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ORIGINAL ARTICLE

BeEAM conditioning with bendamustine-replacing BCNU before autologous transplantation is safe and effective in lymphoma patients

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Abstract BEAM with BCNU is commonly used for conditioning treatment followed by autologous stem cell transplantation (ASCT). However, pulmonary toxicity and availability issues associated with BCNU prompted us to evaluate bendamustine-replacing BCNU (BeEAM). We analyzed 39 lymphoma patients receiving BeEAM conditioning with 200 mg/m^2 bendamustine at days −7 and −6. The median duration until neutrophil recovery was 11 days, and 15 days for platelet recovery (>20 g/L). The most common grade 3/4 non-hematologic toxicities comprised mucosal side effects (27 pts.). Pulmonary toxicity was observed in one patient (2.5%), and one patient died of septic complications. The CR rate increased from 33% to 74% 100 days after ASCT. After a median follow-up of 18.5 months, progression and death each occurred in 11 patients (28%). Median progression-free and overall survival at 2 years were 69% and 72%. Our data suggest that BeEAM conditioning using bendamustine is safe and results in promising survival rates.

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Introduction

Despite usually being chemotherapy sensitive malignancies, many patients with aggressive non-Hodgkin lymphomas (NHL) or advanced Hodgkin lymphoma either relapse or never achieve a remission [1–3]. The outcome in such patients is commonly dismal when conventionally dosed chemotherapy salvage concepts are applied [1–3]. In contrast, high-dose chemotherapy (HDCT) supported by autologous stem cell transplantation (ASCT) is improving both disease-free (DFS) and overall survival (OS) in patients with chemosensitive-relapsed lymphomas and, consequently, is the preferred therapeutic option for relapsed/refractory lymphoma patients considered to be fit for this procedure [4–14]. This notion has been supported by recent advances in conditioning regimens and supportive care reducing ASCT-related mortality to less than 10% [3, 9, 10, 13, 14].

Numerous HDCT regimens followed by ASCT have been reported, with DFS and OS rates varying between 34% and 72% and from 26% to 46%, respectively [4–14]. However, only a limited number among them are comparative randomized trials, with no HDCT regimen having ever shown superior efficacy to another. In addition, each HDCT regimen is associated with its own specific toxicities, related to the compounds or modalities used. A prominent example is the idiopathic pneumonia syndrome (IPS), which encompasses non-infectious pneumonitis caused by high-dose alkylating treatment such as with BCNU. IPS thereby represents the major pulmonary

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toxicity after HDCT, with incidences of 2–64% in various regimens containing BCNU [15–18]. In summary, all commonly applied HDCT regimens have their advantages as well as risks, and improved conditioning strategies are considered an unmet clinical need.

BEAM with BCNU is one of the most commonly used conditioning regimens followed by ASCT. However, the idiopathic pneumonia syndrome and increasingly also availability issues associated with BCNU led us and others to evaluate alternative candidate compounds replacing BCNU within the BEAM regimen. Visani et al. reported a phase I/II study in 43 lymphoma patients investigating bendamustine at three dose levels, with the other three compounds of the BEAM regimen at standard dosing [14]. The highest dose level of 200 mg/m^2 of bendamustine was considered to be safe and was assessed in the subsequent phase II study. Recently updated results indicate a promising 3-year progression-free survival (PFS) of 72% [14]. In this retrospective single-center study, we report tolerance and outcome in a series of 39 consecutive lymphoma patients treated with bendamustine, etoposide, cytarabine, and melphalan (BeEAM) conditioning followed by ASCT. Our data confirm the favorable long-term results reported by the Italian group and indicate that a prospective comparison of BeEAM and BEAM is warranted.

Patients and methods

Patient population

In this single-center retrospective study, we analyzed consecutive patients with Hodgkin lymphoma (HL) or NHL who have been treated with BeEAM conditioning followed by autologous stem cell transplantation between September 2013 and April 2015 at the University Hospital in Bern, Switzerland. All patients gave written informed consent, and this study was approved by the local ethics committee of Bern, Switzerland (decision number no. 281/14). The detailed patient characteristics at diagnosis and the regimens used for induction and salvage treatment are summarized in Table 1.

Treatment

Bendamustine at 200 mg/m^2 was given as a single 2-h infusion in 500-mL 0.9% NaCl supported by forced hydration on days −7 and −6. On days −5 to −2, 200 mg/m^2 cytarabine and 150 mg/m^2 etoposide were administered every 12 h as a 30-min infusion each in 500-mL 0.9% NaCl. Finally, 140 mg/m^2 melphalan was given as a single 1-h infusion in 500-mL 0.9% NaCl supported by the usual forced hydration on day −1. At least 2.0 × 10^6 CD34+ cells/kg body weight (b.w.) was reinfused on day 0.

All patients received weight-adapted G-CSF (filgrastim at 5 μg/kg b.w.) starting at day +6 after ASCT until neutrophils exceeded 0.5 g/L for three consecutive days. Patients routinely received antiviral (oral acyclovir 500 mg twice daily) and antifungal prophylaxis (oral fluconazole 400 mg once weekly and oral sulfamethoxazole/trimethoprim 800/160 mg three times per week). No antibiotic prophylaxis was given. Hyperuricemia prophylaxis was applied from days −7 to −1 with 300 mg daily oral allopurinol. Patients received platelet or red cell transfusions when platelets decreased below 10 g/L or hemoglobin below 80 g/L, respectively. Patients were hospitalized for the entire procedure starting with the application of HDCT and were dismissed after hematologic and adequate physical recovery.

Measurements and definitions

Initial staging of patients was according to the Ann Arbor classification, and the International Prognostic Index (IPI) was determined for risk assessment. Histology, immunohistochemistry, and molecular studies, as required, were based on biopsy considered adequate in quality and quantity. Bone marrow infiltration was assessed in all patients with aspirate and biopsy. Bulky disease in this study described tumors in the chest that occupied at least one third of the chest width or tumors in other areas with a diameter larger than 10 cm. Toxicities were graded using CTCAE 4.0 criteria (Common Terminology Criteria for Adverse Events). Data on late-onset toxicities or infections after discharge from hospital were collected until 1 May 2016 (data cutoff of this study).

OS was defined as the time from ASCT until death from any cause or last follow-up. PFS was defined as the time from ASCT until first relapse/progression, death, or last follow-up, whichever occurred first. Remission status was based on CT assessment since PET data were not routinely available for the majority of the patients in this study. All patients had CT assessments before HDCT/ASCT and 100 days after ASCT. CT scans were scheduled during follow-up every 3 months in year 1, every 6 months in years 2 and 3, and annually in years 4 and 5, or earlier whenever clinically indicated. CR lasting less than 3 months was defined as progressive disease (PD). The RECIST 1.1 criteria were adopted to determine the status of remission.

Statistical analysis

Survival curves were calculated using the method of Kaplan and Meier and compared using the log-rank test. p values of <0.05 were considered statistically significant. All reported p values were from two-tailed Fisher's or unpaired t tests,

Table 1 Patient characteristics at diagnosis ($n = 39$)

Age (median, year (range))	60	(16–71)
Gender (male, *n* (%))	27	69%
Histology (*n* (%))		
Hodgkin lymphoma (HL)	6	15%
Non-Hodgkin lymphoma (NHL)	33	85%
Diffuse large B cell lymphoma (DLBCL)	16	
Mantle cell lymphoma (MCL)	8	
Follicular lymphoma (FL)	4	
Peripheral T cell lymphoma, NOS (PTL)	2	
Nodal marginal zone lymphoma (MALT)	1	
Primary mediastinal B cell lymphoma (PMBCL)	1	
Small lymphocytic lymphoma (SLL)	1	
Stage (*n* (%))		
I	2	5%
II	7	18%
III	8	20%
IV	22	56%
IPI (median (range))	2	(0–3)
0 (low risk; *n* (%))	4	10%
1 (low risk; *n* (%))	15	38.5%
2 (low-intermediate risk; *n* (%))	15	38.5%
3 (high-intermediate risk; *n* (%))	5	13%
Bone marrow infiltration (*n* (%))	16	41%
Infiltration (median, % (range))	50%	10–90%
Bulky disease (*n* (%))	6	15%
CNS infiltration (*n* (%))	0	0%
B symptoms (*n* (%))	14	36%
Time from diagnosis to HDCT (median, months (range))	10	(2–104)
Lines of previous therapy before HDCT (median (range))	2	(1–5)
Previous therapies (detailed)		
CHOP	23	
DHAP	15	
DHAP/CHOP alternating	8	
Bendamustine	7	
ICE	4	
ABVD	3	
BEACOPP	3	
Others[a]	12	
Rituximab[b]	34	
Radiotherapy	7	

IPI international prognostic index, *CNS* central nervous system, *HDCT* high-dose chemotherapy, *CHOP* cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone, *DHAP* dexamethasone, high-dose cytarabine, and platinol, *ICE* ifosfamide, carboplatin, and etoposide, *ABVD* adriamycin, bleomycin, vinblastine, and dacarbazine, *BEACOPP* bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone

[a] FCR (2), ABVD + BEACOPP (1), chlorambucil, vincristine, prednisolon (1), R-CVP (1), IGEV (1), ESAP (1), R-CVP (1), cisplatin, gemcitabine, dexamethasone (1), bortezomib, rituximab, dexamethasone (1), vinorelbine, gemcitabine, bendamustine (1), fludarabine, mitoxantrone, and rituximab + DHAP (1)

[b] Use of rituximab together with chemotherapy

and a value of $p < 0.05$ was considered statistically significant. Survival analysis was performed using the log-rank method, and analyses were performed using GraphPad Prism® Version 7 (GraphPad Software, Inc., La Jolla, CA).

Results

High-dose treatment

Our study comprised 39 lymphoma patients, including 6 (15%) Hodgkin lymphomas and 33 (85%) non-Hodgkin lymphomas. At initial diagnosis, the median age was 60 years. Patients were predominantly male (69%) and had stage IV disease (56%). The median duration from first diagnosis to ASCT was 10 months, and patients had a median of two previous lines of treatment before admission to ASCT. The detailed patient characteristics are summarized in Table 1.

All 39 patients received BeEAM conditioning as planned, without dose modifications. Peripheral blood was the source of autologous stem cells in all patients, and selection of CD34+ cells after stem cell collection was performed in 31 patients (80%). A median of 3.2×10^6 CD34+ cells/kg body weight (range, 2.02–6.38) was transfused. All patients received G-CSF for a median of 7 days, and the median hospitalization duration was 27 days (range, 20–45 days).

Hematologic recovery

Details on hematologic engraftment are depicted in Table 2. Patients received a median of four red blood cell transfusions and six platelet transfusions. Neutrophils recovered above 0.5 g/L after a median of 11 days (range, 9–13), and the median time until platelets increased above 20×10^9, 50×10^9, and 100×10^9/L was 15 days (range, 11–46), 23 days (range, 12–205), and 35 days (range, 12–205), respectively. All patients ultimately achieved complete hematologic recovery.

Infections during hospitalization

All patients had at least one febrile episode (≥38.0 °C), with a median number of 5 days with fever. In 79% of all patients, a causative agent could be identified. Most infections were of bacterial origin (77%), with coagulase-negative staphylococci species (12 patients), *Escherichia coli* species (nine patients), and streptococci species (six patients) being the predominant bacterial agents. Four patients required temporary transferal to the intensive care unit following septic complications, and one patient ultimately died 14 days after ASCT due to multiorgan failure following septic shock syndrome. In 18% of the patients, a viral infection, predominantly respiratory syncytial virus (RSV), could be demonstrated, and three patients had proven fungal infections with aspergillus species. In 41% of the patients, multiple germs were identified.

Non-hematologic toxicities during hospitalization

Mucosal toxicity was the predominant (69%) side effect, with clinically significant dysphagia observed in seven patients. The median weight loss during hospitalization was 2.85 kg (range, −12.6 to +3.8 kg). Accordingly, most patients received total parenteral nutrition (87%). Apart from mucosal side effects, grade III or IV toxicities were noted in 12 (31%) patients according to the CTCAE 4.0 criteria, and 10 of these 12 patients had multiple toxicities (Table 2).

Grade III/IV renal toxicity with acute renal failure was observed in four patients, with one patient transiently requiring dialysis; however, the impairment of renal function was fully reversible in all patients. Three patients suffered from cardiac complications including two patients with symptomatic supraventricular tachyarrhythmia and one patient with acute coronary syndrome (NSTEMI). Clinically relevant gastrointestinal toxicity (gastric hemorrhage) occurred in three patients. Additional toxicities included metabolic impairment (severe hyponatremia and tumor lysis syndrome in one patient each), ototoxicity with transient hearing impairment due to serous otitis media in one patient, and ocular toxicity with keratoconjunctivitis and transient decrease of vision in one patient.

Complications after hospitalization

Thirteen (33%) patients experienced at least one febrile episode following discharge and within 100 days after ASCT, requiring re-hospitalization in 10 of 13 patients. An infectious agent was identified in 9 of the 13 patients. Two patients had RSV infection, and one patient each had parainfluenza infection, CMV reactivation, and Varicella Zoster reactivation. Bacterial infections were identified in four patients. No fungal infections were observed.

Of particular interest was the assessment of toxicities occurring during follow-up. We identified three (8%) patients with toxicities after hospitalization for ASCT. One patient suffered from a transient cerebral ischemia with significant underlying stenosis of the right internal carotid artery. The neurological symptoms resolved completely. A second patient experienced retinal and intravitreal bleeding, most likely due to prolonged thrombocytopenia. Finally, one patient was diagnosed with non-febrile interstitial pneumopathy starting with dry coughing and dyspnea 4 to 6 weeks after ASCT. Pulmonary function (DLCO) was worsening, partially improved after steroid treatment, but remained impaired at last follow-up 22 months after ASCT.

Outcome

Details on the response to HDCT/ASCT treatment and the survival rates are summarized in Table 3. The rate of complete remission (CR) increased from 33% prior to HDCT to 74% at the assessment 100 days after ASCT. At last follow-up, 72% of the patients were in ongoing CR, after a median follow-up after ASCT of 18.5 months (range, 0.5–30.5 months), whereas 11 (28%) patients have relapsed at the cutoff time. The median

Table 2 High-dose chemotherapy, engraftment, infections, and toxicities

BeEAM chemotherapy given (*n* (%))		39 (100%)	
Full dose given as planned (*n* (%))		39 (100%)	
Transplanted CD34+ cells (median, ×10e6/kg (range))		3.2 (2.02–6.38)	
CD34+ selection (*n* (%))		31 (80%)	
Median time to engraftment (days (range))			
Tc >20 g/L		15 (11–46)	
Tc >50 g/L		23 (12–205)	
Tc >100 g/L		35 (12–205)	
Lc >0.5 g/L		10 (8–14)	
Lc >1.0 g/L		11 (9–16)	
Lymph >0.5 g/L		27 (10–205)	
Lymph >1.0 g/L		43 (13–213)	
ANC >0.5 g/L		11 (9–13)	
G-CSF (median, days (range))		7 (3–27)	
Hospitalization (median, days (range))		27 (20–45)	
Total parenteral nutrition (TPN) (*n* (%))		34 (87%)	
Units of red blood cell transfusions (median, *n* (range))		4 (0–15)	
Units of platelets transfusions (median, *n* (range))		6 (1–25)	
Weight[a] change (median, kg (range))		−2.85 (−12.6 ± 3.8)	
Infections			
At least one febrile episode of ≥38.0° (*n* (%))		39 (100%)	
Median days with fever (range)		5 (1–24)	
Patients with at least one identified germ (*n* (**%**))		31 (79%)	
Bacteria gram + (%)		47%	
Bacteria gram – (%)		30%	
Viral (%)		18%	
Fungal (*Aspergillus* sp.; %)		5%	
Patients with positive blood cultures (*n* (%))		25 (64%)	
Patients with multiple germs identified (*n* (%))		16 (41%)	
Antibiotics used for infection (*n* (%))		39 (100%)	
Toxicities			
Patients with toxicities (all grades; *n* (%))		21 (54%)	
Patients with grade 3/4 toxicities (*n* (%))		12 (31%)	
Patients with >1 toxicity (all grades; *n* (%))		11 (28%)	
Type of toxicity		Total (*n*)	
Mucosal (*n* (%))		27 (69%)	
Dysphagia (*n* (%))	7 (18%)	Grades I–II	Grades III–IV
Cardiac (*n*)	6	3	3
Ear (*n*)	1	0	1
Eye (*n*)	3	2	1
Gastrointestinal (*n*)	4	1	3
Metabolism and nutrition (*n*)	2	0	2
Musculoskeletal (*n*)	1	1	0
Nervous system (*n*)	3	3	0
Renal and urinary (*n*)	11	7	4
Skin and subcutaneous tissue (*n*)	2	2	0
Vascular (*n*)	2	2	0

Tc platelets count, *Lc* leucocyte count, *Lymph* lymphocyte count, *ANC* absolute neutrophil count, *G-CSF* granulocyte-colony stimulating factor, *RBC* red blood cells

[a] Weight loss was defined by change of weight from admission to discharge from hospital

Table 3 Outcome

Follow-up (median, months (range))		18.5 (0.5–30.5)	
Overall survival at 2 years (median (%))		72%	
Progression-free survival at 2 years (%)		69%	
Relapse (*n* (%))		11 (28%)	
Time since ASCT (median, months (range))		5 (0–22.5)	
Deaths (*n* (%))		11 (28%)	
Time since ASCT (median, months (range))		4.5 (0.5–11)	
Due to progression (*n*)		9	
Due to other causes (infections; *n*)		2	
TRM (*n* (%))		1 (2.5%)	
Remission status	Before ASCT (day 0)	At day 100	At last follow-up
CR	13 (33%)	29 (74%)	28 (72%)
PR	22 (57%)	7 (18%)	5 (13%)
SD	2 (5%)	0 (0%)	0 (0%)
PD	2 (5%)	3 (8%)	6 (15%)

ASCT autologous stem cell transplantation, *TRM* treatment-related (ASCT) mortality, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PD* progressive disease

OS and PFS were not reached in the patients in our series. The 2-year OS was 72%, and the 2-year PFS was 69% as depicted in Fig. 1. Eleven (28%) patients have died until now; nine patients due to progression and two patients due to infectious complications (14 days after ASCT and following pneumonia 6 months after ASCT).

Discussion

The PARMA study analyzed salvage DHAP chemotherapy alone with the combination with subsequent HDCT and ASCT, and the event-free and overall survival were both found to be improved in the ASCT group [7]. Since then, HDCT with ASCT has become the preferred option for patients with chemosensitive relapsed aggressive lymphoma. In the rituximab era, the rate of relapsing patients with aggressive lymphoma varies between 20% and 30% in the case of one aaIPI factor, and between 25% and 35% for patients with two or three factors, while being somewhat higher for patients above 60 years of age [19–21]. Since the introduction of rituximab for first-line treatment, however, a significant proportion of patients with early relapse who are refractory to any available treatment is observed. Salvage therapy using HDCT/ASCT alone is clearly inefficient for these patients and improved regimens are needed. For patients responding to salvage regimen, HDCT/ASCT remains the best choice of treatment [22].

There are few data to guide the selection between the various HDCT regimens available prior to ASCT for patients with HL and NHL. A large retrospective analysis compared BEAM, CBV, BuCy, and TBI-containing regimens, and CBV was divided into CBV^{high} and CBV^{low} based on the dose of BCNU. [10] Compared with BEAM, CBV^{low} was associated with lower mortality in follicular lymphoma, and CBV^{high}

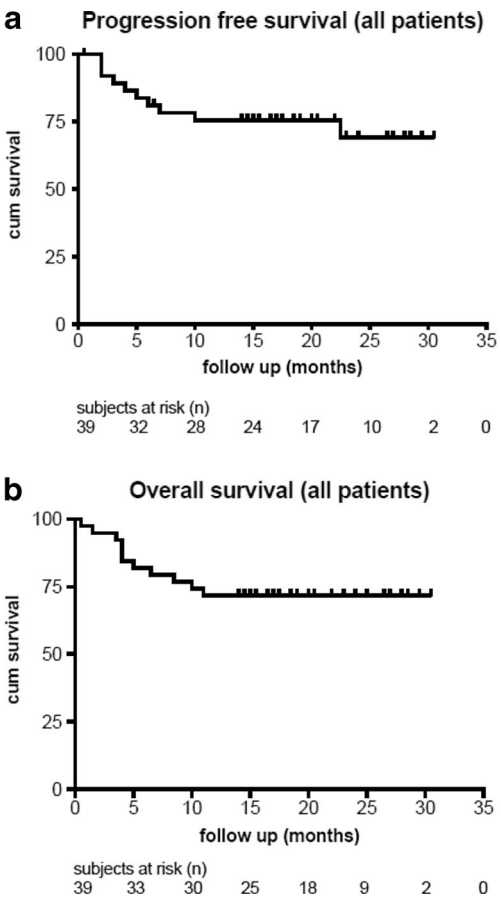

Fig. 1 Kaplan-Meyer survival curves are depicted comparing the survival of 39 lymphoma patients receiving BeEAM conditioning followed by ASCT after a median follow-up of 18.5 months. **a** Progression-free survival; **b** overall survival

with higher mortality in diffuse large B cell lymphoma. For patients with HL, BEAM conditioning was superior. Recently, 184 lymphoma patients with ASCT following BuCyE (busulfan, cyclophosphamide, and etoposide) were compared in a matched control analysis to controls who received BEAM [23]. Toxicity and transplant-related mortality (TRM) appeared to be comparable between the groups, and outcomes for patients with NHL were equivalent between BuCyE and BEAM. In addition, the combination of etoposide, cytarabine, and melphalan together with thiotepa-replacing carmustine (TEAM) has recently been compared in a large retrospective analysis, and no significant differences were found between the two groups for any survival end points [24]. These results indicate that thiotepa-based high-dose therapy represent an alternative to BEAM in lymphoma patients.

Finally, investigators have incorporated newer agents into traditional high-dose regimens. Several trials combined 131-Iodine tositumomab with BEAM for ASCT, but no clear advantage was observed [25, 26]. Other trials have studied Gem-Bu-Mel (gemcitabine, busulfan and melphalan) [27], Bu-Mel-TT (busulfan, melphalan, and thiotepa) [28], and the addition of (90)Y-ibritumomab tiuxetan [29], or bortezomib [30], respectively, to BEAM conditioning. Clearly, prospective randomized trials will be needed to finally determine whether incorporation of one of these newer agents into HDCT regimens provides an added value. Furthermore, such trials will also have to take into account the differences in outcome based on the histology of the lymphoma.

Visani et al. conducted a phase I/II study on 43 patients using BeEAM conditioning for ASCT for relapsed lymphoma patients, and they reported an impressive CR rate of 81% after a median follow-up of 18 months [13]. Recently, the authors updated their data after a follow-up of 41 months after ASCT; the median PFS and OS were still not reached, and the 3-year PFS was 72%. Interestingly, lymphoma subtype (HL versus NHL) at transplant did not affect PFS or OS [14].

The BeEAM regimen offers the option of replacing BCNU by bendamustine, thereby possibly eliminating the pulmonary toxicity notoriously associated with higher doses of BCNU. Based on these considerations, the BeEAM regimen was implemented in our center starting September 2013 as a standard conditioning regimen for lymphoma patients before ASCT. A total of 39 patients were treated until April 2015. Their results are summarized in this paper and lead to the first report aiming to verify the results of the Italian group. Of note, our BeEAM regimen differed slightly since etoposide and cytarabine were given twice a day at a dose of 150 and 200 mg/m^2, respectively, at days −5 to −2, whereas bendamustine and melphalan were administered identically.

We observed an acceptable tolerance of this HDCT regimen, with a transplant-related mortality of 2.5% compared with 0% in the Italian group [13]. The complete remission rate after ASCT, as determined by CT assessments in all patients, was 74%, and it was comparable with the 81% reported by Visani et al. [13]. Median PFS and OS were not reached in both, our and in the Italian cohort. At 2 years, the median PFS and OS were 69% and 72%, respectively, and, thus, similar to the 3-year PFS of 72% observed by Visani et al., and they compared favorably with the corresponding survival rates of other HDCT regimens [4–12].

Of particular concern is the renal toxicity associated with the use of high-dose bendamustine in our cohort. Despite a forced hydration regimen accompanying bendamustine treatment and a prolonged (2 h) application procedure, a transient decrease of the renal function was a common side effect observed in 11 (28%) patients of which four patients had a grade III/IV renal toxicity with one patient transiently requiring dialysis. However, this decrease in renal function was fully reversible within 1 week, and no dose modification of the other components of the BeEAM regimen was necessary. Renal toxicity was not reported in the series of Visani et al. but was common after high-dose bendamustine treatment in our cohort of lymphoma patients [13]. In addition, we observed no renal toxicity grade III/IV in a previous series of 62 consecutive lymphoma patients treated with BEAM HDCT [31]. Thus, the renal toxicity observed with the BeEAM regimen is obviously caused by high-dose bendamustine.

Other grade III/IV side effects of the BeEAM regimen are within the range of expected toxicities associated with HDCT, such as cardiac events (7.5%) or gastrointestinal hemorrhage (7.5%). Transiently impaired vision was reported in three (7.5%) patients, and another 7.5% of patients experienced neurologic side effects including seizure, fully reversible transient ischemic attack, and prolonged tremor. No secondary malignancies were detected in our series during follow-up so far.

IPS is the major pulmonary toxicity after HDCT, and it is caused by high-dose alkylating chemotherapy (e.g., BCNU) or total body irradiation (TBI) [10, 15–18, 32]. The reported incidence of IPS after ASCT varies widely and prompt initiation of steroids can often result in clinical improvement [10, 15–18, 32]. Risk factors associated with the development of IPS are the type of HDCT regimen, diagnosis of Hodgkin lymphoma, female gender, chemotherapy-resistant disease at time of ASCT, and age above 55 years [10]. Patients with IPS have a higher rate of TRM, shorter PFS and OS [10]. In our cohort, we observed a single patient (2.5%) with IPS, with a modest improvement of symptoms following steroid treatment and with persisting dyspnea at slight physical activity at the last follow-up 22 months after ASCT. Our data suggest that IPS after BeEAM conditioning can occur, but it seems to be a rare event.

Pulmonary toxicity of bendamustin has been previously reported, most likely due to the alkylating activity of the mustard group of bendamustine. However, in vitro data suggested that bendamustine has a very different pharmacologic profile

from alkylating agents. In particular, activation of apoptotic pathways was reported to be a key element of the bendamustine activity [33]. Bendamustine is also effective when apoptotic pathways were dysfunctional (e.g., p53-independent cytotoxic effects) by causing a mitotic dysfunctional state in malignant cell lines, and it has activity in resistant cell lines that do not respond to treatment with other alkylating agents [33]. Given its efficacy in the treatment of chronic lymphocytic leukemia (CLL) and indolent NHL, bendamustine emerged as an obvious candidate to be studied in HDCT regimens [34–37].

In conclusion, our study supports a previous report of promising activity of the BeEAM HDCT regimen before ASCT in lymphoma patients, with a CR rate of 74% and a 2-year PFS and OS of 69% and 72%, respectively. Based on these data, we initiated a prospective randomized multicenter trial (BEB trial; NCT02278796) aiming to directly compare BEAM versus BeEAM in lymphoma patients in first or second remission. The trial is actively recruiting since early 2016.

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Author's contributions S.G. performed research, analyzed data, and wrote the paper; U.N., B.M.T., G.M.B., K.L., Y.B., T.Z., D.B., T.E., and D.R. contributed relevant data, reviewed the manuscript, and were involved in the final writing of the paper; T.P. designed research, analyzed data, and wrote the paper.

Conflict of interest The authors declare that they have no conflict of interest.

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