Annals of Hematology
https://doi.org/10.1007/s00277-018-3379-5

ORIGINAL ARTICLE

Brentuximab vedotin as salvage treatment in Hodgkin lymphoma naïve transplant patients or failing ASCT: the real life experience of Rete Ematologica Pugliese (REP)

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Received: 12 June 2017 / Accepted: 21 May 2018

Abstract

Brentuximab vedotin (BV) shows a high overall response rate (ORR) in relapsed/refractory (R/R) Hodgkin lymphoma (HL) after autologous transplant (ASCT). The aim of this multicenter study, conducted in nine Hematology Departments of Rete Ematologica Pugliese, was to retrospectively evaluate the efficacy and safety of BV as salvage therapy and as bridge regimen to ASCT or allogeneic transplant (alloSCT) in R/R HL patients. Seventy patients received BV. Forty-five patients (64%) were treated with BV as bridge to transplant:16 (23%) patients as bridge to ASCT and 29 (41%) as bridge to alloSCT. Twenty-five patients (36%), not eligible for transplant, received BV as salvage treatment. The ORR was 59% (CR 26%). The ORR in transplant naïve patients was 75% (CR 31%). In patients treated with BV as bridge to alloSCT, the ORR was 62% (CR 24%). In a multivariate analysis, the ORR was lower in refractory patients ($p < 0.005$). The 2y-OS was 70%. The median PFS was 17 months. Ten of the 16 (63%) naïve-transplant patients received ASCT, with 50% in CR before ASCT. In the 29 patients treated with BV as bridge to alloSCT, 28 (97%) proceeded to alloSCT with 25% in CR prior to alloSCT. The most common adverse events were peripheral neuropathy (50%), neutropenia (29%) and anemia (12%). These data suggest that BV is well tolerated and very effective in R/R HL, producing a substantial level of CR. BV may also be a key therapeutic agent to achieve good disease control before transplant, improving post- transplant outcomes, also in refractory and heavily pretreated patients, without significant overlapping toxicities with prior therapies.

Keywords Relapsed/refractory Hodgkin lymphoma · Brentuximab vedotin salvage treatment · Autologous and allogeneic stem cell transplant

Introduction

Historically, the standard treatment for relapsed and primary refractory Hodgkin lymphoma (HL) is salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (ASCT). This treatment achieves long-term remission in almost 50% of patients [1, 2]. Nevertheless ASCT is a treatment option limited to younger patients, and the outcomes

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Published online: 27 July 2018

remain poor among those with refractory disease, where long-term survival rarely exceeds 25% [3, 4]. The most relevant prognostic factor is the disease status before ASCT [5–7].

Brentuximab vedotin (BV), an antibody-drug conjugates (ADC) targeting CD30, a cell-surface antigen expressed on malignant Hodgkin Reed–Sternberg cells of classical HL, consists of a CD30-targeted monoclonal antibody (cAC10) covalently linked to the microtubule disrupting agent, monomethyl auristatin E (MMAE) by a protease-cleavable linker [8, 9]. BV has shown a high overall response rate in relapsed or refractory (R/R) HL after ASCT [8, 9]. In the pivotal phase II study, in R/R HL patients after ASCT, 75% of patients achieved an objective response, and 34% of patients achieved a complete response (CR) [10]. Recent updates of the pivotal study have shown that BV can induce complete lasting remission, also without additional consolidation therapies, in HL pretreated cases suggesting that BV may be curative for some patients [11]. Few data are available regarding BV before ASCT or allogeneic transplant (alloSCT), but preliminary results are encouraging [12, 13, 23]. Recently, updated data on survival after alloSCT from a single institution were presented, showing that the improved responses occurred in recent years and the reduced morbidity may be attributable to the use of BV as a safer and more effective salvage alternative before alloSCT [24]. Diversly, in a more recent report from the EBMT Lymphoma Working Party, patients allografted for HL after prior exposure to BV do not have a superior outcome after allogeneic SCT. However, patients with BV-induced remission prior to transplant do not do worse than chemosensitive patients, implying that BV may improve the outlook of allogeneic SCT by helping refractory patients to achieve a more favorable disease status, facilitating allotransplant success [25]. A multicenter, retrospective analysis was conducted in nine Hematology Departments of Rete Ematologica Pugliese (REP), to analyze the outcomes and toxicity of BV as salvage therapy, in the real-life setting. Herein, we evaluated the role of BV as bridge to ASCT or to reduced intensity allogeneic transplant (RIC alloSCT).

Patients and methods

Study design and treatment

From April 2012 to January 2016, in nine hematology centers of REP, BV was used in R/R HL patients, aged ≥ 18 years, as bridge to transplant (SCT) or as salvage treatment. Patients received BV at standard dose (1.8 mg/kg intravenous infusion over 30 min, once every 3 weeks) for a maximum of 16 cycles. Patients candidate for SCT were to receive four BV cycles, as a planned bridge to SCT, and responsive patients underwent SCT. Additional BV cycles were given to patients waiting for the SCT procedure. Patients not elegible for transplant, due to age/bad performance status, lack of donor availability, insufficient CD34 cells harvest, chemo-refractory disease or relapse after previous SCT, received BV as salvage treatment (Fig. 1).

The primary endpoint was overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), the eligibility to proceed to SCT after BV, ORR post transplant, and safety profile of BV. ORR included complete response (CR) and partial response (PR). PFS was defined as the time from the date of treatment initiation to the date of progression or relapse; patients alive without relapse or progression were censored at the time of last contact. OS was defined as death from any cause.

Statistical analysis

Descriptive statistics were computed for demographic as well as baseline variables. *P*-values were based on the Wilcoxon rank sum test. Categorical variables were compared using the χ^2 test. p value were considered significant when < 0.05. OS and PFS survival probabilities were calculated by the Kaplan-Meyer method [14] and $p < 0.05$ defined statistical significance. Analyses were computed using SPSS Software version 20.0.

Study assessments

Response was scored using standard criteria [13]. The disease response was assessed by PET scans at cycles 4, 10, 16, and at the end of therapy. The post transplant evaluation of disease status occurred at + 90 days, by PET/TC and/or CT scans. Safety and tolerability were evaluated by recording the incidence, severity, and type of any adverse event (AE) according to the National Cancer Institute Common Terminology Criteria for AEs v4.0.

Results

Patient characteristics

Demographic and baseline clinical characteristics of the 70 patients are summarized in Table 1. The patients in this study were heavily pretreated, and 46 (66%) underwent high-dose chemotherapy and HSCT before BV. The median number of prior regimens was 3 (range, 2–6), and 64% received ≥ 3 prior chemotherapies. Median time from SCT to relapse was 5 months (range, 1–73), and 52% of patients relapsed in the first 6 months. PET scans were

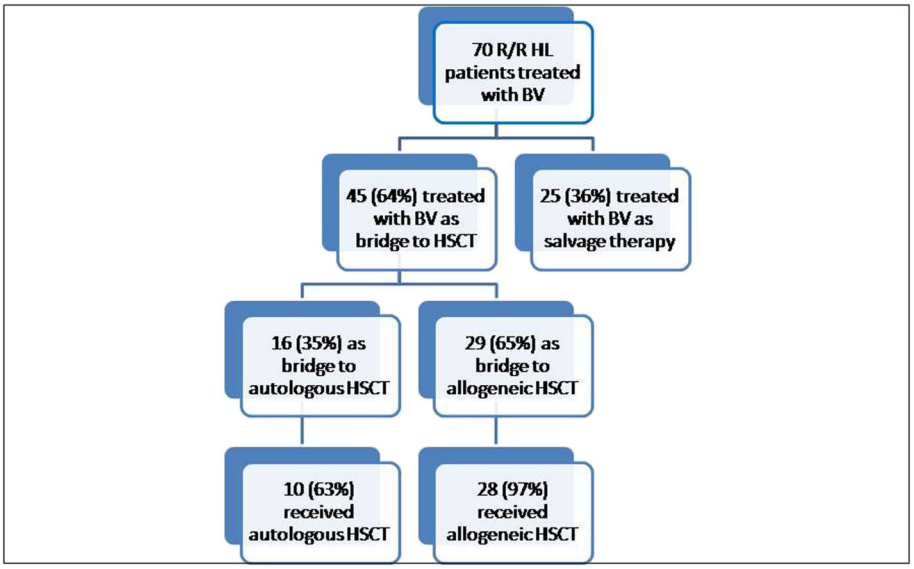

Fig. 1 Study schema. Patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL) treated with brentuximab vedotin (BV) as bridge to transplant (HSCT) or as salvage therapy

positive in all 70 patients (100%). Thirty-three (47%) had refractory disease. No differences in baseline characteristics were observed between the different cohorts of patients, except for the median age (older patients in the salvage group: median age 52 (16–84) and the median number of prior chemotherapy regimens which was lower in the cohort of patients treated with BV as bridge to ASCT (2 vs 3; $p < 0.001$).

Table 1 Demographics and baseline clinical characteristics at enrollment

	No. of patients (%) ($n = 70$)	Bridge to auto SCT ($n = 16$)	Bridge to allo SCT ($n = 29$)	Salvage therapy ($n = 25$)	p
Median age, yrs. (range)	34 (15–84)	30 (15–65)	32 (22–54)	52 (16–84)	
> 50 yrs	19 (28)	5 (31)	2 (7)	12 (50)	0.001
Disease status at BV					
Refractory	33 (47)	6 (37)	13 (45)	14 (56)	0.48
Relapsed	37 (53)	10 (63)	16 (55)	11 (44)	
ECOG performance status					
0	42 (60)	10 (62)	20 (69)	11 (44)	0.38
1–2	28 (40)	6 (38)	9 (31)	14 (56)	
Baseline B symptoms	39 (57)	12 (75)	14 (48)	13 (56)	0.22
Extranodal disease at diagnosis	29 (44)	7 (47)	10 (37)	12 (59)	0.6
Bulky disease	22 (33)	6 (40)	12 (44)	4 (16)	0.09
III–IV stage	44 (64)	11 (69)	16 (55)	17 (71)	0.68
Median prior chemotherapy regimens, (range)	3 (1–6)	2 (2–3)	3 (2–5)	3 (1–6)	0.001
≥ 3	42 (64)	4 (27)	23 (82)	15 (66)	
First remission < 12 months	41 (68)	12 (80)	17 (68)	12 (60)	0.45
Median time from diagnosis to BV, months (range)	17 (3–111)	14 (5–111)	20 (4–86)	19 (3–104)	0.08
≥ 17	30 (43)	4 (27)	17 (61)	9 (56)	
Prior radiation	16 (23)	2 (12)	8 (28)	6 (26)	0.48
Prior Auto-SCT	40 (57)	NA	28 (97)	12 (48)	0.001
Prior Allo-SCT	6 (9)	NA	NA	6 (100)	0.002
Median time from auto to-relapse, months (range)	5 (1–73)	NA	5 (1–44)	5	0.71
< 6 months	21 (52)		9 (32)	1 (8)	

No number, *ECOG* Eastern Cooperative Oncology Group, *yrs. years*, *BV* brentuximab vedotin, *ASCT* autologous stem cell transplant, *AlloSCT* allogeneic stem cell transplant, *NA* not applicable

Table 2 Key response results

	Whole cohort ($n = 70$) No. (%)	Bridge to ASCT ($n = 16$)	Bridge to allo SCT ($n = 29$) No. (%)	Salvage therapy ($n = 25$)	p
Objective response	41 (59)	12 (75)	18 (62)	11 (44)	0.31
Complete remission	18 (26)	5 (31)	7 (24)	6 (24)	
Partial remission	23 (33)	7 (44)	11 (38)	5 (20)	
Progressive disease	29 (41)	4 (25)	11 (38)	14 (56)	

ASCT autologous stem cell transplant, *AlloSCT* allogeneic stem cell transplant, *No.* number

Efficacy

A total of 45 patients (64%) were treated with BV as bridge to SCT; 16 (23%) and 29 (41%) patients as bridge to ASCT and RIC alloSCT, respectively. Twenty-five (36%) patients, not eligible for transplant, received BV as salvage treatment (Fig. 1). Responses and outcomes (PFS and OS) are summarized in Tables 2, 3, and 4 and Figs. 2 and 3.

The ORR of the whole group was 59% including 26% CR. Twenty-nine patients (41%) were not responsive to BV.

Univariate analyses revealed that the ORR was lower in patients with early first-relapse (45 vs 76%; $p < 0.03$), in refractory patients (29 vs 72%; $p < 0.005$), and in patients treated with BV 17 months post- diagnosis (39 vs 65%, $p < 0.05$) (Table 3). In multivariate analysis, the only prognostic variable was refractory disease ($p < 0.005$).

Fifty of the 70 patients (71%) were alive and 34 (68%) free of documented progressive disease after a median observation time of 20 months, (range 1–82). Twenty (29%) patients died, including 9 (12%) for progressive disease. The 2y-OS for the whole group was 70%. A Kaplan-Meyer plot of OS is presented in Fig. 2a. The estimated median PFS for whole group on this study was 17 months, (range 1–82) (Fig. 2b). The 2y-PFS in early relapse patients was 43%, lower than the 2y-PFS of patients who relapsed after 12 months (82%; $p < 0.04$) (Fig. 3a). The 2y-PFS was 73 and 48% in chemosensitive and refractory disease, respectively, $p < 0.03$ (Fig. 3b).

ORR and PFS of BV as salvage therapy In patients treated with BV as salvage therapy, the ORR was 44% (24% CR; 20% PR), Table 2. The median PFS was 9 months (range, 1–82) (Fig. 3c).

ORR and PFS of BV as bridge treatment to SCT The ORR in transplant naïve patients was 75% after four BV cycles, with 5 (31%) CR and 7 (44%) PR. In patients treated with BV as bridge to RIC alloSCT, the ORR was 62% (24% CR; 38% PR), Table 2. No differences in ORR after BV were observed between the different cohorts of patients ($p = 0.31$).

Eligibility to proceed to SCT, ORR, and PFS post-transplant At the time of this analysis, ten of the 16 naïve transplant patients

Table 3 Univariate and multivariate analysis of whole group

	Univariate analysis			Multivariate analysis
	No. of patients (%)			
	ORR	No ORR	p	p
Median age > 50 yrs	10 (25)	9 (32)	0.9	
Extranodal disease at diagnosis	17 (42)	12 (46)	0.66	
Bulky disease	17 (42)	5 (19)	0.09	
Prior radiation	8 (20)	8 (30)	0.44	
III–IV Stage	26 (64)	18 (64)	0.39	
Naïve -SCT	17 (42)	13 (64)	0.4	
Prior AlloSCT	2 (5)	4 (13)	0.29	
First remission < 12 months	13 (45)	19 (76)	0.03	
N. prior CHT-BV ≥ 3	24 (64)	18 (62)	0.096	
Time to BV < 17 months	14 (39)	15 (65)	0.05	
Refractory disease	12 (29)	21 (72)	0.005	0.005

Yrs years, *No* number, *SCT* stem cell transplant, *AlloSCT* allogeneic stem cell transplant, *BV* brentuximab vedotin, *CHT* chemotherapy

Table 4 Post transplant key response results

	No. of patients (%)	
	Bridge to ASCT ($n = 16$)	Bridge to alloSCT ($n = 29$)
Transplanted patients	10/16 (63)	28/29 (97)
Objective response	10 (90)	14 (52)
Complete remission	4 (40)	8 (30)
Partial remission	5 (50)	6 (22)
Stable disease	NA	1
Progressive disease	NA	12
Not evaluable	1	2

No number, *ASCT* autologous stem cell transplant, *AlloSCT* allogeneic stem cell transplant, *NA* not applicable

(63%) received ASCT, with 5 (50%) in CR before ASCT. The ORR at + 90 days post- ASCT was 90% (40% CR), Table 4. The median PFS was 11 months and 2y-PFS was 81% (Fig. 3c). In the 29 patients treated with BV as bridge to RIC alloSCT, 28 (97%) patients proceeded to alloSCT with 25% in CR prior alloSCT. The conditioning regimen was Thiotepa-fludarabine-Endoxan plus anti-thymocyte globulin in unrelated and/or mismatched donors. The ORR at + 90 days was 52% (30% CR and 22% PR), Table 4. The median PFS was 18 months and 2y-PFS was 68% (Fig. 3c).

Safety

All patients enrolled in this retrospective analysis received at least one BV infusion with a median of 4 (range, 1–6) and 6 cycles (range, 2–8) in patients treated with BV as bridge to ASCT and alloSCT, respectively. In patients of BV salvage cohort, the median number of cycles was 8 (range, 2–16). In Table 5 are listed the drug-related adverse events of any grade. The most common (≥ 10%) treatment-related adverse events were peripheral neuropathy (50%), neutropenia (29%), and anemia (12%). A total of 18 patients experienced adverse events of grades 3–4. Peripheral neuropathy (sensory/motor) of grades 3–4 was observed only in 7% of patients; four patients improved with BV dose reduction ($n = 3$) or delayed administration ($n = 1$). Fever occurred in 8% of cases. BV therapy was delayed and/or dose-reduced in 3 (5%) and 4 patients (6%), respectively. Safety was highly acceptable in all different cohorts of patients without statistical difference, Table 6. Peripheral neuropathy was lower in patients treated with BV as bridge to ASCT, 5 (7%) patients compared to those treated with BV as bridge to AlloSCT, 11 (18%) patients, or as salvage treatment, 14 (20%) patients, without statistical significance Table 6.

Discussion

In this study, we retrospectively analyzed real-life experience data regarding BV use in R/R HL patients in a multicenter approach in REP. We reported an ORR of 59% with 26% of

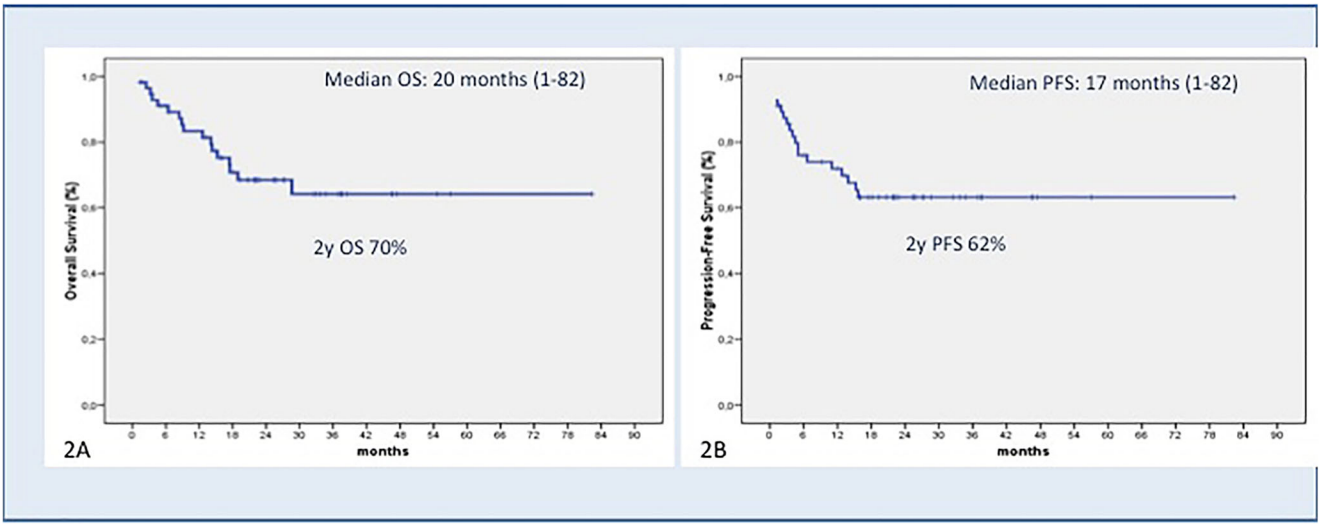

Fig. 2 Kaplan-Meier plots of probabilities of overall survival (OS) (**a**) and progression-free survival (PFS) (**b**) of the whole group

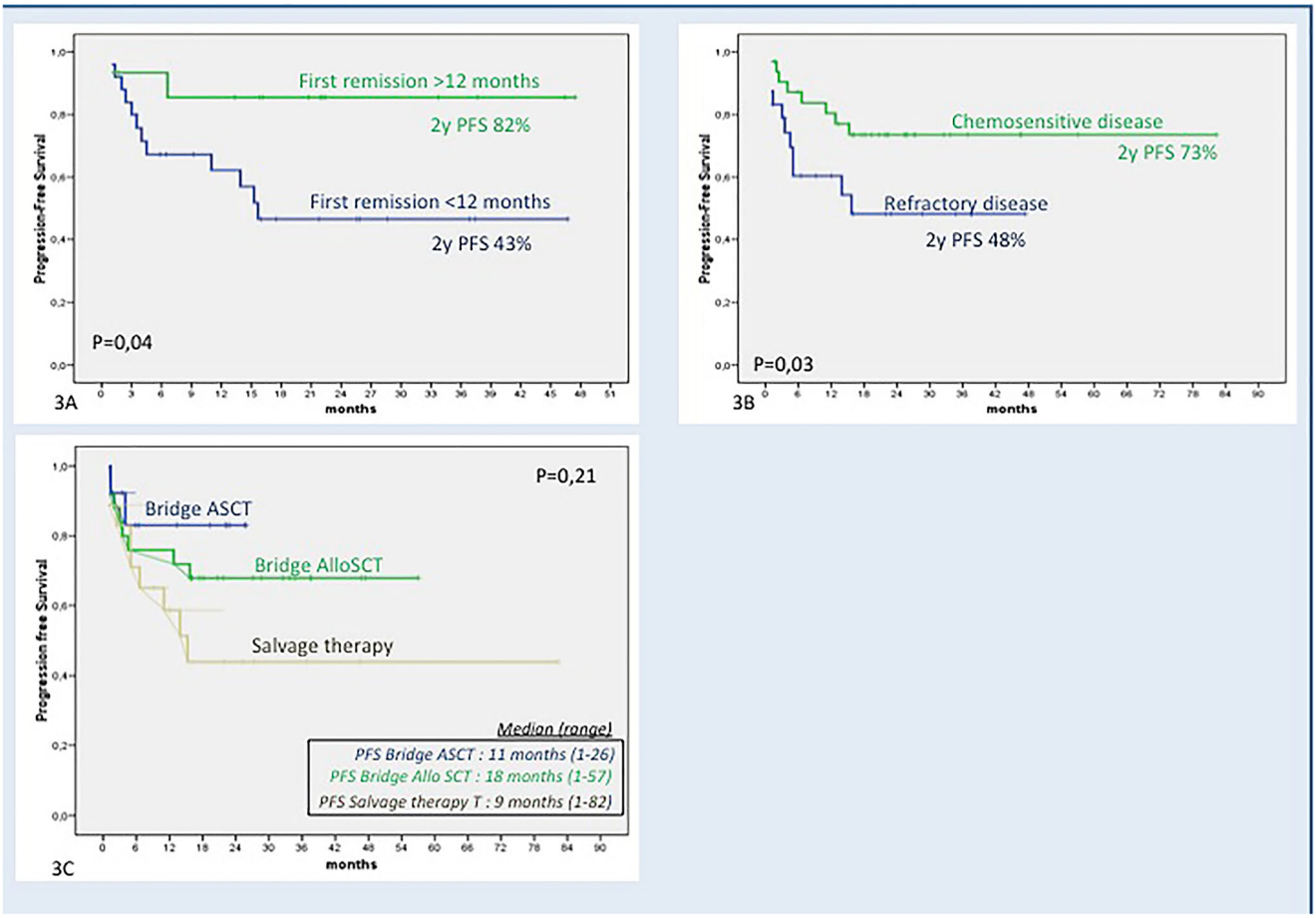

Fig. 3 Progressions free survival (PFS) **a** according to time to relapse, **b** to refractory disease, and **c** to timing of brentuximab vedotin (BV)

patients reaching CR, although considering that these patients had unfavorable prognostic characteristics. Indeed, refractory disease was documented in 47% of cases, and 68% experienced relapse within 12 months after front-line therapy. Furthermore, 66% of patients underwent ASCT or alloSCT before BV with median time to relapse after SCT of only 5 months. These rates of ORR and CR were notable for a single-agent therapy. In the pre-BV era, standard conventional salvage therapy includes ICE (ifosfamide, carboplatin, etoposide), GIFOX (gemcitabine, ifosfamide, oxaliplatin), or DHAP (dexamethasone, high-dose cytarabine, cisplatin). These regimens produce an ORR of about 60–80% (15–20% of CR) but can have significant myelosuppression, grades 3–4 thrombocytopenia, febrile neutropenia or grades 3–4 anemia [15–19]. BV had an acceptable toxicity profile, with no treatment-related deaths. In our cohort of pretreated patients, the most clinically meaningful events were peripheral neuropathy (all grades 50%, grade 3 in 7%), neutropenia (all

Table 5 Drug-related adverse events

	No. of patients (%)		
	Any grade events	Any grade 1–2 events	Any grade 3–4 events
Peripheral sensory/motor neuropathy	35 (50)	30 (43)	5 (7)
Pyrexia	6 (8)	4 (6)	2 (3)
Neutropenia	20 (29)	12 (17)	8 (12)
Anemia	8 (12)	5 (7)	3 (5)
Trombocytopenia	3 (5)	NA	3 (5)
Delayed administration	3 (5)		
Dose reduction BV	4 (6)		

No number, *BV* brentuximab vedotin, *NA* not applicable

Table 6 Drug-related adverse events in the different groups of patients

	Bridge to allo SCT ($n = 29$)		Bridge to ASCT ($n = 16$)		Salvage therapy ($n = 25$)		p
	No. of patients (%)						
	Any grade events	Any grade 3–4 events	Any grade events	Any grade 3–4 events	Any grade events	Any grade 3–4 events	
Median BV cycles, range	6 (2–8)		4 (1–6)		8 (2–16)		0.32
Peripheral sensory/motor neuropathy	11 (18)	2 (3)	5 (7)		14 (20)	3 (5)	0.19
Pyrexia	3 (5)	2 (3)	1 (2)	NA	2 (3)	NA	0.23
Neutropenia	11 (18)	3 (5)	5 (7)	2 (3)	4 (6)	3 (5)	0.38
Anemia	4 (6)	2 (3)	1 (2)	NA	3 (5)	1 (2)	
Trombocytopenia	3 (5)	2 (3)	NA		2 (3)	1 (2)	
Delayed administration	1 (2)		1 (2)		1 (2)		0.81
Dose reduction BV	2 (3)		NA		2 (3)		0.16

No number, *BV* brentuximab vedotin, *ASC* autologous stem cell transplant, *AlloSCT* allogeneic stem cell transplant, *NA* not applicable

grades 29%, grade 3 in 12%), and anemia (all grades 12%, grade 3 in 5%). These results are comparable to those reported in the literature [10–13, 21–23].

Recent data have strongly supported the role of BV as a potent "bridge" therapy to ASCT [20, 21] or alloSCT [12, 13, 23–25]. Our results confirm that BV can effectively bridge patients to transplant, with the ability to improve post transplant ORR and PFS. BV produced 75% ORR with 63% who proceeded to ASCT. The post- ASCT ORR was 90%, and 40% of patients were in continuous CR with a 2y-PFS of 81%. In a previous study, patients received BV as second-line therapy, and those who achieved a CR proceeded directly to ASCT. This strategy resulted in an ORR of 68% and CR rate of 35% [20]. In another trial conducted by Zinzani et al., the authors obtained similar results in a group of 30 patients with R/R HL and PET-positive disease after conventional salvage therapy. BV normalized PET status in 30% of patients and nine proceeded to transplant [21].

In literature, the BV impact on alloSCT is less known. In a retrospective study, 18 patients with R/R HL were treated with BV before alloSCT, and it does not appear to adversely affect engraftment, GVHD, or survival. The 1y-OS was 100% and PFS was 92% [11]. In a recent trial 40 R/R HL patients underwent alloSCT, 26 (65%) received BV before alloSCT, and ORR before alloSCT was 65% in brentuximab-treated patients versus 42% in brentuximab-naive patients [23]. The authors concluded that exposure to brentuximab vedotin allowed more patients to reach allogeneic stem cell transplantation in complete remission, with over 50% of patients progression-free at 3 years. A recent study by Hegerova et al. reported a 3-y OS of 84% and 3-y PFS of 49% in a period from 2009 to 2013. PFS and OS for alloSCT for R/R HL have more than doubled in the recent BV era [24]. In a more recent report from the EBMT Lymphoma Working Party, the outcome of 210 HL patients who received BV prior to allogeneic SCT has been compared with that of 218 patients who did not receive BV. Patients allografted after prior exposure to BV do not have a superior outcome after allogeneic SCT except for a lower risk of chronic GvHD. However, Bazarbachi et al. concluded that BV could improve the outlook of allogeneic SCT by helping refractory patients to achieve a more advantageous disease status as a prerequisite for successful allotransplant [25]. In our cohort of patients candidate for allogeneic transplant, BV pretreatment produced very satisfactory results with an ORR of 60 and 97% of patients subsequently proceeded to transplant. The ORR post- alloSCT was 52% (30% CR) with a 2y-PFS of 68%.

In conclusion, BV is well tolerated and very effective among different cohorts of R/R HL patients, producing a substantial level of CR. BV may also be a key therapeutic agent to achieve a good disease control before ASCT or alloSCT, improving post- transplant outcomes, also in refractory and heavily pretreated patients, without significant overlapping toxicities with previous therapies.

Acknowledgments The authors would like to thank Dr. Stefania Citiso who contributed to the collection of clinical data, Dr. Melania Biasi for her collaboration, all the patients, families, caregivers, clinicians of REP, especially Dr. Giuseppina Greco, nurses, and AIL staff who contributed to this study.

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