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Autologous

A Comparison of the Conditioning Regimens BEAM and FEAM for Autologous Hematopoietic Stem Cell Transplantation in Lymphoma: An Observational Study on 1038 Patients From Fondazione Italiana Linfomi

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A B S T R A C T

BEAM (carmustine [bis-chloroethylnitrosourea (BCNU)]-etoposide-cytarabine-melphalan) chemotherapy is the standard conditioning regimen for autologous stem cell transplantation (ASCT) in lymphomas. Owing to BCNU shortages, many centers switched to fotemustine-substituted BEAM (FEAM), lacking proof of equivalence. We conducted a retrospective cohort study in 18 Italian centers to compare the safety and efficacy of BEAM and FEAM regimens for ASCT in lymphomas performed from 2008 to 2015. We enrolled 1038 patients (BEAM = 607, FEAM = 431), of which 27% had Hodgkin lymphoma (HL), 14% indolent non-Hodgkin lymphoma (NHL), and 59% aggressive NHL. Baseline characteristics including age, sex, stage, B-symptoms, extranodal involvement, previous treatments, response before ASCT, and overall conditioning intensity were well balanced between BEAM and FEAM; notable exceptions were median ASCT year (BEAM = 2011 versus FEAM = 2013, $P < .001$),

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Sorror score ≥3 (BEAM = 15% versus FEAM = 10%, $P = .017$), and radiotherapy use (BEAM = 18% versus FEAM = 10%, $P < .001$). FEAM conditioning resulted in higher rates of gastrointestinal and infectious toxicities, including severe oral mucositis grade ≥3 (BEAM = 31% versus FEAM = 44%, $P < .001$), and sepsis from Gram-negative bacteria (mean isolates/patient: BEAM = .1 versus FEAM = .19, $P < .001$). Response status at day 100 post-ASCT (overall response: BEAM = 91% versus FEAM = 88%, $P = .42$), 2-year overall survival (83.9%; 95% confidence interval [CI], 81.5% to 86.1%) and progression-free survival (70.3%; 95% CI, 67.4% to 73.1%) were not different in the two groups. Mortality from infection was higher in the FEAM group (subhazard ratio, 1.99; 95% CI, 1.02 to 3.88; $P = .04$). BEAM and FEAM do not appear different in terms of survival and disease control. However, due to concerns of higher toxicity, fotemustine substitution in BEAM does not seem justified, if not for easier supply.

INTRODUCTION

The first series of patients transplanted with autologous marrow for lymphomas was reported in 1978, using the BACT (carmustine [bis-chloroethylnitrosourea (BCNU)]-cytarabine-cyclophosphamide-thioguanine) regimen [1]. Many variants were derived from the same chemotherapy backbone, among which was the BEAM (BCNU-etoposide-cytarabine-melphalan) regimen, first reported in 1986 [2].

The BEAM regimen had strong conceptual points favouring its widespread application: it used readily available well-known drugs; it appeared highly effective in relapsed and refractory Hodgkin lymphoma (HL) [3] and non-Hodgkin lymphoma (NHL) [4], while also having acceptable extrahematologic toxicities. These consisted mostly in severe mucositis, chemotherapy-induced nausea and vomiting, diarrhea, hepatotoxicity, and nephrotoxicity [4-7]. Moreover, noninfective toxic pulmonary complications were reported in BCNU-containing regimens, involving 16% to 64% of patients among different studies [8]. Despite these limitations, in the last 40 years there have been few, if any, real alternatives to challenge BEAM as the standard conditioning regimen for lymphomas undergoing autologous stem cell transplantation (ASCT) [9].

Unexpectedly, though, after 2010 the oncological and hematological community faced the novel and unpredicted issue of shortage of some essential chemotherapy drugs, among which was BCNU. Physicians were thus forced to change their standards for those regimens in which a component was no longer available: a common solution was to replace the missing drug with a similar substitute molecule, trusting that the modified regimen would lead to similar results in terms of efficacy and toxicity [10].

Although reasonable, such an approach was prone to dangerous risks: a national U.S. survey in 2013 showed that use of surrogate drugs could have induced medication errors and increased unexpected toxicity [11]; reduced efficacy has also been reported when substituting one component of a consolidated regimen with a "similar" agent [12].

BCNU shortage was reported in Italy in the same years [13]: fotemustine, a third-generation nitrosourea with thrombocytopenia as main dose-limiting toxicity, was chosen as a potential substitute. As it was developed for treatment of brain tumors, fotemustine had been engineered as a molecule with enhanced lipophilia, to ensure high cellular and central nervous system penetration [14]. The first retrospective study to test the fotemustine-substituted BEAM (FEAM) reported promising results in 84 patients with HL and NHL: in this series, the overall survival (OS), progression-free survival (PFS), and nonrelapse mortality (NRM) at 2 years were 85%, 73%, and 2.4%, respectively [15]. A prospective study focusing on HL had been recently reported by the same authors, with similar results [16]: in 122 patients, FEAM-conditioned ASCT yielded a 2-year PFS of 73.8%; the 100-day treatment-related mortality was 2.5%, in all cases attributable to multiorgan failure secondary to sepsis from Gram-negative bacteria.

These encouraging data, together with the persistent difficulties of supply for BCNU, contributed to the ever-increasing fortune in Italy of FEAM conditioning, even if comparative studies between fotemustine and BCNU, especially in the context of ASCT, were missing.

The present study was therefore designed to fill this gap and to compare the efficacy, safety, and toxicity of the BEAM and FEAM regimens. We chose to consider data retrospectively from the experience, already available to 18 Italian ASCT units up to now, for several reasons. Although, theoretically, a randomized comparison would have been preferable, the main reason for switching from BEAM to FEAM (ie, BCNU shortage) would have threatened the feasibility of such a study. Moreover, we reasoned that the purely logistic and nonclinical choice of the treatment allocation between BEAM and
FEAM would reduce the selection bias attributable to a nonrandomized comparison. Finally, we needed to achieve a prompt answer to concerns of toxicity regarding a widely used treatment, and that appeared more easily met by using retrospective data.

METHODS

An extended Methods section is reported in Supplementary Data.

This is a cohort multicenter retrospective study enrolling all consecutive patients undergoing ASCT for lymphomas from January 1, 2008, to December 31, 2015, conditioned with BEAM or FEAM regimen [4].

The study was approved by the institutional review board of the coordinating center and of all participating centers. The primary study endpoint was the frequency (intended as proportion of patients) of severe infectious events (grade 3 or 4 according to Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) occurring in the first 100 days after transplantation. The secondary endpoints were: the overall response rate evaluated 100 days after ASCT (defined according to standard lymphoma response criteria [17]); OS, PFS, cumulative incidence of relapse (RI) and nonrelapse mortality (NRM); engraftment of neutrophils (defined as the first of 3 consecutive days with a neutrophil count > 500 cells/μL) and platelets (defined as the first of 3 consecutive days with unsupported platelets count ≥20,000 cells/μL); the frequency of severe adverse events of any type (grades 3 and 4 according to CTCAE version 4.0); and the frequency of mucositis according to the World Health Organization criteria [18].

Severe infectious events (SIEs) were categorized as: SIE with microbiological identification (SIEM$^+$); severe event of presumed infectious origin but without microbiological identification (SIEM$^-$) (eg, pneumonia or neutropenic enterocolitis); and febrile neutropenia (FN) [19].

Treatment Protocols

Patients were treated with either the BEAM regimen [4], consisting of BCNU (300 mg/m^2 i.v., day – 7), etoposide (200 mg/m^2 days – 6 to – 3), cytarabine (400 mg/m^2 days – 6 to – 3), and melphalan (140 mg/m^2 day –2), or the FEAM regimen, with substitution of BCNU with fotemustine 150 mg/m^2

i.v. days –7 and –6); variations in timing and fractionation of the drug doses were allowed, provided that the cumulative dose was maintained.

Supportive Measures

Supportive measures were given per local policy and declared in a survey among participating centers. In general, post-transplant granulocyte colony-stimulating factor (Filgrastim in most cases) was started shortly after reinfusion (day 3) and continued until neutrophil recovery; antimicrobial prophylaxis consisted of oral fluconazole, ciprofloxacin or levofloxacin, and acyclovir, started on day 0; fluconazole and fluoroquinolones were generally stopped at hematologic recovery or 1 month after reinfusion; acyclovir was continued for 3 months after transplant. Cotrimoxazole was administered for *Pneumocystis jiroveci* pneumonia prophylaxis from hematologic recovery until 3 months after reinfusion (or when CD4 were ≥200/mm^3). In case of fever and absolute neutrophil count <.5 × 10^9/L, empiric broad-spectrum i.v. antibiotics were administered (piperacillin/tazobactam in most cases). Packed RBC and platelet transfusions were administered in case of a hemoglobin level <80 g/L and platelet count 15,000 <10^9/L.

Statistical Considerations

We performed a power analysis to measure the minimum effect size of the primary endpoint likely to be detected with our planned sample: basing on an expected enrollment of 900 patients (BEAM = 600; FEAM = 300) and considering an expected frequency of SIEs equal to 50%, and a type I error set at .05, we estimated that such sample would allow to identify a 1.5-fold increased odds of SIEs in FEAM with a power of .805 [20].

Statistical tests were used to compare baseline characteristics or outcome measures between the BEAM and FEAM groups. OS and PFS were computed using the Kaplan-Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards method. The cumulative incidence method was applied to compute the RI, NRM, and cause-specific mortality in a competing risks setting. Predictive analyses for RI and NRM were based on the proportional hazards model for subdistribution of competing risk. Univariate and multivariate analyses were performed using Gray's test and the proportional subdistribution hazard regression model developed by Fine and Gray [21].

All tests were 2 sided. The type I error rate was fixed at .05. Analyses were performed using Stata 12.0 (StataCorp, College Station, Texas).

RESULTS

Baseline Characteristics

A total of 1038 patients (607 treated with BEAM and 431 treated with FEAM) were included in the study, enrolled from 18 Italian centers (Table 1). There were no differences in the baseline characteristics of the patients with respect to age (53.1 and 52.7 years in the BEAM and FEAM groups, respectively; $P = .51$), sex or disease distribution: the main indication for ASCT in both groups was aggressive NHL (BEAM 57% versus FEAM 61.7%), with diffuse large B cell lymphoma representing the largest disease category (BEAM 30.1% versus FEAM 30.4%), followed by mantle cell lymphoma (BEAM 12.5% versus FEAM 16%); the remainder were HL (BEAM 27% versus FEAM 26.5%) and indolent NHL (BEAM 15.5% versus FEAM 11.6%). Also, disease characteristics at diagnosis were similar between the 2 groups: most patients were in advanced stage (BEAM 80.7% versus FEAM 77.7%) and about one-third had bone marrow involvement (BEAM 33.6% versus FEAM 34.6%); central nervous system involvement at diagnosis was rare (BEAM 1.7% versus FEAM 3.3%).

The therapeutic history of the patients did not differ in the 2 groups with respect to the number of previous chemotherapy courses (median 2 lines of therapy for both groups); however, radiotherapy use was more frequent in the BEAM group, both at any site (BEAM 18.1% versus FEAM 9.7%, $P < .001$) and to the mediastinal region (BEAM 8.4% versus FEAM 2.1%, $P < .001$). The rate of refractoriness to first-line treatment was not different in the 2 groups (BEAM 14.8% versus FEAM 13.9%), but there were more complete responses (CRs) recorded in the BEAM group (BEAM 60.8% versus FEAM 50.3%, $P = .001$); likewise, overall response rate before transplantation was similar in both groups (BEAM 92.7% versus FEAM 91%), but marginally more patients in the BEAM group accessed to transplant with a CR (BEAM 65.2% versus FEAM 59.2%, $P = .05$). However, in the patients evaluable for metabolic response before ASCT (BEAM = 471; FEAM = 288), the rate of positron emission tomography positivity was not different in the 2 groups (BEAM 29.3% versus FEAM 33%).

The comorbidity burden measured by hematopoietic cell transplantation specific comorbidity index was significantly higher in BEAM-conditioned patients (hematopoietic cell transplantation specific comorbidity index ≥3: BEAM 15.3% versus FEAM 10.1%, $P = .02$), as it was the rate of pulmonary comorbidity (BEAM 19.5% versus FEAM 7.8%, $P < .001$). The time frame of ASCT was not the same in the 2 groups, with 2011 the median year of transplantation for BEAM patients and 2013 for FEAM patients. Overall dose intensity was similar for BEAM and FEAM conditioning (ratio ≥90% between delivered and standard dose: BEAM 80.7% versus FEAM 80.9%), as it was the addition of the anti-CD20 antibody rituximab (BEAM 5.3% versus FEAM 7.4%). The number of reinfused CD34$^+$ cells × 10^6/kg was slightly higher in the FEAM group (median 5.5 versus 5.3, $P = .045$).

Toxicities

Toxicities between 2 groups are summarized in Table 2. FEAM patients had a higher gastrointestinal toxicity, as shown by a higher rate of grade ≥3 mucositis (BEAM 31% versus FEAM 44%, $P < .001$), grade ≥3 nausea and vomiting (BEAM 12% versus FEAM 17%, $P = .03$), and grade ≥3 (BEAM 21% versus FEAM 28%, $P = .007$) and ≥4 (BEAM 2.4% versus FEAM 5%, $P = .03$) diarrhea. No other statistically significant extrahematological toxicities emerged (Table 2).

Overall SIEs (by definition of grade ≥3) did not differ between BEAM and FEAM patients (BEAM 71% versus FEAM 71%, $P = .94$), but grade ≥4 SIEs (BEAM 5% versus FEAM 11%, $P < .001$) were higher in the FEAM group. In detail, in the FEAM group there were more grade ≥4 FN events (BEAM 1.5% versus FEAM 6.3%, $P < .001$) and a higher rate of grade ≥3 and ≥4 SIEM$^+$ (BEAM 30% versus FEAM 36%, $P = .05$; BEAM 2.6% versus FEAM 5.6%, $P = .006$). Among SIEM$^+$, the FEAM group had higher incidence of infections with Gram-negative bacteria (mean isolates/patient: BEAM .10 versus FEAM .19, $P < .001$) or fungi (mean isolates/patient: BEAM .015 versus FEAM .039, $P = .01$) (Table 3).

Neutrophil engrafment was similar between the 2 groups, but there was a delayed median platelet engrafment in FEAM patients (BEAM 12 days versus FEAM 13 days, $P < .001$) with higher need of platelet transfusions. Furthermore, hospital stay (BEAM 21 days versus FEAM 23 days, $P < .001$) and need of total parenteral nutrition were higher in the FEAM group (BEAM 52% versus FEAM 64%, $P < .001$) (Table 3).

Outcome

Disease assessment at day 100 did not show any difference between the FEAM and BEAM groups (CR + partial response: BEAM 91% versus FEAM 88%, $P = .42$). Furthermore, among CR patients, the rate of acquired CR (ie, patients achieving post-transplant CR from pretransplant partial response or less) was similar (BEAM 22.6% versus FEAM 23.7%). Early death rate (for any cause, at day 100) was slightly higher in the FEAM group (BEAM 3.5% versus FEAM 5.3%, $P = .14$) without reaching statistical significance.

OS and PFS at 2 years in the whole cohort were 83.9% (95% confidence interval [CI], 81.5% to 86.1%) and 70.3% (95% CI, 67.4% to 73.1%), respectively, without significant differences

Table 1
Basal Characteristics of the Enrolled Patients

Basal characteristics	BEAM	FEAM	*P* Value
Evaluable patients	n = 607	n = 431	
Female	244 (40.2%)	169 (39.2)	.75
Age, y	53.1 (16.5–79.5)	52.7 (17.2–77.8)	.51
Disease	n = 607	n = 431	.16*
Hodgkin lymphoma	164 (27.0)	114 (26.5)	
Indolent NHL	94 (15.5)	50 (11.6)	
Aggressive NHL	346 (57.0)	266 (61.7)	
DLBCL	183 (30.1)	131 (30.4)	
MCL	76 (12.5)	69 (16.0)	
PTCL	52 (8.6)	39 (9.0)	
Other	35 (5.8)	27 (6.3)	
Disease characteristics at diagnosis	n = 607	n = 431	
Advanced stage (Ann Arbor stage III–IV)	490 (80.7)	335 (77.7)	.24
B symptoms	235 (38.7)	157 (36.4)	.45
BM involvement	204 (33.6)	149 (34.6)	.75
CNS involvement	10 (1.7)	14 (3.3)	.09
Pretransplant evaluation			
Sorror score	n = 603	n = 424	.017†‡
0	372 (61.7)	290 (68.4)	
1–2	139 (23.1)	91 (21.5)	
≥3	92 (15.3)	43 (10.1)	
Lung comorbidity	n = 603	n = 424	<.001§
Mild	66 (11.0)	30 (7.1)	
Moderate-severe	51 (8.5)	3 (.7)	
Therapeutic history	n = 607	n = 431	
Median previous chemotherapy courses	2	2	.43
Line of treatment	n = 607	n = 431	
Upfront ASCT (first line)	180 (29.7)	121 (28.1)	.58‖
After salvage (second line)	339 (55.9)	242 (56.2)	
After ≥3 lines of treatment	88 (14.5)	68 (15.8)	
Radiotherapy before transplant	n = 607	n = 431	
Yes, any site	110 (18.1)	42 (9.7)	<.001†
Mediastinal	51 (8.4)	12 (2.8)	<.001†
Response to first line:	n = 607	n = 431	.70¶
CR	369 (60.8)	217 (50.3)	
PR	147 (24.2)	152 (35.3)	
RD	90 (14.8)	60 (13.9)	
Response before ASCT:	n = 607	n = 431	.55¶
CR	396 (65.2)	255 (59.2)	
PR	167 (27.5)	137 (31.8)	
RD	41 (6.8)	33 (7.7)	
ND	3 (.5)	6 (1.4)	
Metabolic response before ASCT	n = 471	n = 288	
PET positive	138 (29.3)	95 (33.0)	.29
Interval diagnosis	n = 607	n = 431	
Transplant, mo	13.0 (2–223)	13.5 (2.8–185)	.80
Conditioning and transplant	n = 607	n = 431	
Median year of transplant	2011	2013	<.001‡
Full dose (≥90% delivered/standard)	n = 471	n = 288	
BCNU/fotemustine	476 (79.1)	374 (87)	.001‡
Etoposide	490 (81.4)	380 (88.6)	.002‡
Cytarabine	498 (82.7)	350 (81.6)	.64
Melphalan	497 (82.6)	368 (85.6)	.17
Overall	486 (80.7)	347 (80.9)	.95
Rituximab addition to conditioning regimen	n = 607	n = 431	
Yes	32 (5.3)	32 (7.4)	.16
Stem cell source	n = 607	n = 431	
Peripheral blood	598 (98.5)	430 (99.8)	.05
Reinfused $CD34^+ \times 10^6$/kg	5.3 (1.1–22)	5.5 (2.0–27)	.045‡

Data are presented as n (%) or median (range).
DLBCL indicates diffuse large B cell lymphoma; MCL, mantle cell lymphoma; PTCL, peripheral T cell lymphoma; BM, bone marrow; CNS, central nervous system; PR, partial response; RD, resistant disease; ND, not done; PET, positron emission tomography.
* Comparison among major disease categories (HL, indolent NHL, aggressive NHL).
† Statistical significance <.05.
‡ Comparison between Sorror score <3 versus ≥3.
§ Comparison between no lung comorbidity versus mild + moderate + severe.
‖ Comparison between upfront ASCT versus after ≥2 lines of treatment.
¶ Comparison between CR + PR versus RD.

between the BEAM and the FEAM groups (Figure 1A,B). Median follow-up was 42 months for both groups, and it was longer for BEAM-treated patients (BEAM 50 months versus FEAM 34 months, $P < .001$).

The cumulative RI (BEAM 18.4% versus FEAM 20.7%, $P = .49$) and NRM (BEAM 2.6% versus FEAM 3.8%, $P = .27$) at 1 year did not differ between the 2 groups (Figure 1C,D). Main death causes in the whole cohort were lymphoma relapse or

Table 2
Main Extra-Hematological Toxicities According to CTCAE version 4.0

Toxicity	BEAM	FEAM	*P* Value
Mucositis (World Health Organization scale)	n = 591	n = 388	
Grade 1	16.9%	9.3%	
Grade 2	34.5%	23.7%	
Grade 3	21.1%	34.8%	<.001*
Grade 4	9.8%	9.0%	.68
Nausea and vomiting (CTCAE 4.0)	n = 591	n = 387	
Grade 3	10.7%	16.1%	.03*
Grade 4	1.5%	1.0%	.58
Diarrhea (CTCAE 4.0)	n = 591	n = 403	
Grade 3	18.4%	23.3%	.007*
Grade 4	2.4%	5.0%	.03*
Other toxicities (CTCAE 4.0)	n = 607	n = 431	
Pulmonary (with grade ≥3)	.7%	.7%	1
Renal (with grade ≥3)	1.3%	.7%	.38
Hepatic (with grade ≥3)	2.0%	3.0%	.31
Cardiac (with grade ≥3)	3.1%	1.6%	.16
Cutaneous (with grade ≥3)	.7%	1.2%	.5
Other GI (with grade ≥3)	1.2%	1.2%	1
Neurological (with grade ≥3)	.5%	.5%	1
Vascular (with grade ≥3)	.2%	.7%	.31
Other (with grade ≥3)	.8%	1.2%	.75
All toxicities, excluding infectious and major GI (with grade ≥3)	9.2%	9.5%	.88

GI indicates gastrointestinal.
* Statistical significance <.05.

Table 3
Transplant Outcomes in the First 100 Days after Reinfusion

	BEAM	FEAM	*P* Value
Infectious events			
FN	n = 607	n = 431	
Grade 3	45.1%	40.8%	.86*
Grade 4	1.5%	6.3%	<.001†‡
Grade 5	.16%	.23%	
Mean number of episodes	.57	.54	.86
Without microbiological identification	n = 607	n = 431	
Grade 3	8.2%	8.6%	.97*
Grade 4	1.7%	1.4%	.81†
Grade 5	.16%	0%	
Mean number of episodes	.10	.11	.99
With microbiological identification	n = 607	n = 431	
Grade 3	27.4%	29.7%	.05*†
Grade 4	2.6%	5.6%	.006†‡
Grade 5	0%	.46%	
Mean number of isolates	.34	.46	.02†
Gram-negative bacteria	.097	.190	<.001†
Gram-positive bacteria	.183	.165	.48
Fungal	.015	.039	.01†
Viral	.035	.051	.25
Other (intracellular, parasites, etc)	.015	.016	.86
Any infectious event	n = 607	n = 431	
Grade 3	65.7%	59.2%	.94*
Grade 4	4.9%	11.4%	<.001†‡
Grade 5	.33%	.70%	
Mean number of episodes	1.02	1.10	.15
Engraftment			
Days to neutrophils $>.5\times10^3$/L	n = 600	n = 429	
Median (range)	10 (5–NR)	10 (6–NR)	.09
Days to platelets $>.5\times10^3$/L	n = 553	n = 400	
Median (range)	12 (3–NR)	13 (7–NR)	<.001†
Transfusional support	n = 595	n = 375	
Median RBC units	2	2	.74
Median platelets units	2	3	.018†
Use of total parenteral nutrition	n = 582	n = 365	
Yes	52.2%	63.6%	.001†
Need for intensive care unit	n = 604	n = 430	
Yes	1.5%	2.3%	.32
Length of stay in hospital	n = 602	n = 420	
Median days (range)	21 (1–82)	23 (1–71)	<.001†
Response at 100 days after ASCT	n = 607	n = 431	.42§
CR	84.2%	79.8%	
PR	6.4%	7.7%	
RD	5.4%	5.8%	
ND	.5%	1.2%	

* Comparison between experiencing ≥1 event of grade ≥3 versus not.
† Statistical significance <.05.
‡ Comparison between experiencing ≥1 event of grade ≥4 versus not.
§ Comparison between CR + PR versus RD.

progression in 138 patients, infection in 34, other treatment-related causes in 35, secondary malignancy in 8, and other or unknown cause in 11. There were no differences in all death causes between the 2 groups, but mortality from infection was significantly higher in the FEAM group (subhazard ratio, 1.99; 95% CI, 1.02 to 3.88; $P = .04$).

Time-dependent outcomes were also evaluated according to major diagnostic categories (Supplementary Figures S1–S3): when the 2 conditioning regimens were compared within aggressive NHL, indolent NHL, and HL, there was no significant difference for OS, PFS, RI, and NRM (Supplementary Figure S2). However, there was a trend for a worse outcome of the FEAM group in PFS (hazard ratio, 1.44; 95% CI, .96 to 2.16; $P = .08$) and RI (hazard ratio, 1.50; 95% CI, 1.00 to 2.27; $P = .051$) (Figure S2B,C) in HL patients.

Multivariate analyses (MVAs) for OS and PFS confirmed the negative roles of already known poor prognostic factors, such as older age, an increasing treatment burden, and suboptimal quality of response before transplant (see Table 4). Interestingly, the category of aggressive NHL was a poor independent predictor for OS but not for PFS; conversely, bone marrow involvement at diagnosis, primary refractory patients, a reduced BCNU/fotemustine dose, and transplantation in a FEAM-oriented center (BEAM/FEAM ratio <25%) emerged as independent factors for PFS but not for OS.

The factors independently associated with a higher relapse occurrence faithfully reproduced those seen for PFS, with the exception of age. Finally, for NRM, the category of HL emerged as a strong protective factor, together with CR before ASCT and more recent time of transplantation; conversely, ASCT after 2 lines of treatment and use of FEAM conditioning was independently associated with worse NRM.

DISCUSSION

Our results suggest a comparable efficacy of FEAM and BEAM conditioning in terms of survival and disease control for lymphoma patients treated with high-dose chemotherapy and ASCT. However, we also observed higher rates of severe gastrointestinal toxicities and of infectious events (mainly from Gram-negative bacteria) in patients transplanted after FEAM.

The BEAM chemotherapy has become the standard conditioning regimen for lymphoproliferative diseases in the last decades. In fact, a large retrospective study from the Center for International Blood and Marrow Transplant Research reports BEAM as increasingly used in the last 20 years, from 13.4% of all conditionings regimens in 1995 to 1999 to 64.1% in 2005 to 2008, with cyclophosphamide, BCNU, and VP-16, busulfan, cyclophosphamide, and total body irradiation–based regimens as main alternatives [22].

A known concern related to BCNU is the development of pulmonary fibrosis, which has been reported especially

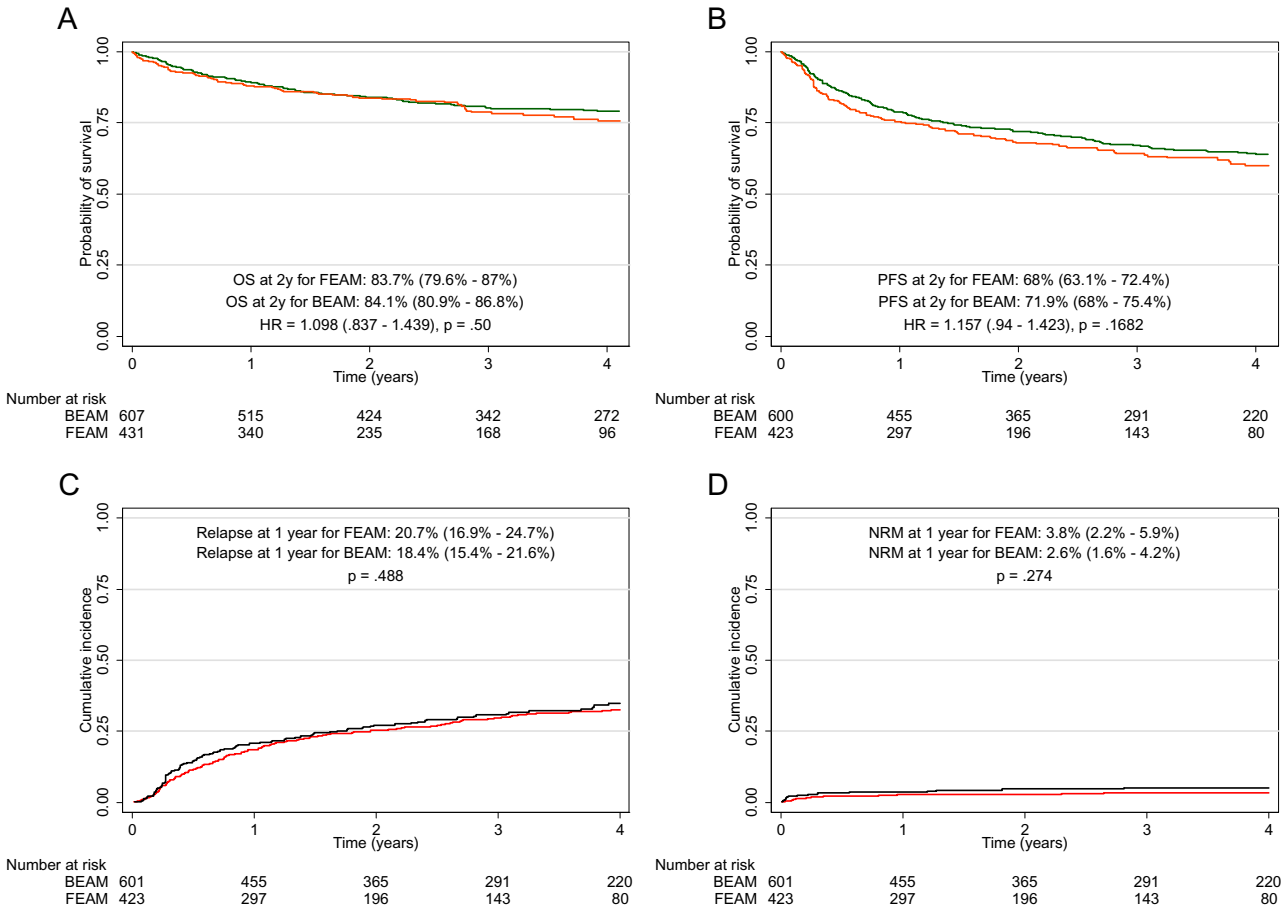

Figure 1. (*A*) OS, (*B*) PFS, (*C*) cumulative RI, and (*D*) NRM, according to type of conditioning.

in regimens with higher BCNU doses (ie, cyclophosphamide, BCNU, and VP-16) than those scheduled in BEAM [22] or when BCNU was combined with cyclophosphamide [8]. Thus, substitution of this component with other drugs, namely thiotepa (TEAM) [23], lomustine (LEAM) [24], fotemustine (FEAM) [15,16], and, most recently, bendamustine (BeEAM) [25] has been proposed: all these alternatives to BEAM were reported to be apparently equally or more effective in controlling lymphoma and equally or less toxic than the original regimen. However, such claims were inferred from comparisons with historical cohorts or studies, done in different populations with different baseline risk factors, while no direct comparison in the same cohort has been conducted so far. A single exception, to our knowledge, is represented by an ongoing prospective trial confronting the BeEAM regimen with the BEAM regimens [26], the results of which are still unavailable.

Despite belonging to the same drug class, one theoretical advantage of fotemustine over BCNU is the apparent lack of pulmonary toxicity [27]: such a difference is explained by the reduced interference with the glutathione system, whose inhibition, driven by the carbamoylation activity of BCNU [28], leads to unopposed production of reactive oxygen species and lung fibrosis. In the 2 studies testing FEAM [15,16], no immediate or late pulmonary toxicity was reported. In our data, we observed a similarly low rate of pulmonary toxicity in both groups: considering that BEAM-conditioned patients had more lung comorbidities before ASCT and had a longer follow-up, it is unlikely that BCNU causes a significantly higher pulmonary toxicity.

Another compelling reason to search for alternatives to BEAM was the shortage of several chemotherapy drugs, a matter of the last decade [10]. As example, the shortage of melphalan was routinely managed by substitution with cyclophosphamide (BEAC regimen); however, in 2016, 4 patients with lymphoma treated with BEAC faced severe complications in a single stem cell transplant center in France. This prompted a retrospective survey by European Group for Blood and Marrow Transplantation on 383 patients treated with BEAC, which were matched to 766 BEAM-treated patients. Although the OS was similar (78% BEAC versus 77% BEAM), cardiac deaths were 32% in the BEAC group compared with 23% in the BEAM group [29]; however, this difference was not statistically significant, and the authors concluded that BEAC was safe as a conditioning regimen.

For BCNU, the whole thing exploded from 2012 onward [13], when increasing difficulties to find BCNU determined a dramatic shift in the use of FEAM in Italy, forcing several hematology units to switch to the new regimen, even if evidence of equivalence was lacking. Moreover, BCNU shortage made it impossible to promote a prospective comparison with the new alternative; conversely, the growing experience with fotemustine in Italy and the existence of good quality databases in many Italian transplant centers, suggested the feasibility and the opportunity of a retrospective comparative analysis of FEAM and BEAM. Finally, given the absence

Table 4
Multivariate Analysis for Overall Survival, Progression-Free Survival, Cumulative Incidence of Relapse and Non-Relapse Mortality

OS		HR (95% CI)	*P* Value
Age at transplant	Each year more	1.02 (1.009–1.03)	<.001
Aggressive NHL	Versus indolent NHL and HL	1.85 (1.346–2.543)	<.001
ASCT after 1 salvage	Versus upfront ASCT	1.495 (1.035–2.158)	.032
ASCT after >1 salvage	Versus upfront ASCT	2.89 (1.835–4.553)	<.001
PR pre-ASCT	Versus RD	.374 (.256–.547)	<.001
CR pre-ASCT	Versus RD	.152 (.102–.225)	<.001
PFS		**HR (95% CI)**	***P* Value**
Age at transplant	Each year more	1.012 (1.004–1.02)	.003
BM involvement at diagnosis	Versus not	1.293 (1.039–1.61)	.022
ASCT after >1 salvage	Versus upfront/only 1 salvage	1.819 (1.401–2.362)	<.001
Primary refractory	Versus response at first line	1.478 (1.115–1.959)	.007
PR pre-ASCT	Versus RD	.45 (.32–.631)	<.001
CR pre-ASCT	Versus RD	.225 (.159–.317)	<.001
Full-dose BCNU/fotemustine	Versus reduced dose	.757 (.581–.987)	.04
FEAM-oriented center	Versus BEAM-oriented or equally oriented	1.312 (1.039–1.656)	.022
Relapse incidence		**SHR (95% CI)**	***P* Value**
BM involvement at diagnosis	Versus not	1.348 (1.071–1.696)	.011
ASCT after >1 salvage	Versus upfront/only 1 salvage	1.732 (1.296–2.315)	<.001
Primary refractory	Versus response at first line	.718 (.523–.987)	.041
PR pre-ASCT	Versus RD	.501 (.328–.767)	.001
CR pre-ASCT	Versus RD	.28 (.185–.423)	<.001
Reduced (<70%) BCNU/fotemustine dose	Versus dose >70%	2.125 (1.488–3.034)	<.001
FEAM-oriented center	Versus BEAM oriented or equally oriented	1.308 (1.018–1.679)	.035
NRM		**SHR (95% CI)**	***P* Value**
Hodgkin lymphoma	Versus others	.266 (.106–.67)	.005
ASCT after >1 salvage	Versus upfront/only 1 salvage	2.293 (1.174–4.478)	.015
Year of transplant	Each year later	.805 (.699–.927)	.003
CR pre-ASCT	Versus RD	.313 (.167–.585)	<.001
FEAM conditioning	Versus BEAM	1.861 (1.023–3.385)	.042

Center orientation: BEAM-oriented center (BEAM/FEAM ratio >75%); FEAM-oriented center (BEAM/FEAM ratio <25%); equally oriented center (BEAM/FEAM ratio 25% to 75%.
SHR indicates subhazard ratio.

of direct comparisons, and nonetheless, the increasing use of fotemustine in Italy, such a study was ethically due, aimed at least to exclude the possibility of a higher toxicity of the FEAM new regimen compared with the standard.

In our study, we recognized several signals of increased mucosal damage with FEAM: severe diarrhea resulting from intestinal mucositis (grade ≥3: BEAM 20.8% versus FEAM 28.3%, $P = .007$) and oral mucositis (grade ≥3: BEAM 30.9% versus FEAM 43.8%, $P < .001$) were in fact more frequent than in the BEAM group. Such a difference persists if we stratify our analysis by the attitude of centers (ie, those using predominantly 1 of the 2 regimens and those switching intermittently between the 2), making a measurement or performance bias (due to fotemustine "novelty") unlikely. The reason for an increased mucotoxicity of fotemustine is not obvious: both nitrosoureas do not usually cause mucositis if used in monotherapy [14,30]; however, when used in combination, the occurrence of severe oral mucositis is relevant, with a reported occurrence of 42% [31] for BEAM and 15% to 30% for FEAM [15,16]. While the major determinant for mucositis severity is the type of chemotherapy regimen used [32], yet there are no univocal pharmacological properties predicting its mucotoxicity. Drug distribution in mucosal tissues has its role, given the established efficacy of cryotherapy in preventing oral mucositis [33], by decreasing the exposure of mucosal tissue to cytotoxic agents through vasoconstriction. In this respect, the enhanced lipophilicity and tissue penetration of fotemustine [14] may represent a drawback and contribute to the increased mucotoxicity observed with FEAM.

Mucositis is a complex phenomenon, originated by DNA damage induced by chemo- or radiotherapy, in which however proinflammatory cytokines play an important role in boosting local injury. In this respect, the new concept of "febrile mucositis" has emerged, highlighting the fact that chemotherapy-induced fever may also result from the inflammation arising in the context of mucositis, and not just from gut-derived bacteremia [34]. Thus, a significant proportion of prior labeled FNs may represent epiphenomena of aseptic mucosal inflammation, carrying a different prognosis and requiring different treatments. In our study, we found a similar occurrence of SIEs in patients treated with BEAM or FEAM. However, the rate of very severe FN (grade ≥4: BEAM 1.5% versus FEAM 6.3%) and SIEM$^+$ (grade ≥4: BEAM 2.6% versus FEAM 6.0%) was higher in the FEAM group. This observation may be traced back to the higher mucotoxicity seen with the FEAM chemotherapy, and possibly related to a different damage determined by this regimen on the enteric mucosa, leading to enhanced disruption of the enteric/blood barrier and easier translocation to the bloodstream of Enterobacteriaceae and resident anaerobes, resulting in bacteremia and sepsis. In fact, the increased occurrence of SIEM$^+$ in the FEAM group is attributable to more frequent isolation of Gram-negative bacteria (mean isolates/patient: BEAM .1 versus FEAM .19, $P < .001$), and in particular of Enterobacteriaceae (mean isolates/patient: BEAM .07 versus FEAM .13, $P = .002$). This, in turn, may explain the higher mortality for infection found in the FEAM group.

In favor of this hypothesis, an association between transplant-related mortality and Gram-negative infections has

also been described in a previous experience with FEAM [16]. Interestingly, an increased occurrence of bacteremias, but with similar rate of overall infectious events, has been reported for another more lipophilic substitute of BCNU (ie, thiotepa; BEAM = 75, TEAM = 47; rate of infectious complications: BEAM 47% versus TEAM 53%; rate of sepsis/bacteremia: BEAM 13% versus TEAM 32%) [23].

An alternative explanation could be the spread of multiresistant Gram-negative bacteria in Italian transplant centers in more recent years [35]. However, in our data, the excess isolates of Enterobacteriaceae observed with FEAM were confirmed restricting the analysis after 2011 (mean isolates/patient: BEAM .07 versus FEAM .13, $P = .009$).

Our study has several limitations, the main one being related to its design: retrospective cohort studies are considered at the lowest level of evidence in the hierarchy of comparative research, with randomized controlled trials (RCTs) being at the opposite end [36]. However, RCTs may not be feasible in several situations and, owing to their interventional nature, they are often restricted to a subset of the population of interest, thereby affecting their external validity [36].

On the contrary, the main threaten for evidence gathered from cohort studies is related to their internal validity, due to risk of selection bias [37]. Although statistical techniques have been developed to control for known imbalances between the groups that are compared, they cannot obviate for unknown factors that are neutralized by randomization. However, if treatment allocation results from factors independent of clinical decision, one might expect more easily 2 prognostically homogeneous groups, thereby allowing a more reliable comparison between them. In our study, the choice between BEAM and FEAM regimen resulted from random variability of BCNU supply, differing among centers and time periods. Such variability mirrored the logistic ability of the centers to procure themselves with BCNU, which in turn generally hindered the pharmacy attitude to find alternative ways to get BCNU (ie, foreign import). Indeed, in our study, centers' attitude was pretty evenly distributed between those who were always able to get BCNU without major interruptions using alternative channels (BEAM/FEAM ratio >75%, n = 8), those who started to use steadily fotemustine since they experienced the first difficulties to get BCNU (BEAM/FEAM ratio <25%, n = 5), and those who switched between the 2 owing to intermittent BCNU shortage (BEAM/FEAM ratio 25% to 75%, n = 5). Therefore, most of the basal characteristics were balanced between BEAM and FEAM, without use of matching or other statistical techniques. The only significant differences were year of transplant (later for FEAM), Sorror score (higher in BEAM), use of radiotherapy (more for BEAM), dose intensity of BCNU/fotemustine and etoposide (higher in FEAM), and number of reinfused $CD34^+$ cells $\times 10^6$/kg (more for FEAM). Although it is expected that some (5%) statistical tests will result significant owing to chance, the observed imbalances likely reflect different policies for transplantation used in different centers, rather than preferential allocation to one of the 2 groups. Center disparities may confound results even in RCTs if the randomization procedure does not account for center stratification. In our analysis, we accounted for the center effect by adding to the MVA a variable coding for center attitude toward the 2 conditioning regimens. Interestingly, in the MVA for PFS and RI, the variable coding for center attitude was more informative than type of conditioning regimen and thus, in the final model, the worse outcome related to FEAM conditioning appears to be limited to FEAM-oriented centers (BEAM/FEAM ratio <25%). Conversely, in the MVA for NRM, type of conditioning emerged as a significant independent predictor, while center attitude was not: thus, it is likely that FEAM conditioning itself contributes to higher treatment-related mortality. In our opinion, such interpretation appears credible and is consistent with the other data, suggesting a higher toxicity induced by substitution of fotemustine in the BEAM regimen. However, given the discussed caveats and the limited size effect observed, there is no absolute confidence about this finding.

In conclusion, we compared 2 groups belonging to the same cohort of patients and differing for one treatment variable, aiming to add evidence to the increasing trend of fotemustine substitution in the BEAM conditioning regimens in lymphomas: our results exclude substantial differences between the 2 treatments in terms of survival and disease control. However, considering that no advantages of FEAM over BEAM emerged, but rather concerns of higher toxicity did, fotemustine substitution in BEAM may not be completely neutral, and thus its use in conditioning does not appear justified when BCNU is available.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.05.018.

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