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REVIEW

Hematopoietic Stem Cell Transplantation and Brentuximab Vedotin for Patients with Relapsed or Refractory Hodgkin Lymphoma and Systemic Anaplastic Large-Cell Lymphoma

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ABSTRACT

Brentuximab vedotin (BV) is an antibody–drug conjugate that has demonstrated effectiveness as a monotherapy for patients with relapsed or refractory Hodgkin lymphoma and systemic anaplastic large-cell lymphoma via several clinical trials. Salvage chemotherapy followed by autologous or allogeneic hematopoietic stem cell transplantation (HSCT) has been performed as a second- or later-line regimen for improving the survival of patients with lymphoma. In particular, the effectiveness of autologous HSCT and the importance of achieving a complete response prior to autologous HSCT are established in Hodgkin lymphoma. Several clinical trials have reported that salvage chemotherapy followed by autologous HSCT showed high response rates, although significant treatment-related hematological toxicity was observed. In the present article, we review clinical reports for assessing the efficacy and safety of relatively less toxic BV as a bridging therapy before HSCT or as a consolidation therapy post-HSCT in patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large-cell lymphoma. Generally, the reported BV regimens seem to be effective and well tolerated in such patients, and no significant influence of BV treatment is noted on hematopoietic stem cell harvest before HSCT. Large-scale clinical studies and long-term follow-up are expected to establish the safety and efficacy of these regimens.
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Keywords: Anaplastic large-cell lymphoma; Antibody–drug conjugate; Brentuximab vedotin; Bridging therapy; Consolidation therapy; Hematopoietic stem cell transplantation; Hodgkin lymphoma

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INTRODUCTION

The term malignant lymphoma refers to a group of tumors of the lymphoid tissues. Lymphomas are classified into several types based on the origin and differentiation of tumor cells.

Hodgkin lymphoma (HL) is generally a curable disease with a favorable prognosis; however, approximately 5–10% of patients with HL

are refractory to initial treatment and 10–30% of patients relapse after achievement of initial complete remission [1]. There are treatment options for patients with HL who relapse after first-line therapy or those who are refractory to first-line therapy. In general, salvage chemotherapy is provided for these patients and high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HDC/Auto-HSCT) is recommended for patients who show good response to salvage chemotherapy. In patients with relapsed or refractory HL, the 3-year freedom from treatment failure rate was 55% for those who underwent HDC/Auto-HSCT after salvage chemotherapy and 34% for those who received salvage chemotherapy only [2]. In addition, allogeneic HSCT (Allo-HSCT) may be offered to patients with HL who relapse after HDC/Auto-HSCT [3]. A study of major histocompatibility complex-matched Allo-HSCT in patients with relapsed or refractory HL who had no prior Auto-HSCT showed no significant difference in the event-free survival rate and relapse rate between patients who received Auto-HSCT and those who received Allo-HSCT [4]; however, a high rate of transplant-related mortality is a major concern for Allo-HSCT [3].

Systemic anaplastic large cell lymphoma (sALCL) is classified as anaplastic lymphoma kinase (ALK)-positive and ALK-negative depending on the expression of ALK protein, which is based on chromosomal translocation involving 2p23 where the *ALK* gene is located; the treatment strategies and outcomes for ALK-positive and ALK-negative sALCL are different [5]. For ALK-positive sALCL, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy is historically recommended and favorable outcomes with CHOP regimen have been reported in some studies. CHOP has also been widely used as a primary treatment for ALK-negative sALCL; however, the outcomes in ALK-negative sALCL were poorer than those in ALK-positive sALCL (5-year failure-free survival rate, 36% vs. 60%; 5-year overall survival rate, 49% vs. 70%) [6]. Salvage chemotherapy is provided for relapsed or refractory sALCL, whereas HDC/Auto-HSCT or Allo-HSCT may be offered depending on the individual case characteristics; however, there is limited evidence to support the available treatment options.

Brentuximab vedotin (BV) is an antibody–drug conjugate wherein an anti-CD30 monoclonal antibody is conjugated to vedotin comprising microtubule-disrupting agent, monomethyl auristatin E (MMAE), with a linker. After BV binds to CD30, it is internalized into the cell by endocytosis, followed by the release of MMAE from anti-CD30 antibody in the lysosome. Released MMAE subsequently binds to tubulin in the cell and exerts an antitumor effect by inducing cell cycle arrest at the G2/M phase and apoptosis [7].

CD30 is considered to be a highly selective tumor-specific antigen of HL and ALCL cells. CD30 antigen is highly expressed on these cells, whereas its expression on normal cells is restricted to the thymic medulla and activated B and T lymphocytes. In a pivotal phase II study of BV monotherapy in patients with relapsed or refractory HL after HDC/Auto-HSCT, the overall response (OR) rate was 75% with complete response (CR) in 34% of patients after treatment with BV (1.8 mg/kg, i.v. every 3 weeks per cycle for up to 16 cycles) [8]. Another pivotal phase II study of BV monotherapy in patients with relapsed or refractory sALCL showed that 86% and 57% of patients achieved OR and CR, respectively; in addition, comparable effects were observed between ALK-positive (OR 81%; CR 69%) and ALK-negative patients (OR 88%; CR 52%) [9]. Peripheral neuropathy and hematologic toxicity, including lymphocytopenia, neutropenia, and leukopenia, are some of the reported common side effects of BV [8–10]. On the basis of the results of these clinical trials, BV has been widely used in clinical practice for the treatment of relapsed/refractory HL and sALCL. Moreover, BV in a combination therapy decreased the cumulative 2-year combined risk of progression, death, or incomplete response and use of subsequent anticancer therapy in the treatment of patients with advanced-stage untreated HL [11]. In recent years, there has been an increased interest in the use of BV as a bridging therapy prior to HSCT following relapse of HL and ALCL and as a consolidation therapy post-HSCT. In this article, we review the recent clinical studies of BV for HSCT.

STUDY SELECTION AND COLLECTED INFORMATION

We performed a PubMed search in December 2018 with the following query: "brentuximab and stem and (cells or cell) and (Hodgkin or anaplastic large-cell lymphoma) not reviews not (a case report)" and retrieved 124 articles. In addition, BV studies that were presented at conferences and had not been published in PubMed were searched among major international conferences, including American Society of Hematology annual meetings, American Society of Clinical Oncology annual meetings, Congress of The European Hematology Association, and International Conference on Malignant Lymphoma. Updated data by follow-up report or publication until April 2019 were utilized for reviewing. We then determined whether each study met the inclusion criteria. The inclusion criteria for eligible studies were clinical trials of BV prior to HSCT with clear results regarding the safety and effectiveness of BV in adult patients and prospective study in Auto-HSCT. In addition, retrospective studies that focused on Allo-HSCT were included because few prospective studies reported on allogeneic studies. The exclusion criteria were pediatric studies, review articles, meta-analysis, reports other than evaluation for effectiveness of BV therapy, case reports, guidelines, statements, or non-English articles. Through screening the titles, abstracts, and contents, we selected eight studies on salvage therapy for Auto-HSCT, three studies on salvage therapy for Allo-HSCT, and two studies on consolidation therapy, which were reported only in conferences. Collected information was study design, sample size, study phase, common clinical outcome, and safety data.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

BRIDGING THERAPY TO HSCT

Anthracycline-containing regimens such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) [12] and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) [13] are historically used with or without radiotherapy as the first-line treatment of HL. Therefore, non-anthracycline chemotherapy regimens with limited cross-resistance are used in the salvage chemotherapy for relapsed or refractory HL; the available options include platinum-based combination regimens, such as ifosfamide, carboplatin, and etoposide (ICE) [14], dexamethasone, cisplatin, and cytarabine (DHAP) [15], etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP), or gemcitabine-containing combination regimens such as gemcitabine, dexamethasone, and cisplatin (GDP), ifosfamide, gemcitabine, vinorelbine (IGeV), and bendamustine, gemcitabine, and vinorelbine (BeGV) chemotherapy [16]. These regimens typically yield OR rates of approximately 45–90% and CR rates of approximately 13–26% [14–17]; however, they may also cause significant myelosuppression and a number of patients may require red blood cell and platelet transfusion [14–17]. BV therapy is expected to control lymphoma and remains well tolerated until the administration of HSCT based on the low incidence of hematological toxicity observed in several clinical trials that evaluated the efficacy and safety of bridging therapy with BV. Clinical trials of BV monotherapy versus combination therapy prior to Auto-HSCT in patients with relapsed/refractory HL are summarized below.

Salvage Therapy Before Auto-HSCT, BV Monotherapy Followed by Chemotherapy (Sequential Combination)

Positron emission tomography (PET) assessment is useful to predict outcomes of Auto-HSCT in patients with HL, and it is important to obtain a negative result in PET assessment before proceeding to Auto-HSCT [18]. Three studies were performed to assess the activity and safety of a novel, sequential, PET-adapted salvage in patients with relapsed or refractory Hodgkin lymphoma (Table 1). One trial was a

Table 1 Clinical reports of BV followed by Auto-HSCT

Phase	Disease (number of patients, % relapsed, % refractory)	Number of prior therapies	Salvage treatment regimen	OR and CR rates	OS, PFS, and EFS	References
Sequential combination regimen						
II	HL (n = 45, 44%, 56%)	1	BV followed by augmented ICE[a]	BV monotherapy: CR = 27% (of 45 patients) [additional therapy: CR = 69% (of 32 patients)] Overall CR = 76% 98% (44 patients) proceeded to HSCT	2-year OS = 95% 2-year EFS = 80%	Moskowitz [19]
II	HL (n = 37, 35%, 65%)	1	BV followed by other chemotherapy[b]	BV monotherapy: OR = 68%, CR = 35% (of 37 patients) [additional therapy: OR = 83%, CR = 61% (of 18 patients)] Overall OR = 86%, Overall CR = 65% 89% (33 patients) proceeded to HSCT	NR	Chen [20]
IV	HL (n = 60)	Median 2 (1–7)	BV followed by other chemotherapy[c]	BV monotherapy: OR = 50%, CR = 12% (of 60 patients) 47% (28 patients) proceeded to HSCT (BV monotherapy,10; additional therapy, 18)	NR	Walewski [21]
Concurrent combination regimen						
II	HL (n = 66, 39%, 61%)	1	BV + ESHAP[d]	OR = 91%, CR = 70% 91% (60 patients) proceeded to HSCT	Estimated 30-month OS = 91% Estimated 30-month PFS = 71%	Garcia-Sanz [22]
I	HL (n = 12, 83%, 17%)	1	BV + DHAP[e]	CR = 100% (of 12 patients)	NR	Hagenbeek [23]
I/II	HL (n = 23, 39%, 61%)	1	BV + augmented ICE[f]	CR = 87% (of 23 patients): ongoing 86% (19 patients) proceeded to HSCT (of the evaluable 22 patients)	NR	Cassaday [24, 25]
I/II	HL (n = 55 enrolled, 49%, 51%)	1	BV + bendamustine[g]	OR = 92%, CR = 74% (of the 53 evaluable patients) 75% (40 patients) proceeded to HSCT	Estimated 2-year OS = 95% Estimated 2-year PFS = 70%	LaCasce [26]

Table 1 continued

Phase	Disease (number of patients, % relapsed, % refractory)	Number of prior therapies	Salvage treatment regimen	OR and CR rates	OS, PFS, and EFS	References
I/II	HL (n = 62 enrolled, 55%, 45%)	1	BV + nivolumab[h]	OR = 82%, CR = 61% (of 61 treated patients)	Estimated 6-month PFS = 89%	Herrera [27]
			Part 1 & 2	69% (42 patients) proceeded to HSCT directly;		
				20% (12 patients) subsequently after additional salvage		
			Part 3	OR = 93%, CR = 80% (of 30 patients)	Estimated 9-month PFS = 88%	Advani [28]
				83% (25 patients) proceeded to HSCT directly		

Auto-HSCT autologous hematopoietic stem cell transplantation, *OR* overall response, *CR* complete response, *OS* overall survival, *PFS* progression-free survival, *EFS* event-free survival, *NR* not reported, *GND* gemcitabine, navelbine, and doxorubicin liposomal

[a] BV: BV 1.2 mg/kg on days 1, 8, and 15 for two 28-day cycles. ICE: 2 doses of ifosfamide 5 g/m^2 in combination with mesna 5 g/m^2 continuous infusion over 24 h, days 1 and 2; 1 dose of carboplatin AUC 5, day 3; 3 doses of etoposide 200 mg/m^2 every 12 h, day 1, for up to two 28-day cycles

[b] BV: BV 1.8 mg/kg every 3 weeks for a total of 4 cycles. Other chemotherapy: ICE, DICE, IGeV, or GND

[c] BV: BV 1.8 mg/kg every 3 weeks for up to 16 cycles. Other chemotherapy: not reported

[d] BV 1.8 mg/kg/day (day 1 and day 21 [final day of cycle 3]), etoposide 40 mg/m^2/day (days 1–4), methylprednisolone 250 mg/day (days 1–4), high-dose cytarabine 2 g/m^2 (day 5), and cisplatin 25 mg/m^2/day (days 1–4) in a 21–28-day cycle

[e] BV 1.8 mg/kg with 3 courses of DHAP at 3 dosing levels (DL), i.e., dexamethasone 40 mg [days 1–4] + cisplatin (CP) [day 1] + 2 doses of cytarabine [day 2]; dosing levels (DLs) of CP and cytarabine: CP 75%/cytarabine 75% = DL1; CP75%/cytarabine 100% = DL2; CP 100% (100 mg/m^2)/cytarabine 100% (2 g/m^2) = DL3

[f] BV 1.2–1.5 mg/kg on day 1 and day 8, etoposide 100 mg/m^2/day on days 1–3, ifosfamide 5 g/m^2 in combination with mesna 5 g/m^2 on day 2, and carboplatin AUC 5 (capped at 800 mg) on day 2 for two 21-day cycles

[g] BV 1.8 mg/kg on day 1 plus bendamustine 90 mg/m^2 on day 1 and day 2 for up to six 3-week cycles

[h] Part 1 & 2: BV 1.8 mg/kg (day 1 of cycles 1–4) and nivolumab 3 mg/kg (day 8 of cycle 1 and day 1 of cycles 2–4) in a 21-day cycle; Part 3: BV + nivolumab (day 1 of cycles 1–4) in a 21-day

non-randomized, open-label, single-center, phase II trial of sequential salvage therapy comprising BV monotherapy (regimens are presented in the footnote of Table 1) as first salvage treatment and subsequent augmented ICE for patients with PET-positive residual disease. Of the 45 initial patients, 12 patients became PET-negative (CR) after two BV cycles alone. Of the 32 remaining patients who proceeded to HDC using augmented ICE, 22 patients became PET-negative. In the end, a high proportion of patients (98%) proceeded to HDC/Auto-HSCT. The 2-year overall survival and event-free survival rates reached high levels of 95% and 80%, respectively [19]. The second study was a multicenter phase II trial of BV monotherapy followed by other sequential salvage chemotherapy as a bridging therapy prior to Auto-HSCT. Among the 37 patients, 13 patients achieved CR and 12 patients achieved partial response (PR) as evaluated by PET assessment after BV treatment. Overall 33 patients (89%) were able to proceed to Auto-HSCT with 18/33 patients straight after completion of BV therapy and 15/33 patients with additional salvage chemotherapy [20]. The third was a phase IV study evaluating BV in 60 patients who were not suitable for HSCT or multi-agent chemotherapy, including ABVD, ICE, or DHAP. Of them, 7 patients achieved CR and 23 patients achieved PR. Ten patients directly went on to have HSCT and 18 patients received subsequent therapy post-BV and prior to HSCT. Overall 28 (47%) patients proceeded to Auto-HSCT [21].

Thus, even in patients who were initially considered to be ineligible for HSCT, BV monotherapy or BV followed by combination chemotherapy can effectively bridge to HDC/Auto-HSCT and optimize the chance of cure. BV as a second-line therapy is effective with a mild toxicity profile.

Salvage Therapy Before Auto-HSCT, Concurrent Combination of BV with Chemotherapy

The reported clinical trials of BV combination therapy prior to Auto-HSCT are outlined below and summarized in Table 1. A multicenter, open-label, phase II trial of ESHAP salvage chemotherapy combined with BV demonstrated that the OR, CR, and PR rates before Auto-HSCT were 91%, 70%, and 21%, respectively, in 66 patients [22]. Another multicenter phase I trial of DHAP chemotherapy combined with BV prior to Auto-HSCT was performed to determine an optimal dose of DHAP. All 12 patients achieved CR after three dosing levels of treatment and a regimen of BV combined with DHAP at the full dose was recommended for phase II of the study [23].

Following the phase II trial of sequential salvage therapy with BV and augmented ICE described above [19], a phase I/II trial to evaluate the efficacy of ICE and BV combination therapy is ongoing to obtain a higher CR rate prior to Auto-HSCT. To date, 23 patients with relapsed or refractory HL have received the combination therapy. The CR rate was 87% (20 patients) and 19 patients were able to proceed to Auto-HSCT [24, 25].

BV combination therapy with bendamustine was also investigated in a multicenter, open-label, phase I/II trial. The OR rate in 53 patients who received BV plus bendamustine combination therapy was 92% (CR 74%; PR 19%). Overall, 40 of 53 (75%) patients proceeded to Auto-HSCT. Of these 40 patients, 25 patients received additional BV monotherapy (up to 16 total doses) after Auto-HSCT. The estimated 2-year overall survival and progression-free survival (PFS) were 95% and 70%, respectively, in those who underwent Auto-HSCT [26]. Moreover, another multicenter phase I/II study evaluated the administration of BV with an anti-PD1 antibody–drug, nivolumab, prior to HSCT. This study comprised three parts. In parts 1 and 2, a total of 62 patients received up to four 21-day cycles of staggered dosing of BV and nivolumab (cycle 1) followed by concurrent dosing thereafter. The OR rate was 82% (CR 61%) in 61 patients, of whom 54 patients received Auto-HSCT. Of the 54 patients, 42 patients (69%) underwent Auto-HSCT directly after treatment with BV and nivolumab [27]. In part 3, 30 patients received up to four 21-day cycles of concurrently dosed BV plus nivolumab on day 1. The OR and CR rates for part 3 were

93% and 80%, respectively, and 25 patients (83%) directly proceeded to Auto-HSCT [28]. These studies demonstrated the tolerability and efficacy of BV plus nivolumab in outpatients.

Collectively, concurrent combination chemotherapy with BV may also effectively bridge to HDC/Auto-HSCT. In addition, most of them were tolerated. However, as the number of patients in each study was smaller than 100, we should interpret the results of these studies with caution. Further studies are needed to elucidate the effectiveness and safety profile.

Peripheral Blood Stem Cell Harvest After BV Chemotherapy

A sufficient amount of harvested hematopoietic stem cells before Auto-HSCT is required to allow successful engraftment and swift hematopoietic recovery. Therefore, salvage chemotherapy before Auto-HSCT needs to provide high numbers of harvested stem cells as well as high treatment efficacy. Table 2 summarizes reports of hematopoietic stem cell harvests after BV therapy, including yield of hematopoietic stem cells, required harvesting time, complications, and time to engraftment.

A retrospective analysis compared 42 patients with malignant lymphoma (including HL, ALCL, and others) who underwent Auto-HSCT with prior BV treatment and 125 patients with malignant lymphoma who underwent Auto-HSCT without prior BV treatment. No significant difference was observed in the median number of collected $CD34^+$ cells between the two cohorts (with prior BV 5.46×10^6 cells/kg; without prior BV 5.1×10^6 cells/kg; $p = 0.38$). The mobilization regimens for patients who received BV therapy included chemotherapy/G-CSF in 32 patients (76%) and

Table 2 Peripheral blood stem cell harvest post BV chemotherapy

Disease	Mobilization regimen (number of patients)	$CD34^+$ cell yield (median, $\times 10^6$ cells/kg)	References
$CD30^+$ lymphoma	Overall (42)	5.46	Afable [29]
	Chemotherapy/G-CSF (32)	5.53	
	Plerixafor/G-CSF (10)	4.81	
HL	Cyclophosphamide/G-CSF (22)	6.0	Chen [20]
	G-CSF (2)		
	Plerixafor following cyclophosphamide/G-CSF (9)		
HL	G-CSF (64)	5.75	Garcia-Sanz [22]
HL	G-CSF (12)	5.3	Hagenbeek [23]
HL	G-CSF with/without plerixafor (37)	4.2 (of 39 patients)	LaCasce [26]
	Cyclophosphamide/G-CSF (4)		
HL	G-CSF (23)	4.7	Herrera [27]
	Cyclophosphamide/G-CSF (14)		
	Plerixafor/G-CSF (5)		
	Chemotherapy/G-CSF (2)		

plerixafor/G-CSF in 10 patients (24%). In most patients, stem cell harvest was completed at the first attempt. These mobilization regimens led to similar numbers of collected $CD34^+$ cells. All patients who received BV therapy engrafted neutrophils and platelets at a median time of 10 days (range 9–13 days) and 10.5 days (range 7–35 days), respectively. This study suggested that BV before HDC/Auto-HSCT does not adversely affect peripheral blood stem cell mobilization and subsequent engraftment in a cohort of heavily pretreated patients with $CD30^+$ lymphomas [29].

In addition, the results of peripheral blood stem cell harvest after BV therapy from the earlier described clinical trials of BV monotherapy and combination chemotherapy have also been reported. In a phase II trial of BV as a second-line therapy, all 33 patients who underwent Auto-HSCT successfully mobilized stem cells, using cyclophosphamide (1.5 g/m^2) and G-CSF (10 μg/kg) (22 patients), G-CSF only (2 patients), or plerixafor (9 patients). None of the patients required a second round of mobilization. The median cell dose collected was 6.0×10^6 CD34 cells (range 2.6–34 $\times$ 10^6). The median number of days required for collection was 2 (range 1–6). The median time to neutrophil engraftment was 11 days (range 10–12) and median time to platelet engraftment was 13 days (range 9–23) [20].

As shown in Table 2, similar results were reported in other trials of combination therapies, including BV plus ESHAP [22], BV plus DHAP [23], BV plus bendamustine [26], and BV plus nivolumab [27].

These studies indicate feasibility of stem cell harvest after BV monotherapy or combination chemotherapy of BV with HDC/followed by Auto-HSCT, and it is believed that BV would not significantly affect the stem cell harvesting efficacy.

BV Monotherapy Before Allo-HSCT

Because no prospective studies were reported when we searched studies in PubMed, three retrospective studies were reviewed (Table 3). One study extracted a subset of patients who underwent Allo-HSCT in two phase II trials of HSCT following BV treatment for relapsed/refractory HL and sALCL as second-line treatment. A total of 15 outpatients (HL 7 patients; sALCL 8 patients) obtained an objective response with CR in 12 patients (5 with HL and 7 with sALCL) and proceeded to Allo-HSCT. The estimated 2-year PFS rate was 66% and the estimated 2-year survival rate was 80% [30]. According to another case-series study, the OR rate with BV was 67% (CR in 11 patients and PR in 5 patients) in 24 patients with relapsed and/or refractory HL; 3 patients underwent Auto-HSCT, 3 patients received tandem Auto-HSCT/Allo-HSCT, 9 patients received Allo-HSCT, and 1 patient was treated with donor lymphocyte infusion (DLI). None of the patients, including those with Allo-HSCT, relapsed or died over a median follow-up of 20 months (range 10.5–43.2) [31]. In addition, the other retrospective study reviewed the cases of Allo-HSCT following intravenous administration of BV as a planned bridge to Allo-HSCT in patients with HL (10 patients) or sALCL (2 patients) who relapsed after prior Auto-HSCT or were not eligible for Auto-HSCT, and did not respond to the most recent line of salvage chemotherapy. The OR rate was 67%, and 2-year PFS and post-Allo-HSCT overall survival rates were 58% and 92%, respectively, at a median follow-up of 30 months [32].

Although the numbers of patients involved in these reports were quite small, BV could successfully bridge to Allo-HSCT. According to these studies, the safety of BV treatment was consistent with the known safety profile and without adding significant post-transplant toxicity. Therefore, BV would be a bridging option with mild toxicity to Allo-HSCT.

CONSOLIDATION THERAPY WITH BV AFTER HSCT

Auto-HSCT was shown to improve PFS in patients with relapsed HL; however, approximately 50% of patients were still not cured [2]. Several clinical trials have evaluated the efficacy of consolidation therapy where BV was used for improving outcomes after HSCT (Table 4). A

Table 3 Clinical reports of BV followed by Allo-HSCT

Phase	Disease (number of patients)	Median number (range) of prior therapies	Treatment regimen	OR and CR rates	OS and PFS	References
Case series study of phase II	HL (7) ALCL (8)	3 (2–5)	BV monotherapy[a]	OR = 100%, CR = 71% (of 7 HL patients) OR = 100%, CR = 88% (of 8 ALCL patients)	Estimated 2-year OS = 80% Estimated 2-year PFS = 66%	Illidge [30]
Case series study	HL (24)	2 (2–4)	BV monotherapy[b]	OR = 67%, CR = 46% (of 24 patients): Auto-HSCT (3 patients), tandem Auto-HSCT/Allo-HSCT (3 patients), Allo-HSCT (9 patients), donor lymphocyte infusion (1 patient)	OS = 80%* PFS = 67%*	Garciaz [31]
Case series study	HL (10) ALCL (2)	4 (3–6) 3 (3–3)	BV monotherapy[c]	OR = 67%, CR = 33% (of 12 patients)	2-year OS = 92% 2-year PFS = 58%	Mediwake [32]

Allo-HSCT allogeneic hematopoietic stem cell transplantation, *Auto-HSCT* autologous hematopoietic stem cell transplantation, *OR* overall response, *CR* complete response, *OS* overall survival, *PFS* progression-free survival

*Survival for 24 patients, including patients without Allo-HSCT, with a median follow-up of 13 months (range 5.4–43.2)

[a] BV 1.8 mg/kg every 3 weeks for up to 16 cycles

[b] BV 1.8 mg/kg every 3 weeks

[c] BV 1.8 mg/kg every 3 weeks for up to 4 cycles

Table 4 Clinical reports of BV consolidation therapy post-HSCT

Phase	Disease (number of patients)	Treatment regimen	OR and CR rates	PFS	References
Phase III AETHERA study	HL (BV group: 165, placebo group: 164)	BV single-agent consolidation therapy (after Auto-HSCT)	NR	5-year PFS = 59% (BV group), 41% (placebo group)	Moskowitz [34]
Case series study	HL (16)	BV single-agent consolidation therapy (after Allo-HSCT)	OR = 69%, CR = 54% (of 13 patients): patients who relapsed after Allo-HSCT CR = 100% (of 3 patients): patients without progression after Allo-HSCT	NR	Tsirigotis [36]

Allo-HSCT allogeneic hematopoietic stem cell transplantation, *Auto-HSCT* autologous hematopoietic stem cell transplantation, *OR* overall response, *CR* complete response, *PFS* progression-free survival, *NR* not reported

phase III trial, the AETHERA study, was a randomized, double-blind, placebo-controlled study of consolidation therapy with BV after Auto-HSCT in patients with unfavorable-risk relapsed or primary refractory HL who had undergone Auto-HSCT. Patients who had at least one of the following risk factors for progression after Auto-HSCT were enrolled in this trial: primary refractory HL (failure to achieve complete remission as determined by investigator), relapsed HL with an initial remission duration of less than 12 months, or extranodal involvement at the start of pre-transplantation salvage chemotherapy. Eligible patients were randomly assigned 30–45 days after Auto-HSCT for receiving 16 cycles of BV 1.8 mg/kg or placebo every 3 weeks. At 5-year follow-up, the median PFS with BV (165 patients) was not reached and was 15.8 months with placebo (164 patients). The 5-year PFS rate was 59% in the BV group and 41% in the placebo group (hazard ratio, 0.52). No significant difference was noted between the two groups with respect to mortality. At 5 years, 40 (24%) patients in the BV group and 37 (23%) patients in the placebo group had died. Notably, 77 (87%) of 89 patients in the placebo group subsequently received BV treatment after disease progression [33, 34]. BV maintenance and/or consolidation in BV-naïve high-risk HL is recommended by a consensus project by the American Society for Blood and Marrow Transplantation (ASBMT), Center for International Blood and Marrow Transplant Research (CIBMTR), and the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation (EBMT) [35].

In addition, a case-series study of consolidation therapy with BV after Allo-HSCT has been reported using data sets from four transplant centers. Sixteen patients with advanced HL received BV with (10 patients) or without (6 patients) DLI as consolidation therapy after Allo-HSCT. In the 13 patients who relapsed after Allo-HSCT, the OR rate after BV treatment was 69% (CR, 7 patients; PR, 2 patients). All 3 patients who did not show progression of HL after Allo-HSCT achieved CR after BV treatment. After a median follow-up of 13 months, the survival rate was 81% (13 of 16 patients) and the median PFS was 6 months [36].

Considering these results, consolidative BV after Auto-HSCT is an important treatment alternative for patients with risk factors for relapse or progression after HSCT. Furthermore, consolidative BV in combination with DLI post-

Allo-HSCT seems safe and effective, providing one approach worth considering.

SAFETY

Table 5 summarizes the safety of BV surrounding HSCT and shows whether adverse events were drug-related or not. MMAE contained in BV is a potent microtubule inhibitor, which is known to be associated with a risk of myelosuppression and peripheral neuropathy. Results of recent large-scale BV studies also identified these as the most common adverse effects of BV therapy [37, 38]. In the AETHERA study, grade 3 and higher neutropenia occurred in 49 (29%) of 167 patients in the BV group. Incidence rates of grade 3 and higher infection were 7% in the BV group and 6% in the placebo group; these findings indicate that myelosuppression is unlikely to be a significant risk. Incidence of secondary malignancies was comparable in the two treatment groups (BV 4% vs. placebo 2%). Discontinuation of treatment due to an adverse event occurred in 54 patients (33%) in the BV group, most commonly because of peripheral neuropathy (23%) [33, 34]. Relatively long-term safety evaluation studies of BV therapy have investigated the incidence and recovery of BV-related peripheral neuropathy; the results showed that most patients tend to experience complete resolution (Table 6) [21, 39, 40].

In addition to myelosuppression, peripheral neuropathy, and infection, the commonly reported severe adverse events (≥ grade 3) include gastrointestinal symptoms (nausea, mucositis, diarrhea, and constipation), skin symptoms (pruritus and rash), hepatic disorders (transaminase elevation), metabolism abnormality (hyperglycemia and hypoglycemia), dyspnea, fever, and fatigue. The serious adverse events, death, events leading to discontinuation, and other significant events are unique to each regimen. In sequential salvage therapy with BV followed by augmented ICE as bridging therapy, death related to a serious adverse event occurred after HDC/Auto-HSCT in a patient who received BV and augmented ICE. The patient developed progressive multifocal leukoencephalopathy 5 months after HDC/Auto-HSCT and died 2 months later [19]. In BV therapy in combination with DLI as consolidation therapy after Allo-HSCT, DLI-associated graft-versus-host disease (GVHD) occurred in 7 of 10 patients. Five patients with GVHD required treatment, and in all cases, GVHD resolved after a short course of low-dose steroids [36].

Furthermore, in BV combination chemotherapy for Auto-HSCT, a variety of dose-limiting adverse events have been reported, e.g., ventricular function reduction and pulmonary embolism in BV plus ESHAP combination chemotherapy [22, 41], acute liver failure lasting more than 14 days and atrial fibrillation in BV plus DHAP combination chemotherapy [23], infusion-related reactions in BV plus bendamustine combination salvage chemotherapy [26], and BV plus nivolumab combination chemotherapy [27]. In BV plus ICE combination chemotherapy, dose-limiting toxicity (sepsis) occurred in 9 of 16 patients treated in the dose-escalation phase of BV, in which 1.5 mg/kg was administered on day 1 and day 8 of the 21-day cycle as the maximal tolerated dose of BV in combination with ICE. One patient discontinued the treatment because of an adverse event (neuropathy) [24, 25].

On the basis of those studies, it appears that treatment-related adverse events tend to be more severe when BV is combined with other chemotherapy as bridging therapy prior to Auto-HSCT. Although safety reports for BV combination therapy have been limited, due caution is required when BV is administered in combination with other agents. On the other hand, grade 3 or higher adverse events, including mainly myelosuppression and peripheral neuropathy, have been reported for BV monotherapy before or after autologous/allogeneic HSCT, and there was no significant difference in their types and frequencies as compared with previous safety reports for BV monotherapy.

DISCUSSION

Since the advent of new drugs for malignant lymphoma, there has been a definite increase in

Table 5 Adverse events of BV

Regimen	Monotherapy										Combination therapy							
									(Consolidation)		+ ESHAP		+ DHAP		+ Bendamustine		+ Nivolumab	
Author	Moskowitz [19]		Chen [20]		Walewski [21]		Illidge [30]		Moskowitz [33]		Garcia-Sanz [22]		Hagenbeek [23]		LaCasce [26]		Herrera [27]	
Trial name									AETHERA				BRaVE					
Phase	Phase II		Phase II		Phase IV		Phase II		Phase III		Phase I/II		Phase I		Phase I/II		Phase I/II	
Number of patients	*N* = 45		*N* = 37		*N* = 60		*N* = 15		*N* = 167		*N* = 66		*N* = 12		*N* = 55		*N* = 61	
Drug-related events ONLY	Yes		Yes		No		No		No		Yes		Yes		No		No	
Event grade	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3
Hematological toxicity																		
Anemia	–	–	19%	0%	–	5%	–	–	–	–	94%	19%	–	–	–	–	–	3%
Febrile neutropenia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3%
Neutropenia	11%	0%	16%	5%	10%	5%	47%	47%	35%	29%	96%	50%	–	25%	–	–	–	3%
Thrombocytopenia	18%	0%	8%	0%	–	–	–	–	–	–	100%	47%	–	8%	–	–	–	–
Lymphopenia	–	–	9%	6%	–	–	–	–	–	–	–	–	–	–	–	11%	–	–
Peripheral neuropathy																		
All	–	–	52%	0%	35%	0%	–	–	–	–	22%	0%			24%	0%	–	–
Sensory	49%	0%	–	–	–	–	53%	13%	56%	10%	–	–	33%	0%	–	–	15%	0%
Motor	–	–	–	–	–	–	–	–	23%	6%	–	–	0%	0%	–	–		
Others																		
Alopecia	20%	0%	–	–	–	–	–	–			–	–	–	–	20%	0%	13%	0%
ALT elevation	–	–	38%	0%	–	–	–	–	–	–	–	–	–	8%	–	–	–	–
AST elevation	–	–	40%	3%	–	–	–	–	–	–	–	–	–	8%	–	4%	–	–
Asthenia	–	–	–	–	–	–	–	–	–	–	23%	3%	–	–	–	–	–	–
Constipation	31%	0%	–	–	–	–	–	–	13%	2%	11%	0%	–	–	24%	–	10%	2%
Chills	–	–	–	–	–	–	27%	0%	10%	0%	–	–	–	–	22%	4%	16%	0%

Table 5 continued

Regimen	Monotherapy										Combination therapy							
									(Consolidation)		+ ESHAP		+ DHAP		+ Bendamustine		+ Nivolumab	
Author	Moskowitz [19]		Chen [20]		Walewski [21]		Illidge [30]		Moskowitz [33]		Garcia-Sanz [22]		Hagenbeek [23]		LaCasce [26]		Herrera [27]	
Trial name									AETHERA				BRaVE					
Phase	Phase II		Phase II		Phase IV		Phase II		Phase III		Phase I/II		Phase I		Phase I/II		Phase I/II	
Number of patients	*N* = 45		*N* = 37		*N* = 60		*N* = 15		*N* = 167		*N* = 66		*N* = 12		*N* = 55		*N* = 61	
Drug-related events	Yes		Yes		No		No		No		Yes		Yes		No		No	
ONLY Event grade	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3
Cough	22%	0%	–	–	–	–	–	–	21%	0%	–	–	–	–	–	–	21%	0%
Diarrhea	22%	0%	–	–	10%	0%	47%	7%	20%	2%	–	–	–	–	36%	4%	26%	2%
Dyspnea	11%	0%	–	–	–	–	27%	7%	13%	0%	–	–	–	–	24%	4%	20%	0%
Fatigue	67%	0%	30%	0%	–	–	–	–	24%	2%	–	–	–	–	40%	–	41%	2%
Fever	–	–	–	–	18%	3%	53%	0%	19%	2%	48%	8%	–	–	35%	4%	20%	0%
Headache	–	–	–	–	–	–	–	–	11%	2%	–	–	–	–	–	–	25%	0%
Hyperglycemia	69%	4%	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hypoglycemia	27%	4%	22%	0%	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Mucositis	–	–	–	–	–	–	–	–	–	–	30%	8%	–	–	–	–	–	–
Muscle weakness	–	–	29%	0%	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Nasal congestion	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	20%	0%
Nausea	29%	2%	19%	0%	–	–	33%	0%	22%	3%	–	–	–	–	69%	0%	49%	0%
Pain	–	–	–	–	–	–	–	–	–	–	29%	0%	–	–	–	–	–	–
Pruritus	22%	0%	25%	3%	–	–	–	–	12%	1%	–	–	–	–	–	–	31%	2%
Rash	58%	0%	40%	5%	–	–	–	–	–	–	–	–	–	–	20%	13%	20%	0%

Table 5 continued

Regimen	Monotherapy										Combination therapy							
									(Consolidation)		+ ESHAP		+ DHAP		+ Bendamustine		+ Nivolumab	
Author	Moskowitz [19]		Chen [20]		Walewski [21]		Illidge [30]		Moskowitz [33]		Garcia-Sanz [22]		Hagenbeek [23]		LaCasce [26]		Herrera [27]	
Trial name									AETHERA				BRaVE					
Phase	Phase II		Phase II		Phase IV		Phase II		Phase III		Phase I/II		Phase I		Phase I/II		Phase I/II	
Number of patients	*N* = 45		*N* = 37		*N* = 60		*N* = 15		*N* = 167		*N* = 66		*N* = 12		*N* = 55		*N* = 61	
Drug-related events ONLY	Yes		Yes		No		No		No		Yes		Yes		No		No	
Event grade	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3	Any	≥ 3
URT infection	–	–	–	–	–	–	–	–	26%	0%	–	–	–	–	–	–	–	–
Vomiting	–	–	–	–	–	–	–	–	16%	2%	28%	0%	–	–	35%	0%	21%	0%

Other than hematological toxicity and peripheral neuropathy, adverse events that occurred in at least 20% in any one of the reviewed studies are shown
– not reported, *BV* brentuximab vedotin, *URT* upper respiratory tract, *DHAP* dexamethasone, high-dose cytarabine, cisplatin, *ESHAP* etoposide, methylprednisolone, cytarabine, and cisplatin

Table 6 Recovery of BV-related peripheral neuropathy

	AETHERA study [33, 34]	Pivotal phase II study of BV monotherapy (HL) [39]	Pivotal phase II study of BV monotherapy (ALCL) [40]	Phase IV study BV monotherapy + subsequent chemotherapy [21]
Follow-up period	5 years	~ 3 years into LTFU (5 years)	~ 2 years into LTFU (5 years)	18 months
Incidence	67% [112/167]	55% [56/102]	57% [33/58]	35% [21/60][b]
Complete resolution	73% [82/112]	73% [41/56]	67% [22/33[a]]	57% [12/21]
Improvement	17% [19/112]	14% [8/56]	24% [8/33[a]]	
Residual grade 1 PN	9% [10/112]	20% [11/56]	24% [8/33[a]]	24% [5/21]
Residual grade 2 PN	3% [3/112]	7% [4/56]	9% [3/33[a]]	14% [3/21]
Residual grade 3 PN	1% [1/112]	0%	0%	5% [1/21]

PN peripheral neuropathy, *LTFU* long-term follow-up

[a] Three of 33 patients were not evaluable because of death

[b] Treatment-related PN: 32% [19/60]

options for salvage therapy prior to HSCT. The goal of salvage therapy is to achieve high-quality responses prior to HDC/Auto-HSCT and preserve the number and quality of hematopoietic stem cells. To define an optimal second-line regimen for relapsed or refractory patients, it is important to compare regimens according to the disease status and treatment background of patients.

BV is an antibody–drug conjugate whose therapeutic efficacy as a single-agent chemotherapy for relapsed/refractory HL and sALCL is well established. BV monotherapy prior to Auto-HSCT in patients with relapsed/refractory HL and sALCL has shown high response rates and an acceptable safety profile; moreover, BV treatment does not significantly affect hematopoietic stem cell harvest before Auto-HSCT. In addition, BV therapy has shown high response rates and better outcomes as consolidation therapy post-Auto-HSCT/Allo-HSCT and as bridging therapy prior to Allo-HSCT. BV therapy for HSCT is well tolerated; long-term follow-up results of BV therapy for HSCT showed that peripheral neuropathy (the most common BV-related adverse event) resolved or improved in a majority of the patients. Also, the incidence rate of GVHD following Allo-HSCT was low. Therefore, BV therapy is expected to be effective when used as a bridging therapy prior to HSCT or as a consolidation therapy post-HSCT. However, much of the available evidence pertaining to BV for HSCT has emanated from phase II trials and case-series reports; large-scale clinical studies and long-term follow-up are required for more definitive evidence. In particular, a couple of studies on BV therapy in combination with other drugs prior to Auto-HSCT are limited to conference presentations. As most of these reports showed that BV combination therapy had more serious adverse events, which led to discontinuation, than BV monotherapy, careful

examination of the efficacy and safety of BV combination therapy is a key imperative.

CONCLUSIONS

The clinical trials and case series reviewed in this article suggest that BV is effective and tolerable as a bridging therapy prior to autologous/allogeneic HSCT or as a consolidation therapy post-HSCT for patients with relapsed or refractory HL or sALCL. Moreover, BV treatment would not significantly affect the harvesting of hematopoietic stem cells prior to Auto-HSCT. Further large-scale clinical studies and long-term follow-up are required for confirming the safety and efficacy of each regimen.

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