Received: 10 August 2023 | Revised: 29 September 2023 | Accepted: 30 September 2023

DOI: 10.1111/ejh.14118

ORIGINAL ARTICLE

European Journal of Haematology

WILEY

Identification of clinical factors impacting outcome in patients undergoing autologous hematopoietic cell transplantation after BEAM and TEAM conditioning

Radu-Florian Gherman[1] | Sophie Ewald[1] | Gabriele Ihorst[2] | Tim Strüßmann[1] | Robert Zeiser[1] | Ralph Wäsch[1] | Hartmut Bertz[1] | Daiana Stolz[3] | Justus Duyster[1] | Jürgen Finke[1] | Reinhard Marks[1] | Monika Engelhardt[1] | Jesús Duque-Afonso[1]

[1]Department of Hematology/Oncology/Stem Cell Transplantation, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany

[2]Clinical Trials Unit, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany

[3]Department of Pneumology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany

Correspondence
Jesús Duque-Afonso, Department of Hematology/Oncology/Stem Cell Transplantation, University Medical Center Freiburg, Hugstetterstr 55, D-79106 Freiburg im Breisgau, Germany.
Email: jesus.duque.afonso@uniklinik-freiburg.de

Funding information
German Federal Ministry of Education and Research, Grant/Award Number: BMBF 01 EO 0803; Else Kröner-Fresenius-Stiftung, Grant/Award Number: 2018-A56; German Research Foundation, Grant/Award Numbers: 1287/5-1, 1287/3-1; Forschungskommission of the University of Freiburg Medical School, Grant/Award Number: DUQ1106/16; Berta Ottenstein-Programm for Advanced Clinician Scientists, Faculty of Medicine, University of Freiburg

Abstract

Organ dysfunction, including pulmonary function impairment, plays a key role in the choice of conditioning chemotherapy before autologous hematopoietic stem cell transplantation (auto-HSCT). Replacement of BCNU/carmustine as part of BEAM (BCNU/carmustine, etoposide, cytarabine, and melphalan) conditioning protocol by thiotepa (TEAM) reduces pulmonary toxicity while maintaining efficacy. We retrospectively analyzed the association of clinical characteristics, comorbidities, and organ function with outcomes after conditioning with BEAM or TEAM. Three hundred ninety-six patients undergoing auto-HSCT ($n = 333$ with BEAM; $n = 63$ with TEAM) at our institution between 2008 and 2021 were included in this study. In the multivariate analysis, CO-diffusion capacity corrected for hemoglobin (DLCOcSB) ≤ 60% of predicted, progressive disease (PD) before auto-HSCT, Karnofsky performance score (KPS) ≤ 80%, HCT-CI score ≥ 4, and cardiac disease before auto-HSCT were associated with decreased overall survival (OS) in patients treated with BEAM. In contrast, only PD before auto-HSCT was identified in patients treated with TEAM. Patients conditioned with BEAM and DLCOcSB ≤ 60% had higher non-relapse mortality, including pulmonary cause of death. In summary, we have identified clinical and pulmonary risk factors associated with worse outcomes in patients conditioned with BEAM compared to TEAM. Our data suggest TEAM conditioning as a valid alternative for patients with comorbidities, including pulmonary dysfunction and/or poorer performance scores, before auto-HSCT.

KEYWORDS
autologous stem cell transplantation, cardiac function, conditioning, pulmonary function, TEAM

Novelty Statement

What is the new aspect of your work?

We compared clinical characteristics, outcome variables, and cardiac and lung function parameters in a large cohort of patients with lymphoma conditioned with either BEAM ($n = 333$) or TEAM ($n = 63$) before auto-HSCT at our institution.

What is the central finding of your work?

We identified clinical risk factors including cardiac disease, pulmonary dysfunction, high comorbidity index, and poorer performance status associated with worse outcomes in patients conditioned with BEAM but not with TEAM before auto-HSCT.

What is (or could be) the specific clinical relevance of your work?

Patients with the abovementioned risk factors could undergo auto-HSCT with TEAM as conditioning to reduce organ toxicity and non-relapse mortality.

1 | INTRODUCTION

Conditioning regimens before autologous hematopoietic stem cell transplantation (auto-HSCT) have been developed to eliminate residual malignant cells after several cycles of chemotherapy. Despite new emerging treatments, this procedure has been a standard therapy in patients with lymphomas for decades.[1,2] However, severe adverse effects, such as early complications and organ toxicity, can be a limiting factor to select patients for high-dose conditioning chemotherapy before auto-HSCT. In particular, auto-HSCT has been implemented in elderly patients or patients with comorbidities therefore with caution,[3,4] using low-dose conditioning regimens.[5–7] For this reason, several comorbidity-assessment scores (e.g., HCT-CI) have been developed over the years, to predict outcomes in patients with hematological malignancies undergoing allogeneic stem cell transplantation (allo-HSCT).[8,9] The HCT-CI-score has been also successfully implemented in patients undergoing auto-HSCT[10,11] and potentially adapt conditioning protocols to the individual risks of each patient.[12,13]

BEAM (BCNU, etoposide, cytarabine, and melphalan) protocol is one of the most widely used protocols for conditioning of patients with lymphoma before auto-HSCT.[14,15] Nevertheless, BCNU is known to cause severe side effects and complications, including pulmonary toxicity.[16] Several alternative conditioning regimens[17,18] have been considered to improve outcomes of patients after auto-HSCT. Replacement of BCNU with thiotepa as part of TEAM (thiotepa, etoposide, cytarabine, and melphalan) was initially used in primary central nervous system lymphoma[19] but showed encouraging results in patients with Hodgkin and non-Hodgkin lymphoma as well.[20–22] Although impaired lung function has been proven to critically influence the outcomes of patients after conditioning with BEAM,[23] the effect of pulmonary dysfunction has not been systematically studied in patients receiving treatment with TEAM before auto-HSCT. As part of the HCT-CI score, pulmonary function, age, and comorbidities are yet regarded to be important predictive outcome factors for patients undergoing auto-HSCT.[8,9]

Therefore, we aimed to compare the impact of clinical features including pulmonary function parameters, comorbidities, and disease status on outcomes and early complications of patients conditioned with BEAM or TEAM before auto-HSCT at our institution. Thus, we identified specific risk factors associated with unfavorable outcomes for each conditioning protocol, which might be used to choose the suitable treatment for each specific patient.

2 | PATIENTS AND METHODS

2.1 | Patient characteristics and data collection

All patients receiving BEAM or TEAM conditioning followed by auto-HSCT between May 28, 2008, and December 23, 2021, at the University of Freiburg Medical Center were included in this study. Statistical analysis of prognostic factors was performed as of March 31, 2023. Patient clinical characteristics are detailed in Table 1. Patient comorbidities before auto-HSCT, Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI),[8–10] and early complications after auto-HSCT occurring before discharge from hospital are listed in Table S1. Early toxicity after auto-HSCT was defined according to formerly described criteria[24] and reporting of death causes was based on established definitions.[25] The clinical data were prospectively collected with written informed consent from all patients. This study was carried out in accordance with the Helsinki Declaration and the study protocol was approved by the Institutional Review Board of the University of Freiburg Medical Center (Nr. 22-1490-S1-retro). All authors were provided access to primary clinical trial data. Of note, the analysis of 241 patients from the BEAM cohort was analyzed in our previous publication.[23] We now increased the number of patients conditioned with BEAM included in the study, updated the follow-up and we compared these data with patients conditioned with TEAM in the same time period.

TABLE 1 Clinical characteristics, lung, and cardiac function parameters of patients conditioned with BEAM and TEAM before auto-HSCT.

Variables (*N*)	BEAM (333)	TEAM (63)	*p* Value
Patient characteristics			
Age at diagnosis, median (range)	55.9 (18–78)	54.8 (19–75)	0.40
Age at auto-HSCT, median (range)	56.8 (19–78)	55.7 (22–75)	0.31
Sex female, *n* (%)	129 (38.7)	31 (49)	0.12
KPS ≤80%, *n* (%)	88 (27.2)	24 (39)	0.07
Smoking	**101 (30.3)**	**34 (54)**	**<0.001**
Disease characteristics			
Disease, *n* (%)			
B-NHL	232 (69.7)	43 (68)	
T-NHL	47 (14.1)	9 (14)	
Hodgkin	36 (10.8)	11 (17)	
MM	1 (0.3)		
ALL	1 (0.3)		
Burkitt	16 (4.8)		
B-Symptoms at diagnosis, *n* (%)	110 (33.2)	24 (38)	0.46
Chemotherapy sensitive disease[a] at auto-HSCT, *n* (%)	49 (15)	10 (16)	0.39
Upfront auto-HSCT, *n* (%)	214 (64)	38 (61)	0.55
PD at auto-HSCT, *n* (%)	29 (9)	5 (8)	0.37
Auto-HSCT characteristics			
Days on the ward after auto-HSCT, median (range)	14 (5–49)	15 (10–39)	0.11
CD34+ cells transplanted ($\times 10^6 \times$ kg bw), median (range)	5.8 (0.15–40.9)	5.91 (1.59–14.2)	0.5
Day of engraftment, median (range)			
Neutrophiles	10 (6–72)	10 (8–40)	0.46
Thrombocytes	11 (4–82)	11 (8–16)	0.19
Treatments post auto-HSCT			
Chemotherapy post auto-HSCT, *n* (%)	108 (32.4)	20 (32)	0.92
Radiotherapy post auto-HSCT, *n* (%)	27 (8.1)	8 (13)	0.24
Second auto-HSCT, *n* (%)	6 (2)	0	0.28
Allo-HSCT post auto-HSCT, *n* (%)	35 (11)	10 (16)	0.22
Follow up in months, median (range)	**39 (0.2–163)**	**22 (0.3–74)**	**<0.001**
Pulmonary and cardiac function			
Pulmonary function tests before auto-HSCT, *n* (%)	326 (98)	62 (98)	
FEV1% of predicted[b]	**93 (34–145)**	**85 (45–131)**	**0.002**
FEV1/FVC ratio[b]	**0.79 (0.45–1.33)**	**0.77 (0.57–0.97)**	**0.02**
MEF50% of predicted[b]	75 (12–235)	75 (21–179)	0.44
MEF25% of predicted[b]	**47 (6–386)**	**57 (8–241)**	**0.02**
DLCOcSB % of predicted[b]	**78 (29–126)**	**66 (31–109)**	**<0.001**
RV % of predicted[b]	**107 (45–249)**	**114 (29–236)**	**0.04**
RV/TLC ratio[b]	**0.36 (0.14–0.69)**	**0.37 (0.11–0.75)**	**0.03**
TLC % of predicted[b]	96 (43–134)	97 (57–132)	0.12
Arterial CO_2 mmHg absolute[b]	36 (22–46)	36 (30–46)	0.31
Arterial O_2 mmHg absolute[b]	**81 (53–100)**	**78 (58–100)**	**0.01**
Transthoracic heart echography, *n* (%)	321 (96)	62 (98)	
EF 60%–65%	52 (16)	16 (26)	
EF 55%–59%	228 (71)	36 (58)	

TABLE 1 (Continued)

Variables (*N*)	BEAM (333)	TEAM (63)	*p* Value
EF 50%–54%	26 (8)	5 (8)	
EF ≤ 49%	15 (5)	5 (8)	

Note: Statistically significant patient characteristics are highlighted in bold.
Abbreviations: aCO_2, arterial carbon dioxide; aO_2, arterial oxygen; ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous hematopoietic stem cell transplantation; BEAM, BCNU, etoposide, cytarabine, and melphalan; bw, body weight; DLCOcSB, diffusion capacity of carbon monoxide adjusted for hemoglobin level; EF, ejection fraction; FEV1, forced expiratory volume in 1 s; FEV1/FVC, FEV1/forced vital capacity (FVC); kg, kilogram; MEF25, mid-expiratory flow 25% of vital capacity; MEF50, mid-expiratory flow 50% of vital capacity; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PD, progressive disease; RV, residual volume; TEAM, thiotepa, etoposide, cytarabine, and melphalan; TLC, total lung capacity; VCmax, maximal vital capacity.
[a]Chemotherapy sensitive disease was defined as relapse after 12 months of primary therapy and CR/PR/SD at auto-HSCT.
[b]Data are presented as median (range).

2.2 | Conditioning protocols

Conditioning protocols BEAM (BCNU/carmustine 300 mg/m^2 at day −7, cytarabine 2 × 200 mg/m^2/d from days −6 to −3, etoposide 2 × 100 mg/m^2/d from days −6 to −3 and melphalan 1 × 140 mg/m^2 at day −2) and TEAM (thiotepa 5 mg/kg at day −7, cytarabine 2 × 200 mg/m^2/d from days −6 to −3, etoposide 2 × 100 mg/m^2/d from days −6 to −3 and melphalan 1 × 140 mg/m^2 at day −2) before auto-HSCT were applied intravenously via a central venous catheter. All patients received chemotherapy- and G-CSF-mobilized peripheral blood stem cells. Caring physicians allocated patients to the two protocols depending mainly on age, pulmonary toxicity, and performance status.

2.3 | Pulmonary function assessment

To evaluate pulmonary function according to international standards,[26,27] pulmonary function tests (PFTs) such as single breath diffusion capacity for CO (DLCOcSB), whole-body plethysmography, and arterial blood gas analyses were routinely performed 1 week before auto-HSCT in most of the patients. Percentages of predicted normal values were used to express individual PFT parameters. The former were calculated applying published algorithms,[28] suitable for our patient population (Caucasian, Middle Europe). Cardiac function was evaluated by transthoracic echocardiography performed 1 week before auto-HSCT.

2.4 | Study endpoints, definitions, and statistical analysis

Following the model of our previous study, we considered overall survival (OS) as the time from auto-HSCT until death from any cause, and progression-free survival (PFS) as the time from auto-HSCT until death from any cause or relapse, whichever occurred first. In case, the event of interest for OS or PFS did not occur over the observation period, individuals were censored from the date of last contact. Evidence of disease progression in histopathological samples or radiology after auto-HSCT was defined as relapse. In contrast, death due to other causes than relapse was a competing risk, expressed as non-relapse mortality (NRM). The median follow-up was calculated using the inversed Kaplan–Meier method.[29]

STATA v17.0 was used to perform statistical analyses for patient characteristics, organ function parameters, cumulative incidences, and hazard ratios (HRs). We applied the Cox proportional hazards regression model to calculate HR and corresponding two-sided confidence intervals (CIs) for OS and PFS, as well as to conduct multivariate analyses for OS. The latter included a backward selection process of prognostic factors with a univariate p value < .1, such as clinical features, comorbidities, and organ function tests in patients with BEAM conditioning. The multivariate model with the same variables was applied to patients conditioned with TEAM. Taking competing risks into account, we utilized the Fine and Gray model[30,31] to determine cumulative incidence rates and subdistribution hazard ratios (SHRs) for relapse incidence and NRM rates, respectively.

Statistical differences for categorical variables were calculated with Pearson's chi-square test and Student t test for continuous variables, respectively, assuming a normal distribution.

3 | RESULTS

3.1 | Patient characteristics

Three hundred and ninety-six patients undergoing auto-HSCT (333 patients conditioned with BEAM and 63 patients conditioned with TEAM) were included in this study. The clinical characteristics of patients are shown in Table 1. Comorbidities before auto-HSCT and early complications thereafter are described in Tables S1A and S1B. One hundred and twenty-nine (39%) patients in the BEAM cohort and 31 (49%) patients in the TEAM cohort were female. The median age at auto-HSCT was 57 years (range: 19–78) and 56 years (range: 22–76) for patients conditioned with BEAM and TEAM, respectively (Table 1). The median follow-up of patients conditioned with BEAM was 39 months (range 0.2–163) and for TEAM 22 months (range 0.3–74; p < .001; Table 1).

The most frequent hematological diagnosis among patients receiving BEAM conditioning was B-non-Hodgkin Lymphoma (B-NHL; 70%), followed by T-NHL (14%) and Hodgkin lymphoma (11%). In patients receiving TEAM conditioning, the main indication for auto-HSCT was B-NHL (68%) as well, followed by Hodgkin

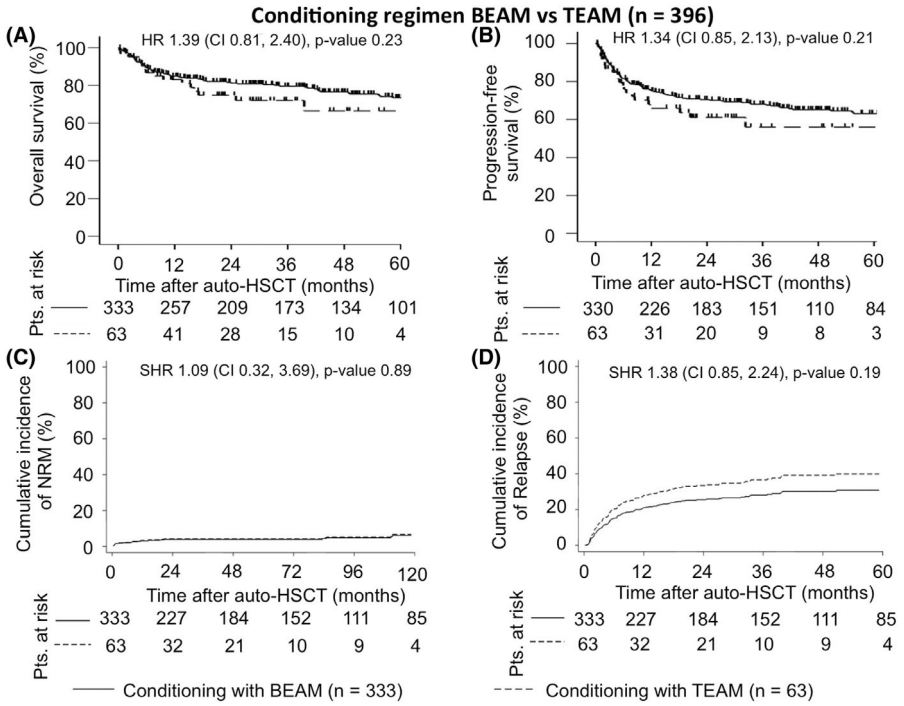

FIGURE 1 Outcome variables by conditioning regimen BEAM or TEAM before auto-HSCT. Kaplan–Meier curves represent (A) overall survival (OS) and (B) progression-free survival (PFS) and cumulative incidence curve represent (C) non-relapse mortality and (D) relapse incidence in patients conditioned with BEAM and TEAM, respectively. Statistical analysis was performed for OS and PFS by log-rank test and for cumulative incidence of non-relapse mortality and relapse by Fine and Gray regression models in the presence of competing risks. HRs and SHRs represent the risk of TEAM compared to BEAM conditioning. auto-HSCT, autologous hematopoietic stem cell transplantation; BEAM, carmustine or BCNU, etoposide, cytarabine, and melphalan; CI, confidence interval; HR, hazard ratio; NRM, non-relapse mortality; Pts., patients; SHR, subdistribution hazard ratio; TEAM, thiotepa, etoposide, cytarabine, and melphalan.

lymphoma (17%) and T-NHL (14%). Forty-nine (15%) patients in the BEAM cohort and 10 (16%) patients in the TEAM cohort had chemotherapy-sensitive disease at auto-HSCT. Nevertheless, 29 (9%) individuals in the BEAM cohort and 5 (8%) in the TEAM cohort had a progressive disease (PD) status at auto-HSCT (Table 1).

Eighty-eight (27%) patients with BEAM conditioning and 24 (39%) with TEAM conditioning had a Karnofsky performance score (KPS) of ≤80% (p value = .07). Notably, current or previous smoking was found in 101 (30%) of patients receiving BEAM and 34 (54%) of those receiving TEAM (p value < .001; Table 1). Twenty-nine patients (9%) conditioned with BEAM and 9 (14%) patients conditioned with TEAM had a history of pulmonary diseases (p value = .17). Forty-eight (14%) patients from the BEAM group and 7 (11%) from the TEAM group had a previous history of heart disease (p value = .49; Table S1A). The median HCT-CI-score[8] before auto-HSCT was 3 in both BEAM (range 0–11) and TEAM patient groups (range 0–12; p value = .01; Table S1B).

PFTs before auto-HSCT were available for most patients (n = 388, 98%), in most cases including DLCOcSB (n = 377, 95%). Patients from the TEAM cohort showed significantly worse PFT values. A highly significant difference between the two groups was observed in DLCOcSB (p value < .001) and FEV1% of predicted (p value = .002), indicating a worse lung function in the TEAM group. In most patients (n = 383, 97%), cardiac function before auto-HSCT was evaluated via transthoracic heart echography, with only a small proportion of patients (n = 15 [5%] in BEAM group and n = 5 (8%) in TEAM group) in each group showing a reduced ejection fraction (<50%; Table 1).

In summary, patients conditioned with TEAM were more frequently current or previous smokers and they had a worse pulmonary function as seen by DLCOcSB and FEV1. A trend for worse KPS in patients with TEAM was observed.

3.2 | Clinical characteristics and organ impairment influencing outcomes

Outcome variables between patients conditioned by BEAM or TEAM were compared by Kaplan–Meier curves and log-rank tests (OS and PFS), cumulative incidence curves, and Cox regression in the presence of competing events (NRM and relapse incidence). Despite higher smoking rates and impaired pulmonary function, no significant outcome difference was observed between patients conditioned with BEAM or TEAM before auto-HSCT (Figure 1).

We evaluated the impact of clinical patient characteristics, lung function parameters, and comorbidities on the outcomes of both conditioning groups by univariate and multivariate analyses for OS using the Cox proportional hazard regression model. In the univariate analysis for the BEAM (Tables 2A and 2B) and TEAM (Tables 3A and 3B), several factors were shown to be associated with a decreased OS. The multivariate analysis for OS indicated DLCOcSB ≤ 60% of predicted (HR = 2.33, p value = .001), KPS ≤ 80% (HR = 1.74, p value = .03), HCT-CI score ≥ 4 (HR = 2.22, p value = .002), and PD status before auto-HSCT (HR = 2.78, p value = .001) as well as cardiac disease before auto-HSCT (HR = 2.13, p value = .007) as independent risk factors for decreased OS in patients receiving BEAM conditioning (Table 2A and Figures S1–S5). From these clinical factors, only PD status before auto-HSCT could be demonstrated to be associated with increased risk of death in the TEAM cohort (HR = 13.99, p value = .001; Table 2B).

Furthermore, the multivariate analysis of patients treated with BEAM revealed age ≥ 65 years (HR = 3.94, p value = .004), an HCT-CI-score ≥ 4 (HR = 7.78, p value = .007), and lung diagnosis before auto-HSCT (HR = 5.53, p value = .001) to be highly significant risk factors for increased NRM, together with DLCOcSB ≤ 60% of predicted (HR = 3.11, p value = .02) and a MEF50 score ≤ 20% of

TABLE 2 Clinical parameters associated with overall survival in multivariate Cox regression analysis after conditioning by (A) BEAM and (B) by TEAM.

Variables	N	HR (95% CI)	p Value
(A) BEAM			
Progressive disease status before auto-HSCT	29	2.77 (1.52–5.04)	.001
Cardiac disease before auto-HSCT	48	2.03 (1.16–3.56)	.01
HCT-CI score ≥ 4	121	2.25 (1.35–3.74)	.002
KPS ≤ 80%	88	1.77 (1.08–2.90)	.02
DLCOcSB ≤ 60% initial	48	2.34 (1.39–3.94)	.001
(B) TEAM			
Progressive disease status before auto-HSCT	5	13.99 (3.08–63.56)	.001
Cardiac disease before auto-HSCT	7	1.09 (0.21–5.70)	.92
HCT-CI score ≥ 4	25	2.83 (0.82–9.72)	.10
KPS ≤ 80%	24	2.64 (0.76–9.22)	.13
DLCOcSB ≤ 60% initial	17	1.66 (0.50–5.54)	.41

Abbreviations: auto-HSCT, autologous hematopoietic stem cell; BEAM, BCNU, etoposide, cytarabine, and melphalan; CI, confidence interval; DLCOcSB, diffusion capacity of carbon monoxide adjusted for hemoglobin level; HCT-CI, hematopoietic cell transplantation comorbidity index; HR, hazard ratio; KPS, Karnofsky performance score; N, number of patients; PD, progressive disease; TEAM, thiotepa, etoposide, cytarabine, and melphalan.

TABLE 3 Multivariate analysis for non-relapse mortality of clinical, lung, and cardiac function parameters in patients conditioned with BEAM before auto-HSCT.

Variables	N	SHR (95% CI)	p Value
BEAM			
Age ≥ 65 years	69	3.94 (1.55–10.02)	.004
HCT-CI score ≥4	121	7.78 (1.77–34.28)	.007
Lung diagnosis before auto-HSCT	29	5.53 (2.04–15.02)	.001
MEF50 ≤ 20% initial	10	4.67 (1.15–18.87)	.03
DLCOcSB ≤ 60% initial	48	3.11 (1.23–7.93)	.02

Abbreviations: auto-HSCT, autologous hematopoietic stem cell; BEAM, BCNU, etoposide, cytarabine, and melphalan; CI, confidence interval; DLCOcSB, diffusion capacity of carbon monoxide adjusted for hemoglobin level; HCT-CI, hematopoietic cell transplantation comorbidity index; MEF50, mid-expiratory flow 50% of vital capacity; N, number of patients; SHR, subdistribution hazard ratio.

predicted (HR = 4.67, p value = .03; Table 3A). Of note, the low numbers of patients conditioned with TEAM and NRM ($n = 3$) precluded univariate and multivariate analysis for NRM.

3.3 | Clinical characteristics including pulmonary function parameters before auto-HSCT and complications after auto-HSCT associated with DLCOcSB ≤ 60% of predicted

We compared the association of DLCOcSB ≤ 60% with clinical characteristics and complications after auto-HSCT in each conditioning group. In patients treated with BEAM, a higher number of chemotherapy lines in median, radiotherapy before auto-HSCT, including mediastinal radiotherapy and current or previous smoking, were associated with DLCOcSB ≤ 60% of predicted (Table S4A). After undergoing auto-HSCT, early complications were more frequent among these patients, thus being more often transferred to the intensive care unit for enhanced treatment (Table S4A). On the contrary, in the TEAM cohort, no correlation was found between DLCOcSB ≤ 60% of predicted and specific clinical characteristics or complications after auto-HSCT (Table S4B), but compared to the BEAM group, mucositis did occur more frequently after auto-HSCT (Table S1B). Furthermore, a series of abnormal lung function parameters (reduced FEV1, MEF25, MEF50, TLC, and arterial O_2 mmHg, as well as higher RV/TLC ratio and RV) were commonly observed in patients with BEAM and DLCOcSB ≤ 60% (Table S5A), whereas increased RV/TLC ratio correlated with DLCOcSB≤60% of predicted in patients with TEAM (Table S5B).

3.4 | Cause of death in patients conditioned with BEAM or TEAM after auto-HSCT by CO-diffusion parameters

Cause of death was analyzed by CO-diffusion parameters in both BEAM and TEAM cohorts. In the BEAM cohort, within the median

TABLE 4 Cause of mortality by DLCOcSB> or ≤60% of predicted in patients undergoing auto-HSCT conditioned with BEAM and TEAM.

	DLCOcSB > 60% of predicted	DLCOcSB ≤ 60% of predicted
(A) BEAM		
N	280	48
Alive, *n* (%)	228 (81)	26 (54)
Relapse, *n* (%)	41 (15)	12 (25)
Non-relapse mortality, *n* (%)	7 (3)	8 (17)
Cause of death (months after auto-HSCT)	ARDS (0.5)	Aspergillosis (0.6)
		Multiorgan dysfunction (1.3)
	Pneumonia, hypoxia by aspiration (0.7)	CNS-organic psycho-syndrome (2.1)
	Acute abdomen (3.7)	Subdural hematoma (9.6)
	Pneumonic sepsis (4.0)	Sepsis by *Pseudomonas aeroginosa* (10.2)
	Pneumocystis jiroveci pneumonia (5.6)	ST-elevated myocardial infarction (17.8)
	Pneumonitis associated with immunotherapy (67.5)	PD secondary malignoma (41.7)
	Septic shock (72)	Secondary malignoma (55.3)
Unknown cause of death, *n* (%)	4 (1)	2 (4)
(B) TEAM		
N	45	17
Alive, *n* (%)	34 (76)	12 (71)
Relapse, *n* (%)	7 (16)	4 (24)
Non-relapse mortality, *n* (%)	3 (7)	1 (5)
Cause of death (months after auto-HSCT)	Septic shock (25)	Septic shock in neutropenia (0.3)
	Cardiogenic shock (5.9)	
	Pneumonia by aspiration and septic shock (0.5)	
Unknown cause of death, *n* (%)	0	0

Note: DLCOcSB values before auto-HSCT from 16 patients (5.2%) before conditioning with BEAM and from 2 patients (4%) before conditioning with TEAM were not available.

Abbreviations: auto-HSCT, autologous hematopoietic stem cell; ARDS, acute respiratory distress syndrome; BEAM, BCNU, etoposide, cytarabine, and melphalan; CNS, central nervous system; DLCOcSB, diffusion capacity of carbon monoxide adjusted for hemoglobin level; TEAM, thiotepa, etoposide, cytarabine, and melphalan.

observation period of 39 months, 41 (15%) patients with relapse in the DLCOcSB > 60% of predicted and 12 (25%) patients died in the DLCOcSB ≤ 60% of predicted group. However, 21 patients (6%) treated with BEAM before auto-HSCT died without relapse (NRM): 11 patients (4%) in the DLCOcSB > 60% of predicted and 10 patients (21%) in the DLCOcSB ≤ 60% of predicted group (Table 4A). In the group conditioned with TEAM, within the median observation period of 22 months, seven (16%) patients with relapse in the DLCOcSB > 60% of predicted and four (24%) patients died in the DLCOcSB ≤ 60% of predicted group. In contrast, three patients (7%) died without relapse in the DLCOcSB > 60% of predicted and one non-relapse-death occurred among patients with DLCOcSB > 60% of predicted treated with TEAM before auto-HSCT (Table 4B).

3.5 | Impact of conditioning and auto-HSCT on pulmonary and cardiac function

To assess the influence of the auto-HSCT on cardiac and pulmonary function (Table S6), we analyzed patients with available cardiac echocardiographies and PFTs before and after auto-HSCT in both BEAM ($n = 101$, 30%) and TEAM ($n = 14$, 22%) cohorts. Remarkably, the most significant decrease showed DLCOcSB % of predicted in both, patients conditioned with BEAM (median 76% vs. 67% of predicted, p value ≤ .001) and TEAM (median 69% vs. 57% of predicted, p value = .02; Table S6). A statistically significant decrease in EF after auto-HSCT was only identified in patients conditioned with BEAM (Table S6).

4 | DISCUSSION

Treatment with BCNU/carmustine in patients with malignancies is known to cause lung toxicity,[16,32] such as pulmonary fibrosis[33] or diffuse alveolar damage.[34] The association between conditioning with BEAM before auto-HSCT and increased mortality has already been described in patients with impaired lung function, especially with reduced CO diffusion capacity,[23] and in patients previously treated with lung-toxic substances.[35,36] For this reason, several alternatives to BCNU/carmustine emerged over the years to reduce adverse effects

while maintaining the same efficacy.[37–39] BCNU replaced by thiotepa as part of TEAM conditioning regimen has promising activity.[20–22] However, an observational study described the BEAM protocol to be superior in terms of clinical outcomes,[40] whereas a recent study shows similar results between BEAM and TEAM.[41] We hypothesize that organ dysfunction might play a crucial role in the outcomes of patients undergoing auto-HSCT and only selected patients might profit from TEAM conditioning before auto-HSCT. Therefore, we assessed the impact of lung and cardiac function impairment in patients conditioned with BEAM or TEAM before auto-HSCT at our institution.

Overall, conditioning with BEAM protocol was not superior to conditioning with TEAM protocol regarding any of the study endpoints (Figure 1). However, a trend for shorter OS (HR = 1.39, $p = .23$), shorter PFS (HR = 1.34, $p = .21$), and higher cumulative incidence of relapse (HR = 1.38, $p = .19$) was observed in patients treated with TEAM, suggesting a trend for better clinical outcome for patients treated with BEAM in the whole cohort. Studies with larger patient numbers and longer follow-ups are required to address this research question.

Interestingly, reduced CO diffusion capacity defined as DLCOcSB ≤ 60% was associated with decreased OS, DFS and increased NRM in patients conditioned with BEAM (Figure S1), but not in patients conditioned with TEAM before auto-HSCT. Similarly, cardiac disease before auto-HSCT led to a decreased OS and PFS among patients treated with BEAM (Figure S2), but not those treated with TEAM. These findings indicate an increased toxicity of BEAM conditioning protocol in patients with impaired lung and cardiac function compared to TEAM, suggesting TEAM conditioning as an alternative for these patients.

In multivariate analysis, KPS ≤ 80% (p value = .027), PD before auto-HSCT (p value = .001), DLCOcSB ≤ 60% (p value = .001), and HCT-CI score ≥ 4 (p value = .002) as well as cardiac disease before auto-HSCT (p value = 0.007) were associated with shorter OS in patients conditioned with BEAM, but not in patients conditioned with TEAM. A limitation of our study is the relatively smaller number of patients treated with TEAM ($n = 63$) compared to BEAM ($n = 333$), which might explain the lack of identification of clinical parameters including pulmonary function tests in the multivariate analysis. However, only PD before auto-HSCT (p value = .001) could be demonstrated to be associated with patients conditioned with TEAM (Table 2). These data confirm the dismal prognosis of patients with progressive disease undergoing auto-HSCT and these patients should be considered for more effective alternative therapies as CAR-T cells[42] and bispecific antibodies.[43]

In subgroup analysis, among patients with upfront auto-HSCT after primary therapy, OS of the BEAM group was superior to the TEAM group (Figure S6). A higher proportion of patients with Hodgkin lymphoma were transplanted with TEAM due to pulmonary toxic substances in chemotherapy protocols for Hodgkin lymphoma (bleomycin and brentuximab), having similar outcomes as patients treated with BEAM before auto-HSCT (Figure S7), suggesting TEAM conditioning to be a valid alternative for patients with Hodgkin lymphoma.

Interestingly, patients conditioned with TEAM developed more frequently mucositis than in BEAM (32% vs. 44%, p value = .05; Table S1). Patients conditioned with fludarabine/thiotepa/melphalan (FTM) suffered more frequently from mucositis than patients conditioned with fludarabine/BCNU/melphalan (FBM) before allo-HSCT (40% vs. 64%, $p < .001$).[37] Therefore, our previous observations that thiotepa is associated more often with mucositis than BCNU were validated in this study in an auto-HSCT setting.

Overall, 254 (76%) patients treated with BEAM and 46 (73%) patients treated with TEAM before auto-HSCT were alive at the last follow-up. In contrast, 15 (5%) patients conditioned with BEAM and 4 (6%) individuals after conditioning with TEAM and auto-HSCT died during the observation period due to NRM. In the BEAM cohort, 53 (16%) and in the TEAM cohort 11 (17%) of patients suffered a relapse. Even considering the unbalanced characteristics among the two cohorts, the results indicate the therapy with both BEAM or TEAM conditioning followed by auto-HSCT has high curative rates and low morbidity and mortality in patients with lymphoma.

This study has several limitations. First, the cohort conditioned with TEAM included a considerably smaller number of patients and a shorter follow-up than the cohort conditioned with BEAM, which impacts the statistical precision of our results, especially the clinical outcomes and the multivariate analysis. As discussed before, clinical studies with larger patient numbers and longer follow-ups are urgently needed. Second, we did not randomize patients to both conditioning protocols. The conditioning protocol was chosen by the caring physicians. Therefore, patient characteristics before auto-HSCT were unbalanced between both groups and the comparison of results should be interpreted with caution. Further limitations include the retrospective, single-center study design. Future prospective randomized multicenter controlled clinical trials are needed to correct potentially biased results and elucidate the most suitable conditioning protocol for specific patient populations.

In summary, pulmonary function impairment, alongside preexisting cardiac diseases, coexistent comorbidities, and performance status before auto-HSCT, has a crucial impact on the outcomes of patients undergoing auto-HSCT. Our data suggest TEAM conditioning as a valid alternative for patients with several comorbidities including cardiac and lung dysfunction and/or poor performance score as well as for patients with Hodgkin Lymphoma.

AUTHOR CONTRIBUTIONS

Study concept and design: Radu-Florian Gherman and Jesús Duque-Afonso. *Acquisition of data*: Radu-Florian Gherman, Sophie Ewald, Robert Zeiser, Tim Strüßmann, Ralph Wäsch, Hartmut Bertz, Daiana Stolz, Justus Duyster, Jürgen Finke, Reinhard Marks, Monika Engelhardt, and Jesús Duque-Afonso. *Analysis and interpretation of data*: Radu-Florian Gherman, Gabriele Ihorst, Monika Engelhardt., and Jesús Duque-Afonso. *Critical revision of the manuscript for important intellectual content*: Radu-Florian Gherman, Sophie Ewald, Gabriele Ihorst, Tim Strüßmann, Robert Zeiser, Ralph Wäsch, Hartmut Bertz, Daiana Stolz, Justus Duyster, Jürgen Finke, Reinhard Marks, Monika Engelhardt, and Jesús Duque-Afonso. *Statistical analysis*: Radu-Florian Gherman, Jesús Duque-Afonso, and Gabriele Ihorst.

ACKNOWLEDGMENTS

We thank J. Urban for managing the data bank of transplanted patients, the medical technicians in the Stem Cell Transplantation Unit and Pulmonary Function Test Unit of the University Medical Center Freiburg, and all the patients and staff on the Löhr, Holthusen, and Thannhauser wards. This project was supported by a grant from the German Federal Ministry of Education and Research (BMBF 01 EO 0803). Jesús Duque-Afonso, Monika Engelhardt., and Gabriele Ihorst received support from Else Kröner-Fresenius-Stiftung (Nr. 2018-A56). Jesús Duque-Afonso received research support from the German Research Foundation (Deutsche Forschungsgemeinschaft, ref. DU 1287/3-1 and 1287/5-1), from the Forschungskommission of the University of Freiburg Medical School (DUQ1106/16) and Berta Ottenstein-Programm for Advanced Clinician Scientists, Faculty of Medicine, University of Freiburg. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicting financial interest with the submission of this article. Jürgen Finke received research support and speakers honoraria from Medac, Neovii, and Riemser. Jesús Duque-Afonso received speaker's honoraria from Roche, Amgen, AstraZeneca, Riemser, Sobi, Lilly, and Ipsen and travel support from Gilead, Sobi, and Abbvie. Robert Zeiser received speaker's honoraria from Incyte, Novartis, Roche, and Mallinckrodt.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analyzed during the current study are available upon reasonable request from the corresponding author.

ORCID

Robert Zeiser https://orcid.org/0000-0001-6565-3393
Monika Engelhardt https://orcid.org/0000-0003-0405-1676
Jesús Duque-Afonso https://orcid.org/0000-0002-8287-5673

REFERENCES

1. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359(9323):2065-2071.
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.
3. de la Rubia J, Saavedra S, Sanz GF, et al. Transplant-related mortality in patients older than 60 years undergoing autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;27(1):21-25.
4. Jantunen E. Autologous stem cell transplantation beyond 60 years of age. *Bone Marrow Transplant*. 2006;38(11):715-720.
5. Duque-Afonso J, Ihorst G, Waterhouse M, et al. Impact of lung function on bronchiolitis obliterans syndrome and outcome after allogeneic hematopoietic cell transplantation with reduced-intensity conditioning. *Biol Blood Marrow Transplant*. 2018;24(11):2277-2284.
6. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. *Blood*. 2014;124(3):344-353. doi:10.1182/blood-2014-02-514778
7. Brunstein CG, Pasquini MC, Kim S, et al. Effect of conditioning regimen dose reduction in obese patients undergoing autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2019;25(3):480-487.
8. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106(8):2912-2919.
9. Sorror ML, Storb RF, Sandmaier BM, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2014;32(29):3249-3256.
10. Berro M, Arbelbide JA, Rivas MM, et al. Hematopoietic cell transplantation-specific comorbidity index predicts morbidity and mortality in autologous stem cell transplantation. *Biol Blood Marrow Transplant*. 2017;23(10):1646-1650.
11. Martínez C, Jorge AS, Pereira A, et al. Comorbidities, not age, are predictive of survival after autologous hematopoietic cell transplantation for relapsed/refractory Hodgkin's lymphoma in patients older than 50 years. *Ann Hematol*. 2017;96(1):9-16.
12. Farina L, Bruno B, Patriarca F, et al. The hematopoietic cell transplantation comorbidity index (HCT-CI) predicts clinical outcomes in lymphoma and myeloma patients after reduced-intensity or non-myeloablative allogeneic stem cell transplantation. *Leukemia*. 2009;23(6):1131-1138.
13. Graf SA, Vaughn JE, Chauncey TR, et al. Comorbidities, alcohol use disorder, and age predict outcomes after autologous hematopoietic cell transplantation for lymphoma. *Biol Blood Marrow Transplant*. 2016;22(9):1582-1587.
14. 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;13:588-595.
15. Caballero MD, Rubio V, Rifon J, et al. BEAM chemotherapy followed by autologous stem cell support in lymphoma patients: analysis of efficacy, toxicity and prognostic factors. *Bone Marrow Transplant*. 1997;20:451-458.
16. Durant JR, Norgard MJ, Murad TM, Bartolucci AA, Langford KH. Pulmonary toxicity associated with bischloroethylnitrosourea (BCNU). *Ann Intern Med*. 1979;90(2):191-194.
17. Damaj G, Cornillon J, Bouabdallah K, et al. Carmustine replacement in intensive chemotherapy preceding reinjection of autologous HSCs in Hodgkin and non-Hodgkin lymphoma: a review. *Bone Marrow Transplant*. 2017;52(7):941-949.
18. Isidori A, Christofides A, Visani G. Novel regimens prior to autologous stem cell transplantation for the management of adults with relapsed/refractory non-Hodgkin lymphoma and Hodgkin lymphoma: alternatives to BEAM conditioning. *Leuk Lymphoma*. 2016;57(11):2499-2509.
19. Schorb E, Kasenda B, Atta J, et al. Prognosis of patients with primary central nervous system lymphoma after high-dose chemotherapy followed by autologous stem cell transplantation. *Haematologica*. 2013;98(5):765-770.
20. Sellner L, Boumendil A, Finel H, et al. Thiotepa-based high-dose therapy for autologous stem cell transplantation in lymphoma: a retrospective study from the EBMT. *Bone Marrow Transplant*. 2016;51(2):212-218.
21. Duléry R, Lebras L, Choquet S, et al. TEAM conditioning (thiotepa, etoposide, cytarabine, melphalan) prior to autologous hematopoietic stem cell transplantation for Hodgkin and non-Hodgkin lymphoma: final results from a prospective multicenter study. *Blood*. 2019;134-(Suppl_1):S786. doi:10.1182/blood-2019-130651
22. Frietsch JJ, Miethke J, Linke P, et al. Treosulfan plus fludarabine versus TEAM as conditioning treatment before autologous stem cell transplantation for B-cell non-Hodgkin lymphoma. *Bone Marrow Transplant*. 2022;57:1164-1170.
23. Duque-Afonso J, Ewald S, Ihorst G, et al. The impact of pulmonary function in patients undergoing autologous stem cell transplantation

[published correction appears in blood adv. 2022;6(6):1865]. *Blood Adv*. 2021;5(21):4327-4337.
24. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol*. 1988;6:1562-1568.
25. Copelan E, Casper JT, Carter SL, et al. A scheme for defining cause of death and its application in the T cell depletion trial. *Biol Blood Marrow Transplant*. 2007;13(12):1469-1476.
26. American Thoracic Society. Single-breath carbon monoxide diffusing capacity (transfer factor). Recommendations for a standard technique—1995 update. *Am J Respir Crit Care Med*. 1995;152:2185-2198.
27. Culver BH, Graham BL, Coates AL, et al. Recommendations for a standardized pulmonary function report. An official American Thoracic Society technical Statement. *Am J Respir Crit Care Med*. 2017;196:1463-1472.
28. Zaiss AW, Matthys H. A multi user system for whole body plethysmographic measurements and interpretation. *Lung*. 1990;168:1185-1192.
29. Korn EL. Censoring distributions as a measure of follow-up in survival analysis. *Stat Med*. 1986;5:255-260.
30. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.
31. Dignam JJ, Kocherginsky MN. Choice and interpretation of statistical tests used when competing risks are present. *J Clin Oncol*. 2008;26:4027-4034.
32. 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.
33. O'Driscoll BR, Hasleton PS, Taylor PM, Poulter LW, Gattameneni HR, Woodcock AA. Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. *N Engl J Med*. 1990;323(6):378-382.
34. Rossi SE, Erasmus JJ, McAdams HP, Sporn TA, Goodman PC. Pulmonary drug toxicity: radiologic and pathologic manifestations. *Radiographics*. 2000;20(5):1245-1259.
35. Reece DE, Nevill TJ, Sayegh A, et al. Regimen-related toxicity and nonrelapse mortality with high-dose cyclophosphamide, carmustine (BCNU) and etoposide (VP16-213) (CBV) and CBV plus cisplatin (CBVP) followed by autologous stem cell transplantation in patients with Hodgkin's disease. *Bone Marrow Transplant*. 1999;23(11):1131-1138.
36. Scarlata S, Annibali O, Santangelo S, et al. Pulmonary complications and survival after autologous stem cell transplantation: predictive role of pulmonary function and pneumotoxic medications. *Eur Respir J*. 2017;49(3):1601902.
37. Duque-Afonso J, Ihorst G, Waterhouse M, et al. Comparison of reduced-toxicity conditioning protocols using fludarabine, melphalan combined with thiotepa or carmustine in allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2021;56(1):110-120.
38. Grisariu S, Shapira MY, Or R, Avni B. Thiotepa, etoposide, cyclophosphamide, cytarabine, and melphalan (TECAM) conditioning regimen for autologous stem cell transplantation in lymphoma. *Clin Lymphoma Myeloma Leuk*. 2018;18(4):272-279.
39. 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.
40. Marchesi F, Capria S, Pedata M, et al. BEAM conditioning regimen ensures better progression-free survival compared with TEAM but not with FEAM in lymphoma patients undergoing autologous stem cell transplant. *Leuk Lymphoma*. 2020;61(9):2238-2241.
41. Deveci B, Ateşoğlu EB, Bayrak E, et al. Comparative efficacy and safety of BEAM and TEAM conditioning regimens for autologous stem cell transplantation in lymphoma patients. *Transplant Proc*. 2023;55(1):235-241.
42. Westin JR, Oluwole OO, Kersten MJ, et al. Survival with Axicabtagene Ciloleucel in large B-cell lymphoma. *N Engl J Med*. 2023;389(2):148-157.
43. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2022;387(24):2220-2231.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gherman R-F, Ewald S, Ihorst G, et al. Identification of clinical factors impacting outcome in patients undergoing autologous hematopoietic cell transplantation after BEAM and TEAM conditioning. *Eur J Haematol*. 2024;112(3):350-359. doi:10.1111/ejh.14118