Impact of pre- and/or post-autologous stem cell transplantation exposure to brentuximab vedotin on survival outcomes in patients with high-risk Hodgkin lymphoma.

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ABSTRACT

The AETHERA trial demonstrated that brentuximab vedotin (BV) consolidation after autologous stem cell transplantation (ASCT) in patients with Hodgkin lymphoma (HL) at high risk of relapse/progression increases progression-free survival (PFS). Patients previously exposed to BV were excluded from that trial. However, BV alone or in combination with chemotherapy is frequently used as front-line treatment and/or pre-ASCT salvage therapy. We analyzed data from 156 patients with high-risk HL who underwent ASCT with (BV-CON, n=62) or without (non-BV, n=94) BV consolidation. Fifty-seven patients received BV-based salvage regimens before ASCT. The 3-year overall survival and PFS for all patients were 91.6% and 70.0%, respectively. Multivariate analysis showed that BV-CON was associated with better PFS (HR 0.39, p=0.01), whereas positive PET at transplant leaded to worse PFS (HR 2.71, p=0.001). BV-CON improved PFS in PET positive patients (72.2% vs. 43.0%, p=0.05), with a beneficial trend observed in PET negative (88.8% vs. 75.2%, p=0.09). BV-CON patients with or without BV exposure pre-ASCT had a significantly better PFS than non-BV with or without BV pretransplant treatment (HR 0.36, p=0.004). The efficacy of real-life BV consolidation therapy was similar to that in the AETHERA trial. This therapeutic strategy improves survival independently of BV exposure prior to ASCT.

INTRODUCTION

The gold standard treatment for patients with classical Hodgkin lymphoma (HL) who fail first-line treatment is high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) [1-4]. Disease relapse remains the most frequent cause of treatment failure and death following ASCT. Risk factors predictive of disease relapse after transplantation include low performance status, primary refractory disease, relapse after an initial remission duration of <12 months, extranodal disease at relapse, and metabolically active disease by positron emission tomography (PET) before transplantation [5-9].

Most patients with HL who relapse do so within the first 1–3-years following ASCT, providing a rationale for post-transplant maintenance and/or consolidation strategies to mitigate relapse risk. In the AETHERA trial, HL patients at high risk of relapse or progression, defined as having one or more trial-specified risk factors (primary refractory disease, complete remission (CR) <12 months, or extranodal involvement at the start of salvage chemotherapy), were randomized to consolidation with brentuximab vedotin (BV) or placebo [10]. The results showed that BV consolidation improved progression-free survival (PFS) compared with placebo, with 5-year PFS rates of 59% and 41%, respectively (hazard ratio [HR] 0.57, *P*=0.001) [10, 11]. BV was subsequently approved by the United States Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for this indication [12, 13].

The approval of BV for the treatment of relapsed/refractory (R/R) HL after ASCT and for post-ASCT consolidation, along with other highly effective drugs such as checkpoint inhibitors, has revolutionized the management of HL patients. In recent years, these agents have been utilized as earlier lines of therapy, including front-line treatment and pre-ASCT salvage therapy inside or outside clinical trials. This shift in practice means that more HL patients who were previously treated with BV, either as monotherapy or in combination with chemotherapy, are potential candidates for BV consolidation after ASCT. Whereas the AETHERA trial excluded patients who previously received BV, four recent real-life studies assessing BV consolidation included many patients who had been exposed to BV before ASCT [14-17]. Another limitation of

AETHERA trial was that PET scanning was not routinely done for disease assessment before ASCT. However, pre-transplant PET status is an important determinant of patient prognosis and currently it is recognized as the standard of care to evaluate response to salvage therapy prior to transplant.

These findings suggest that the patients included in the AETHERA trial may not have been fully representative of real-life patients receiving BV consolidation treatment. The present study was therefore designed to evaluate the efficacy and safety profile of BV as consolidation treatment after ASCT in patients with high-risk HL in a real-life context and to analyze the impact of BV omission and pre- and/or post-transplant exposure to BV on PFS.

PATIENTS AND METHODS

Study design and patients

This multicenter, retrospective study included all consecutive patients with high-risk R/R HL who underwent ASCT with and without BV consolidation therapy between January 2013 and March 2021 and 17 centers in Spain belonging to GELTAMO (*Grupo Español de Linfoma y Trasplante de Médula Ósea*) and GETH (*Grupo Español de Trasplante Hematopoyético*). High-risk HL was defined, according to the criteria in the AETHERA trial, as patients with HL having at least one of the following risk factors for progression after ASCT: primary refractory HL (failure to achieve CR after first-line therapy), relapsed HL with an initial remission duration <12 months, or extranodal involvement at the start of pretransplantation salvage chemotherapy. The following additional risk factors were also recorded: bulky disease at relapse, B symptoms at relapse, ≥2 salvage therapy lines, and positive PET at transplant. Patients treated with at least one cycle of BV as consolidation therapy after ASCT were assigned to the BV consolidation group (BV-CON). The decision to use BV maintenance was made by the attending physician on an individual basis. BV was approved and reimbursed in Spain on November 27th 2019 for the treatment of HL patients relapsing after ASCT and for those refractory to ≥2 chemotherapy lines. After the impressive results of AETHERA trial, several centers started BV maintenance after ASCT in high-risk patients in an "out of indication" program in Spain, until its approval on September 1st 2019. Individual data were collected retrospectively by chart review at each center and reported to GELTAMO-GETH specifically for this study. The protocol was approved by the GELTAMO-GETH review boards and by an independent reference ethics committee.

Statistical analysis

The primary study endpoint was PFS after ASCT. Lymphoma status assessment was based on local PET/CT results and on previously published recommendations and response criteria [18, 19]. A positive PET was defined as a Deauville score ≥4. At the time of evaluating prognostic factors on disease progression after ASCT, results of PET/CT were considered separately from the remaining risk factors.

Continuous and ordered variables were reported as medians and ranges and statistically compared by Mann-Whitney U tests. Categorical variables were reported as frequencies and proportions and compared by chi-squared tests. Time-to-event curves were estimated by the Kaplan-Meir (KM) method and compared statistically by log-rank tests. The effect of BV consolidation on the study endpoints was adjusted for possible confounders by means of multivariable Cox regression, with the results presented as HRs and 95% confidence interval (CIs). Median follow-up after ASCT was estimated by the inverse KM method. All statistical calculations were performed using SPSS Statistics version 25 (SPSS INC, Chicago, Illinois, USA) and Stata version 14 (www.stata.com) software.

RESULTS

Characteristics of patients

Of the 156 patients included in this study, 62 received BV consolidation (BV-CON group), and 94 did not (non-BV group). Baseline characteristics are shown in Table 1. ABVD (adriamycin + bleomycin + vinblastine + dacarbazine) was the most frequently front-line treatment regimen. The two groups had similar rates of the following adverse risk factors: primary refractory HL, disease relapse <12 months from the completion of front-line therapy, B symptoms, extranodal disease, and $\geq$2 lines of salvage therapy (Table 1). The median number of lines of salvage therapy (detailed in Table 1) was 2 (range 1-6) for both groups. A total of 57 (36.5%) patients were treated with BV alone or in combination with chemotherapy before ASCT as part of first or subsequent salvage treatments (Figure 1). The proportion of patients with PET negative CR prior to transplant was significantly higher in the BV-CON than in the non-BV group (75.8% vs. 57.7%, p=0.02).

BV-CON group: treatment and safety of BV consolidation

The median time from ASCT to first dose of BV consolidation was 53.5 days (range, 26–287 days), and 48 (77.4%) of the 62 patients in the BV-CON group were treated within 3 months of ASCT. Except for three patients in partial response (PR), all patients were in CR at the time of BV initiation. The median number of BV consolidation cycles was 14 (range, 2–16). As expected, the number of BV consolidation cycles was higher for patients who had not been treated with BV before ASCT (16 [2-16] vs. 12 [3-16], p=0.03). Thirty-five patients (56.5%) finished all BV cycles in accordance with their treatment plans before transplantation, with 23 patients receiving 16 BV doses each, and the other 12 patients receiving doses based on those administered before transplantation. Treatment was interrupted in 21 patients (32.3%) due to BV related adverse events (AEs), in four (6.5%) due to disease progression, and in two (3.2%) due to physician decision. Fifteen patients (24.2%) required BV dose adjustments due to drug toxicity. All patients had discontinued treatment at the time of data analysis.

Peripheral sensory neuropathy was reported in 38 (61.3%) patients starting at a median 16.9 weeks (range, 2.4–55 weeks) after initiation of BV consolidation. Severity of neuropathy was grade 1 in 12 (19.4%) patients, grade 2 in 11 (17.7%), grade 3 in ten (16.1%), grade 4 in three (4.8%), and unknown in two (3.2%). Twelve (19.4%) patients experienced a combination of sensory and motor neuropathy. Treatment consisted of monotherapy or combinations of antiseizure drugs (gabapentin or pregabalin) in 20 patients, amitriptyline in three, and vitamin B complex in ten. At the last follow-up, 17 (44.7%) patients showed complete resolution of neuropathy, 14 (36.8%) showed a reduction in symptom severity, and six (15.8%) had persistent symptoms (unknown in one patient). Of these 20 patients with ongoing neuropathy, all except for one had a grade of 1 or 2. The median time to resolution was 48 weeks (range, 13–107 weeks). The incidence of peripheral neuropathy (66.7% vs. 54.8%, p=0.71) and the incidence of grade 3–4 neuropathy (23.3% vs. 19.4%, p=0.89) did not differ significantly in patients who did and did not receive BV as salvage therapy prior to ASCT.

Twenty-four (38.7%) patients experienced neutropenia, including ten (16.1%) with grade 1, four (6.5%) with grade 2, eight (12.9%) with grade 3, and two (3.2%) with grade 4. Twelve (50%) patients required granulocyte colony-stimulating factor (G-CSF) support. Episodes of febrile neutropenia were not reported. At the last follow-up, all but two patients presented with complete resolution of neutropenia. Other AEs related to BV are shown in Table 2. Three episodes of severe infection were observed, including two of *Pneumocystis jirovecii* pneumonia and one of colecystitis, along with two episodes of organizing pneumonia.

Survival

The median follow-up for the entire study cohort was 4.7 years (95% CI, 4.2–5.3-years). Twenty-one patients died, all in the non-BV group, including seven due to disease progression, six due to infection, and three due to complications of allogeneic transplantation; causes of death were not reported in the other five patients, although two experienced disease relapse after ASCT. Ten (16.1%) patients in the BV-CON group and 41 (43.6%) in the non-BV group relapsed. The 3-year OS and PFS for all patients were 91.6% (95% CI 85.6-95.1) and 70.0% (95% CI 61.9-76.8), respectively.

The 3-year PFS rate was significantly higher in patients who did receive BV consolidation after ASCT than those who did not (81.2% vs. 61.2%; *p*=0.003; Figure 2). PFS according to the number of high-risk factors (excluding PET), and pre-ASCT disease's status evaluated by PET, are shown in Figure 3A and B, respectively. Risk factors other than PET status at transplant had no significant influence on the ASCT outcome (Figure 3A). On the contrary, a positive PET before ASCT implied a significant decrease in the subsequent PFS (Figure 3B). The prognostic impact of BV consolidation was confirmed after adjustment for other potential prognostic factors and confounders (age, male sex, $\geq$2 lines of salvage therapy, BV before ASCT, number of risk factors other than PET, and the result of pre-ASCT PET) (HR 0.39, 95% CI: 0.21-0.80; *p*=0.01) (Table 3). In patients with positive PET (n=57), 3-year PFS was higher for those receiving BV consolidation than for those who did not (72.2% vs. 43.0%, respectively, *p*=0.05) (Figure 4A). In patients with negative PET (n=99), a trend for better PFS was also observed for BV-CON patients in comparison to non-BV group (88.8% vs. 75.2%, respectively, *p*=0.09) (Figure 4B).

The 23 patients who discontinued BV consolidation therapy due to AEs or physician decision received a median of 12 cycles (range, 2–15 cycles) of consolidation treatment. Those patients had a significantly lower 3-year PFS than those who completed consolidation treatment (80.3% vs. 97.6%; *p*=0.02).

To assess whether patients receiving BV-based salvage therapy prior to ASCT benefited from BV consolidation therapy, four groups of patients were compared: patients who never received BV (n=68), patients who received only pretransplant BV as part of a salvage regimen (n=26), patients who received BV only as post-transplant consolidation (n=31), and patients who received both pre- and post-transplant BV (n=31) (Figure 1). The 3-year PFS rates overlapped between patients who never were exposed to BV or only pre-ASCT (64.4% and 52.5%, respectively; *p*=0.4), on the one hand, and patients who received BV consolidation post-ASCT with or without BV pre-ASCT (88.9% and 80.5%, respectively; *p*=0.3), on the other (Figure 5). This later group of patients had a significantly better PFS than those never exposed to BV or exposed only pre-ASCT (HR 0.36, 95% CI: 0.18-0.72; *p*=0.004).

Management of disease relapse after ASCT

In the non-BV group, relapsed patients were treated with BV alone or in combination with chemotherapy (n=15), chemotherapy (n=8), radiotherapy (n=8), or checkpoint inhibitors (n=7) (unknown n=3). Treatment of patients in the BV-CON group after relapse included BV-Bendamustine (n=4), chemotherapy alone (n=2), and checkpoint inhibitors (n=6). Some patients received more than one option simultaneously or sequentially. The number of patients who underwent allogeneic HSCT after salvage therapy was significantly higher in the non-BV than in the BV-CON group (19 [20.4%] vs. 3[4.8%], *p*=0.006).

DISCUSSION

This retrospective multicenter study analyzed real-life outcomes of BV consolidation therapy after ASCT in R/R high-risk HL patients. The safety and efficacy of BV in this study were similar to those in the AETHERA trial. PFS rates were significantly higher in patients who underwent BV consolidation than in patients who did not, including those who were exposed to BV-based salvage regimens prior to ASCT.

Three large retrospective studies have published real-world results of BV consolidation after ASCT in patients with high-risk HL [14-16]. These studies reported 2 year PFS rates of 75% and 68%, and a 3-year PFS rate of 62% [14-16], findings comparable to the 2 and 5 year PFS rates of 63% and 59% [10, 11], respectively, of patients in the AETHERA trial. The present study found that the 3-year PFS rates in the BV-CON and non-BV groups were 81.2 % and 61.2%, respectively, with these rates being higher to those in the BV consolidation and placebo groups in the AETHERA trial. The characteristics of the patients included in this real-life study were quite similar to those of patients in the AETHERA. As in that trial, most patients in the present study were treated with front-line ABVD, and the proportions of patients presenting with high-risk factors for disease relapse, such as primary refractory disease, early relapse, and extranodal relapse, were similar. These studies differed, however, in two main characteristics. First, in contrast to AETHERA, several patients in the present study, including those in both the non-BV and BV-CON groups, had received BV-based salvage regimens. Second, the percentage of patients with metabolic CR at ASCT was higher in the present study, being 54.6% in the non-BV cohort compared with 35% in the AETHERA placebo group and 74.2% in the BV-CON group compared with 34% in the AETHERA BV group. Both of these factors could have contributed to the better PFS results in the present study.

BV consolidation treatment was found to benefit patients independent of prior exposure to the drug. PFS rates were lower in patients who were never treated with BV and those who only received pretransplant BV than in patients who received BV consolidation with/without pretransplant BV. Treatment with BV-based salvage regimens, however, did not affect the completion of BV consolidation. This was

relevant because PFS was poorer in patients who did prematurely stop BV consolidation due to AEs than in those who did not.

Although BV consolidation showed long-term clinical benefits in the AETHERA trial, this treatment is not without side effects and economic cost. Thus, it was of interest to identify patients who would benefit most from this treatment. In the AETHERA trial, the benefit of BV consolidation was more pronounced in patients with additional risk factors with HRs of 0.424 and 0.390 in those with $\geq$2 and $\geq$3 risk factors, respectively. In our study, similarly to that reported by Marouf et al [15], only absence of metabolic CR at transplant significantly correlated with reduced PFS. BV consolidation significantly improved outcome in PET positive patients but also, a trend for better PFS was observed in those with negative PET at transplant, suggesting a potential benefit of BV consolidation independently of PET status.

It is not yet known whether BV consolidation therapy has a positive impact on the OS. In contrast to the results of the AETHERA trial, the present study found that OS rates were higher in the BV-CON than in the non-BV group. Effective novel drugs such as BV with/without chemotherapy and checkpoint inhibitors were used to treat patients in the non-BV group who relapsed after ASCT. HL progression and complications resulting from salvage therapies, including allogeneic HSCT, were the leading causes of death. Therefore, increases in OS for BV-CON patients may be attributed to the use of BV consolidation and its effect on the reduction of relapses after transplantation.

Safety outcomes of BV consolidation in the present study were similar to those in the AETHERA trial [10, 20]. The most common AE of any grade in the present study was peripheral neuropathy, with most AEs being sensory in type and grade 1-2 in severity. The incidence of neuropathy and the median time to symptom onset after the first dose of BV consolidation were similar to those reported in AETHERA. However, 20.9% of patients in the present study, compared with 13% in AETHERA, had grade 3-4 neuropathy (grade 4, 4.8% vs. 0%, respectively) [19]. In addition, although most patients (81.5%) showed improvements in symptoms, time to neuropathy resolution was longer in the present study (48 weeks) than in AETHERA (25.9 weeks).

These differences may be explained by the higher severity of neuropathy observed in the present study. Moreover, in contrast to AETHERA, 50% of the patients in the BV-CON cohort of the present study had been exposed to BV before ASCT. However, the incidence and severity of neuropathy did not differ when compared with patients who did not receive BV-based salvage regimens. The incidence of peripheral neuropathy in real-life studies, which have included a variable number of patients previously exposed to BV (23% to 70%), was found to range from 21% to 43% which could reflect a poorer and/or heterogeneous management of neuropathy in real life compared to clinical trials. Neuropathy was observed to be more frequent in patients receiving pretransplant BV, without affecting treatment discontinuation rate [15]. Other studies reported, however, that the safety profile of BV consolidation was unaffected by prior exposure to BV [14, 16].

The main limitations of this study were its retrospective design and multicenter nature, as well as the absence of a centralized review of the PET results. However, this study is the first real-world study to compare BV vs. non-BV consolidation in high-risk patients who underwent ASCT and to examine the impact of BV exposure prior to ASCT on post-transplant survival outcomes.

In conclusion, this real-life study of BV consolidation after ASCT for high-risk HL patients reproduced the safety profile reported in the AETHERA trial. BV consolidation was associated with increased PFS and OS. This therapeutic strategy can improve survival outcomes, in both patients who are and are not previously exposed to BV.

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Author contributions: C.M. conceived and designed the study, collected and assembled data, and wrote the manuscript; C.M. and A. P. performed the statistical analysis and interpreted the results; and all coauthors are physicians from GELTAMO-GETH centers who performed the transplants, took care of the patients, collected local data of patients, and made significant contributions to the discussion of the results. All authors approved the final version of the manuscript.

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TABLES

Table 1. Baseline clinical characteristics of patients included in this study.

	Non-BV cohort N = 94	**BV-CON cohort N = 62**	***P***
ASCT period	January 2013 to March 2018	May 2015 to March 2021	-
Age, years, median (range) at ASCT	35.5 (16–67)	35 (16–70)	0.86
Sex			
Male	50 (53.2%)	32 (51.6%)	0.81
Female	44 (46.8%)	30 (48.4%)	
Front-line chemotherapy			
ABVD	85 (90.4%)	58 (93.5%)	0.36
Other	9 (9.3%)	4 (6.5%)	
Primary refractory disease	48 (51.1%)	34 (54.8%)	0.64
Early relapse (≤12 months)	17 (18.1%)	16 (25.8%)	0.25
Advance stage at relapse/progression	55 (58.5%)	32 (51.6%)	0.45
B symptoms at relapse/progression	18 (19.1%)	15 (24.2%)	0.5
Bulky disease at relapse/progression	8 (8.5%)	2 (3.2%)	0.18
Extranodal disease at relapse/progression	43 (45.7%)	22 (35.5%)	0.24
First salvage therapy			
Platinum-based	56 (59.6%)	35 (56.5%)	-
Gemcitabine-based	10 (10.6%)	1 (1.6%)	
BEACOPP	2 (2.1%)	2 (3.2%)	
Radiotherapy	3 (3.1%)	2 (3.2%)	
BV-ESHAP	4 (4.4%)	11 (17.7%)	
BV-Bendamustine	0 (0%)	4 (6.5%)	
BV	2 (2.1%)	0 (0%)	
Other	17 (18.1%)	7 (11.3%)	
Second salvage therapy			
BV-Bendamustine	0 (0%)	9 (14.5%)	-
BV	17 (18.1%)	4 (6.5%)	
Platinum-based	12 (12.8%)	3 (4.8%)	
Gemcitabine-based	3 (3.2%)	3 (4.8%)	
Other	3 (3.2%)	0 (0%)	
Third salvage therapy			
BV-Bendamustine	2 (2.1%)	3 (4.8%)	-
BV	2 (2.1%)	1 (1.6%)	
Other	7 (7.5%)	0 (0%)	
No of salvage therapy lines pre-ASCT, median (range)	62 (63.9%)	43 (69.4%)	0.48
1	35 (36.1%)	19 (30.6%)	
≥2			
Pretransplant BV	26 (27.7%)	31 (50%)	0.005
Disease status at ASCT			
CR	54 (57.4%)	47 (75.8%)	0.054
PR	35 (37.2%)	14 (22.6%)	
No response	5 (5.3%)	1 (1.6%)	
Pre-ASCT PET status			
Positive	40 (42.6%)	15 (24.2%)	0.02
Negative	54 (57.4%)	47 (75.8%)	
Number of high-risk factors			
3 vs. >3	63 (64.9%) vs. 34 (35.1%)	49 (79%) vs. 13 (21%)	0.058
Conditioning regimen			
BEAM	83 (88.3%)	61 (98.4%)	0.06
CBV	5 (5.3%)	1 (1.6%)	
Other	6 (6.4%)	0 (0%)	
Median (range) follow-up after	73 (6-104)	33 (11-81)	<0.001

ASCT, months

BV, brentuximab vedotin; BV-CON, brentuximab vedotin consolidation; ASCT, autologous stem cell transplantation; CR, complete remission.

Table 2. Adverse events among patients receiving BV consolidation, excluding neuropathy and neutropenia.

AEs	Grade 1–2	Grade 3	Total
Alopecia	1	0	1
Fever	3	0	3
Organizing pneumonia	1	1	2
Arthralgia	1	0	1
Infection	10	3	13
Anemia	2	0	2
Thrombocytopenia	2	0	2
Abdominal pain	1	0	1
Nausea-vomiting	4	1	5
Rash	3	0	3
Cognitive impairment	1	0	1

Table 3. Multivariate analysis of factors significantly associated with progression-free survival (PFS).

Variable	Hazard ratio	95% confidence interval	*P*-value
Age at transplant	0.99	0.97–1.02	0.98
Sex: male	1.24	0.70–2.18	0.46
Lines of salvage therapy ≥2	0.88	0.40–1.96	0.76
BV before ASCT	1.30	0.63–2.68	0.47
No of risk factors	1.13	0.83–1.55	0.43
Positive PET	2.71	1.54-4.79	0.001
BV consolidation	0.39	0.21–0.80	0.01

FIGURES

Figure 1. Disposition of patients according to the type of salvage therapy before ASCT (with or without BV) and to the BV consolidation after ASCT.

Figure 2. Kaplan-Meier analysis of progression-free survival (PFS) in patients with and without brentuximab vedotin (BV) consolidation treatment.

Figure 3. Kaplan-Meier analysis of progression-free survival (PFS) according to the number of high-risk factors (A) and pre-ASCT PET status (B).

Figure 4. Kaplan-Meier analysis of progression-free survival (PFS) according to pre-transplant PET status (A, PET positive; B, PET negative) and BV consolidation.

Figure 5. Kaplan-Meier analysis of progression-free survival (PFS) in patients exposed to brentuximab vedotin (BV) before and/or after transplantation.