of ifosfamide, carboplatin and etoposide (ICE) was developed at Memorial Sloan Kettering Cancer Center[8,112] and is one of the most commonly used salvage regimens for HL. In a cohort of 65 patients with relapsed/refractory HL, two cycles of ICE given every 2 weeks were associated with an OR rate of 88% and resulted in a long-term EFS of 68% in 57 patients who proceeded to ASCT incorporating involved-field radiation therapy.[8] An augmented ICE regimen with intensified doses of ifosfamide and etoposide has also been employed for patients with unfavorable risk factors.[74,113] Other commonly used salvage regimens include combinations of platinum agents with cytarabine, such as dexamethasone, cisplatin and cytarabine (DHAP),[114] or etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP).[115,116] Gemcitabine-based chemotherapy regimens have also been developed, such as gemcitabine, dexamethasone and cisplatin (GDP),[117] gemcitabine and vinorelbine (GV),[118] GV with doxorubicin (GVD)[119] or ifosfamide, gemcitabine and vinorelbine (IGeV).[120] Such gemcitabine-based regimens offer the advantage of outpatient administration, and there is some evidence that may achieve similar response rates and superior PFS compared to mini-BEAM, with less toxicity.[111]

The advent of new targeted or immunotherapy agents for relapsed/refractory HL (detailed in the "Novel therapeutic approaches for primary refractory and early relapsed HL" section) has been embraced with enthusiasm, because they offer the potential for effective salvage therapy without excessive toxicity, in contrast to conventional cytotoxic chemotherapy. There is currently no consensus with regard to the optimal salvage strategy for patients with relapsed/refractory HL. However, given the importance of pretransplant disease status for posttransplant outcomes, it is reasonable to attempt a second non-cross-resistant regimen in patients with inadequate response to first salvage, with the goal to achieve CR prior to ASCT.

A variety of conditioning regimens have been used for ASCT in patients with relapsed or refractory HL, but there is no agreement with regard to optimal regimen. The two Phase III prospective randomized studies that established the role of ASCT in such patients used BEAM conditioning,[106,107] which remains one of the most commonly used regimens to date. Other common regimens include cyclophosphamide, carmustine and etoposide (CBV) with various dosing modifications[121–125]; busulfan-based regimens such as busulfan and cyclophosphamide (BuCy),[126] busulfan and melphalan (BuMel),[127] busulfan, etoposide and cyclophosphamide (BuCyE)[128,129] a or triple alkylator regimen of busulfan, melphalan and thiotepa (BuMelTt).[130,131] total body irradiation (TBI) (or total lymphoid irradiation [TLI])-based regimens have also been used as conditioning regimens in previously nonirradiated patients[8,113,123,132,133]; however, there

has been a swift away from such regimens over time due to concerns for increased associated risk of secondary malignancies and long-term toxicity. Based on registry analyses, BEAM appears to be superior to CBV, TBI-based therapies, or BuCyE as a preparative regimen in patients with HL undergoing ASCT.[129,134]

Prognostic factors for patients with relapsed/refractory HL undergoing ASCT

Considering different combinations of salvage and conditioning regimens, many single-arm studies or retrospective analyses support the role of ASCT in patients with relapsed and/or refractory HL, which was previously established by two prospective Phase III studies in relapsed HL patients.[135–138] Moreover, several such studies have sought to identify prognostic factors for ASCT outcomes. Prognostic factors can be divided into patient-related, disease-related at the time of disease relapse or progression, and factors related to disease status prior to ASCT. Age and performance status are the most important patient-related factors and likely influence the risk of TRM.[139–141] Factors at the time of disease relapse or progression that have been associated with clinical outcomes include duration of remission, anemia, B-symptomatology, stage IV disease or extranodal involvement and bulky disease.[8,139,140,142–144] Although primary refractory HL is thought to confer worse prognosis, such patients may also derive benefit from ASCT, depending on the risk factors present.[145,146]

Importantly, pre-ASCT factors such as the number of salvage chemotherapy lines, stage and response to salvage therapy are important prognostic factors for post-ASCT outcomes.[138,147] Functional imaging by Gallium scans in the past or, most commonly, by fluorodeoxyglucose (FDG)-positron emission tomography (FDG-PET) is preferred over computed tomography (CT) for assessment of response to salvage therapy, because it can differentiate viable tumor from residual fibrotic tissue in patients with PR to therapy by CT.[142] Moreover, several groups have shown that normalization of pre-ASCT functional imaging and, in particular, FDG-PET is an independent prognostic factor for post-ASCT risk of relapse, PFS and possibly OS, and may be superior to other risk factors at the time of relapse.[141,148–151] These findings were corroborated in a recent meta-analysis.[152] Based on the notion that FDG-PET response to salvage therapy is predictive of clinical outcomes, MSKCC has performed two Phase II studies of PET-adapted sequential salvage therapy,[74,113] in which patients with relapsed or refractory HL who did not achieve CR to first salvage therapy were switched to a different salvage regimen prior to ASCT. PET-adapted salvage strategies may increase the proportion of patients achieving FDG-PET negativity and consequently leading to higher chances of cure. However, such strategies may be limited by the inadequate sensitivity and specificity of the test.[152]

ASCT for frontline consolidation of patients with high-risk HL

In view of the improved outcomes of ASCT in relapsed or refractory HL and early data in the preemptive setting,[153] subsequent randomized clinical trials tested ASCT as a consolidation strategy for patients with unfavorable high-risk HL in first CR or PR, in comparison with standard induction chemotherapy[154,155] or intensified induction with or without radiotherapy.[156] Despite the different definitions of adverse risk factors, neither study showed a failure-free or a survival benefit in patients receiving frontline ASCT, suggesting that a large fraction of patients with nonchemorefractory unfavorable HL are cured with standard induction chemotherapy or effectively salvaged with ASCT at the time of relapse. Consequently, despite prior controversy,[153,157–159] ASCT is not recommended for frontline consolidation in patients with advanced or high-risk HL responding to induction chemotherapy.

Intensification of salvage and sequential high-dose chemotherapy (SHDCT)

Approximately 30–50% of patients with relapsed or refractory HL undergoing ASCT will eventually develop disease progression after transplant. The risk is influenced by the presence of disease-related risk factors and, possibly, by the type of the conditioning regimen.[134,160,161] Some investigators have favored more intensive salvage regimens prior to ASCT[135,162] with variable results. However, in the absence of prospective comparative trials, such approaches have not been widely adopted. A Phase III European intergroup study investigated whether SHDCT – consisting of sequential high doses of cyclophosphamide, methotrexate and etoposide administered to patients responding to two cycles of ESHAP before BEAM ASCT – might decrease the risk of post-ASCT relapse.[163] The intervention was proven toxic without survival benefit. Thus, intensification of conditioning did not lead to improved ASCT outcomes.

Tandem ASCT for relapsed/refractory ASCT

The use of tandem ASCT has also been investigated as a strategy to improve the outcomes in patients with relapsed

or refractory HL. In the prospective Phase II GELA/SFGM H96 trial, poor-risk patients[164] received salvage treatment followed by tandem ASCT 45–90 days apart.[165] The first conditioning was CBV with mitoxantrone (CBVM) or BEAM, and the second was TBI, cytarabine (Ara-C) and melphalan (TAM) or busulfan, cytarabine (Ara-C) and melphalan (BAM) in patients who had received prior irradiation. Long-term follow-up results of the trial showed 46% and 57% freedom from second failure and OS at 5 years, and 41% and 47% at 10 years, respectively, which were comparably favorable to the historic rates especially in patients not achieving CR to cytoreductive therapy.[165,166] Other groups using different salvage and conditioning regimens[167,168] have similarly suggested that tandem ASCT may be an effective treatment strategy for primary refractory or poor-risk-relapsed HL. However, in the absence of randomized studies and considering the advent of newer effective agents that can be used for salvage or post-ASCT maintenance, tandem ASCT is not routinely performed and has no role in the management of standard risk patients in particular.

Post-ASCT maintenance

An alternative strategy to improve the outcomes of ASCT consists of the use of post-ASCT consolidation or maintenance. Early attempts with the use of cytotoxic chemotherapy[169] or immunotherapeutic agents (rIL-2 and IFN-α)[170] were not widely adopted due to lack of efficacy or tolerability. In contrast, the multicenter Phase III AETHERA trial evaluated the use of brentuximab vedotin as post-ASCT maintenance therapy in 329 patients with primary refractory or unfavorable-risk-relapsed HL, defined as <12 month initial remission duration or extranodal involvement prior to salvage chemotherapy.[142] Patients were randomized to receive brentuximab vedotin for up to 1 year versus placebo. Patients randomized to the treatment arm had significantly improved 2-year PFS of 63% by independent review compared to 51% in the placebo group. The PFS benefit of brentuximab vedotin maintenance was consistent across subgroups, although less notable in patients who achieved PET-negative remission before ASCT. No OS benefit was observed, but the majority of control patients received brentuximab vedotin at the time of progression. Based on the results of the AETHERA trial, brentuximab vedotin has received FDA approval for post-ASCT maintenance in patients with HL at high risk for relapse or progression. The use of other targeted agents, including HDAC inhibitors and PD-1 inhibitors, for consolidation is appealing given the high response rates and favorable side- effect profile of such agents, but their role in this setting remains to be shown.

Allogeneic stem cell transplantation (alloHCT)

Patients who relapse after ASCT have poor prognosis and, in general, they are not considered curable with standard chemotherapy.[10,14] Perhaps the only exception includes patients with truly localized disease that may be salvaged with radiation.[171] A second ASCT may be considered for post-ASCT-relapsed HL patients,[172] especially in those who have had a long remission interval following first ASCT. However, alloHCT has been most commonly considered for such patients as a potentially curative intervention.

Early experience with myeloablative (MAC) alloHCT in HL patients was associated with limited success due to high rates of TRM and relapse, likely due to the inclusion of heavily pretreated or advanced HL patients.[173,174] Moreover, alloHCT was not found to be superior to ASCT in terms of survival outcomes.[175,176] Consequently, alloHCT is not recommenced in lieu of ASCT in the management of relapsed/refractory HL and is reserved for carefully selected medically fit patients relapsing after ASCT.

More recently, reduced intensity conditioning (RIC) alloHCT, commonly with the use of fludarabine and melphalan or BEAM conditioning, with or without in vivo T-cell depletion, has been embraced by many centers due to the lower risk of TRM and is considered the recommended approach for patients with relapsed HL who are candidates for alloHCT.[177–181] This recommendation is also supported by a retrospective analysis by the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation, which demonstrated significantly lower TRM and improved OS survival with RIC compared to MAC alloHCT.[182] Prognostic factors for TRM included chemorefractory disease, poor performance status and age >45 years, whereas PFS and OS determinants included performance status and disease status at transplant.[183] However, it should be noted that in a more recent analysis, MAC alloHCT was associated with a nonsignificant improvement in PFS due to somewhat better disease control and decreasing TRM in recent years. Consequently, the issue of conditioning intensity may be revised in the future.[184] Despite recent improvements, the optimal conditioning regimen for patients undergoing alloHCT for HL remains undetermined, and relapse continues to be a common cause of treatment failure. Finally, patients who relapse after alloHCT have limited treatment options including donor lymphocyte infusions (DLIs), second alloHCT, radiation

therapy and palliative chemotherapy, and, in general, their prognosis is grim.[185,186]

There is conflicting evidence regarding the susceptibility of HL to graft versus lymphoma (GVL) effect, which is more crucial in the setting of RIC alloHCT. In support of a potent GVL effect, some studies have shown high rates of clinical responses in heavily treated allografted HL patients to DLI[187,188] and a reduction in relapse risk in allografted patients developing acute or chronic graft versus host disease (GVHD).[175,182,183] However, a large Center for International Blood and Marrow Transplant Research (CIBMTR) study showed no association between GVHD and reduction of relapse risk after MAC or RIC alloHCT for HL arguing against a potent GVL effect in these patients.[189] Moreover, relapse risk remains high for allografted HL patients (especially in comparison with indolent lymphomas).[190]

Although most of the alloHCT experience for HL (and other lymphomas) is based on patients transplanted with HLA-matched related or unrelated donors, several patients lack suitable HLA-matched donors. Alternative graft sources including mismatched unrelated donors, haploidentical-related donors and unrelated cord blood have extended allograft access to patients with lymphoma (including HL), with acceptable and largely comparable results to matched unrelated donor transplants.[191–193] Similarly, although data specific to HL patient cohorts allografted with alternative donors are more limited, they support the notion that all graft sources can be considered in patients who are felt to be candidates for a potentially curative alloHCT.[194–198]

In view of the development of novel targeted agents with high activity against HL and favorable side-effect profiles, it is likely that alloHCT may play a lesser role in the management of such patients in the proximate future. Moreover, questions remain unanswered regarding the incorporation and optimal sequence of new agents in the treatment plan, without compromising safety. As an example, brentuximab vedotin has been successfully used prior to allogeneic transplantation[199,200] as a single agent or in combination with DLI for post-alloHCT relapse.[201,202] In contrast, PD-1 blockade prior to or after alloHCT may exacerbate GVHD due to prolonged or permanent inhibition of pathways with a key role in the induction of self-tolerance.[203,204]

Summary and future directions

In summary, HL is a highly curable disease, but ~25%–30% of patients will progress during or following first-line chemotherapy and will require further treatment. High-dose chemotherapy followed by ASCT remains the standard of care for patients with relapsed or refractory HL who respond to salvage therapy, and affords long-term PFS in ~50% of such patients, but ASCT success varies widely depending on the risk factors present and pre-ASCT disease status. There is presently not enough evidence to support a routine role of upfront ASCT in high-risk HL, SHDCT or tandem ASCT. HL relapsing after ASCT is associated with adverse prognosis, and alloHCT in that setting is the only potentially curative treatment modality, although historically limited by high rates of TRM and associated morbidity. Recent advancements in the understanding of HL pathogenesis and the development of novel targeted therapies with promising efficacy and favorable toxicity profiles have provided hope for improving the outcomes of patients with relapsed or refractory HL. Such novel therapies, including brentuximab vedotin and PD-1 inhibitors, have been successfully incorporated in the current treatment paradigm, specifically as salvage therapy of HL patients relapsing after frontline therapy, as post-ASCT maintenance for relapsed or refractory HL with high-risk features and as bridge therapy prior to ASCT or AlloSCT, either alone or in combination with other agents. Moreover, in view of the promising results of such agents, the role of AlloSCT for the management of relapsed or refractory HL might need to be revised. Nevertheless, although the development of numerous novel agents with activity against HL is exciting, further studies are required to determine their long-term efficacy and the optimal combination or sequence of such therapies, ideally in a risk-adapted fashion.

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Disclosure

Vassiliki A Boussiotis has patents on the PD-1 pathway licensed by Bristol-Myers Squibb, Roche, Merck, EMD-Serono, Boehringer Ingelheim, AstraZeneca, Novartis and Dako. The authors report no other conflicts of interest in this work.

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