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Review Article

Advances in CD30- and PD-1-targeted therapies for relapsed or refractory Hodgkin lymphoma

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Abstract: The current standard approach for relapsed or refractory (R/R) Hodgkin lymphoma (HL) is salvage chemotherapy, followed by autologous stem cell transplantation (ASCT). However, this therapeutic regimen is successful in only half of patients with relapsed or refractory classical HL. In addition, some patients with R/R HL are ineligible for ASCT. To improve survival time and quality of life and decrease the acute and long-term toxicities of therapy, many schemes for the treatment of R/R HL have emerged. Recently, the use of targeted therapy and immunotherapy represents an important advance in the treatment of R/R HL. The CD30 antibody drug conjugate brentuximab vedotin (BV) and programmed death-1 (PD-1) receptor checkpoint inhibitors nivolumab and pembrolizumab are effective and well-tolerated treatments for R/R HL patients, broadening treatment options for these patients. BV and anti-PD-1 antibodies can be used as monotherapy or combined with other chemotherapy regimens for rescue treatment, consolidation treatment and second-line treatment of R/R HL. In this article, we review current pathobiology knowledge of R/R HL and summarize recent advances in therapy schemes.

Keywords: Relapsed or refractory Hodgkin lymphoma, brentuximab vedotin, PD-1 inhibitor, therapy

Introduction

HL is usually derived from mature B cells [1], in which rare malignant Hodgkin and Reed-Sternberg (HRS) cells of classical HL and lymphocyte-predominant Hodgkin lymphoma (NLPHL) lymphocytes become infiltrated by extensive but invalid inflammatory immune cells [1, 2]. Although HRS cells originate from B cells, they do not express typical B cell markers (such as CD19 and CD20) [3, 4]. HRS cells are also characterized by constitutive activation of the NF-κB and JAK-STAT pathways, downregulation of MHC-I and nonfunctional part of MCH II (**Figure 1**), all of which allow HRS cells to escape the immune response [5, 6]. HL accounts for 8.6-13% of all lymphoma cases in mainland China [7] and 50% of all lymphoma cases in children and adolescents in Western countries [8]. Age at diagnosis has a bimodal distribution, with the highest incidence at 15-34 years and the other peak after 60 years [9]. Approximately 70-80% of patients will be cured by frontline therapy, such as ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) and radiotherapy, which is a high cure rate for lymphoma [10, 11]. However, among cured cases, short- and long-term toxic effects related to treatment, including the risk of serious pulmonary toxic effects from bleomycin exposure and second solid cancers as a result of radiation therapy, remain a significant concern. In addition, approximately 10-15% of early-stage and 15-30% of advanced-stage HL patients experience relapse or primary refractoriness [12]. Primary refractory HL is defined as progression or nonresponse during induction treatment or within 3 months of completing treatment [13]. Relapse HL is defined as induction therapy achieving complete remission (CR) at least 1 month after the reappearance of HL. HRS cells normally die by apoptosis due to loss of expression of B-cell surface proteins; however, HRS cell survival and growth rely on upregulation or downregulation signaling pathways that are associated with immune evasion [2].

High-dose chemotherapy (HDCT) followed by ASCT is the standard of care for most cases of R/R HL. However, not all patients are eligible or

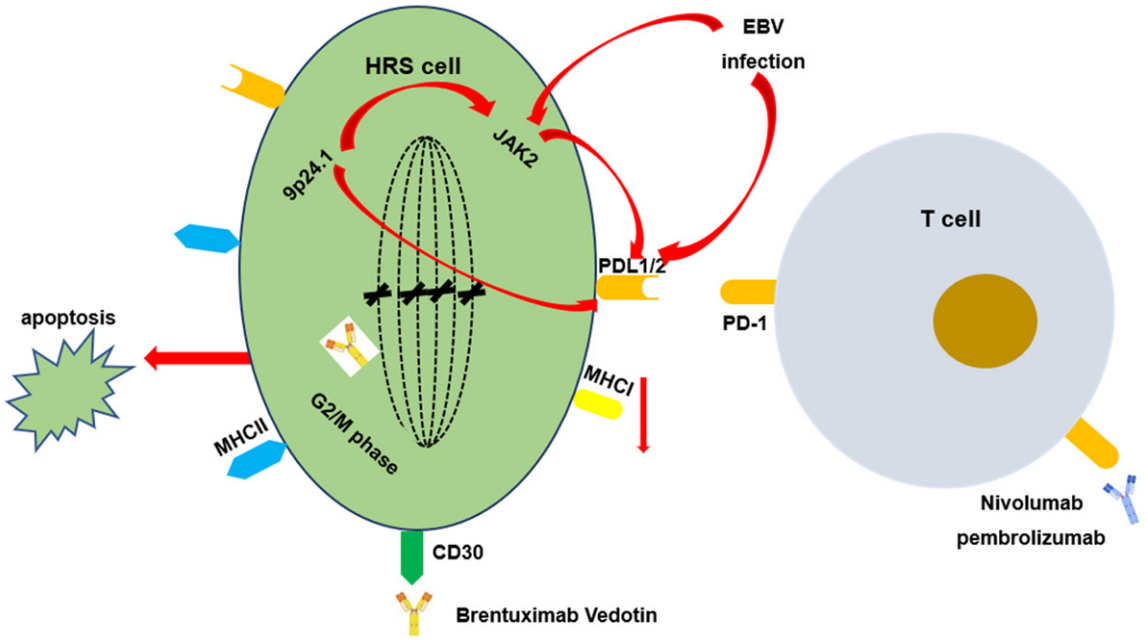

Figure 1. The mechanisms of immune escape and the mechanisms of action of brentuximab vedotin and PD-1 inhibitors. Chromosome 9p24.1 amplification and EBV infection in HRS cells result in PD-L1, PD-L2 and JAK2 overexpression. Enhanced JAK-STAT signaling can also lead to upregulation of PD-L1 expression. Upregulation of PD-L1 expression and downregulation of MHC-I and the nonfunctional part of MCH II cause HRS cells to escape the immune response. Brentuximab vedotin binds to CD30 on the HRS cell surface and is internalized to further release cytotoxic MMAE, which leads to G2/M phase cell growth arrest and apoptosis. The PD-1 inhibitors nivolumab and pembrolizumab bind to PD-1 and block interaction of PD-1 with PD-L1 or PD-L2, releasing T cell inhibition, enhancing antitumor immune responses and inhibiting tumor immune evasion.

benefit from ASCT; compared to younger patients, elderly patients have increased treatment-related mortality and poor event-free survival after ASCT [14]. Therefore, R/R HL treatment continues to face huge challenges. Since several novel therapies have emerged in recent years, the landscape of R/R HL treatment has changed significantly. There are two major therapy drugs. One is BV, a CD30 antibody-drug conjugate that was FDA approved in 2011 for the treatment of R/R HL patients who experience ASCT failure or are transplant-ineligible after at least two prior lines chemotherapy. The other is anti-PD-1 antibodies, as the receptor for programmed death-ligand 1 (PD-L1) is overexpressed in HRS cells as well as the HL microenvironment due to chromosome 9p24.1 amplification, resulting in an ineffective immune response [15]. Overall, the roles of BV and anti-PD-1 antibodies in the treatment of HL are evolving. They have shown promising efficacy as salvage treatment, consolidation treatment and second-line therapy for HL.

With a growing understanding of immune escape mechanisms and the interaction between HRS cells and the tumor microenvironment in recent years, CD30- and PD-1-targeted therapies have yielded exciting results for R/R HL. The aim of this review is not only to assess BV or anti-PD-1 antibody monotherapy but also to discuss the prospect of combining BV or anti-PD-1 antibody monotherapy with traditional chemotherapy.

Salvage chemotherapy

For R/R HL, most studies [16, 17] have demonstrated a significant correlation between pretransplant patient status and posttransplant progression-free survival (PFS) time, with the selection of salvage chemotherapy before transplantation being crucial. However, there are no randomized clinical trials to confirm which salvage treatment regimen is most effective. Several studies of traditional chemotherapy and BV combined with traditional chemotherapy are listed below (**Table 1**).

Traditional salvage chemotherapy

Armando Santoro [18] and colleagues conducted a multicenter, open-label, phase II prospec-

Table 1. Salvage chemotherapy

Therapeutic Regimens	Study Characteristics	N	ORR	CR (%)	ASCT (%)	PFS	OS	Median follow time	References
BeGEV	Phase II	59	83.0%	43 (73.0)	43 (73.0)	2-year PFS 62.2%	2-year OS 77.6%	29.1 months	[18]
IGEV	Retrospective analysis	12	100%	7 (58.0)	12 (100.0)	5-year EFS 83%	5-year OS 90%	71.0 months	[19]
ESHAOx	Phase II	36	72.2%	12 (33.3)	Not ASCT	Median TTP 34.9 months	Median OS not reached	18.9 months	[59]
BV+ICE	Ongoing phase I/II	23	NR	20 (87.0)	19 (86.0)	NR	NR	NR	[20]
BV+DHAP	Phase II	52	90%	42 (81.0)	47 (85.0)	2-year PFS 73.5%	2-year OS 73.5%	27 months	[21]
BV+ESHAP	Phase I-II	66	91%	46 (70.0)	60 (91.0)	30-month PFS 71%	30-month OS 91%	27 months	[22]

N, number of patients enrolled; ORR, overall response rate; CR, complete remission; ASCT, autologous stem cell transplant; PFS, progression-free survival; OS, overall survival; NR, not reported; EFS, event-free survival; TTP, time to progression; BeGEV, bendamustine, gemcitabine, and vinorelbine; IGEV, ifosfamide, vinorelbine, gemcitabine, methylprednisolone; ESHAOx, etoposide, methylprednisolone, high-dose cytarabine, oxaliplatin; ICE, Ifosfamide, Carboplatin, and Etoposide; DHAP, dexamethasone, cytarabine and cisplatin; ESHAP, etoposide, solumedrol, AraC, and cisplatin.

tive study of R/R HL. Fifty-eight patients met the inclusion criteria and were included in this study. The treatment regimen was BeGEV (bendamustine, gemcitabine, vinorelbine). After 4 cycles of treatment, 43 (73%) patients reached complete remission (CR), 6 (10%) partial remission (PR), 1 achieved stable disease (SD), and 8 had progressive disease (PD). The overall response rate (ORR) was 83%. Finally, 43 people successfully underwent ASCT. After a median follow-up of 29.1 months, the 2-year PFS (progression-free survival) and OS (overall survival) were 62.2% and 77.6%, respectively. Kristin Marr [19] recently reported a study of 12 pediatric patients with R/R HL treated with salvage IGEV, with 58% achieving CR and 42% PR and an ORR of 100%. All patients received subsequent ASCT. Some received consolidated radiotherapy after ASCT. After long-term follow-up, the secondary EFS (event-free survival) and OS at 5 years were 83% and 90%, respectively. Therefore, ASCT is a preferred option for young patients with R/R HL who have achieved CR after salvage treatments, and IGEV is a better regimen for pediatric patients (**Table 1**).

BV combined with traditional chemotherapy before ASCT

The combination of BV with ICE chemotherapy was evaluated in 23 patients with R/R HL, and the PET-based CR rate was 87% (20 patients) by investigator review and 70% (16 patients) by central independent review. A total of 86% (19/22) of patients were able to proceed to ASCT. Grades 3-4 nonheme toxicity were reported in 48% of patients, and peripheral neuropathy was seen in 30% [20]. In total, 55 R/R cHL patients were enrolled in a phase II HOVON/LLPC Transplant BRaVE study, and all of them received BV and DHAP. Finally, 81% (42/52) achieved a metabolic complete response (mCR), 9.6% (5/52) achieved a metabolic partial response (mPR), and 9.6% (5/52) had PD. Through a long period of tracking, the patients' 2-year PFS was 74%, and OS was 95%. BV-DHAP is an effective salvage regimen for patients with R/R cHL, but toxicity should be closely monitored [21]. In a multicenter, open-label, phase I-II trial, 66 patients were recruited and accepted the BV plus ESHAP regimen. The ORR before ASCT was 91%, including a CR rate of 70%; 64 patients underwent stem-cell mobilization, all with success, and 60 patients underwent ASCT. Twenty-eight (42%) patients presented grades 3-4 hematological toxicity [22] (**Table 1**).

Brentuximab vedotin

BV, a CD30 antibody-drug conjugate, is mainly composed of three parts: the chimeric IgG1 antibody cAC10, which targets the CD30 antigen, the microtubule destabilizing agent monomethyl auristatin E (MMAE), and the cleat bridge of the protease covalently attaching MMAE to cAC10 [23, 24]. CD30 is expressed in HRS cells but not in most cells outside the immune system. Under nonpathological conditions, CD30 expression is usually limited to activated B and T lymphocytes and NK cells, with generally lower levels of activated monocytes and eosinophils [25]. Infiltrating inflammatory cells in the tumor microenvironment and HRS cells express high levels of CD30 and CD30L, indicating that autocrine and paracrine loops play an important role in the pathogenesis of HL. CD30 combined with CD30L causes HRS cell proliferation and survival [24, 26]. BV can block ligand-receptor interactions and in-

Table 2. Clinical trials of BV or BV plus bendamustine as second-line therapy before ASCT in R/R HL

Study Characteristics	Therapeutic Regimens	N	ORR	CR	ASCT	References
Phase II	4 cycles BV (1.8 mg/kg) or 2 cycles BV (1.8 mg/kg) followed by salvage chemotherapy (ICE/DICE/IGEV/GND)	37	68%[1]	13[2] (35%)	33 (89%)	[28]
Phase IV	16 cycles BV (1.8 mg/kg) until PD/unacceptable toxicity or BV followed by other therapy[3]	60	50%	7 (12%)	28 (47%)	[29]
Phase II	2 cycles BV (1.2 mg/kg)[4] or 2 cycles BV followed by 2 cycles augmented ICE[5]	45	NR	12 (27%)	44 (98%)	[30]
Phase 1/2 study	BV (1.8 mg/kg day 1) + Bendamustine (90 mg/m^2 days 1 and 2)	53	92.5%	39 (73.6%)	40 (75%)	[31]
Phase 1 trial	BV (1.2 mg/kg or 1.8 mg/kg day 1) + Bendamustine (70 mg/m^2, 80 mg/m^2, or 90 mg/m^2 days 1 and 2)	27	59%	5 (19%)	NR	[32]
Phase 2 trial	BV (1.8 mg/kg day 1) + Bendamustine (90 mg/m^2 days 1 and 2)	37	78%	16 (43%)	NR	[32]

N, number of patients enrolled; ORR, overall response rate; CR, complete remission; ASCT, autologous stem cell transplant. [1]ORR after two 21-day cycles BV (1.8 mg/kg, on day 1) treatment. [2]CR after two 21-day cycles BV (1.8 mg/kg, on day 1) treatment. [3]All patients who are not suitable for stem cell transplant or multiagent chemotherapy before the trial. [4]1.2 mg/kg on days 1, 8 and 15 for two 28-day cycles. [5]Augmented ICE: two doses of ifosfamide 5000 mg/m^2 in combination with mesna 5000 mg/m^2 continuous infusion over 24 h, days 1 and 2; one dose of carboplatin AUC 5, day 3; three doses of etoposide 200 mg/m^2 every 12 h, day 1.

ternalization after binding to CD30, leading to the release of the microtubule-destabilizing agent MMAE [24]. MMAE shows cytotoxic activity, causing growth arrest and apoptosis in the G2/M phase of HRS cells and infiltrating inactive inflammatory and immune cells in the tumor microenvironment (**Figure 1**) [27].

BV as salvage therapy

Three clinical trials have investigated the activity and safety of a novel, sequential, PET-adapted salvage therapy before ASCT in R/R HL patients (**Table 2**). A multicenter phase II trial examined the activity and tolerability of BV as second-line therapy before ASCT in R/R HL, in which 37 patients with R/R HL received BV (1.8 mg/kg) infusion on day 1 of four 21-day cycles. The ORR was 68% (25), including 13 CR cases and 12 PR cases. Eighteen patients received BV and salvage chemotherapy prior to ASCT. Thirty-three (89%) were able to proceed to ASCT, including 18 patients after BV monotherapy and 15 patients with additional salvage chemotherapy [28]. The second trial was a phase IV study (NCT01990534) evaluating BV (1.8 mg/kg every 3 weeks) in 60 patients who were considered unsuitable for SCT/multiagent chemotherapy. The ORR was 50%, with 12% (7 patients) CR and 38% (23 patients) PR. The median PFS was 48 months, and the median duration of CR was 61 months. Twenty-eight patients (47%) ultimately proceeded to AutoHSCT, of whom 10 (17%) received direct SCT after BV treatment and 18 BV and subsequent therapy [29]. The third study was a non-randomized, open-label, single-center, phase 2 trial. In this trial, 45 patients received BV monotherapy (1.2 mg/kg on days 1, 8, and 15 for two 28-day cycles) as first-line salvage chemotherapy; 12 patients (27%) were PET negative and proceeded to HDT/ASCT. Subsequently, 32 PET-positive patients received augICE (ifosfamide, carboplatin, etoposide), with 22 (69%) being PET negative and undergoing HDT/ASCT. Ultimately, 34 patients (76%) achieved PET negativity, and 44 of 45 (98%) were able to undergo ASCT [30].

BV plus bendamustine as salvage therapy

Patients with CR before ASCT have a good prognosis. To improve the efficacy rate of second-line salvage chemotherapy, BV plus bendamustine was carried out in several studies. A multicenter, open-label, phase 1/2 study evaluated the combination of BV plus bendamustine as a first salvage regimen in R/R HL. The ORR in 53 patients was 92.5%, with a CR rate of 73.6%. Overall, 40 patients (75%) underwent ASCT, and the ORR of ASCT patients was 95% (38/40). After long-term follow-up, the 2-year OS rates of the ASCT patients and overall patients were 94.9% and 94.2%, respectively, and the 2-year PFS rates were 69.8% and 62.6%, respectively [31]. The prognosis of patients with these experimental data were significantly better than that for those who underwent BV monotherapy, but the data may vary greatly in different experiments. For example, 64 patients with CD30-positive R/R HL were enrolled in an international, multicenter, single-arm, phase 1-2 trial; in phase 1, 27 patients received BV (1.2 mg/kg or 1.8 mg/kg) on day 1 and bendamustine (70 mg/m^2, 80 mg/m^2, or 90 mg/m^2) on days 1 and 2 of a 21-day cycle. In phase 2, 37 patients received BV (1.8 mg/kg) on day 1 plus bendamustine (90 mg/m^2) on

Table 3. Common toxicities of BV therapy [28, 30, 60, 61]

	Any Grade-% of patients
Neutropenia	16%-22%
Thrombocytopenia	10%-18%
Peripheral neuropathy	22%-52%
Fatigue	30%-49%
Nausea	13%-42%
Rash	26%-29%
Anemia	19%-33%

days 1 and 2. The ORRs of phase 1 and phase 2 were 59% (CR 19%) and 78% (CR 43%), respectively. The median duration of response was 4.3 months and 3.95 months in phase 1 and phase 2, respectively. In total, the ORR was 70% (45/64), with 33% (21/64) achieving CR and 37% (24/64) achieving PR [32]. This may be due to the different conditions of the patients, and the ORR and CR of the first experiment were higher than those of the second experiment [32]. In a real-life study, 20 R/R cHL patients received BV (1.8 mg/kg d 1) combined with bendamustine (120 mg/kg days 2 and 3) for 4 courses, and 80% of patients had deep metabolic responses achieving a Deauville score ≤2. Finally, 18 (90%) patients received hematopoietic stem cell transplantation (HSCT). After a median follow-up of 27 months, the 2-year PFS was 93.7% [33]. In general, the effect of BV plus bendamustine as salvage treatment for R/R HL is better than that of BV monotherapy, but its toxicity and side effects are higher. Therefore, for elderly patients, the BV plus bendamustine regimen should be used carefully while weighing risks and benefits (**Table 2**).

BV as consolidation therapy

In R/R HL, some patients relapse after stem cell transplantation. To reduce the recurrence rate, BV monotherapy as a consolidation therapy also shows a good effect. In a randomized, double-blind, placebo-controlled, phase 3 trial, 329 patients were randomly assigned to the BV group (n=165) or the placebo group (n= 164), and the former received 16 cycles of 1.8 mg/kg BV every 3 weeks. The PFS of patients in the BV group was significantly increased compared with that in the placebo group. The median PFS was 42.9 months in the BV group and 24.1 months in the placebo group. The 2-year rate of PFS was 63% in the BV group and 51% in the placebo group. Therefore, BV-based consolidation therapy is a good choice for patients with primary refractory disease, relapse within 1 year after frontline treatment and extranodal invasion [34].

Safety of BV

The most common toxicities of BV are neutropenia and peripheral neuropathy, but these side effects are not serious and can be controlled. In addition, BV therapy has no significant effect on hematopoietic stem cell collection before ASCT. Common side effects of BV are summarized in **Table 3**. In the phase 3 AETHERA study, neutropenia occurred in 58 (35%) of 167 patients, and peripheral neuropathy occurred in 94 (56%). The incidence rates of fatigue were 24% in the BV group and 18% in the placebo group [34, 35].

PD-1-targeted immunotherapy

Classic Hodgkin's lymphoma (cHL) is characterized by scattered RS cells surrounded by a dense rosette-like infiltrate of dysfunctional inflammatory cells that are unable to produce an antitumor response [36]. Normally, upregulation of PD-L1 and PD-L2 in tissue is a physiological response to inflammation. The binding of PD-L1 and PD-L2 to PD-1 on the T cell surface can inhibit T cell signal transduction and prevent excessive tissue damage [37, 38]. However, in addition to CD30 expression in HRS cells [39], Shipp and his colleagues reported that chromosome 9p24.1 amplification (**Figure 1**) in HRS cells is a recurrent genetic abnormality in HL, resulting in overexpression of genes (including PD-L1, PD-L2 and JAK2) in this region [40, 41]. In addition, EB virus (EBV) infection, AP1 activation and enhanced JAK-STAT signaling in HL can lead to upregulation of PD-L1 expression [11, 42, 43]. EBV infection in HL patients may further amplify the JAK/STAT and NF-kB pathways via the LMP1A protein [44]. PD-L1 is also overexpressed in inflammatory immune cells in the HL tumor microenvironment [45]. PD-L1 expressed on HRS cells and inflammatory cells in the tumor microenvironment binds to PD-1 expressed on T cells, which induces immune checkpoint inhibition and leads to T cell depletion [46]. 9p24.1 gene alterations range from polyploidy (the median of an extra copy) to increases and amplifica-

Table 4. Clinical trials of nivolumab and pembrolizumab therapy

Therapeutic Regimens	Study Characteristics	Patient Characteristics	N	ORR	CR	PR	Median DOR	PFS	OS	References
Nivolumab	Phase II	Failure of ASCT therapy	243	69%	40 (16%)	128 (53%)	16.6 months	Median PFS 14.7 months	1-year OS rate was 92%	[48]
Nivolumab	Phase II	Failure of both ASCT and BV therapy	80	66.3%	7 (9%)	46 (58%)	7.8 months	Median PFS 10.0 months	6-month OS rate 98.7%	[49]
Nivolumab	Ongoing study	78% relapse following ASCT and 78% relapse following BV	23	87%	4 (17%)	16 (70%)	NR	NR	Median OS not reached	[55]
Nivolumab	Phase II	All prior to BV therapy	16	87.5%	5 (31.3%)	9 (56.3%)	8.5 months	Median PFS 11.7 months	3-year OS rate 80.4%	[53]
Nivolumab	Retrospective analysis	NR	86	70%	31 (36%)	29 (34%)	NR	Median PFS 31.5 months	1-year OS rate 78.7%	[54]
Nivolumab	Retrospective analysis	Failing after ASCT and/or BV and ASCT-naïve	99	64%	31 (31%)	33 (33%)	NR	Median PFS 19.4 months	Median OS not reached	[62]
Pembrolizumab	Phase II	3 cohort	210	69%	47 (22.4%)	98 (46.7%)	Median DOR was not reached	9-month PFS rate 63.4%	9-month OS rate 97.5%	[47]
Pembrolizumab	Phase Ib	Progressed on or after treatment with BV	31	65%	5 (16%)	15 (48%)	NR	24-week PFS rate 69%	24-week OS rate 100%	[57]

N, number of patients enrolled; ORR, overall response rate; CR, complete remission; PR, partial response; DOR, duration of response; PFS, progression-free survival; OS, overall survival; NR, not report.

tion of a higher copy number (more than 6-10 additional copies). PD-L1/PD-L2 amplification is associated with advanced disease, poor progression-free survival and a higher response rate [40, 47]. Therefore, interaction of PD1-PD1 ligands provides a unique target for the treatment of HL.

Nivolumab and pembrolizumab are immunoglobulin G4 monoclonal antibodies that act as checkpoint inhibitors, binding to PD-1 and blocking interaction of PD-1 with PD-L1 or PD-L2, thereby releasing inhibition of T cells, enhancing antitumor immune responses and suppressing tumor immune evasion.

Nivolumab was the first anti-PD-1 antibody approved by the FDA for the treatment of R/R HL. In a multicenter, single-arm, phase II study, 243 patients with R/R cHL were enrolled after ASCT treatment failure, all of whom received nivolumab 3 mg/kg every 2 weeks. The overall ORR was 69%, including 16% (40 patients) of patients who achieved CR and 53% (128 patients) who achieved PR. The median duration of the response (DOR) was 16.6 months, the median PFS was 14.7 months, and the 1-year OS rate was 92% (88% to 95%). In this study, drug-related AEs of any grade were fatigue (23%), diarrhea (15%), and infusion-related reactions (14%). Finally, 29 patients died, but all deaths were considered unrelated to nivolumab. The long-term clinical benefits of anti-PD-1 checkpoint inhibition are not limited to CR patients, even those who did not achieve an objective response may gain clinical benefits [48]. In another single-arm phase 2 study, 80 patients with cHL after failure of both ASCT and BV treatment were recruited; all patients received nivolumab at 3 mg/kg every 2 weeks, and the median number of doses received was 17. The objective response assessed by an independent radiological review committee (IRRC) was 53 patients; CR occurred in 9% (7 patients) and PR in 58% (46 patients); SD and PD rates were 23% and 8%, respectively. The median DOR and median PFS assessed by IRRC were 7.8 months and 10.0 months, respectively [49]. Other clinical trials of nivolumab therapy are shown in **Table 4**.

In a multicohort phase 2 study, 30 patients received pembrolizumab treatment within 21 days after ASCT, 200 mg every 3 weeks for up to 8 cycles. Overall, pembrolizumab improved PFS at 18 months after ASCT from 60% to

Table 5. Common PD-1-related AE [47-50, 53-58]

Treatment-related AEs	Any grade-% related to study drug
Hypothyroidism	8.1%-16.0%
Pyrexia	9.0%-14.0%
Cough	6.0%-6.7%
Fatigue	6.0%-29.2%
Diarrhea	3.5%-16.0%
Vomiting	3.8%-10.0%
Neutropenia	5.2%-9.0%
Rash	7.6%-16%
Pruritus	3.8%-10.4%
Headache	6.2%-7.6%
Arthralgia	3.0%-14.0%
Pneumonitis	2.0%-10.0%

AE, adverse events.

82%; therefore, pembrolizumab is successful as post-ASCT consolidation for high-risk R/R cHL patients [50]. In a single-arm phase II study, 210 patients were enrolled and treated with pembrolizumab. Patients received a median of 13 treatment cycles, and the ORR was 69%, with CR and PR rates of 22.4% (47 patients) and 46.7% (98 patients), respectively. The 9-month PFS rate and OS rate were 63.4% and 97.5%, respectively (**Table 4**) [47].

Treatment-related adverse events of PD-1

Nivolumab and pembrolizumab are well tolerated, but because of immune activation, treatment-related adverse events (AEs) can occur [51, 52]. Common treatment-related AEs of PD-1 inhibitors are hypothyroidism, pyrexia, fatigue, diarrhea, rash, pneumonitis and neutropenia, and only approximately 4-6.3% of patients discontinue treatment because of treatment-related AEs [47-50, 53-58]. PD-1 inhibitors can increase the incidence of graft versus host disease (GVHD) in patients undergoing allogeneic hematopoietic stem cell transplantation (**Table 5**).

Conclusion

Since the FDA approved BV for the treatment of R/R HL, the therapeutic landscape for R/R HL has changed greatly. After ASCT, most cases experienced as CR or PD and generally did not SD. As most studies [16, 17] have confirmed a significant association between pretransplant patient status and posttransplant PFS time, ASCT is also a better option for patients with R/R HL who have achieved CR after salvage therapy. However, for patients with PR, SD or PD, BV and PD-1 inhibitors are new and better choices that can be implemented. BV alone or in combination with other regimens has achieved remarkable results as salvage and consolidation therapy of R/R HL. Immunotherapy with PD-1 inhibitors is still an option after the failure of BV treatment. When using PD-1 inhibitors, even if the patient does not achieve CR, long-term benefits may still be obtained. Immunotherapy can remove minimal residual lesions, improve the cure rate, and achieve a complete cure. BV and PD-1 inhibitors provide new targets for the treatment of patients with R/R HL and offer new hope. Nevertheless, many challenges remain in the treatment of R/R HL. The effect of the combination of BV and traditional chemotherapy is better than that of monotherapy, but treatment-related AEs will also increase; thus, the dose of each drug, the sequence of medication, and the advanced treatment-related AEs are particularly important. The efficacy and safety of PD-1 inhibitors combined with chemotherapy, PD-1 inhibitors combined with epigenetic drugs, and PD-1 inhibitors combined with immunopotentiators (IL-2, vaccine, etc.) need to be further explored.

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Disclosure of conflict of interest

None.

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