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ORIGINAL ARTICLE

Brentuximab vedotin and ESHAP is highly effective as second-line therapy for Hodgkin lymphoma patients (long-term results of a trial by the Spanish GELTAMO Group)

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Background: In this work, we assessed the efficacy and safety of brentuximab vedotin (BV) plus ESHAP (BRESHAP) as second-line therapy for Relapsed/Refractory Hodgkin lymphoma (RRHL) to improve the results before autologous stem-cell transplantation (ASCT).

Patients and methods: This was a multicenter, open-label, phase I–II trial of patients with RRHL after first-line chemotherapy. Treatment had three 21-day cycles of etoposide, solumedrol, high-dose AraC, and cisplatin. BV was administered at three dose levels (0.9, 1.2, and 1.8 mg/kg) intravenous on day −1 to 3 + 3 cohorts of patients. Final BV dose was 1.8 mg/kg. Responding patients proceeded to ASCT, followed by three BV courses (1.8 mg/kg, every 21 days). Main end points for evaluation were maximum tolerable dose and overall and complete response (CR) before ASCT.

Results: A total of 66 patients were recruited (median age 36 years; range 18–66): 40 were primary refractory, 16 early relapse and 10 late relapse. There were 39 severe adverse events were reported in 22 patients, most frequently fever ($n = 25$, 35% neutropenic), including 3 deaths. Grade 3–4 hematological toxicity presented in 28 cases: neutropenia ($n = 21$), thrombocytopenia ($n = 14$), and anemia ($n = 7$). Grade ≥3–4 extrahematological adverse events (≥5%) were non-neutropenic fever ($n = 13$) and hypomagnesaemia ($n = 3$). Sixty-four patients underwent stem-cell mobilization; all collected >2×10e6/kg CD34+ cells (median 5.75; range 2.12–33.4). Overall response before transplant was 91% (CI 84% to 98%), including 70% (CRs 95% CI 59% to 81%). 60 patients were transplanted with no failure engraftments. Post-transplant response was CR in 49 patients (82% CI 73% to 91%) and partial responses in six (10% CI 5% to 15%). After a mean follow-up of 27 months, the 30-month time to treatment to failure was 74% (95% CI 68% to 80%), progression-free survival 71% (95% CI 65% to 77%), and overall survival 91% (CI 84% to 98%).

Conclusion: BRESHAP looks a safe and effective pre-transplant induction regimen, does not jeopardize transplant and allows long-term remissions and survival.

Key words: Hodgkin lymphoma, refractory, polychemotherapy, brentuximab vedotin, transplant

Introduction

Most patients with classical Hodgkin's lymphoma (cHL) can be successfully treated with standard chemo/radiotherapy, with 70% of them remaining alive 10 years after diagnosis [1]. However, in patients with refractory disease or those relapsing after first-line therapy, conventional-dose chemotherapy regimens are associated with low remission rates, and long-term disease-free survival rates no higher than 10% of patients [2].

High-dose chemotherapy (HDT) followed by autologous stem-cell transplantation (ASCT) has become the gold standard treatment of these patients, as shown by two prospective randomized studies, as well as by some other studies [3–10]. This treatment approach results in long-term remissions in 40%–50% of relapsed patients, and 25%–30% of those with primary refractory disease. The probability of cure depends on prognostic factors, such as duration of the initial remission, disease extension, prior chemotherapy regimen, B symptoms, and previous chemotherapy lines. However, in almost all series, the strongest prognostic factor is the disease status before ASCT [6, 9, 10]. Patients with cHL who do not achieve complete remission (CR) after induction chemotherapy and those with unresponsive relapse have a very poor prognosis. Therefore, the choice of a highly active pre-transplant salvage chemotherapy regimen is extremely important to improve results after ASCT. This activity should also be combined with a good stem-cell mobilizing potential and a low-toxicity profile.

Pre-transplant salvage regimens for refractory or relapsed HL that are currently used have overall response (OR) and CR rates of 67%–89% and 21%–71%, respectively [5, 11–14], with a median CR percentage around 30% and no randomized trial has yet compared their relative effectiveness. Accordingly, treatment units must use the regimen with which they have most experience. In Spain, the most common regimen is ESHAP (etoposide, methylprednisolone, cytosine arabinose, cisplatin), which yields OR and CR rates of around 75% and 50%, respectively, with fewer than 5% toxic deaths [3, 11, 12, 15].

Brentuximab vedotin (BV) is an antibody-drug conjugate that delivers the antimicrotubule agent monomethylauristatin E to CD30-positive Hodgkin and Reed-Sternberg [16–18]. BV is approved for the treatment of patients with cHL after failure of ASCT or of at least two previous multi-agent chemotherapy regimens in patients who are not ASCT candidates, and as a consolidation therapy in patients at high risk of relapse after ASCT.

The efficacy of BV in cHL has stimulated the development of clinical trials in which the drug can be positioned early in cHL therapy, especially in combination before ASCT [19–21]. In the present study, a combination of ESHAP plus BV as a pre-transplant therapy was evaluated with the aim of improving the CR rate before ASCT.

Methods

Study design and participants

This was a multicenter, single-arm, prospective, phase I and II trial, sponsored by the Spanish Lymphoma Group and Bone Marrow Transplantation (*GELTAMO, Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea*). Patients were recruited from 14 Spanish institutions (supplementary material, available at *Annals of Oncology* online).

Main inclusion criteria included written informed consent according to the Helsinki declaration and the ethics committee, relapsed or refractory cHL after first-line chemotherapy (mandatory CD30+; lymphocyte-predominant Hodgkin's lymphoma was formally excluded), acceptable performance status and organ function, no prior history of main malignant diseases, and life-expectancy >3 months. The criteria for relapsed or refractory cHL were used by the investigator based on the 2007 International Working Group Guidelines (IWGG) [22], although the concepts of the Lugano Revision [23] could also be taken into account when they became available. More specifically, Early relapse was defined as a re-growth (>50% increase in size) or re-positivization of a prior negative PET-CT scan within the first year after the CR achievement. Primary refractory HL was defined either by progression at any time during first-line chemo-radiotherapy, or by early relapse up to 3 months after the end of treatment. Patients with persistent FDG-avidity at the end of therapy had to demonstrate a second test with evidences of progression or a positive biopsy for HL. Exclusion criteria included concomitant relevant hepatic, psychiatric, cardiac, neurological, or infectious disorders that could interfere with participation in the clinical study, prior use of anti-CD30 monoclonal antibodies, and concomitant pregnancy or breast-feeding, as well as any risk of conception. The complete lists of inclusion and exclusion criteria can be seen in the clinical protocol that is provided with supplementary material, available at *Annals of Oncology* online.

Treatment protocol

Induction therapy: BV plus ESHAP. The ESHAP regimen consisted of: etoposide 40 mg/m^2/day, saline solution 0.4 mg/ml, 2 h intravenous (i.v.) infusion, days 1–4; methylprednisolone 250 mg/day, 100 ml saline solution, 15 min i.v. infusion, days 1–4; cisplatin 25 mg/m^2/day, 500 ml saline solution, days 1–4, 24 h continuous perfusion; cytarabine 2 g/m^2, 500 ml 5% glucose solution, 2 h i.v. infusion, day 5. A total of three cycles every 21 days were planned (Figure 1). Filgrastim or peg-filgrastim were recommended after chemo to reduce the risk of neutropenia.

BV was administered on day 1 of every BV plus ESHAP (BRESHAP) course 1 h before the start of conventional chemotherapy, following the label instructions. A fourth dose of BV alone was given 21 days after the third BV dose to facilitate the response evaluation before the transplant (Figure 1). During phase I, BV was administered at three different doses according to a standard 3 + 3 dose-escalation design to one of the three cohorts. The cohorts were designed to be expanded by three patients until the maximum tolerated dose (MTD) was met. Patients in cohort 1 received 0 ×9 mg/kg BV intravenously on day 1, which was escalated to 1×2 mg/kg in cohort 2, and to 1×8 in cohort 3. Dose limiting toxicity (DLT) was defined before the transplant as any non-hematological toxicity episode ≥3, or any hematological toxicity episode of ≥4 lasting for >21 days from presentation. If the phase I demonstrated the feasibility of the protocol, patients from phase I would be included in the phase II of the study and continued with the same procedures for all patients since that moment.

After three cycles of BRESHAP, patients assessed as having a complete response (CR) or a partial response (PR) according to the IWGG [22] underwent high-dose therapy followed by APBSCT.

Peripheral blood hematopoietic stem-cell collection. All patients were required to have sufficient peripheral blood hematopoietic stem cells (PBSCs) collected to enable ASCT. PBSC collection was scheduled for day +14 of one the three BRESHAP courses. Mobilization was done with subcutaneous G-CSF, 5 μg/kg/12 h, days +10 to +14. Apheresis was done according to each institution's standard operating procedures, requiring the collection of a minimum of 2×10e6 CD34+ cells/kg of body weight. The PBSC product was cryopreserved in DMSO and frozen according to the institution's stem cell processing standards.

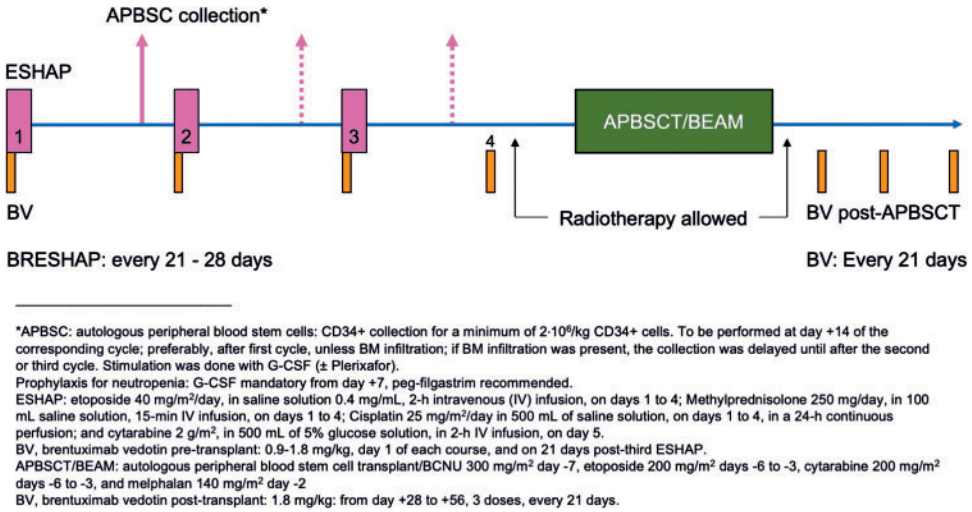


Figure 1. Protocol scheme.

HDT followed by APBSCT. Patients achieving progression or stable disease after BRESHAP were dropped from the protocol. The conditioning regimen was BEAM [3] BCNU 300 mg/m^2, day –7; Etoposide 200 mg/m^2, days –6 to –3; Ara-C 200 mg/m^2 on days –6 to –3; Melphalan 140 mg/m^2, day –2. APBSCs were infused on day 0. The preparative regimen administration, the infusion of APBSCs, the supportive and transfusion care, and the management of infections were carried out according to the institution's standard operating guidelines.

Additional consolidation with BV. A fifth dose of BV was given between days 28 and 35 post-transplant based on the recovery of PB cell counts, followed by two additional doses every 3 weeks, to complete a total of seven BV infusions (four pre-transplant and three post-transplant). The three last courses were provided at the conventional dose of 1.8 mg/m^2.

Evaluation procedures

All patients were evaluated with IWGG [22], but adding the Deauville score (DS) [24]. A score of 1–3 was required to define CR. After informed consent had been provided, a complete patient evaluation and baseline PET-CT was carried out. Patients were followed-up every week until a second PET-CT was done at least 2 weeks after the third cycle and 3–5 weeks before the HDT start. A third PET-CT scan was scheduled between days 90 and 100 post-transplant. After this evaluation, patients were followed-up according to their institution standards.

Efficacy analyses

Aims. There were two main end points: MTD assessment for phase I and response rate for phase II.

To determine the MTD of BRESHAP in relapse/resistant HL patients, we evaluated three groups of patients with the standard scheme of three-patient cohorts of Simon et al. [25, 26]. MTD was assessed over a 21-day observation period, evaluating the toxicity results of the first course. The second primary objective was the response rate after BRESHAP before ASCT.

Secondary objectives were overall survival (OS), progression-free survival (PFS), and time to tumor progression (TTP) [22]. An intention-to-treat (ITT) approach was taken for the analysis. Survival rates were estimated by the Kaplan–Meier method.

Statistical hypotheses and simple size calculation. The primary statistical hypothesis for efficacy was that the addition of BV to the standard ESHAP would not result in a significant increase of toxicity and that the MTD would be the same for the combination as it had been observed for the separate components. The outcomes were measured as OR and CR rates and BRESHAP was inspected to increase the historical response rate.

The sample size was calculated to be 66 patients. Previous results with O-ESHAP [12] showed that 44/59 patients had achieved an objective response (CR + PR, 74.6%). For a targeted objective response rate of 90%, 65 subjects were needed to obtain a 95% confidence interval of 81%–99% (alpha level 5%; power 90%). To minimize a potential unexpectedly low activity of the regimen, a two-stage design for phase II clinical trials was also adopted [26], with a first stage requiring at least 22 responses out of 28 cases, and a second stage with 53 responses out of 66 cases. Other similar reports included a similar number of patients: N = 61 [12], N = 53 [20], and N = 59 [14].

All patients were recruited in 17 months. This trial was registered at ClinicalTrials.gov, number NCT02243436.

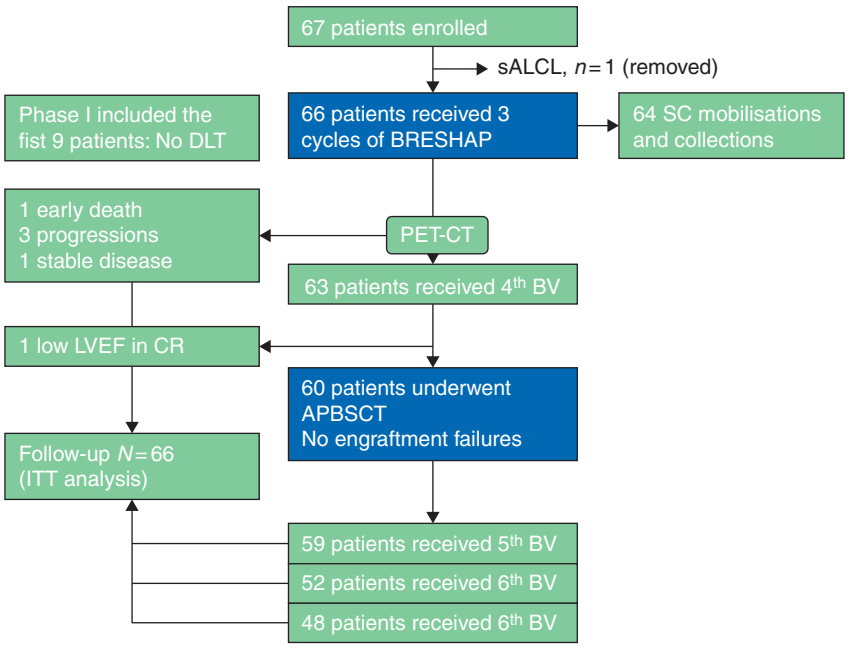
Results

Patient characteristics

Sixty-seven patients were enrolled between 16 November 2014 and 28 April 2015. One patient had systemic anaplastic large cell lymphoma in the final pathological review and was excluded from the study. The 66 patients remaining in the study were assessed for the primary end points (Figure 2 and Table 1). There were 35 females and 31 males, with a median age of 36 years (range 18–66 years). At inclusion, 40 patients were primary refractory, 16 were early relapses (CR lasting <1 year), and 10 were late relapses (CR of ≥1 year).

Phase I

Phase I of the trial involved the first nine patients (three cohorts of three patients) who were included between 16 November 2014 and 30 March 2015. These patients received ESHAP with the first group of three patients receiving BV at 0.9 mg/kg, the second group at 1.2 mg/kg and the third at 1.8 mg/kg. None of them experienced DLT. During the first four cycles, four of them had severe adverse reactions (SAEs): two non-neutropenic fevers,



sALCL, systemic anaplastic large cell lymphoma; DLT, dose-limiting toxicity; SC, stem cell; PET-CT, positron emission tomography & computerized tomography; BV, brentuximab vedotin; CR, complete response; LVEF, left ventricular ejection fraction; APBSCT, autologous peripheral blood stem cell transplant

Figure 2. Patient disposition.

pneumothorax, and febrile neutropenia. Three patients presented grade 4 hematological toxicity: neutropenia ($n=2$) and thrombocytopenia ($n=1$). All nine patients underwent stem-cell mobilization after the first or second treatment cycle, all collecting >2×10e6/kg peripheral blood CD34+ cells (median 6.25, range 3.4–27.5), with no grade 3–4 toxicity. There were one ($n=7$) or two ($n=2$) harvesting procedures. All nine patients received a transplant, and took a median of 9 and 10 days for neutrophil and platelet recovery to occur, respectively. No evidence of disease progression was detected before the transplant, one with residual FGD uptaking areas (metabolic CR: 89%). After the ASCT, six patients were in CR, one in PR and two in progression.

Since no DLT was observed, phase II of the trial commenced on 12 April 2015, with BV at the recommended dose of 1.8 mg/kg per course.

Phase II

Completion of the study. By the time of the data-lock, all patients had completed the protocol. The first three cycles were given to all 66 patients, with a median time of 21 days (range 18–41 days) between the first and second cycles, and of 21 days (range 20–38 days) between the second and third cycles. The fourth BV single dose was given to 63 patients after 22 days (range 20–35 days). The fourth cycle was not given in the case of two progressions and one case of concomitant depressive syndrome.

Mobilization was tried in 64 patients and transplant in 60 patients, with no failures in any case (see below). The median time between the fourth BV dose and SC infusion was 36 days (range 21–102 days), which means that the time between the fourth dose and patient hospitalization for transplant was 29 days (range 14–95 days). The three post-transplant consolidation doses of BV were given to 55, 51, and 48 patients (fifth, sixth, and seventh doses, respectively), with a duration of up to 36 (20–92), 23 (19–39), and 22 (19–30) days, respectively. Eighteen patients did not receive the projected consolidation due to toxicity (cytopenias, $n=4$; neuropathy, $n=3$), progression ($n=6$), patient refusal ($n=3$), or death ($n=2$).

Response to the protocol. An OR before transplant was observed in 60 patients, providing an intention to treat OR rate of 91% (CI 84% to 98%), distributed in 70% CR (CI 59% to 81%) and 21% PR (CI 11% to 31%). Six patients were non-responders: one who died before any evaluation, two with stable disease and three progressions. According to DS, pre-transplant PET-CT was scored as 1 in 8 cases, 2 in 35, 3 in 7, 4 in 11, and 5 in 4. CR was less frequently achieved in patients who progressed under first-line therapy, had bone marrow involvement or were in stage IV at inclusion (Table 2).

Responses at 4 months after transplant were CR in 49 patients, PR in 6 and PD in 10, plus 1 patient who died before any evaluation. The post-transplant response was closely related to the response before the transplant, as expected. There were seven patients in CR/PR at transplant that were in progression at day +120. In contrast, seven patients upgraded their response from PR to CR after the transplant, and six maintained the same status after the transplant.

Survival. After a mean follow-up of 27 months, 16 patients had progressed and 3 had died without progression, providing a 30-month TTF and PFS of 74% (95% CI 68% to 80%) and 71% (95% CI 65% to 77%), respectively (Figure 3A and B). Six patients had died: three due to progression and three from causes

Table 1. Characteristics of the patients (n = 66)

Characteristic	At diagnosis No.	%	At inclusion No.	%
Age, years				
Median	31		36	
Range	17–62		18–66	
Sex				
Male	31	46%	31	46%
Female	35	54%	35	54%
Ann Arbor stage				
I	1	1%	4	6%
II	26	40%	26	40%
III	12	18%	13	20%
IV	27	41%	21	33%
B symptoms	–			
Yes	38	58%	19	30%
No	28	42%	45	70%
Bulky disease				
Yes	15	23%	4	6%
No	51	77%	62	94%
Primary therapy				
ABVD	64	97%	–	
eBEACOPP	2	3%	–	
Radiotherapy in front-line				
Yes	12	18%	2	3%
No	54	82%	64	97%
Extranodal sites of disease				
Yes	29	44%	24	36%
No	37	56%	40	64%
Type of refractoriness				
Relapsed disease	–		26	39%
CR <1 year	–		16	24%
CR ≥1 year	–		10	15%
Primary refractory	–		40	61%

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CR, complete remission.

Table 2. Parameters influencing the probability of achieving metabolic complete response before the transplant

	n	CR	No CR	*P* value
Characteristic	65	71%	29%	–
Progression under first-line therapy	16	37%	63%	0.002
Bone marrow infiltration at inclusion	8	37%	63%	0.041
Stage IV at inclusion	23	57%	43%	0.058
Extranodal disease at inclusion	24	58%	42%	0.065
LDH at Inclusion above normal	19	58%	42%	0.089
Extranodal disease at diagnosis	29	62%	38%	0.134
B symptoms at inclusion	18	67%	33%	0.406
Bulky disease at inclusion	4	75%	25%	0.679
ECOG ≥1 at inclusion	20	70%	30%	0.895

unrelated to progression. The projected OS was 91% at 30 months (95% CI 84% to 98%; Figure 3C).

Several factors influenced the time to treatment failure after the global strategy: response to BRESHAP (equivalent to pre-transplant status), hemoglobin at inclusion below 12.5 g/dl, extranodal disease at inclusion, and bone marrow involvement at inclusion. There were no differences in TTF or PFS between DS 2 and DS 3.

Stem-cell mobilization and transplant development

Sixty-four patients underwent stem-cell mobilization after the first ($n = 15$), second ($n = 36$), or third ($n = 13$) cycle, collecting more than 2×10e6/kg CD34+ peripheral blood cells (median 5.75, range 2.12–33.4) in all of them. Two patients were not mobilized due to death and progression before apheresis. The number of harvesting procedures was 1 in 48 patients, 2 in 13 patients, 3 in 2 patients, and 4 in 1 patient. There was a direct relationship between cycle number and the abundance of cells collected: the earlier the procedure was carried out, the more CD34+ cells were collected (Figure 4). Six patients could not receive a transplant due to early death, LVEF reduction in pre-transplant evaluation, and, in four patients (3 PD and 1 SD), lack of sufficient response. Transplant after BRESHAP was carried out in 60 patients, all of whom engrafted and took a median of 11 and 12 days for neutrophil and platelet recovery, respectively.

Toxicity

During the study follow-up, 39 SAEs were reported in 22 patients (hospitalizations and AEs around the transplant were not considered SAEs), the most frequent being fever ($n = 25$, 35% neutropenic), hypomagnesaemia and gastrointestinal symptoms ($n = 3$). Three SAEs led to death, one each from pneumonia in the absence of neutropenia (day +110 post-ASCT), abdominal sepsis as a late surgical complication (day +67 post-ASCT) and pulmonary embolism related to a catheter insertion (day +8 of third BRESHAP). All deaths were judged as not related with the inclusion of BV in the protocol and none of these patients demonstrated signs of HL during their final evaluations. Apart from ASCT, grade 3–4 hematological toxicity was noted in 28 cases: neutropenia ($n = 21$), thrombocytopenia ($n = 14$), and anemia ($n = 7$). The cases of grade 3–4 extra-hematological adverse events present in ≥5% of cases (Table 3) comprised non-neutropenic fever ($n = 13$) and hypomagnesaemia ($n = 3$). PNP was never present before transplant, except in one case who developed a grade 2 PNP after the third BRESHAP and did not receive the fourth dose. Three other patients developed grade 2 neuropathy after the fifth ($n = 2$) and seventh ($n = 1$) cycles, two of whom discontinued BV after presentation and one who was managed with dose reductions. In total, only three patients discontinued BV due to PNP.

Discussion

In this phase I–II trials, we have evaluated the safety and effectiveness of the addition of BV to a conventional polychemotherapy

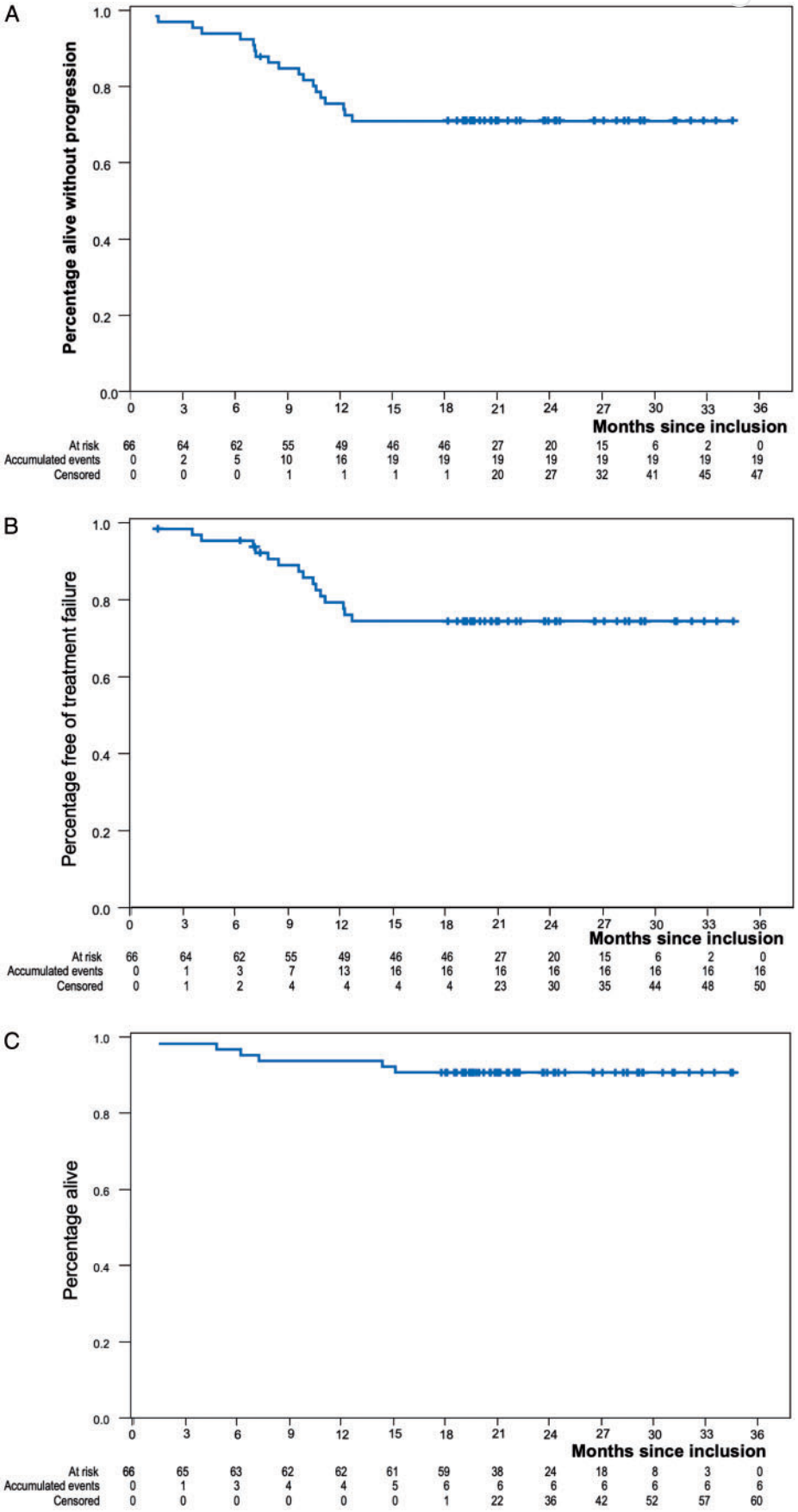


Figure 3. (A) Progression-free survival; (B) time to treatment failure; (C) overall survival.

scheme, ESHAP, that is frequently used in Europe to treat patients with Relapsed/Refractory Hodgkin lymphoma (RRHL) [11, 12, 15, 27]. This combination led to a CR rate of 71%, which is expected to be higher than historical results. The BRESHAP scheme did not cause significant complications during the transplant procedure, and provided an estimated TTF of 74% and PFS of 71% 2.5 years after the inclusion in the trial. The trial benefits from: (i) the homogeneous series of 66 RRHL patients in which the phase I part assessed the correct dose combination for some drugs that had never been combined before; (ii) the effective transplantation in most recruited patients; (iii) the long-term follow-up that corroborates the outcome in terms of PFS; and (iv) the use of PET-CT scan to evaluate all responses.

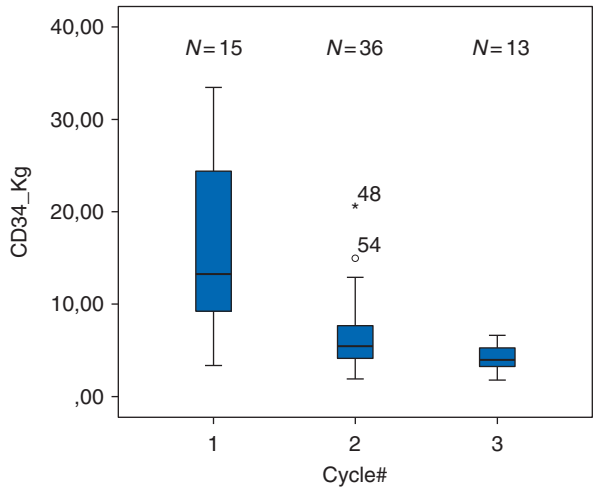


Figure 4. CD34+ cells per kilogram of weight in 64 patients who were mobilized after one, two or three cycles of BRESHAP. Results are expressed as conventional boxplots: boxes span percentiles 25 to 75, lines span percentiles 5–95 and the thick horizontal line indicates the median. Outliers are expressly written. *N* is the number of patients collected after each cycle. All patients collected, and all of them with one attempt that required 1 ($n = 48$), 2 ($n = 13$), 3 ($N = 3$), and 4 ($N = 1$) procedures.

Single-agent BV is approved as a third-line therapy for patients with RRHL because of its demonstrated efficacy in a phase II trial in patients who had failed after ASCT [17]. This efficacy has prompted several attempts to implement its use from the late stages of the disease to first- and second-line therapy [19, 28]. One such attempt was the use of BV in second-line therapy, immediately before ASCT. However, BV monotherapy yields poor CR rates [19, 21] and requires the frequent use of sequential polychemotherapy to achieve CR before the transplant. Alternatively, BV could be used before the transplant in combination with chemotherapy. Until now, most BV combinations with chemotherapy have involved bendamustine [20, 29], and the outcome has been highly dependent on the line of therapy, because the CR rate among patients treated beyond the second line is around 35% [29]. In contrast, bendamustine with BV in second-line therapy, just before the transplant, increased the CR rate up to 71% [20]. However, concerns have recently emerged about the toxicity of bendamustine combinations [30], and a prospective trial in second-line therapy resulted in only 73% of patients able to receive a transplant [20], so alternatives

Table 3. Adverse events related to brentuximab vedotin plus ESHAP

Toxicity		During BRESHAP ($n = 66$)				Post-transplant ($n = 59$)			
Hematologic	Grade any	1	2	3	4	1	2	3	4
Thrombocytopenia	100%	17%	36%	33%	14%	21%	12%	3%	0%
Neutropenia	96%	42%	8%	31%	19%	29%	15%	2%	0%
Anemia	94%	19%	42%	19%	0%	12%	7%	2%	0%
Non-hematologic									
Fever	48%	11%	8%	8%	0%	10%	3%	2%	3%
Mucositis	30%	8%	11%	8%	0%	3%	0%	0%	0%
Pain	29%	19%	6%	0%	0%	4%	0%	0%	0%
Vomiting	28%	14%	6%	0%	0%	8%	0%	0%	0%
Asthenia	23%	11%	6%	3%	0%	4%	0%	0%	0%
Hyporexia	14%	8%	6%	0%	0%	0%	0%	0%	0%
PNP	22%	8%	4%	0%	0%	6%	4%	0%	0%
Constipation	11%	11%	0%	0%	0%	0%	0%	0%	0%
Renal dysfunction	9%	6%	3%	0%	0%	0%	0%	0%	0%
Hypotension	3%	0%	0%	3%	0%	0%	0%	0%	0%
CMV reactivation	3%	0%	3%	0%	0%	0%	0%	0%	0%
Hypomagnesemia	5%	2%	3%	0%	0%	0%	0%	0%	0%

Only grade 1–2 events affecting >5% of participants are included, unless grade 3–4 events also occurred. Data are expressed in percentages, over 66 patients who received at least three cycles before the transplant, and over 59 patients who received at least one additional BV administration after the transplantation. In addition to this data, there were three patients who died without progression: pulmonary embolism (day +8 post-third BRESHAP), abdominal sepsis as late surgical complication (day +67 post-APBSCT), and pneumonia (day +110 post-APBSCT).

combining conventional chemotherapy and BV would be welcome. In our study, we demonstrate that the combination of ESHAP with BV is feasible and yields a good pre-transplant status in patients without hampering the collection of SC and transplant procedures. After demonstrating that the dose of 1.8 mg/kg is safe, the extension of the trial recruited up to 66 patients in whom no SC toxicity was observed and ll patients in whom SC collection was attempted ($n = 64$) provided sufficient CD34+ SC for transplant.

Transplantation was carried out in 60 patients and all of them quickly engrafted with no major complications during hospitalization. These results are better than those of our old series [3] and quite similar to those of more recent ESHAP studies [11, 12].

The OR rate was 91%, similar to other BV combinations [20] and seems to be higher than that reported with ESHAP alone [11, 12, 15, 27], or with other conventional chemotherapeutic schemes [31]. Notably, this OR rate was accompanied by a high CR rate (70% for ITT; 71% of assessable patients), which was a good predictor of CR after the transplant. Responses were evaluated according to PET-CT as the standard for evaluating the response in first-line therapy, which seems logical looking at the current results of second-line therapy in HL demonstrating that patients who are PET-negative before HDT are more likely to be cured [32–34]. In our study, 71% of patients who received BRESHAP became PET-CT-negative. This response was 21% higher than the response we observed in a retrospective analysis of patients treated with ESHAP [11], and 27% higher than that observed in another prospective trial using ofatumumab plus ESHAP [12], although retrospective comparisons should always be considered cautiously.

The survival analyses gave results consistent with the response, with a projected 30-month PFS of 71%. This estimate would be close to the patient cure rate, since a mean follow-up of 27 months is sufficient guarantee for a disease in which relapses beyond the second year of follow-up are extremely rare [18]. Accordingly, the TTF was more favorable for patients (74% at 3 years). Other survival analyses (DR, DFS, and EFS) did not differ from the PFS and TTF, being consistent with a cure probability of around 75% and a 3-year OS of 91%.

The BRESHAP regimen was considered to have good tolerability, like conventional polychemotherapeutic schemes [11, 31]. The only different effect compared with our previous ESHAP regimen was an increase in the grade 3–4 neutropenia, although this did not translate into a higher rate of febrile neutropenia. Despite the potential risk of peripheral neuropathy with BV plus platinum, PNP was not a major problem during the pre- and post-transplant phases of the protocol, since it was present in 5% of cases (grade 2), and were resolved with BV dose reduction or discontinuation.

In conclusion, the BRESHAP combination is a safe and efficient therapeutic option for RRHL patients who are candidates for ASCT, since it combines a high metabolic CR rate, high mobilization potential, low toxicity profile, and high long-term PFS.

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Disclosure

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