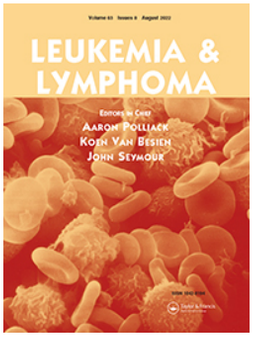

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ORIGINAL ARTICLE

Final results of brentuximab vedotin combined with ifosfamide-carboplatin-etoposide in first refractory/relapsed Hodgkin lymphoma: a lymphoma study association phase I/II study

Aspasia Stamatoullas[a], Hervé Ghesquières[b], Pierre Feugier[c], Marc André[d], Fabien Le Bras[e], Anne-Claire Gac[f], Cécile Borel[g], Thomas Gastinne[h], Philippe Quittet[i], Franck Morschhauser[j], Vincent Ribrag[k], Stephanie Guidez[l], Emmanuelle Nicolas-Virelizier[m], Alina Berriolo-Riedinger[n], Thierry Vander Borght[o], Véronique Edeline[p] and Pauline Brice[q]

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ABSTRACT

This phase I/II study assessed the combination of brentuximab vedotin (BV) with ifosfamide-carboplatin-etoposide (ICE) as a second-line therapy in refractory/relapsed (R/R) classical Hodgkin lymphoma (cHL) patients. Phase I study was designed to determine the maximum tolerated dose (MTD) of BV (10 patients) and phase II evaluated the rate of complete metabolic response (CMR) after 2 cycles of BV-ICE (42 patients). There were no dose-limiting toxicities (DLT) during phase I recommending BV 1.8 mg/kg for phase II. Twenty-six patients (61.9%) achieved CMR after 2 cycles of BV-ICE and 37 patients (88%) were transplanted. With a median follow-up of 38 months, the 3-year progression free survival (PFS) and overall survival (OS) rate were 64.3% and 100%, respectively. Hematological toxicities (81%) and infections (21%) were the most frequent adverse event encountered BV-ICE regimen is feasible with manageable toxicities and could be an alternative to other salvage treatments.

Trial Registration: ClinicalTrials.gov identifier: NCT02686346

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Introduction

Most patients with classical Hodgkin lymphoma (cHL) can be cured with standard chemo/radiotherapy. However, 15–30% of patients fail to respond or relapse (R/R) after primary conventional therapy [1,2]. For the last 30 years, the standard of care for these patients has been salvage chemotherapy followed by high-dose therapy (HDT) [3,4] and ASCT. However, 20–30% of all these patients will relapse within 3 years after ASCT, and most of them will ultimately die from the disease [5,6]. The CMR assessed by PET-CT before transplantation is currently the strongest predictor of outcome [7,8] and has become the goal of the majority of salvage chemotherapy.

Brentuximab vedotin, a CD30-directed antibody conjugated to the highly potent anti-microtubule agent monomethyl auristatin E, has shown significant monotherapy activity in R/R HL patients, but the CR rate was below 40% with a median duration of response for those in CR of 20.5 months [9–11]. These results led to combining BV with other treatments in salvage situations with no standard second-line therapy.

Among salvage chemotherapies, there is no standard of care and the ICE based-regimen (ICE/augICE) allows sufficient CMR (60%) [7,12] without peripheral polyneuropathy and seems to be a good candidate to be combined with BV. This combination has already been tested by Moskowitz et al. [13] with consecutive

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administration of BV and ICE chemotherapy (BV-augICE) and recently by Lynch and colleagues in a combining concomitant administration of BV (1.5 mg/kg) on Days 1 and 8 of each ICE cycle [14] (D-d-BV-ICE). In our study, BV was added to the ICE regimen on day one of each cycle at 1.2 mg/kg or 1.8 mg/kg depending on the stage of the study.

As assessing disease status by PET-CT before HDT and ASCT appear to be the most important factor in predicting outcome, the current trial was meant to increase the CR rate and furthermore to improve the PFS and OS. We present the final results of this phase I-II study (NCT02686346) combining concomitant BV with ICE regimen in first relapsed or primary refractory cHL patients eligible for transplantation.

Methods

Study design and treatment

Study design

This study was a phase I/II prospective multicenter study. The key inclusion criteria were as follows: first R/R [15,16] CD30-positive cHL patients, aged 18–65 years, eligible for ASCT with PET-positive disease at relapse. Patients with peripheral neuropathy grade 2 or more or treated with BV in first-line therapy were excluded (all inclusion/exclusion criteria in Supplemental Data p.1–3).

The primary objective of the phase I study was to determine the maximum tolerated dose (MTD) of BV combined with ICE chemotherapy to propose the recommended phase II dose (RP2D) of BV. Therefore, the primary analysis was based on safety parameters and particularly on the incidence of dose-limiting toxicities (DLTs) after cycle 1. The secondary objectives were the safety and tolerability of BV-ICE as well as preliminary antitumor activity (all definitions in Supplemental Data p.3).

The primary objective of the phase II study was to establish the CMR rate at PETC2 according to the Lugano criteria [15] (Deauville score 1–3) among the full analysis set (FAS) and according to local assessment.

Secondary endpoints were the toxicity profile of BV-ICE, the feasibility of harvesting stem cells, the overall metabolic response (OMR defined as patients in CMR or PMR), the fraction of patients transplanted, and the PFS and OS at 3 years of follow-up.

Exploratory analyses to identify predictive factors of response, PFS and OS were performed. Baseline clinical, hematologic and PET-CT volume measures were considered as potential predictors. Post-hoc confirmatory analyses were performed on the exploratory set (ExS) (48 patients from Phase I and II patients treated with BV: 1.8 mg/kg) to increase statistical power in the analyses.

The trial (ClinicalTrials.gov #NCT02686346) was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki.

Treatment

Patients received 3 cycles of 21 days of BV (1.2 mg/kg or 1.8 mg/kg IV capped at 100 kg) on Day 1 combined with the ICE regimen (etoposide 100 mg/m^2 on Days 1–3, carboplatin AUC (5) max 800 mg and ifosfamide + mesna 5 g/m^2 on Day 2). The fourth injection of BV 1.8 mg/kg was performed on Day 21 from cycle 3 (Treatment regimen in practice in Supplemental Data p.3–4). In phase II, the treatment was the same using the BV dose determined during phase I (Figure 1). Patients with no CMR at PETC2 were considered out of the study and could receive either BV-ICE or other salvage chemotherapy.

Assessment

Local and central assessments of PET-CT at baseline, after 2 cycles of BV-ICE and before ASCT (PET0, PETC2, and PETEOT) were performed according to the Lugano criteria classification. A central review was performed by a panel of 3 nuclear physicians in anonymized Digital Imaging and Communications in Medicine format. TMTV was computed using the free semiautomatic software Beth Israel Fiji (http://petctviewer.org) [17].

Procedure and statistical methods

Phase I was a standard 3 + 3 dose escalation design. The starting dose of BV was 1.2 mg/kg followed by 1.8 mg/kg if no DLT was observed. For the phase II part of the study, a two-stage Simon's design [18] was used to determine the efficacy of BV-ICE after PETC2 (with interim analysis after 13 patients).

The CMR rate is considered to be no better than 50% if the observed rate is $<$54% at the interim analysis or $<$61% at the final analysis. The response rates are expressed with 90% confidence limits according to the Pearson-Clopper method. Survival times are expressed using Kaplan-Meier estimates with 95% CIs.

Baseline factors that were considered potentially predictive of response to treatment (response after 4 cycles according to local assessment and central review) and PFS were investigated. For analyses using imaging measures, the standardized uptake volume maximum (SUV max) and TMTV according to a 41% threshold of SUVmax to calculate lesion volumes were measured at baseline and 2 patients were excluded

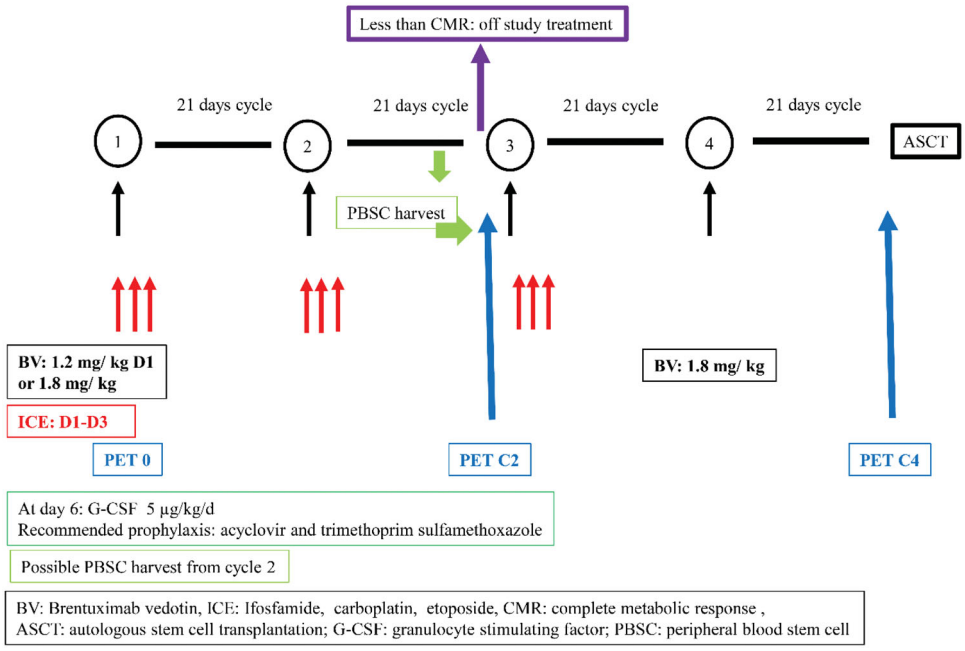

Figure 1. Trial design. BV: Brentuximab vedotin, ICE: Ifosfomide, carboplatin, etoposide, CMR: complete metabolic response, ASCT: autologous stem cell transplantation; G-CSF: granulocyte stimulating factor; PBSC: peripheral blood stem cell.

due to missing data. Patients were classified according to the median for both measures and for TMTV by the cutoff value of 109.5 cm^3 reported to be prognostic for EFS by Moskowitz et al. [19].

Odds ratios for complete metabolic response at end of treatment (EOT) were calculated *via* logistic regression. Association with PFS was tested using the log-rank test and calculation of hazard ratios. A *p*-value of $\leq$.05 was considered statistically significant.

To examine the prognostic importance of response at each evaluation (cycle 2 and EOT), PFS was re-calculated from the landmark date of the evaluation. Only patients considered 'surviving' (i.e. without a progression at the landmark date) are considered in each landmark analysis. Patients with a missing evaluation but later shown to be progression-free are included in the analysis.

To confirm the exploratory findings of the FAS, analyses were performed on Phase I/II 1.8 mg set of 48 patients (ExS), combining the 42 patients of the Phase II set and 6 patients in the Phase I set who received the 1.8 mg dose. Statistical analyses used SAS 9.3 software.

Results

Phase I

Between March 2016 and January 2017, ten patients were enrolled: 4 patients in the 1.2 mg/kg BV dose group (the fourth patient was treated with 1.2 mg/kg BV instead of 1.8 by investigator's mistake and was not excluded) and 6 in the 1.8 mg/kg BV dose group (Figure 2). The median age was 29.5 years (range: 22–55), 60% were men, 70% of patients received first-line treatment with ABVD, 30% were primary refractory to frontline chemotherapy and 10% relapsed within 1 year of CR. Patient characteristics are summarized in Table 1.

None of the four 1.2 BV dose patients experienced DLT after cycle 1 as defined earlier, leading to the recommendation of the usual dose of 1.8 mg/kg of BV to combine with ICE chemotherapy for the second part of the study.

Nine patients (4 in the 1.2 BV dose group and 5 in the 1.8 BV dose group) experienced grade 3–4 adverse events after cycle 3 or 4, mainly hematological toxicity (Table 2: grade 3–4 AEs of at least 10% of patients, all grade 3–4 AEs and SAEs are reported in Supplemental Data Table S1 p 5). The median duration of grade 3–4 neutropenia, febrile neutropenia, and thrombocytopenia were 4 days (1–15), 8 days (2–13) and 5 days (1–13), respectively. Nine serious adverse events (SAEs) were reported in 4 patients: 3 thrombocytopenia, 2 febrile neutropenia, 2 infections, 1 anemia and 1 neutropenia.

Grade 3–4 toxicity induced at least one decrease in BV dose mainly after cycle 3 or 4 for patients treated with BV 1.8 mg/kg. In addition, 3 patients experienced at least one cycle delay (1/4 BV1.2 and 2/6 BV 1.8). Stem cell harvest was performed on 9 patients.

Eight patients achieved CMR at PETC2 (3/4 in the 1.2 mg/kg BV dose group and 5/6 in the 1.8 mg/kg BV

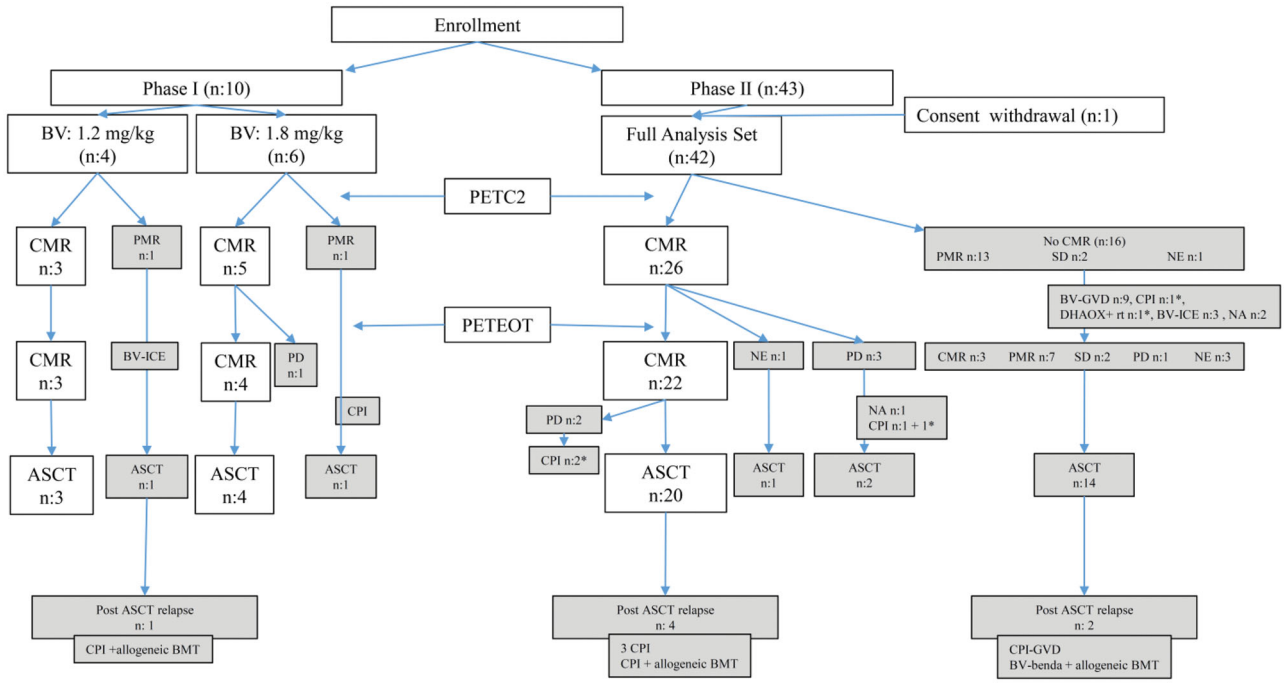

Figure 2. Patient set. BV; Brentuximab vedotin, PETC2: PET-SCAN after 2 cycles of BV-ICE, PETEOT: PET-SCAN before ASCT, CMR: complete metabolic response, PR: partial response, SD: stable disease, PD: progressive disease NE: not evaluated, ASCT: autologous stem cell transplantation, *No ASCT; CPI: checkpoint inhibitor; BV-GVD: brentuximab vedotin-gemcitabine-vinorelbine-liposomal doxorubicin; DHAOX: dexamethasone, cytarabine, oxaliplatin; rt: radiotherapy; BV-benda: brentuximab vedotin bendamustin; Gray boxes indicate: off study patients.

Table 1. Patients characteristics.

Characteristics	Phase I (n:10)	Phase II (n:42)
Age (years)	29.5 (22–55)	30 (18–65)
Sex, male	6 (60%)	27 (64.3%)
Pathology at diagnosis		
Nodular sclerosis	7 (70%)	35 (83.3%)
Mixed cellularity	1 (10%)	3 (7.1%)
Unclassified	2 (20%)	3 (7.1%)
Other	–	1 (2.4%)
Frontline chemotherapy		
ABVD	7 (70%)	17 (40%)
eBEACOPP	2 (20%)	21 (50%)
OEPA-COPDAC	–	2 (5%)
PVAB	–	1 (2.5%)
CHOP	–	1 (2.5%)
MOPP/ABV	1 (10%)	–
Refractory to frontline chemotherapy	3 (30%)	12 (28.6%)
Relapse	7 (70%)	30 (71%)
Relapse within 1 year	1 (10%)	16 (38%)
Stage at enrollment		
I	3 (30%)	3 (7.1%)
II	3 (30%)	11 (26.2%)
II	1 (10%)	6 (14.3%)
IV	3 (30%)	22 (52.4%)
B symptoms	4 (40%)	10 (23.8%)
ECOG PS		
0–1	10 (100%)	41 (97.6%)
2		1 (2.4%)

n: number of patients; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; eBEACOPP: escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; OEPA-COPDAC: vincristine, etoposide, prednisone, doxorubicin-cyclophosphamide, vincristine, prednisone, dacarbazine; PVAB: prednisone, vinblastine, doxorubicinbendamustine; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; MOPP/ABV: mechlorethamine, vincristine, procarbazine, prednisone/ doxorubicin, bleomycin, Vinblastine; ECOG PS: Eastern cooperative oncology group performance score.

Table 2. Phase I/II grade 3–4 Aes in $\geq$ 10% of patients.

Event	Phase I (n:10) BV 1.2 mg/kg (n:4) + BV 1.8 mg/kg (n:6)	Phase II (n:42)
Hematological toxicity	8 (80%) (3 + 5)	34 (81%)
Thrombocytopenia	4 (40%) (1 + 3)	26 (61.9%)
Anemia	5 (50%) (2 + 3)	19 (45%)
Neutropenia	6 (60%) (2 + 4)	17 (40.5%)
Leucopenia	5 (50%) (2 + 3)	12 (28.6%)
Febrile neutropenia	1 (10%) (0 + 1)	8 (19%)
Infection	2 (20%) (2 + 0)	9 (21%)
Anxiety	1 (10%) (0 + 1)	–
Hepatic toxicity	–	6 (14.2%)

n: number of patients, Aes: adverse events.

dose group), and 9 patients were transplanted after HDT (4 in the 1.2 BV dose group and 5 in the 1.8 BV dose group). Two patients in the 1.8 BV dose group progressed after PETC2 and received additional chemotherapy (Figure 2).

Phase II

Between June 2017 and March 2018, 43 patients were enrolled. One patient withdrew informed consent before being treated (Figure 2). The main characteristics of the 42 remaining patients (FAS) are summarized in Table 1. The median age was 30 years (range 18–65), 64% were men, and 67% were primary refractory or relapsed within one year of first CR. The

median time from the end of prior treatment to inclusion in the BV-ICE study was 7.4 months (range 0.9–252). Twenty-one patients (50%) received frontline treatment with at least 2 cycles of escalated BEACOPP (eBEACOPP) as induction therapy (11 patients received only 2 cycles followed by ABVD [20], and 10 patients received >2 cycles), and 4 more patients received eBEACOPP after ABVD [21].

According to local assessment, 26 patients (61.9%) achieved CMR at PETC2 (Figure 2). This result was above the prespecified critical threshold of 61% and was confirmed in a sensitivity analysis in evaluable patients without protocol deviation (25/39 evaluable patients (64%)). A comparison of local and central review responses in FAS and ExS patients is provided in Supplemental Data Table S2 p.5.

At PETEOT, 7 patients and 25 patients exhibited PMR and CMR, respectively, giving an OMR of 76%. The toxicity profile was comparable to that in phase I. The grade 3–4 AES occurring in at least 10% of patients are listed in Table 2 (details of SAEs and all grade 3–4 AEs are listed in Supplemental Data Table S1 p.5). One hundred and sixty-seven events were reported in 35 patients (83%), and 16 patients (38%) experienced 29 SAEs. As expected, hematological toxicity (81%: thrombocytopenia:61.9%, neutropenia:40.5%; anemia:45% and febrile neutropenia:19%) and infection (21%) were the most important grade 3–4 AEs reported. The main extra-hematological toxicity was gastro-intestinal disorders (9.5%). There were no grade 3–4 peripheral polyneuropathy and no toxic death.

Adverse events (one ileus and two hematological toxicities) led to dose reduction for 3 patients with doses reduced between 11 and 33%. Sixteen patients had minor dose reductions due to changes in weight and dose calculation, without being directly related to an AE. One delay of chemotherapy was also observed in 19/42 patients (median time: 10 days range 3–37).

Apart from toxicity, peripheral blood stem cell mobilization and administrative reasons induced a delay in 2 out of the 19 patients. Only 11 grade 1–2 AEs were reported, including one grade 2 peripheral neuropathy. Four further cases of grade 1 peripheral neuropathy were recorded at clinical exams during the study without meeting the criteria to be reported as AEs.

Stem cell harvest was performed with GCSF (and plerixafor in 3 patients) in 41/42 patients (97.6%). The median number of apheresis sessions was 2 (range: 1–5), and the median number of CD34+ cells/kg was 7.75 10^6/kg (range: 4–24). Harvesting failed for one patient. Thirty-seven patients (88%) were transplanted (Figure 2). Four patients with CMR at PETC2 progressed at PETEOT.

Twenty patients underwent ASCT directly after they complete all study therapy (CMR at PETC2 and PETEOT). Seventeen additional patients considered "off study" were also transplanted (1 patient not evaluated at PETEOT, 2 patients progressive after PETEOT and 14 patients in no CMR at PETC2. Among these 14 patients in no CMR at PETC2, 10 received additional salvage chemotherapy: 9 BV-GVD (brentuximab vedotin, gemcitabine, vinorelbine, liposomal doxorubicin) and 1 checkpoint inhibitor (CPI). Finally, 25 patients achieved CMR according to local assessment.

The BEAM regimen (carmustine, etoposide, cytarabine and melphalan) was used as HDT for all of these patients. Five patients did not receive the transplant. The reasons for the lack of transplantation were progressive disease ($n = 3$), alteration of pulmonary function ($n = 1$) and no harvesting for the last patient. Four received treatment with a checkpoint inhibitor (CPI), and the last patient received DHAOx (dexamethasone, cytarabine, oxaliplatin) and radiotherapy (Figure 2).

Thirteen patients considered at high risk of relapse received post-transplant BV maintenance and 5 patients received radiotherapy. Six patients relapsed after ASCT; five of them were treated with CPI. Two patients underwent allogeneic bone marrow transplantation, one after CPI and one after BV-bendamustine.

With a median follow-up of 38 months (18–41), the 3-year progression-free survival and overall survival rate were 64.3% and 100%, respectively (95% CI 47.9–76.7) (Figure 3A,B). The exploratory objectives assessed the prognostic factors of response and PFS. No analyses were performed on OS due to the absence of any OS event.

In such a small cohort there is limited power to detect a significant effect. More than 2 cycles of BEACOPP versus 0–2 cycles appears to reduce the odds of achieving CR at EOT according to central review, with a significant result in analyses on the FAS (Supplemental Data Table 3 and 4 p.6) and ExS (Supplemental Data Table 5 and 6 p.7), however, this does not translate to a significant difference in PFS.

Patients with TMTV above the median (76 cm^3) had significantly reduced PFS in the FAS, but this was not confirmed in analyses on the ExS. In landmark analyses, the EOT response according to the central review was found to be prognostic for PFS (Figure 3C). Patients considered to be in CMR (21 patients) [2] had an 85.7% (95% CI 62.0–95.2) PFS rate at 24 months after EOT compared with 56.3% (95% CI 29.5–76.2) for

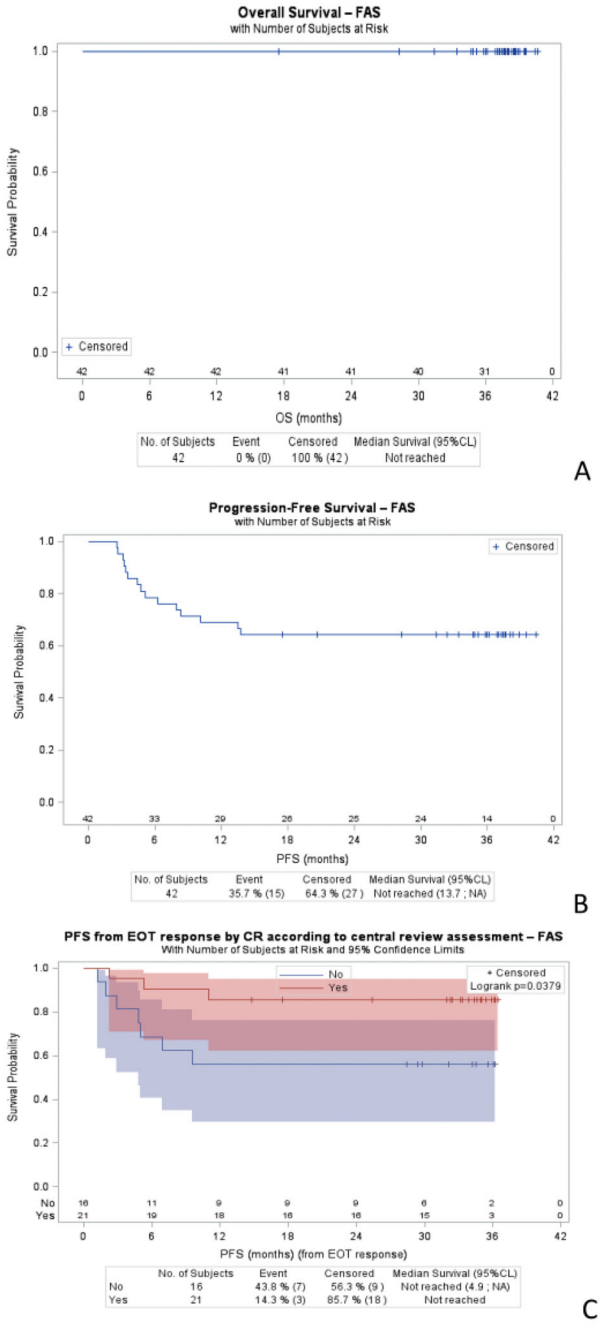

Figure 3. OS (A) and PFS (B) full analysis set, PFS from EOT by CR (C). FAS: Full analysis set, OS: Overall survival, PFS: Progression free survival, EOT; end of treatment; CR: Complete response.

patients in less than CMR (log-rank p: 0.038 and HR 0.263 95% CI 0.007–1.02) These results were confirmed in analyses on the ExS.

Disease stage III-IV, refractory or progression within one year, prior BEACOPP treatment, and elevated TMTV were associated with increased risk of progression but did not achieve significance. There is no evidence that treatment delay was associated with an increased risk of progression ($p = 0.66$ HR = 1.24 95% CI 0.48–3.20). In this small cohort, the power to detect a significant difference was limited. All three patients with bone marrow involvement experienced hematologic toxicity. Prior eBEACOPP and refractory status appeared to increase the odds of hematologic toxicity, but do not achieve significance.

Discussion

In this phase I-II study, we combined BV on day 1 of each cycle of the ICE regimen. The dose of BV was evaluated during the dose escalation phase (Phase I) which demonstrates that the usual dose of BV (1.8 mg/kg) could be combined with ICE chemotherapy.

Our study was designed to assess the rapid effect of 2 cycles of BV-ICE judged by PET-CT in order to detect early refractory disease in those who could benefit from alternative third-line therapy. HDT followed by ASCT was allowed after the completion of the whole treatment (3 BV-ICE and 1 BV). Approximately 62% of patients achieved CMR according to local assessment. However, we have to point out that approximately 50% of our patients had refractory disease or relapsed within one year of the first treatment, more than 50% had the advanced-stage disease and 50% were treated with eBEACOPP as front-line therapy.

This CR rate seems lower than other salvage regimens including BV combination (ICE [12], IVOX [22], BeGEV [23], BV-augICE [13], BV-bendamustine [24,25], BV-ESHAP [26], BV-Nivolumab [27,28], BV-DHAP [29], D-d-BV-ICE [14]), with a CMR rate before HDT of between 60% and 80% (BV-bendamustine: 73.6%, BV-ESHAP: 70%, BV-nivolumab: 61%, and BV-DHAP: 81%). The comparison between all these regimens remains difficult for several reasons including the heterogeneity of baseline clinical characteristics such as the type of first-line chemotherapy (50% of our patients were treated with eBEACOPP, which is not as frequently reported in other series), the total dose and schedule of BV administration [13,14], concomitant administration or sequential administration [13,14], and the time to response evaluation (after 2 or 3 cycles of treatment or before HDT). However, none of these salvage BV regimens has truly demonstrated its superiority.

The recent use of salvage CPI combined with chemotherapy appears more efficient. Indeed,

Moskowitz et al. published their phase II trial combining pembrolizumab with GVD [30] and showed impressive results with a 95% rate of CR with good tolerability (comparison of selected salvage chemotherapy in Supplemental Data Table S7, p8). In the future, the choice of salvage chemotherapy will have to take into account the use of BV [30,31] and CPI [32] in frontline therapy.

The safety profile of BV-ICE was expected: as in other BV-chemotherapy combination [13,14,25,28], hematological toxicities (mainly neutropenia and thrombocytopenia) and infection were the most important toxicities encountered despite the use of GCSF and antibiotic prophylaxis. AEs induced treatment delay in only 3 patients. This delay was not associated with an increased risk of progression.

Importantly, no grade 3–4 peripheral polyneuropathy was observed, in contrast to other BV chemotherapy regimens [13,14,28]. Furthermore, the absence of neurological events allows the use of BV in post-transplant maintenance [31] (13 patients in our study). Only a few common and well-known extra hematological toxicities such as gastrointestinal and hepatic toxicities were reported. We also note that there was no skin reaction [23,24], no infusion-related reaction [23,24,26,27,29] and no immune-related AEs [26,27,29] usually reported when BV is combined with CPI treatment. Finally, all patients recovered from AE and SAE with no sequelae, and there were no toxic deaths.

Another issue in this context of R/R patients is the evaluation of the residual disease responsible for relapse. Indeed, in our series, some patients progressed after achieving CMR at PETC2. A potential explanation for these progressions could be the presence of radiologically subdetectable disease, which could not be visualized by PET-CT. The combination of PET-CT with some biological markers already tested (cytokine profile [13], circulating tumor DNA [32] or tumor mutation [33] could probably help to better discriminate those patients with minimal residual disease who escape radiological evaluation and finally relapse.

ASCT was performed in the majority of patients (88%) even after additional chemotherapy. Indeed, BV-GVD and CPI treatment helped some patients to achieve a better response before transplantation. In addition, CPI treatment was also used for patients not transplanted or for post-transplant relapse with well-known benefit [34,35].

With a median follow-up of 38 months, the PFS was disappointing (64.3%). Only the EOT response according to the central review was found to be prognostic for PFS. Advanced stage disease, refractory or relapse disease within one year of treatment; prior eBEACOPP and elevated TMTV were associated with increased risk of progression but did not reach significance. Regarding eBEACOPP, the use of more than 2 cycles appears to reduce the chance of achieving CR at EOT but it is not a significant prognostic factor in PFS analyses. Furthermore, no difference in the outcome of patients relapsing after ABVD versus eBEACOPP has been shown [2]. The results of TMTV support the findings of Moskowitz et al. [19] that elevated baseline TMTV calculated according to a 41% threshold of SUVmax can be considered a risk factor for subsequent progression, but determining the optimal value of TMTV would require further study in a larger cohort than the current study. However, these analyses suffer from a lack of statistical power due to the small number of patients. The excellent OS (100%) could be explained by the efficiency of other salvage therapies including CPI even for patients who did not undergo transplant [14,29].

In conclusion, this study achieved a CMR of 62% with BV-ICE, in R/R cHL patients regardless of frontline treatment. Toxicity was manageable, with no grade 3–4 peripheral neuropathy and no toxic death. It could be an alternative to other salvage chemotherapies according to baseline characteristics and frontline therapy (eBEACOPP, BV [36,37] or CPI [38] treatments).

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Authors contributions

PB and VR designed the study; all authors collected the data; AS and PB analyzed the data; wrote the manuscript with contributions from all authors, who also read, commented on, and approved the final version of the manuscript; ABR, TVB and VE performed the central PET-CT review; AS and PB supervised the study.

Disclosure statement

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