BendaEAM versus BEAM as conditioning regimen for ASCT in patients with relapsed lymphoma (BEB): a multicentre, randomised, phase 2 trial

Felix Keil,[a,*] Antonia M. S. Müller,[b,c] Andrea Berghold,[d] Regina Riedl,[d] Veronika Buxhofer-Ausch,[e,f] Judith Schuster,[g] Corinne Vorburger,[h] Alexandra Böhm,[i] Michael Panny,[a] Thomas Nösslinger,[a] Richard Greil,[g,j,k,l] Panagiotis Samaras,[m] Celine Bencker,[a] Markus Rütti,[c] and Thomas Pabst[h]

[a]3rd Medical Department for Haematology and Oncology, Hanusch Hospital, Vienna, Austria
[b]Department of Transfusion Medicine and Cell Therapy, Medical University of Vienna, Vienna, Austria
[c]Department of Medical Oncology and Haematology, University Hospital Zurich, Zurich, Switzerland
[d]Institute for Medical Informatics, Statistics, and Documentation, Medical University Graz, Graz, Austria
[e]Department of Internal Medicine I with Haematology, Stem Cell Transplantation, Haemostaseology and Medical Oncology, Ordensklinikum Linz Elisabethinen, Linz, Austria
[f]Medical Faculty, Johannes Kepler University Linz, Linz, Austria
[g]Austrian Group Medical Tumor Therapy (AGMT), Salzburg, Austria
[h]Department of Medical Oncology, Inselspital, Bern University Hospital, Bern, Switzerland
[i]Haematological Health Care Centre of the ÖGK Mariahilf, Vienna, Austria
[j]Cancer Cluster Salzburg (CCS), Salzburg, Austria
[k]III[rd] Medical Department with Haematology and Medical Oncology, Haemostaseology, Rheumatology and Infectious Diseases, Oncologic Centre, Paracelsus Medical University, Salzburg, Austria
[l]Salzburg Cancer Research Institute with Laboratory of Immunological and Molecular Cancer Research and Centre for Clinical Cancer and Immunology Trials (CCCIT), Salzburg, Austria
[m]Clinic for Haematology and Oncology Hirslanden Zurich, Zurich, Switzerland

eClinicalMedicine 2023;66: 102318
Published Online xxx https://doi.org/10.1016/j.eclinm.2023.102318

Summary

Background Replacement of carmustine (BCNU) in the BEAM regimen (BCNU, etoposide, cytarabine, melphalan) with bendamustine (BendaEAM) before autologous stem cell transplantation (ASCT) is feasible in lymphoma. However, randomised trials are lacking. Here, we present the first trial addressing this topic.

Methods This multicentre, randomised, phase 2 study (BEB-trial) conducted at four haematological centres in Austria and Switzerland compares BEAM with BendaEAM in patients with relapsed lymphoma. Both regimens were administered intravenously before ASCT, in BEAM according to the standard protocol (300 mg/m^2 BCNU on day −6), in BendaEAM, BCNU was replaced by 200 mg/m^2 bendamustine given on days −7 and −6. Eligible patients were aged 18–75 years and had mantle cell lymphoma, diffuse large B-cell lymphoma, or follicular lymphoma in first or second remission or chemosensitive relapse. The primary endpoint of the study was to evaluate whether replacement of BCNU by bendamustine reduces lung toxicity, defined as a decrease of the diffusion capacity of the lung for carbon monoxide by at least 20% at three months after ASCT. Data analyses were performed on an intention-to-treat basis. This study is registered with ClinicalTrials.gov, number NCT02278796, and is complete.

Findings Between April 20, 2015, and November 28, 2018, 108 patients were enrolled; of whom 53 were randomly assigned to receive BendaEAM (36 male, 17 female) and 55 to receive BEAM (39 male, 16 female). All patients engrafted rapidly. Lung toxicity did not differ between groups (BendaEAM: n = 8, 19.5%; BEAM: n = 11, 25.6%; risk difference = −6.1%: 95% confidence interval: −23.9% to 11.7%). Acute toxicities of at least grade 3 were comparable in both groups (BendaEAM: 35.8%, BEAM: 30.9%). Overall survival (BendaEAM: 92.5%, BEAM: 89.1%) and complete remission (BendaEAM: 76.7%, BEAM: 74.3%) after 1 year (median follow-up: 369 days) were similar. No difference in quality of life was observed.

Interpretation Results were similar for both regimens in terms of survival and response rates. A phase 3 non-inferiority study is required to investigate whether BendaEAM can be considered as an alternative to BEAM.

*Corresponding author. KeilHanusch Hospital, 3 rd Medical Department for Haematology and Oncology, Heinrich-Collin-Straße 30, 1140, Vienna, Austria.
E-mail address: felix.keil@oegk.at (F. Keil).

Funding Mundipharma.

Keywords: Lymphoma; Autologous stem cell transplantation; Conditioning regimen; BEAM; Bendamustine

Research in context

Evidence before this study

Before conducting this trial, we searched PubMed between database inception and December 8, 2014, using the terms "bendamustine" AND "conditioning regimen" AND "autologous stem cell transplantation" AND "lymphoma" to identify clinical trials investigating bendamustine as part of a conditioning regimen prior to autologous stem cell transplantation (ASCT) in the treatment of lymphoma. The results yielded the dose-finding study by Visani et al. on which our protocol for BendaEAM (bendamustine, etoposide, cytarabine, melphalan) was based. No published data were found from a randomised phase 2 clinical trial on the use of the BendaEAM regimen in lymphoma, underscoring the unmet clinical need that we addressed with our study, the BEB-trial.

Added value of this study

The BEB-trial represents the first randomised clinical phase 2 trial challenging BEAM (carmustine, etoposide, cytarabine, melphalan) as standard conditioning regimen with BendaEAM prior to ASCT in the treatment of relapsed lymphoma that has reported results. The primary outcome, lung toxicity, did not differ between groups (BendaEAM [n = 8], 19.5%; BEAM [n = 11], 25.6%; risk difference = −6.1%: 95% CI: −23.9% to 11.7%). Acute toxicities of at least grade 3 were comparable in both groups (BendaEAM: 35.8%, BEAM: 30.9%). Our findings provide novel insights into BendaEAM as a potential alternative regimen to BEAM. Given the high use of BEAM in the treatment of lymphoma worldwide and the recent supply shortages of BCNU, viable alternatives are of great importance, especially in areas where access to newer therapeutic options such as chimeric antigen receptor (CAR-)T cell therapy is limited.

Implications of all the available evidence

Results from the BEB-trial suggest that replacing BCNU with bendamustine is similarly effective in the treatment of relapsed lymphoma and has a manageable toxicity profile. These findings align with evidence from non-randomised data and could, with more research, have important implications for clinical practice. Future research is required and should more thoroughly compare the efficacy and toxicity of both therapeutic regimens by conducting phase 3 trials.

Introduction

High-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) is an established standard treatment for patients with relapsed non-Hodgkin lymphoma, achieving long-term remission and possibly cure.[1,2] Each year, about 10,000 patients in Europe receive ASCT for the treatment of lymphoma, and about 16,000 worldwide.[3,4]

Carmustine (BCNU)-containing BEAM (BCNU, etoposide, cytarabine, melphalan) is the most frequently used conditioning regimen prior to ASCT in patients with lymphoma.[2,5] To our knowledge, to date, there are no reported results of randomised clinical trials, challenging BEAM with other conditioning regimens.

Bendamustine is an effective drug in the treatment of lymphoma and a promising alternative to BCNU as a conditioning regimen prior to ASCT.[6–8] Visani et al.[9] were the first to demonstrate efficacy and feasibility of the BendaEAM regimen before ASCT, replacing BCNU by 200 mg/m^2 bendamustine, given on day −7 and day −6 before transplantation. These results have been supported by subsequent trials, including a study by our institution.[10–12]

For both, BEAM and BendaEAM there are conflicting results in terms of efficacy and toxicity. Regarding the BendaEAM regimen, renal toxicity may be a potential concern, as has been reported in several studies.[11–13] Among the most frequently observed complications of high-dose BCNU-containing regimens is pulmonary toxicity, resulting in an incidence of idiopathic pneumonia syndrome varying from 2% to 64%.[1–3] Other studies indicated lung toxicity associated with BEAM, as reflected by a decrease in lung volume[14] and radiologic findings of lung injury.[15] Reduced diffusion capacity of the lung for carbon monoxide (D_{LCO}) before ASCT was recently defined as a risk factor for treatment-related mortality in patients treated with BEAM.[16] D_{LCO} is a crucial measure for evaluating lung-specific toxicity, reflecting the alveolar membrane's ability to transfer inspired gas into the capillary blood. D_{LCO} values decrease post-transplant following lung-toxic chemotherapy, with the most substantial effects observed around 100 days after ASCT.[17] In our study, 20% reduction of D_{LCO} was considered a clinically significant impairment of pre-transplant values. This decision was based on other

studies investigating chemotherapy-related pulmonary toxicity.[18,19]

To investigate whether there are specific differences in toxicity between both regimens, we conducted a randomised phase 2 clinical trial comparing the two regimens in patients with lymphoma receiving high-dose chemotherapy before ASCT. Primary endpoint was to evaluate whether replacement of BCNU by bendamustine reduces lung toxicity defined as a D_{LCO} reduction of 20% or more.

Methods

Study design and participants

This multicentre, randomised, phase 2 clinical trial was conducted at four haematological centres in Austria and Switzerland (Krankenhaus der Elisabethinen Linz, Hanusch Hospital in Vienna, Inselspital/University Hospital Bern, and University Hospital Zurich). The study protocol is available in the Supplementary Material.

This study was performed in compliance with the Declaration of Helsinki. Ethics approval was obtained from the ethics commission of the City of Vienna in Austria (reference number: EK 15-009-0215) and the Ethics Commission of the Canton of Bern in Switzerland (reference number: 2016-00005). Written informed consent was obtained from all study participants.

Participants were recruited by screening patients with lymphoma who had been routinely referred to the participating study centres for ASCT. Eligible patients were 18–75 years of age with mantle cell lymphoma (MCL) in first remission, diffuse large B-cell lymphoma (DLBCL) in first or second remission or chemosensitive relapse, or follicular lymphoma (FL) in second remission or second chemosensitive relapse. Further eligibility criteria were a neutrophil count of $\geq 1000/\mu l$ and platelet count of $\geq 100 \times 10^9/l$ and a Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) ≤ 5. Sex was collected by self-report; the options were "female" or "male".

Randomisation and masking

Patients were stratified according to their lymphoma diagnosis and by trial site and subsequently randomised at a 1:1 ratio to the study group (BendaEAM: n = 53) or the control arm (BEAM: n = 55) by using the Randomizer for Clinical Trials tool developed at the Medical University of Graz (www.randomizer.at). As randomisation method, permuted block randomisation with block size 8 was used. Randomisation was performed by the investigators, ensuring allocation concealment. No masking nor blinding was done.

Procedures

Both regimens were administered intravenously over seven consecutive days before autologous stem cells were reinfused. The BendaEAM conditioning regimen, previously described by Visani[9] consisted of 200 mg/m^2 bendamustine on days –7 and –6, 200 mg/m^2 of etoposide from day –5 to day –2, 400 mg/m^2 of cytarabine daily from day –5 to day –2 and 140 mg/m^2 of melphalan given on day –1 before reinfusion of autologous stem cells. The BEAM conditioning regimen differed only in replacing bendamustine with 300 mg/m^2 of BCNU given on day –6. The other three drugs etoposide, cytarabine, and melphalan were administered at the same days at the same doses as in the BendaEAM regimen.

All patients were hospitalised from the start of conditioning. Antiemetics, hydration, and supportive care were given according to local hospital guidelines. According to study protocol, no discontinuation or dose modification was permitted with any of the study compounds. Haematological engraftment after ASCT was defined as the first day of neutrophil counts above $0.5 \times 10^9/l$, and of platelet counts above $20 \times 10^9/l$ in the absence of platelet transfusion in the previous 3 days.

Follow-up assessments were done three months and one year after ASCT. Furthermore, an additional assessment after 10 years is planned.

Outcomes

The primary endpoint of the study was to evaluate whether replacement of BCNU by bendamustine reduces lung toxicity. Lung toxicity was defined as a decrease of the diffusion capacity of the lung for carbon monoxide (D_{LCO}) by at least 20% at three months after ASCT. D_{LCO} was assessed before ASCT (baseline), 3 months after ASCT when recovery of erythropoietin can be expected, as well as 12 months after ASCT. We expected significantly fewer patients to suffer from pulmonary toxicity in the BendaEAM group than in the BEAM group. The Dinakara equation was used for adjusting D_{LCO} for haemoglobin (Hb): $D_{LCO\ adjusted}$ = measured $D_{LCO}/(0.06965 \times Hb)$.[20]

At the same time points, spiroergometry was performed and forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were assessed as secondary endpoints. Additionally, cardiac and renal function were evaluated using echocardiography (ECHO) and electrocardiography (ECG) and by calculating the estimated glomerular filtration rate (eGFR), with values below 60 indicating impaired renal function (chronic kidney disease stage ≥ 3). ECG and ECHO were judged at the discretion of the examining clinician without describing further details. Further secondary endpoints included haematological recovery, engraftment, survival, toxicities, and quality of life. Overall survival (OS) and progression-free survival (PFS) were estimated one year after ASCT. Response rates were originally calculated following the RECIST guideline.[21] After completion of the study, radiological reassessment was

performed according to the Lugano classification system, which is the established standard now.[22] Further, acute (≤35 days after ASCT) and late (>35 days after ASCT) toxicity adverse events (AEs) were assessed during the entire study period, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOC).[23] Cytopenias occurring within the first four weeks after ASCT were considered transplant-related and therefore not counted as AE. Quality of life was assessed at screening, three months after ASCT, and one year after ASCT using the EORTC-Q30 questionnaire, version 3.0.[24]

All outcomes were assessed by the respective study centre.

Statistical analysis

The hypothesis was that <4% of patients in the BendaEAM arm and >25% of patients in the BEAM arm would present with toxic effects to the lung upon administration with the respective conditioning regimen. Applying a statistical power of 80% and a two-sided significance level of 5%, 49 evaluable patients were required in each group to be able to demonstrate a clinically meaningful reduction of lung toxicity. Expecting a drop-out rate of 10%, a total of 108 patients were needed.

For statistical analysis of this study, continuous endpoints were summarised using descriptive statistics. For categorical variables, the number and percentage of patients in each category are presented; for continuous variables, the mean and standard deviation (SD) or median and interquartile range (IQR) are reported. The primary endpoint in the two groups was tested using Fisher's exact test. For group comparisons in the categorical secondary endpoints Fisher's exact test and in the continuous secondary endpoints t-test or Mann-Whitney-U test was used. PFS and OS were assessed by Kaplan-Meier plots and group comparisons were performed using log-rank tests. A post-hoc sensitivity analysis was performed by including the stratification parameter lymphoma diagnosis (MCL, FL, and DLBCL) in the analyses (Cochran Mantel–Haenszel test for categorical endpoints, linear model with lymphoma diagnosis as co-variable for continuous endpoints and stratified log-rank test for survival endpoints; The stratified *P*-values are reported in the results and in the Supplementary Material, Table S14). Further post-hoc analyses include: comparisons of eGFR values, a descriptive presentation of all results by the subtypes MCL, DLBCL and FCL separately, and cumulative incidences of non-relapse mortality. Analyses were performed on an intention-to-treat basis. There was no imputation for missing values.

All tests were two-sided and P <0.05 denoted statistical significance. SAS Version 9.4 software was used for all analyses.

The BEB-trial was registered with the European Medicines Agency (EudraCT number 2014-003629-16), in the WHO International Clinical Trials Registry Platform (ClinicalTrials.gov Identifier: NCT02278796), and the Swiss National Clinical Trials Portal.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

108 patients with lymphoma in first or second remission or chemosensitive relapse were enrolled between April 20, 2015, and November 28, 2018, at the four participating study centres (Krankenhaus der Elisabethinen Linz, n = 13; Hanusch Hospital in Vienna, n = 26; Inselspital/University Hospital Bern, n = 46; University Hospital Zurich n = 23). Participants had either MCL (n = 39), FL (n = 12) or DLBCL (n = 57), three of which were suffering from transformed high malignant lymphoma, and were randomly assigned to the BendaEAM (n = 53) or BEAM (n = 55) regimen. Fig. 1 displays the participant flow from enrolment to follow-up 1 year after ASCT. Time between the measurements (randomisation–HDCT, HDCT–ASCT, ASCT–100 days, ASCT–1 year) was similar in both study groups. Main characteristics of patients including status of disease are listed in detail in Table 1. Age, prognostic indices, and patient conditions were well balanced in both groups. Most frequent comorbidities, according to the HCT-CI, were moderate pulmonary dysfunction (BendaEAM: n = 17, 32.7%, BEAM: n = 19, 34.5%), severe pulmonary dysfunction (BendaEAM: n = 9, 17.0%, BEAM: n = 7, 12.7%), cardiac disorders (BendaEAM: n = 5, 9.4%, BEAM: n = 5, 9.1%), diabetes (BendaEAM: n = 4, 7.5%, BEAM: n = 6, 10.9%), arrhythmia (BendaEAM: n = 3, 5.7%, BEAM: n = 2, 3.6%), mild hepatic insufficiency (BendaEAM: n = 3, 5.7%, BEAM: n = 2, 3.6%), and infection (BendaEAM: *N* = 3, 5.7%, BEAM: n = 2, 3.6%). Remission status before ASCT did not differ between study and control arm. All patients with MCL received ASCT as consolidation within their first line treatment, and patients with FL in second line. 39 of 57 patients with DLBCL (68.4%) received treatment in second line, the remaining 18 patients (31.6%) had high risk lymphoma (either double hit lymphoma, double expressor lymphoma, or high risk NCCN International Prognostic Index) and received first line treatment. Previous first and second line therapies combined and irrespective of lymphoma type consisted of (R)-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)/CHOP-like (41.4%), R-CHOP-R-DHAP (dexamethasone, high-dose cytarabine, cisplatin; 18.5%), R-DHAP/DHAP-like (11.5%), R-Bendamustine (5.7%), Rituximab (4.5%), R-DA-EPOCH/EPOCH

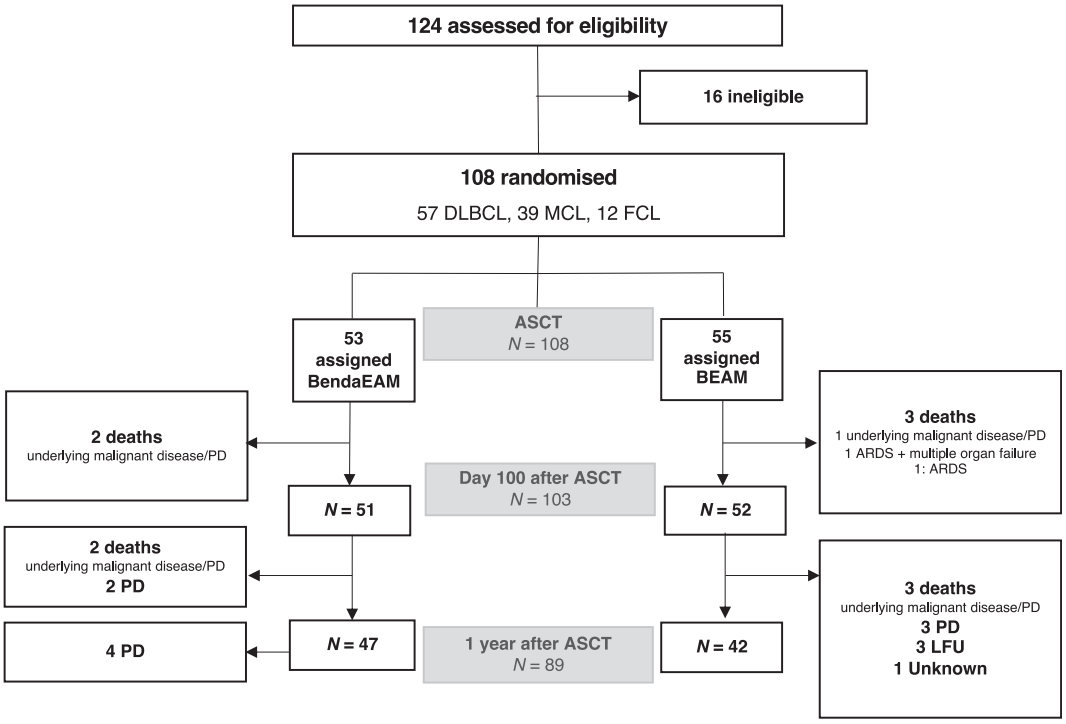

***Fig. 1:* Patient flow**. MCL indicates mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ASCT, autologous stem cell transplantation; LFU, lost to follow-up; PD, progressive disease; ARDS, acute respiratory deficiency syndrome.

(4.5%), R-ICE (ifosfamide, carboplatin, etoposide; 3.2%), and other (10.8%) treatments.

Patients received peripheral blood stem cells and a median number of 4.3×10^6 and 4.6×10^6 CD34+ cells/kg was infused in the BendaEAM and in the BEAM arm, respectively. All patients engrafted with a median time of 10 days (IQR: 10–11) to achieve an absolute neutrophil count $>0.5 \times 10^9$/l. Median time to platelet count $>20 \times 10^9$/l was 12 days (IQR: 11–15). Details for engraftment results per study group see Table 2. Median duration of hospitalisation at bone marrow transplant unit was 21 (IQR: 18–24) and 20 days (IQR: 14–22) in the BendaEAM and BEAM group, respectively. A median of 4 platelet units (IQR: 2–7) were transfused in the BendaEAM arm and 3 (IQR: 2–5) in the BEAM arm. The median number of red blood cell units transfused was 2 (IQR: 2–4) and 2 (IQR: 1–4) in the BendaEAM and BEAM arm, respectively. Median fever days were 1.0 in both study groups, with an interquartile range (IQR) of 1.0–2.5 and 0.0–2.0 in the BendaEAM and BEAM group, respectively.

Lung toxicity, defined as a decrease of $D_{LCO} \geq 20\%$, at three months after ASCT, was observed in 8 from 41 patients (19.5%) in the BendaEAM and in 11 from 43 (25.6%) in the BEAM group, including two lung toxicity deaths, ($P = 0.605$, P *stratified* = 0.34, risk difference BendaEAM–BEAM: –6.1%: 95% CI: –23.9% to 11.7%). There was no difference in lung toxicity between the study groups, thus the primary endpoint was not met. D_{LCO} (%) at baseline and 3 months and 1 year after ASCT is displayed in Fig. 2, the detailed results are shown in Tables 3 and 4. Mean relative reduction of D_{LCO} from baseline to 3 months after ASCT was 4.9% (SD 18.7%) in the BEAM arm (n = 41) vs. 3.2% (SD 21.2%) in the BendaEAM arm (n = 41). There was no significant group difference in any cardiac or pulmonary function parameter at any time point (Table 4). Although two patients died due to treatment-related lung toxicity in the BEAM arm, no clinically significant deterioration in pulmonary function was observed in patients receiving the BCNU-containing BEAM regimen.

Acute toxicities are shown in Table 5. Most patients had at least one adverse event of any severity within the first 35 days after ASCT. Respiratory, thoracic, and mediastinal disorders were only observed in the BEAM arm. In contrast to previous trials, grade 3–5 renal toxicity was low, both in the BendaEAM and BEAM arm. Late toxicity of any kind was observed in 48.1% and 31.5% of the patients in the BendaEAM and BEAM group, respectively ($P = 0.11$, P *stratified* = 0.04). Grade 3–5 late toxicities were more frequent in BendaEAM than BEAM ($P = 0.02$, P *stratified* = 0.03). Table 6 provides details on observed late toxicities. Regarding renal toxicity, no difference between groups was observed at any time. CTCAE grade 3–5 acute renal toxicity was low

	BendaEAM, *N* = 53	BEAM, *N* = 55
	N (%)	N (%)
Age, years		
Mean (SD)	51.8 (1.1)	51.9 (1.1)
Sex		
Male	36 (67.9)	39 (70.9)
Female	17 (32.1)	16 (29.1)
Type of disease		
DLBCL	29 (54.7)	28 (50.9)
IPI, Median (IQR, N = 82)	2.0 (1.5–3.0)	2.5 (2.0–3.0)
FCL	5 (9.4)	7 (12.7)
FLIPI–Median (IQR, N = 8)	2.0 (1.5–4.0)	2.0 (1.5–2.5)
MCL	19 (35.8)	20 (36.4)
MIPI–Median (IQR, N = 22)	5.6 (5.0–6.2)	5.2 (5.0–5.4)
Remission status		
Complete remission	39 (76.5)	36 (67.9)
Partial remission	12 (23.5)	16 (30.2)
Stable disease	–	1 (1.9)
Medical history (MedDRA SOC; > 10% of N)		
Vascular disorders	17 (32.1)	18 (32.7)
Infections and infestations	15 (28.3)	12 (21.8)
Metabolism and nutrition disorders	14 (26.4)	12 (21.8)
Cardiac disorders	10 (18.9)	8 (14.5)
Gastrointestinal disorders	8 (15.1)	10 (18.2)
Surgical and medical procedures	11 (20.8)	7 (12.7)
Neoplasms (benign–malignant–and unspecified)	6 (11.3)	10 (18.2)
Musculoskeletal and connective tissue disorders	9 (17.0)	7 (12.7)
Social circumstances	6 (11.3)	9 (16.4)
Respiratory–thoracic–and mediastinal disorders	6 (11.3)	8 (14.5)
Renal and urinary disorders	5 (9.4)	7 (12.7)
Nervous system disorders	6 (11.3)	5 (9.1)
Comorbidity burden (HCT-CI score)		
0 (no comorbidities)	14 (26.4)	18 (32.7)
1–2	18 (34.0)	18 (32.7)
3–5	21 (39.6)	19 (34.5)
Performance status (ECOG)		
0	38 (77.6)	40 (80.0)
1	11 (22.4)	9 (18.0)
2	–	1 (2.0)
Missing	4	5

DLBCL indicates diffuse large B-cell lymphoma; FL, Follicular lymphoma; MCL, Mantle cell lymphoma; IPI, International Prognostic Index for Diffuse Large B-cell Lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; MIPI, Mantle Cell Lymphoma International Prognostic Index; SD, standard deviation; IQR, interquartile range; MedDRA, Medical Dictionary of Regulatory Activities; SOC, System Organ Classes; HCT-CI, Hematopoietic Cell Transplantation-specific Comorbidity Index.

Table 1: **Patient characteristics at baseline.**

	BendaEAM	BEAM
Median number of CD34+ cells/kg infused x 10^6 (IQR)	4.3 (3.2–6.2)	4.6 (3.3–5.5)
Median time ASCT to engraftment (days, IQR)	12 (11–14)	12 (10–17)
Median time to ANC >0.5 × 10^9/l (days, IQR)	10 (10–11)	10 (10–11)
Median time to PLT >20 × 10^9/l (days, IQR)	12 (11–14)	12 (10–17)

ASCT indicates autologous stem cell transplantation; ANC, absolute neutrophil count; PLT, platelet count; IQR, interquartile range. BendaEAM: *N* = 52–53, BEAM: *N* = 54–55.

Table 2: **Engraftment details per study group.**

in both groups, with only one case in each study group (see Table 5). No grade 3–5 late renal toxicity was observed in either group. Fig. 3 displays the frequency of eGFR values < 60 ml/min, indicating abnormal renal function (chronic kidney disease stage ≥3), with no significant differences between the study groups. Four patients in the BendaEAM and six patients in the BEAM arm experienced an increase >0.3 mg/dl in creatinine from baseline until day 100.

Median follow-up observation period for the whole cohort, defined as the time from ASCT until death of any cause or date of last follow-up, was 369 days (range: 15–540 days). Ten patients died (four in the BendaEAM and six in the BEAM arm). The Kaplan–Meier estimates for one-year overall survival were 92.3% (95% CI: 80.8–97.0) and 88.6% (95% CI: 76.3–94.7) in the BendaEAM and BEAM arm, respectively (log-rank test $P = 0.54$, P *stratified* = 0.46). Two (both in the BEAM arm) out of 10 patients died due to non-relapse mortality, one from acute respiratory distress syndrome (ARDS) and one from ARDS with multiple organ failure (cumulative incidence of non-relapse mortality using relapse mortality as competing event: 3.6%; 95% CI: 0.8%–15.4%). Causes of death are summarised in Table 7. Ten patients in each group had a progression or died during the observational period (log-rank test $P = 0.89$, P *stratified* = 0.66), with a PFS of 72.5% (95% CI: 50.2–86.0) in the BendaEAM arm and 81.7% (95% CI: 68.6–89.7) in the BEAM arm. The corresponding survival curves are shown in Fig. 4. One year after ASCT, 90.0% in BendaEAM and 94.3% in BEAM were in CR, 0.0% and 5.7% in PR, none had stable disease, and 10.0% in BendaEAM had PD.

As shown in Fig. 5, the two study groups did not differ in any of the assessments for global health status and physical functioning, although an increasing trend could be observed in both groups. No differences were found between BendaEAM and BEAM for any of the other subscales of the EORTC-Q30.

Discussion

This is the first randomised phase 2 clinical trial comparing BendaEAM with BEAM as a conditioning regimen prior to ASCT in lymphoma that has reported results. Rapid and stable engraftment and absence of treatment-related mortality in the BendaEAM group were found, confirming previous reports.[9,10,25] However, despite similar survival rates, compared to the BEAM group, increased late toxicity was found in the BendaEAM group.

BCNU has been known to cause lung toxicity, particularly when used in combination with cyclophosphamide or at doses exceeding 600 mg/m^2.[26,27] To reduce lung-related toxicity, replacing BCNU by bendamustine has been proposed. However, the present study did not demonstrate superiority of BendaEAM

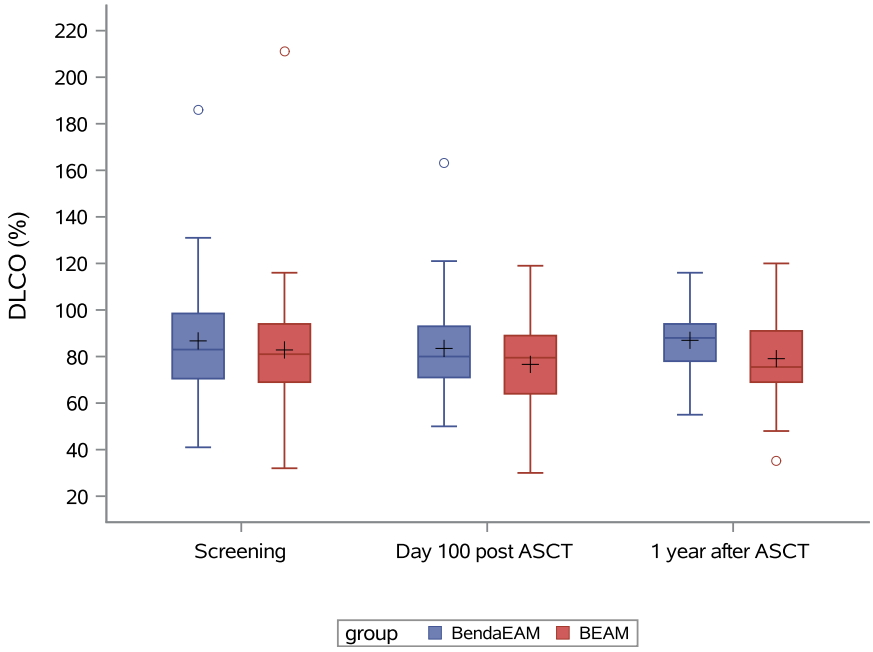

***Fig. 2:* Boxplots for D_{LCO} over the study period.** D_{LCO} indicates diffusion capacity of the lung for carbon monoxide. D_{LCO} (%) is adjusted for haemoglobin; Boxes represent the interquartile range per group and measurement. Horizontal lines dividing the boxes mark the median, crosses indicate the mean. Outliers are represented by dots, lying outside the whiskers.

	BendaEAM *N* (%)	BEAM *N* (%)	*P*
D_{LCO} reduction ≥20%	8 (19.5)	11 (25.6)	0.605
D_{LCO} reduction <20%	33 (80.5)	32 (74.4)	

D_{LCO} indicates diffusion capacity of the lung for carbon monoxide.BendaEAM: *N* = 41, BEAM: *N* = 43.

***Table 3:* Primary endpoint: D_{LCO} reduction 3 months post ASCT.**

over BEAM in terms of pulmonary toxicity: No difference in D_{LCO} reduction was observed between both treatment groups. Thus, the primary endpoint of our trial was not met. Although it should be noted that two patients in the BEAM group died due to treatment-related pulmonary toxicity, suggesting acute severe lung damage rather than slow functional and irreversible deterioration. One patient was found to have pulmonary fibrosis without evidence of infection on post-mortem examination. In the other patient, respiratory failure with cardiac arrest was observed without clear evidence of infection-related death. Both patients received steroids during the period of respiratory failure. Our results therefore support previous findings of a potential increased risk of fatal lung injury with the BCNU regimen. Nevertheless, overall, particularly late toxicities of any kind appear to be more frequent with BendaEAM, confirming previous publications.[13,28] This should be taken into account when considering BendaEAM as an alternative preparatory regimen.

Previous retrospective studies have demonstrated significant bendamustine-related renal toxicity in up to 30% of patients.[10,12,13,25,29,30] In our previously published study,[11] a slight increase in creatinine levels was observed in the majority of patients receiving bendamustine. CTCAE grade 1 renal toxicity occurred in approximately 15% of patients. This was confirmed by recent publications.[28,31] Of note, nearly 10% of patients entered the present trial with pre-existing renal impairment related to comorbidities and/or toxicity of preceding treatments. However, there was no increase in patients suffering from kidney diseases up until one year after ASCT. At 1-year follow-up, no grade ≥3 renal or pulmonary toxicities were observed in either study group. Both are well known risk factors for late non-disease related mortality.[32] As results from meta-analyses indicate, particularly impairment of kidney function is associated with an increase of all-cause and cardiovascular mortality.[33]

Our patient population was heterogeneous but well balanced. Because of limited financial support, we had to restrict the sample size, which affected the statistical power of the trial. Although formal testing was not possible in the current study, it is crucial to consider efficacy of BendaEAM versus BEAM. In our study population, we observed a slight tendency towards lower PFS with the BendaEAM regimen compared to BEAM. No difference in response rates and OS was found between both regimens. It is important to note that prior retrospective

	Screening		3 months post ASCT			1 year post ASCT		
	Mean (SD)		Mean (SD)			Mean (SD)		
	BendaEAM	BEAM	BendaEAM	BEAM	*P*	BendaEAM	BEAM	*P*
Venous BGA								
pH arterial	7.4 (0.0)	7.4 (0.1)	7.4 (0.0)	7.4 (0.0)	0.934	7.4 (0.1)	7.4 (0.0)	0.260
Base excess, mval/l	−0.1 (2.9)	0.3 (5.4)	0.1 (2.2)	−1.6 (3.4)	0.067	−0.5 (2.9)	0.2 (2.0)	0.406
HCO_3, mmol/l	23.9 (2.5)	23.8 (1.8)	24.1 (2.9)	23.3 (2.7)	0.349	24.7 (1.7)	23.7 (1.7)	0.100
SaO_2, %	94.8 (7.6)	93.4 (12.1)	94.3 (7.6)	92.6 (14.7)	0.524	93.1 (12.6)	92.6 (12.8)	0.528
pCO_2, mmHg	37.9 (5.3)	39.3 (4.2)	39.5 (5.6)	37.6 (5.4)	0.185	37.8 (4.0)	38.9 (4.8)	0.417
pO_2, mmHg	72.4 (23.2)	65.5 (19.7)	63.0 (24.3)	69.1 (23.7)	0.333	76.8 (14.1)	73.9 (17.6)	0.576
Pulmonary function								
FVC, l	4.1 (0.9)	4.1 (0.8)	4.1 (0.8)	4.0 (0.9)	0.428	4.2 (0.9)	4.4 (0.9)	0.174
FEV_1, l	3.2 (0.8)	3.2 (0.7)	3.2 (0.7)	3.0 (0.7)	0.149	3.3 (0.8)	3.4 (1.1)	0.518
Diffusion capacity								
D_{LCO}, mmol/min/kPA	9.8 (7.6)	9.4 (3.5)	8.7 (3.3)	8.4 (3.3)	0.654	8.9 (3.8)	9.3 (3.8)	0.668
D_{LCO}, %	86.7 (25.2)	82.8 (25.9)	83.5 (20.6)	76.6 (19.6)	0.110	87.0 (13.5)	79.1 (18.3)	0.054
Spiroergometry								
Watt/kg	1.7 (0.4)	1.7 (0.6)	1.7 (0.6)	1.8 (0.6)	0.734	1.8 (0.5)	2.0 (0.5)	0.176
ECG								
Normal, *N* (%)	44 (84.6)	41 (74.5)	40 (83.3)	34 (77.3)	0.600	27 (79.4)	24 (85.7)	0.740
Abnormal, *N* (%)	8 (15.4)	14 (25.5)	8 (16.7)	10 (22.7)		7 (20.6)	4 (14.3)	
Missing, *N*	1	–	5	11		19	27	
ECHO								
Normal, *N* (%)	35 (68.6)	34 (64.2)	31 (63.3)	29 (63.0)	1	23 (63.9)	26 (76.5)	0.303
Abnormal, *N* (%)	16 (31.4)	19 (35.8)	18 (36.7)	17 (37.0)		13 (36.1)	8 (23.5)	
Missing, *N*	2	2	4	9		17	21	

D_{LCO} indicates diffusion capacity of the lung for carbon monoxide; D_{LCO}, % was adjusted for haemoglobin; ECG and ECHO were judged at the discretion of the examining clinician; ASCT indicates autologous stem cell transplantation; SD, standard deviation; BGA, blood gas analysis; HCO_3, hydrogen carbonate; SaO2, oxygen saturation; pCO2, partial pressure of carbon dioxide; pO2, partial pressure of oxygen; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in 1 s; DLCO, diffusion capacity of the lung for carbon monoxide; ECG, electrocardiography; ECHO, echocardiography. BendaEAM *N* = 17–53, BEAM *N* = 16–55.

Table 4: **Cardiopulmonary function.**

Toxicity	All N (%)		Grade 3–5 N (%)	
	BendaEAM	BEAM	BendaEAM	BEAM
Blood and lymphatic system disorders	7 (13.2)	4 (7.3)	5 (9.4)	4 (7.3)
Cardiac disorders	5 (9.4)	3 (5.5)	3 (5.7)	2 (3.6)
Gastrointestinal disorders	31 (58.5)	25 (45.5)	7 (13.2)	3 (5.5)
General disorders and administration site conditions	22 (41.5)	16 (29.1)	4 (7.5)	2 (3.6)
Infections and infestations	13 (24.5)	15 (27.3)	5 (9.4)	8 (14.5)
Investigations	12 (22.6)	6 (10.9)	5 (9.4)	3 (5.5)
Metabolism and nutrition disorders	14 (26.4)	10 (18.2)	2 (3.8)	5 (9.1)
Renal and urinary disorders	3 (5.7)	2 (3.6)	1 (1.9)	1 (1.8)
Respiratory, thoracic, and mediastinal disorders	7 (13.2)	8 (14.5)	–	3 (5.5)
Any AE	43 (81.1)	37 (67.3)	19 (35.8)	17 (30.9)

≤35 days after autologous stem cell transplantation; AE indicates adverse event. Two grade 5 pulmonary toxicities were observed. BendaEAM *N* = 53, BEAM *N* = 55.

Table 5: **Acute toxicities.**

analyses on the efficacy of BendaEAM versus BCNU-based conditioning regimens have yielded inconclusive results. Some studies found no significant difference between BendaEAM and BEAM in terms of PFS,[10,25,31] while others reported superior PFS rates with BendaEAM.[28] Considering the current state of research, no definitive conclusion can be drawn regarding the efficacy of BendaEAM in comparison to BEAM. A recent meta-analysis of retrospective reports comparing BendaEAM and BEAM found slightly better PFS in BendaEAM.[34]

Toxicity	All N (%)		Grade 3–5 N (%)	
	BendaEAM	BEAM	BendaEAM	BEAM
Blood and lymphatic system disorders	5 (9.6)	5 (9.3)	2 (3.8)	2 (3.7)
Cardiac disorders	4 (7.7)	1 (1.9)	–	–
Gastrointestinal disorders	8 (15.4)	2 (3.7)	3 (5.8)	–
General disorders and administration site conditions	5 (9.6)	2 (3.7)	–	–
Infections and infestations	9 (17.3)	7 (13.0)	2 (3.8)	–
Investigations	7 (13.5)	3 (5.6)	3 (5.8)	1 (1.9)
Metabolism and nutrition disorders	3 (5.8)	2 (3.7)	1 (1.9)	–
Renal and urinary disorders	–	1 (1.9)	–	–
Respiratory, thoracic, and mediastinal disorders	3 (5.8)	3 (5.6)	–	–
Any AE	25 (48.1)	17 (31.5)	11 (21.2)	3 (5.6)

>35 days after autologous stem cell transplantation; AE indicates adverse event. No grade 5 toxicities were observed. BendaEAM: *N* = 52, BEAM: *N* = 54.

Table 6: **Late toxicities.**

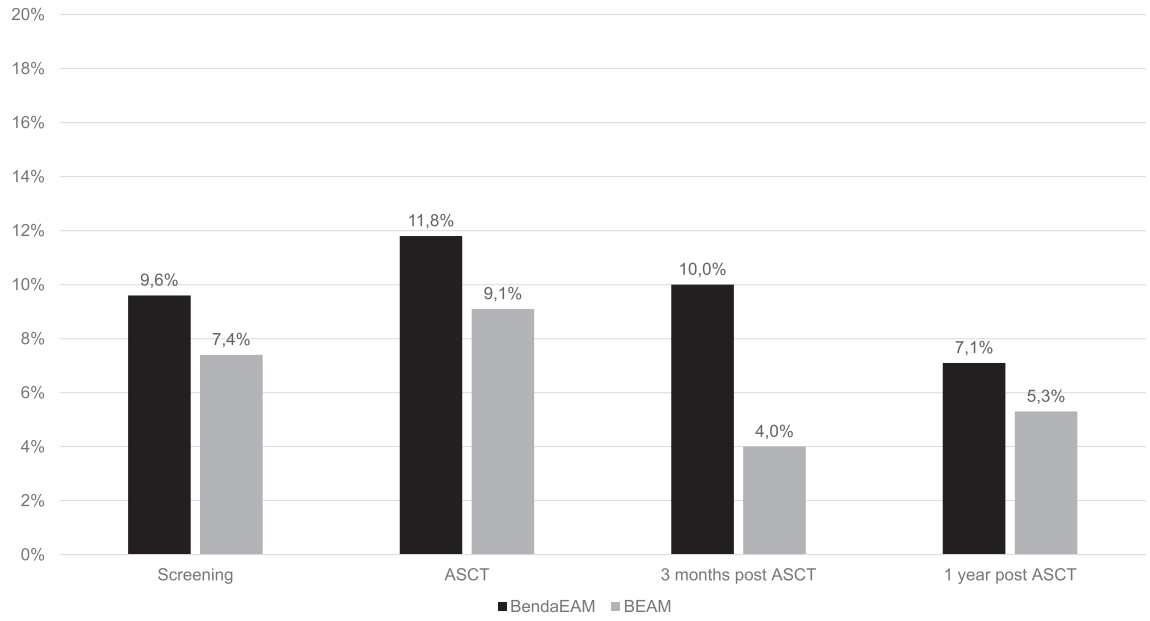

Fig. 3: **Abnormal renal function over time.** Proportion of patients per study group with an estimated glomerular filtration rate (eGFR) below 60 across the study period.

	BendaEAM, *N* = 53 *N* (%)	BEAM, *N* = 55 *N* (%)
Underlying malignant disease/progression	4 (7.5)	4 (7.3)
ARDS	–	1 (1.8)
ARDS + multiple organ failure	–	1 (1.8)
Total number of deaths	**4 (7.5)**	**6 (10.9)**

ARDS indicates acute respiratory distress syndrome.

Table 7: **Causes of death.**

In light of the emerging role of novel cellular therapies such as bispecific antibodies, antibody-drug conjugates, and chimeric antigen receptor (CAR-) T cell therapy in the treatment of relapsed lymphoma, ASCT remains an important treatment option in patients with chemosensitive lymphoma. Retrospective analysis of real-world data of DLBCL patients suggests superior OS at two years and lower rates of relapse or progression after ASCT compared to CAR-T cell therapies in chemosensitive patients.[35] Furthermore, long-term clinical results for ASCT continue to improve as transplant strategies evolve.[32,36]

Considering the occasional limited availability and high costs associated with BCNU, bendamustine might be regarded an alternative to BCNU in the BEAM conditioning regimen. However, the decision to replace bendamustine with BCNU should carefully consider its potentially higher toxicity.

In conclusion, our results should be interpreted in light of the discussed limitations. The observation period of 12 months is not sufficient to evaluate long-term

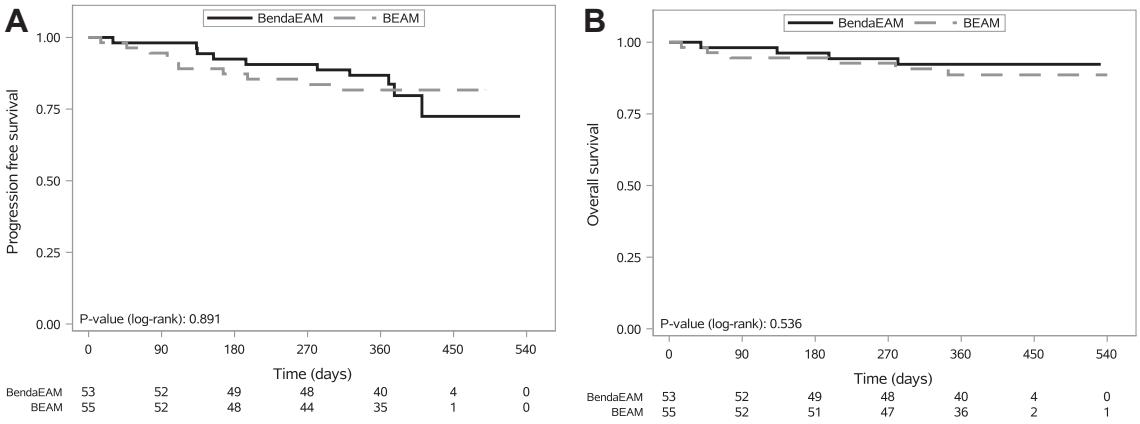

Fig. 4: **Kaplan–Meier Plots for overall and progression-free survival**. (A) Overall survival, one year after autologous stem cell transplantation, was 92.3% (95% CI: 80.8–97.0) and 88.6% (95% CI: 76.3–94.7) in the BendaEAM and BEAM arm, respectively. (B) Progression-free survival was 72.5% (95% CI: 50.2–86.0) in the BendaEAM and 81.7% (95% CI: 68.6–89.7) in the BEAM arm.

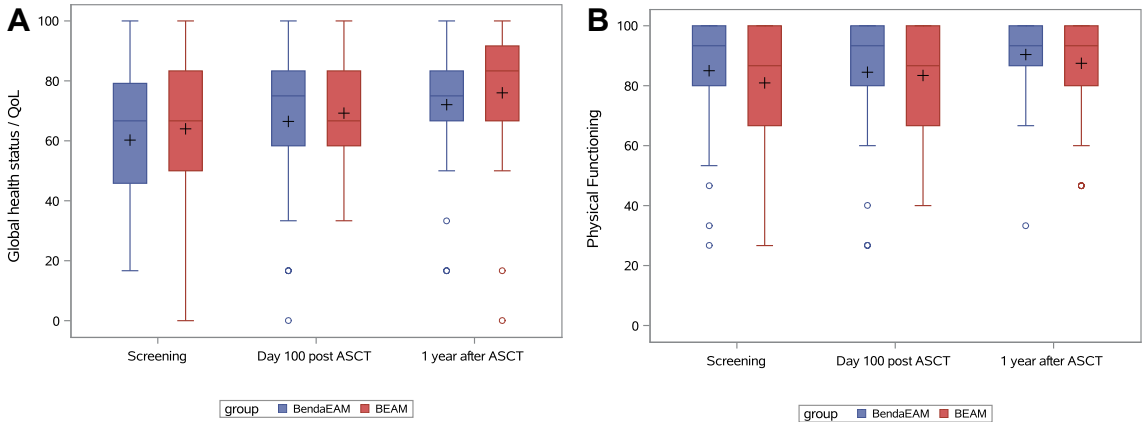

Fig. 5: **Boxplots for quality of life over the study period.** Global health status (A) and physical functioning (B) as assessed by the EORTC-Q30. Vertical lines within the box indicate the median, crosses indicate the mean. Boxes represent the interquartile range per group and measurement. Horizontal lines dividing the boxes mark the median, crosses indicate the mean. Outliers are represented by dots, lying outside the whiskers.

toxicity and survival. However, a long-term follow-up assessment after 10 years is planned. A phase 3 non-inferiority trial could establish whether BendaEAM can be considered a reasonable alternative to BEAM.

Contributors

FK is the principal investigator. He administered and supervised the project, performed research, provided resources, wrote the manuscript (original draft + review), and acquired funding. AMSM, VB-A, CV, ABo, MP, TN, PS, MR contributed with performing research. ABe and RR statistically designed the trial and did the data analysis and visualisation. JS and RG were involved through project administration. JS further contributed by data curation and validation. CB wrote the manuscript (original draft + review & editing), and visualised results. TP contributed by acquiring funding, performing research, and providing resources. All authors reviewed the manuscript, confirmed the completeness and accuracy of the report, and agreed on its submission for publication. All authors had access to the primary data. FK, TP and JS accessed and verified the underlying data.

Data sharing statement

De-identified individual patient data underlying the reported results are available to collaborating researchers for an unlimited period of time. Upon reasonable interest, others may also request the data or extracts from those. Proposals for access should be sent to felix.keil@oegk.at.

Declaration of interests

FK received research funding from Mundipharma and honoraria from Novartis, Gilead, Janssen, Astra Zeneca, Abbvie, Roche, Takeda, BMS, and Incyte. VB-A received honoraria from AOP Orphan, Incyte, Novartis, Gilead, BMS Celgene, Amgen, Takeda, Sanofi, GSK, and Janssen-Cilag. TN received honoraria from Janssen and Roche. RG received honoraria from Celgene, Novartis, Roche, BMS, Takeda, Abbvie, Astra Zeneca, Janssen-Cilag, MSD, Merck, Gilead, Daiichi Sankyo,

Sanofi Amgen, and Sandoz; and holds stock (options) from Novo Nordisk and Lilly. ABe received honoraria from Roche. All other authors declare no competing interests.

Acknowledgements

The authors thank the patients, their families, the participating study centres, and their medical and nursing staff. Furthermore, the authors thank Dr Chantal Y. Manz (ClinaMed, Therwil, Switzerland) for the supply of the study concept and Prof Dr Dominik Schneidawind for his support in data collection and radiological reassessment according to the Lugano criteria. This work was financially supported by Mundipharma.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102318.

References

1 Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28(27):4184–4190. https://doi.org/10.1200/JCO.2010.28.1618.
2 Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333(23):1540–1545. https://doi.org/10.1056/NEJM199512073332305.
3 Passweg JR, Baldomero H, Chabannon C, et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. *Bone Marrow Transplant*. 2021;56(7):1651–1664. https://doi.org/10.1038/s41409-021-01227-8.
4 Niederwieser D, Baldomero H, Bazuaye N, et al. One and a half million hematopoietic stem cell transplants: continuous and differential improvement in worldwide access with the use of non-identical family donors. *Haematologica*. 2021;107(5):1045–1053. https://doi.org/10.3324/haematol.2021.279189.
5 Mills W, Chopra R, McMillan A, Pearce R, Linch DC, Goldstone AH. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol*. 1995;13(3):588–595. https://doi.org/10.1200/JCO.1995.13.3.588.
6 Leoni LM, Bailey B, Reifert J, et al. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. *Clin Cancer Res*. 2008;14(1):309–317. https://doi.org/10.1158/1078-0432.CCR-07-1061.
7 Rummel MJ, Chow KU, Hoelzer D, Mitrou PS, Weidmann E. In vitro studies with bendamustine: enhanced activity in combination with rituximab. *Semin Oncol*. 2002;29(4 Suppl 13):12–14. https://doi.org/10.1053/sonc.2002.34873.
8 Vidal L, Gurion R, Shargian L, Dreyling M, Gafter-Gvili A. Bendamustine for patients with indolent B cell lymphoproliferative malignancies including chronic lymphocytic leukaemia–an updated meta-analysis. *Br J Haematol*. 2019;186(2):234–242. https://doi.org/10.1111/bjh.15901.
9 Visani G, Malerba L, Stefani PM, et al. BeEAM (bendamustine, etoposide, cytarabine, melphalan) before autologous stem cell transplantation is safe and effective for resistant/relapsed lymphoma patients. *Blood*. 2011;118(12):3419–3425. https://doi.org/10.1182/blood-2011-04-351924.
10 Hahn L, Lim H, Dusyk T, et al. BeEAM conditioning regimen is a safe, efficacious and economical alternative to BEAM chemotherapy. *Sci Rep*. 2021;11(1):14071. https://doi.org/10.1038/s41598-021-93516-x.
11 Noesslinger T, Panny M, Simanek R, et al. High-dose Bendamustine-EAM followed by autologous stem cell rescue results in long-term remission rates in lymphoma patients, without renal toxicity. *Eur J Haematol*. 2018;101(3):326–331. https://doi.org/10.1111/ejh.13102.
12 Chantepie SP, Garciaz S, Tchernonog E, et al. Bendamustine-based conditioning prior to autologous stem cell transplantation (ASCT): results of a French multicenter study of 474 patients from LYmphoma Study Association (LYSA) centers. *Am J Hematol*. 2018;93(6):729–735. https://doi.org/10.1002/ajh.25077.
13 Garciaz S, Coso D, Schiano de Collela JM, et al. Bendamustine-based conditioning for non-Hodgkin lymphoma autologous transplantation: an increasing risk of renal toxicity. *Bone Marrow Transplant*. 2016;51(2):319–321. https://doi.org/10.1038/bmt.2015.257.
14 Bou Akl I, Matar M, Khalil PB, et al. Impact of the conditioning regimen dose intensity before autologous stem cell transplantation on the pulmonary function test abnormalities in patients with lymphoma and multiple myeloma: single center experience. *Clin Lymphoma Myeloma Leuk*. 2020;20(6):371–376.e1. https://doi.org/10.1016/j.clml.2019.10.015.
15 Kim YJ, Kim WS, Choi YH, et al. Radiologic evaluation of pulmonary injury following carmustine- and cyclophosphamide-based preparative regimen for autologous peripheral blood stem cell transplantation in children. *Pediatr Radiol*. 2018;48(13):1875–1883. https://doi.org/10.1007/s00247-018-4223-8.
16 Duque-Afonso J, Ewald S, Ihorst G, et al. The impact of pulmonary function in patients undergoing autologous stem cell transplantation. *Blood Adv*. 2021;5(21):4327–4337. https://doi.org/10.1182/bloodadvances.2021004863.
17 Bhalla KS, Wilczynski SW, Abushamaa AM, et al. Pulmonary toxicity of induction chemotherapy prior to standard or high-dose chemotherapy with autologous hematopoietic support. *Am J Respir Crit Care Med*. 2000;161(1):17–25. https://doi.org/10.1164/ajrccm.161.1.9903059.
18 Dimopoulou I, Efstathiou E, Samakovli A, et al. A prospective study on lung toxicity in patients treated with gemcitabine and carboplatin: clinical, radiological and functional assessment. *Ann Oncol*. 2004;15(8):1250–1255. https://doi.org/10.1093/annonc/mdh311.
19 Dimopoulou I, Galani H, Dafni U, Samakovli A, Roussos C, Dimopoulos MA. A prospective study of pulmonary function in patients treated with paclitaxel and carboplatin. *Cancer*. 2002;94(2):452–458. https://doi.org/10.1002/cncr.10182.
20 Shibasaki Y, Katagiri T, Kobayashi H, et al. The Dinakara equation for adjusting DLCO for hemoglobin in the HCT-CI is superior to the Cotes equation for predicting high-risk patients in allogeneic hematopoietic stem cell transplantation. *Am J Hematol*. 2016;91(5):E296. https://doi.org/10.1002/ajh.24318.
21 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. https://doi.org/10.1016/j.ejca.2008.10.026.
22 Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059–3067. https://doi.org/10.1200/JCO.2013.54.8800.
23 National Cancer Institute. *Common terminology criteria for adverse events (CTCAE) version 4.0*. 2010.
24 Aaronson N, Ahmedzai S, Bergmann B, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365–376.
25 Costes-Tertrais D, Hueso T, Gastinne T, et al. Bendamustine-EAM versus R-BEAM after high-dose cytarabine-based induction in newly diagnosed patients with mantle cell lymphoma, a LYSA retrospective study. *Bone Marrow Transplant*. 2022;57(4):627–632. https://doi.org/10.1038/s41409-022-01596-8.
26 Alessandrino EP, Bernasconi P, Colombo A, et al. Pulmonary toxicity following carmustine-based preparative regimens and autologous peripheral blood progenitor cell transplantation in hematological malignancies. *Bone Marrow Transplant*. 2000;25(3):309–313. https://doi.org/10.1038/sj.bmt.1702154.
27 Ager S, Mahendra P, Richards EM, Bass G, Baglin TP, Marcus RE. High-dose carmustine, etoposide and melphalan ('BEM') with autologous stem cell transplantation: a dose-toxicity study. *Bone Marrow Transplant*. 1996;17(3):335–340.
28 Lachance S, Bourguignon A, Boisjoly JA, et al. Impact of implementing a bendamustine-based conditioning regimen on outcomes of autologous stem cell transplantation in lymphoma while novel cellular therapies emerge. *Transplant Cell Ther*. 2022;0(0). https://doi.org/10.1016/j.jtct.2022.10.003.
29 Ghesquières H, Dalban C, Nicolas-Virelizier E, et al. BeEAM (bendamustine, etoposide, cytarabine, melphalan) prior to autologous stem cell transplant for chemosensitive relapses in patients with follicular lymphoma: a prospective multicentre phase II study in Lymphoma Study Association centres. *Br J Haematol*. 2021;192(3):e94–e98. https://doi.org/10.1111/bjh.17279.
30 Prediletto I, Farag SA, Bacher U, et al. High incidence of reversible renal toxicity of dose-intensified bendamustine-based high-dose

chemotherapy in lymphoma and myeloma patients. *Bone Marrow Transplant*. 2019;54(12):1923–1925. https://doi.org/10.1038/s41409-019-0508-2.

31 Frankiewicz A, Saduś-Wojciechowska M, Najda J, et al. Comparable safety profile of BeEAM (bendamustine, etoposide, cytarabine, melphalan) and BEAM (carmustine, etoposide, cytarabine, melphalan) as conditioning before autologous haematopoietic cell transplantation. *Contemp Oncol Poznan Pol*. 2018;22(2):113–117. https://doi.org/10.5114/wo.2018.77046.

32 Bhatia S, Robison LL, Francisco L, et al. Late mortality in survivors of autologous hematopoietic-cell transplantation: report from the Bone Marrow Transplant Survivor Study. *Blood*. 2005;105(11):4215–4222. https://doi.org/10.1182/blood-2005-01-0035.

33 van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int*. 2011;79(12):1341–1352. https://doi.org/10.1038/ki.2010.536.

34 Wu R, Ma L. BeEAM (bendamustine, etoposide, cytarabine, melphalan) versus BEAM (carmustine, etoposide, cytarabine, melphalan) as conditioning regimen before autologous haematopoietic cell transplantation: a systematic review and meta-analysis. *Cell Transplant*. 2023;32. https://doi.org/10.1177/09636897231179364.

35 Shadman M, Pasquini M, Ahn KW, et al. Autologous transplant vs chimeric antigen receptor T-cell therapy for relapsed DLBCL in partial remission. *Blood*. 2022;139(9):1330–1339. https://doi.org/10.1182/blood.2021013289.

36 Bhatia S, Dai C, Landier W, et al. Trends in late mortality and life expectancy after autologous blood or marrow transplantation over three decades: a BMTSS report. *J Clin Oncol*. 2022;40(18):1991–2003. https://doi.org/10.1200/JCO.21.02372.