Bone Marrow Transplantation (2010) 45, 1147–1153

www.nature.com/bmt

ORIGINAL ARTICLE

Fotemustine plus etoposide, cytarabine and melphalan (FEAM) as a new conditioning regimen for lymphoma patients undergoing auto-SCT: a multicenter feasibility study

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BEAM is a widely used conditioning regimen for relapsed/refractory lymphoma patients undergoing auto-SCT. We conducted a multicenter study with an alternative regimen (fotemustine plus etoposide, cytarabine and melphalan (FEAM)) in which BCNU was substituted by the chloroethylnitrosourea fotemustine (FTM). Eighty-four patients with relapsed/refractory Hodgkin's ($n = 20$) and non-Hodgkin's lymphoma ($n = 64$) were conditioned with a FEAM regimen (FTM 150 mg/m^2 on days –7, –6, etoposide 200 mg/m^2 and cytarabine 400 mg/m^2 on days –5, –4, –3, –2 and melphalan 140 mg/m^2 on day –1). Patients were evaluated for toxicity and engraftment parameters. Median times to neutrophil ($> 500 \times 10^9$/l) and plt ($> 20\,000 \times 10^9$/l) engraftment were 11 and 13 days, respectively. Grade 3 mucositis occurred in 19 patients (23%), while G3 nausea/vomiting and G3 diarrhea were observed in 13 (15%) and 6 (7%) patients, respectively. No severe hepatic, renal or pulmonary toxicity was detected. Seven patients (7%) experienced G4 mucositis, while no other G4 toxicities or unexpected adverse events of any grade were recorded. Transplant-related mortality was 2.4%. We conclude that a FEAM regimen is feasible and safe. Although toxicity and engraftment times compared favorably with BEAM, longer follow-up is needed to evaluate fully its efficacy and long-term safety.

Bone Marrow Transplantation (2010) **45,** 1147–1153; doi:10.1038/bmt.2009.318; published online 9 November 2009
Keywords: fotemustine; carmustine; FEAM; BEAM; conditioning; auto-SCT

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Received 14 April 2009; revised 17 September 2009; accepted 29 September 2009; published online 9 November 2009

Introduction

BEAM is a widely adopted conditioning regimen for autologous hemopoietic SCT (ASCT) in patients with Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL), and has an acceptable toxicity and high efficacy.[1] Adverse events associated with carmustine-containing conditioning regimens (that is, BEAM, BEAC) are partly related to BCNU and most commonly include severe mucositis, chemotherapy-induced nausea and vomiting, diarrhea, hepatotoxicity and nephrotoxicity.[1–4] In addition, non-infective toxic pulmonary complications have been reported in 16–64% of patients after carmustine-containing high-dose regimens.[5] Post transplant lung toxicity in patients receiving carmustine-based conditioning has been related to the fact that BCNU inhibits the glutathione reductase tissue detoxification system.[6] As BCNU-related major pulmonary toxicity represents an invalidating and sometimes fatal complication of ASCT, accurate monitoring of respiratory functions, prompt initiation of steroid therapy and even carmustine dose reductions, especially in BCNU plus CY-containing regimens, have been suggested.[5,7]

Fotemustine (FTM) is a third-generation chloroethyl-nitrosourea containing a phosphoalanine carrier group attached to the nitrosourea radical.[8] The phosphoalanine group makes the drug highly lipophilic, as shown by the octanol/water partition coefficient, which is in the optimal range compared with other nitrosoureas such as BCNU and CCNU.[9,10] This characteristic allows FTM to cross the blood-brain barrier (BBB), as shown by experimental studies in animals.[11,12] In addition, as FTM does not significantly alter glutathione reductase activity, a more favorable pulmonary toxicity profile for this agent can be predicted compared with BCNU.[13] In fact, several clinical trials have confirmed that FTM, unlike other nitrosoureas, shows no significant pulmonary toxicity.[14–16]

With regards to antitumor activity, a phase II study by Jacquillat *et al.*,[17] showed that administration of a non-myeloablative schedule of FTM (100 mg/m^2 on days 1, 8

and 15 (induction), followed after 4–5 weeks by a single 100 mg/m^2 maintenance dose, every 21 days), induced objective clinical responses in 7 of 13 heavily pre-treated patients with hematologic malignancies including HL and NHL; thrombocytopenia was the most commonly observed toxicity. In addition, Rigal-Huguet *et al.*[18] conducted an intensification pilot study with autotransplantation of BM in NHL patients in which high-dose FTM was substituted for BCNU in modified BEAM/BEAC-like regimens (FTM, 300 mg/m^2; etoposide 500 mg/m^2; cytarabine, 400 mg/m^2 and melphalan 140 mg/m^2 or CY 6.0 g/m^2).

The aim of this pharmacokinetic study was to show the passage of FTM through the BBB and the feasibility of increasing the dose of the drug.

Given the comparable antitumor activity of FTM with respect to BCNU, in addition to a more favorable safety profile, we conducted a multicenter study of a novel FTM-based high-dose regimen (fotemustine plus etoposide, cytarabine and melphalan (FEAM)) in which BCNU was substituted by an equal dose (300 mg/m^2) of FTM without further modifications of the BEAM platform. The results, in a series of 84 consecutive patients with refractory and relapsed lymphoma, show that FEAM, followed by autologous hemopoietic rescue with peripheral blood progenitor cells, is a feasible conditioning strategy associated with a favorable toxicity profile and timely hemopoietic engraftment.

Patients and methods

Eligibility criteria

In all, 84 eligible patients with relapsed/refractory HL ($n = 20$) or NHL ($n = 64$), were consecutively enrolled. The study was conducted according to the Declaration of Helsinki, and all patients signed a written informed consent form before treatment. Eligible patients were required to have histologically proven relapsed/refractory HL or NHL after first-line chemotherapy. High-risk patient candidates to upfront high-dose consolidation and ASCT were also accrued. Other eligibility criteria included a Karnofsky Performance Status >60, adequate cardiac, pulmonary, hepatic and renal function, and no acute or uncontrolled bacterial or viral infections before transplantation. Patients with uncontrolled comorbid conditions or active toxicity from salvage chemotherapy were considered ineligible.

Conditioning regimen

In all of the cases peripheral blood was used as the source of CD34+ cells for transplantation. CD34+ cells were collected by standard apheresis procedures. The FEAM regimen consisted of FTM 150 mg/m^2 on days –7, –6, etoposide 200 mg/m^2 and aracytin 400 mg/m^2 on days –5, –4, –3, –2 and melphalan 140 mg/m^2 on day –1 (Table 1). Fotemustine (Muphoran, Servier; Thissen Laboratoires, Braine L'alleud, Belgium), was dissolved in the alcoholic solvent, diluted in polyvinyl chloride bags containing 5% dextrose solution, and administered i.v. over a 1-h period. All other drugs were administered according to a standard BEAM regimen.[1] After a day of rest, autologous peripheral blood progenitor cells were infused on day 0, followed by s.c. G-CSF (5 μg/kg) from day 1 of ASCT until 2 consecutive days when the ANCs were $\geqslant 1000 \times 10^9$/l. Prophylaxis for opportunistic infections and antimicrobial therapy in cases of febrile episodes as well as standard supportive measures including blood and plt transfusions were administered according to the standard protocols and policies of each participating center. Similarly, protocols for antiemetic prophylaxis used during FEAM administration, were identical to those currently used for BEAM at participating centers and consisted of serotonin 5-HT3-receptor antagonists and dexamethasone.

Table 1 Dosage and schedule of the FEAM regimen

Drug	*Dose*	*Day*
FTM	150 mg/m^2	–7, –6
Etoposide	200 mg/m^2	–5, –4, –3, –2
Ara-C	400 mg/m^2	–5, –4, –3, –2
Melphalan	140 mg/m^2	–1

Abbreviations: FEAM = fotemustine plus etoposide, cytarabine and melphalan; FTM = fotemustine.

Study definitions, safety and efficacy evaluations

The primary objectives of the study were to assess the feasibility and safety of the FEAM regimen in terms of acute toxicity and hemopoietic engraftment. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria version 3.0 (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf). Transplant-related mortality (TRM) was defined as any death related to a fatal complication in the absence of the underlying disease within 100 days from transplantation. Secondary end points included evaluation of the efficacy of the FEAM regimen in terms of event free survival and overall survival. Disease status at transplantation and response to high-dose chemotherapy, assessed 1 month after ASCT, were evaluated with standard response criteria for lymphoma.[19] Event free survival was defined as the time between ASCT and the occurrence of a serious morbidity (that is, a life-threatening complication requiring hospitalization or prolonging ongoing hospitalization resulting in death or significant disability/incapacity), disease relapse, disease progression or death from any cause. Overall survival was defined as the time from ASCT until death or the date of last follow-up when the patient was known to be alive.

Results

Patient characteristics

From April 2007 to August 2008, a total of 84 consecutive patients from six different institutions were enrolled. Baseline demographics, histology, disease and patient status before ASCT are summarized in Table 2. Twenty patients were affected by HL (24%), and 64 by NHL (76%) with aggressive ($n = 57$) or indolent ($n = 7$) histology. All patients with HL received standard adriamycin, bleomycin, vinblastine, dacarbazine as first-line therapy but in one

Table 2 Patient characteristics

	n (%)
Total no. of patients	84
Age, years	
Median (range)	51 (18–77)
Sex	
Male	53 (63)
Female	31 (37)
Diagnosis	
NHL	64 (76)
Aggressive[a]	57 (89)
Indolent[b]	7 (11)
HL	20 (24)
Stage	
Advanced	68 (81)
Early	16 (19)
Extranodal disease	
Bone marrow	21 (25)
CNS	5 (6)
No. of previous CT lines	
1	17 (20)
2	66 (79)
3	1 (1)
Mediastinal radiotherapy	
Before ASCT	4 (4.8)
After ASCT	13 (15.5)
Disease status at ASCT	
CR	41
PR	32
RD	11

Abbreviations: ASCT = autologous stem cell transplantation; CNS = central nervous system; CT = chemotherapy; HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma; RD = refractory disease.
[a]Including diffuse large B-cell lymphoma, $n=37$; lymphoblastic lymphoma, $n=7$; mantle cell lymphoma, $n=6$; and peripheral T-cell lymphoma, $n=7$.
[b]Including lymphoplasmacytic/small lymphocytic lymphoma, $n=5$ and follicular lymphoma, $n=2$.

case treated with bleomycin, etoposide, adriamycin, CY, vincristine, procarbazine, prednisone whereas upfront chemotherapy included rituximab plus CY, adriamycin, vincristine and prednisone ($n=36$) and rituximab plus CY, adriamycin, vincristine and prednisone-like (Mega-CHOP, ProMACE-CytaBOM, Hyper-CVAD, CODOX-M) regimens ($n=21$) in those with aggressive and very aggressive NHL. Patients with indolent histology were treated upfront with R-fludarabine-based regimens ($n=2$) or rituximab plus CY, adriamycin, vincristine and prednisone ($n=5$).

After first-line chemotherapy, 24 patients were chemorefractory while 60 were considered chemosensitive having attained a CR ($n=39$) or a PR ($n=21$) (Figure 1). Salvage chemotherapy included ifosfamide-based regimens (ifosfamide, carboplatin, etoposide; ifosfamide, epiribicin, vinorelbine; ifosfamide, gemcitabine, etoposide, vinorelbine; and gemcitabine, ifosfamide, oxaliplatin) in 59% of cases, sequential high-dose MTX, cytarabine and etoposide

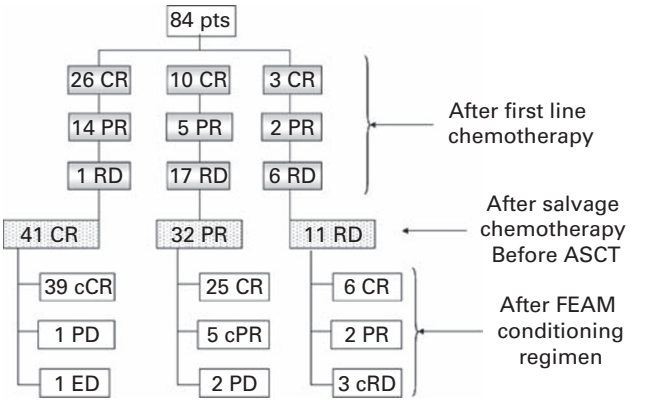

Figure 1 Study flow-chart throughout the treatment and follow-up periods. cCR, continuous CR; cPR, continuous PR; cRD, continuous RD; ED, early death; RD, refractory disease; PD, progression of disease.

in 12% of patients. All remaining patients (27%) were salvaged with the high-dose dexamethasone, cytarabine, cisplatin regimen, whereas bleomycin, etoposide, adriamycin, CY, vincristine, procarbazine, prednisone was used in two patients with HL who received adriamycin, bleomycin, vinblastine, dacarbazine as first-line therapy. A majority of the patients (81%) had advanced disease at relapse with BM (25%) and/or central nervous system involvement (6%). After salvage treatment, 41 patients achieved CR, 32 obtained a PR, while 11 patients underwent FEAM conditioning with non-chemosensitive disease. In all, 4 and 13 patients received mediastinal XRT immediately before and after ASCT, respectively (Table 2). Median days of hospitalization were 24 days (range 14–42), five patients (6%) were admitted in intensive care unit.

Hematopoietic engraftment, transfusion support and febrile neutropenia assessment

All patients showed timely engraftment of infused peripheral blood progenitor cells (Table 3), with a median time to neutrophil recovery ($>500\times10^9$/l) of 11 days (range 9–19 days). Plt recovery ($>20\,000\times10^9$/l) was recorded after a median of 13 days (range 6–105 days). CD34+ cells were collected from peripheral blood and the median number of infused cells per patient was 4.5×10^6/kg.

RBCs and plts transfusion support was required by 65.5 and 98.8% of patients, respectively. Neutropenic fever occurred in 67 patients (79.8%), with a median duration of 4 days (range 1–25). The origin of fever was documented in 29 out of 67 patients (43%) including 10 cases of bacteremia (*Escherichia coli*, $n=4$; *Staphylococcus aureus*, $n=4$; *Enterobacter Cloacae*, $n=2$), 3 cases of catheter-related infection because of coagulase-positive *Staphylococcus* organism ($n=2$) and *Pseudomonas aeruginosa* ($n=1$), 6 cases of enteritis (*Enterococcus faecium*, $n=1$, *E. Coli*, $n=5$), 6 cases of upper respiratory tract infections (*Staphylococcus aureus*, $n=3$; *Streptococcus pneumoniae*, $n=3$) and 4 cases of urogenital tract infections (*Klebsiella*, $n=2$; *E. Coli*, $n=2$).

The remaining 38 patients (56.7%) had negative results on repeated cultures (Table 3).

Treatment-related morbidity and mortality

Treatment-related toxicity, according to National Cancer Institute Common Terminology Criteria, is summarized in Table 4. Overall, FEAM conditioning was well tolerated. Mucositis reached G3/G4 severity in only 30% of cases (median duration 7 days, range 4–14), while G2/G3 chemotherapy-induced nausea and vomiting was documented in 47% of patients, without any G4 episodes. Similarly, 17 and 7% of patients experienced G2 and G3 diarrhea, while no G4 events were observed. Liver and renal toxicity was generally mild and transient, with G2 events being recorded in only 2 and 1% of patients, respectively. There were no episodes of veno-occlusive liver disease. Administration of FEAM was not associated with pulmonary adverse events, except for a single case of G2 toxicity in a patient with a concomitant bacterial respiratory infection, one case of G1 laryngitis, and a single episode of G1 dyspnea. TRM at 100 days occurred in two patients (2.4%); one died of bacterial meningitis at day +25 after transplantation, and the other of bacterial infection at day +51 after having achieved full hematologic recovery.

Patient outcome and survival

As shown in Figure 1 and Table 5, 73 out of 84 patients (86.9%) had chemosensitive disease (41 CR, 32 PR) before ASCT, while in 11 patients (13.1%) the progressing lymphoma was chemorefractory to salvage therapy. Regarding post-FEAM conditioning and ASCT, 70 out of 84 (83.3%) patients attained CR, 7 achieved PR (8.3%), 6 patients (7.2%) showed no response (three because of refractory disease and three because of early progression), and 1 was not assessable as the patient died of TRM. Interestingly, FEAM conditioning was active in partially responsive and chemoresistant diseases as shown by a 78% conversion rate of PR into CR and by the attainment of an objective response (six CR and two PR) in about 70% of patients with chemorefractory lymphoma at transplantation. After a median follow-up of 13 months (range 1–23), 74 patients (88.1%) were alive (Table 5). In particular, of the 70 patients attaining CR, 58 (82.9%) were alive and disease free, 9 were alive with lymphoma progression (occurred at days +164, +179, +226, +304, +370, +375, +379, +413 and +615, post-ASCT), 1 (70-year old) died for TRM at day +51, because of infection, 1 (68-year old) died of disease progression at day +186 and 1 (71-year old) died for cardiac comorbidity at day +175. Among the 84 patients, 10 deaths occurred during a median follow-up of

Table 3 Hematopoietic engraftment, transfusion support therapy, infection and febrile neutropenia

Parameter	*Outcome*
Hematopoietic engraftment	Median (range)
Number of CD34+[a] cells infused ($\times 10^6$/kg)	4.5 (1–21.8)
	Median days (range)
Neutrophils ($>500\times10^9$/l)	11 (9–19)
Neutrophils ($>1000\times10^9$/l)	12 (9–20)
Plts ($>20\,000\times10^9$/l)	13 (6–105)
Plts ($>50\,000\times10^9$/l)	16.5 (10–105)
Transfusion support therapy	n (%)
RBC units[b]	55 (65.5)
Median (range)	2 (1–8)
Plt units[c]	83 (98.8)
Median (range)	2 (1–15)
Febrile neutropenia[d]	*n* (%)
No	17 (20.2)
Yes	67 (79.8)
Median duration days (range)	4 (1–25)
FUO	38 (56.7)
MDF	29 (43.3)
Gram +	13[e] (44.8)
Gram −	16[e] (55.2)

Abbreviations: FUO = fever of unknown origin; MDF = microbiologically documented fever.
[a]CD34+: source of collection was peripheral blood.
[b]The red blood transfusion threshold was a hemoglobin value <8g per 100 ml.
[c]The platelet transfusion threshold was a platelet count $<20\,000\times10^9$/l.
[d]Fever >38 °C and a number of neutrophils $<500\times10^9$/l.
[e]Number of patients with Gram ± infection among patients with FUO.

Table 5 Patient status throughout treatment and follow-up

Status	*Patient status—n (%)*		
	Before ASCT	*After ASCT*	*Follow-up median 13 months (range 1–23 months)*
CR	41 (48.8)	70 (83.3)	58 (69.0)
PR	32 (38.1)	7 (8.3)	4 (4.8)
RD	11 (13.1)	3 (3.6)	0
PD		3 (3.6)	12 (14.3)
Death		1 (1.2)	10 (11.9)

Abbreviations: ASCT = autologous stem cell transplantation; RD, refractory disease; PD = progressive disease.

Table 4 Toxicity associated with the FEAM regimen

Type of toxicity	*Grade 0 (%)*	*Grade 1 (%)*	*Grade 2 (%)*	*Grade 3 (%)*	*Grade 4 (%)*
Mucositis	13 (15)	10 (12)	36 (43)	19 (23)	6 (7)
CINV	18 (22)	26 (31)	27 (32)	13 (15)	0
Diarrhoea	50 (59)	14 (17)	14 (17)	6 (7)	0
Hepatotoxicity	82 (98)	0	2 (2)	0	0
Nephrotoxicity	83 (99)	0	1 (1)[a]	0	0
Pulmonary toxicity	81 (96)	2 (2)[b]	1 (1)[c]	0	0

Abbreviation: CINV = chemotherapy-induced nausea and vomiting.
[a]Transient renal toxicity in a 70-year-old patient.
[b]One episode of laryngitis and one of dyspnea.
[c]Slight thickening of the lungs due to concomitant Klebsiella and Pseudomonas aeruginosa infection.

13 months. Four patients died of disease progression at days +207, +45, +78, +108 at 33, 41, 63, 65 years old, respectively, one patient (52-year old) died of meningitis at day +25, one (39-year old) for hemorrhage at day +112 and one (64-year old) because of comorbidity at day +210.

Discussion

High-dose chemotherapy followed by ASCT is an established treatment modality for recurrent lymphoma that is associated with long-term survival in 30 to 50% of patients with HL and NHL that fail upfront multiagent chemotherapy.[20–23] Clinical outcome and survival of lymphoma patients after ASCT depend, among other factors, on the disease chemosensitivity at transplantation, ability of conditioning regimens to eradicate residual tumor cell clones after salvage chemotherapy, and transplant-related morbidity and mortality.[4,20,22–24] Despite efforts to identify high-dose regimens with increasing antitumor activity and acceptable toxicity to normal tissues, there is not yet clear evidence of a superior conditioning platform that should be applied in the setting of recurring lymphoma patients, at least in terms of tumor-eradicating capacity. Consequently, most recent research has focused on the incorporation of monoclonal antibodies, radioimmunoconjugates and other immunologic manipulations during the early pre- and post transplantation phases.[25–27] However, because some major causes of both early- and long-term mortality after ASCT remain related to the toxicity of the high-dose regimen adopted, efforts to ameliorate tolerability and reduce the extrahematologic toxicity of conditioning regimens may be a further means to improve patient outcomes.

BEAM is the most widely used conditioning regimen for ASCT in patients with HL and NHL, and has acceptable toxicity and high antitumor efficacy.[1–4,28] The early nonhematologic toxicities of BCNU, the nitrosourea component of BEAM, have been fully characterized and mainly represented by mucositis, nausea and vomiting, diarrhea, hepatotoxicity and nephrotoxicity.[1–4,22,28,29] In addition, late-onset toxic pulmonary reactions, mainly interstitial non-infectious pneumonitis, have been reported in 16–64% of patients receiving BCNU-based conditioning regimens, with a fatal outcome in about 9% of cases.[5,7,29–31] BCNU-related pulmonary toxicity appears to be dose related and is probably linked to BCNU-specific inhibition of the glutathione reductase cellular detoxification system.[5,6] Although dose reductions, early steroid therapy and intensive respiratory monitoring have been adopted to manage carmustine-related lung injury in patients receiving carmustine-based conditioning regimens,[5] an alternative approach is to replace BCNU with an equally active agent with a more favorable toxicity profile.

In this study, we report the results of a multicenter study in which 84 consecutive patients with recurring lymphoma were conditioned with a modified BEAM-like regimen (FEAM) in which carmustine was substituted by the third-generation chloroethylnitrosourea FTM.[8,32] In this regard, FTM shows a distinct pharmacologic and safety profile with respect to both first- (lomustine) and second- (BCNU) generation nitrosoureas, which is characterized by a reduced incidence of hepatic and renal complications and by the absence of pulmonary toxicity.[33] In addition, FTM shows antitumor activity that is comparable to BCNU, and preclinical and clinical studies have shown that it has significant cytotoxicity toward malignant lymphoid cells.[17,18,34–39]

All patients showed timely hemopoietic engraftment after FTM-based conditioning, with neutrophil and plt recovery to post transplant intervals that are highly comparable to those reported for most carmustine-based regimens.[1–4,22,28,29] Similarly, the intensity of transfusion support and the rate, type, and severity of neutropenic infectious episodes during the aplastic phase did not substantially differ from those reported for BEAM and BEAM-like regimes,[1–4,22,29] thus confirming the overall safety of FEAM conditioning. This is further confirmed by a TRM of 2.4%, which compares favorably with that reported for similar carmustine-based regimens (0 to 11%) and other types of high-dose conditioning (0 to 25%), with variations being mostly related to patient age and/or comorbidity status.[1–4,22,28–30,40–42]

Regarding the acute toxicity of FEAM, we observed a relatively high incidence of mucositis, which was, however, equal or higher than G3 severity in only 30% of episodes. Although the design of this study did not foresee comparison with standard BEAM, it is noteworthy that a recent investigation reported that 83% of patients receiving BEAM experienced oral mucositis, which was graded G1/G2 in 42% of cases and G3/G4 in the remaining 41% of patients.[42] In our series, we detected a similar overall incidence of mucositis (85%), but the substitution of BCNU with FTM appeared to be associated with a shift toward less severe mucositis (G2, 43%; G3/G4, 30%), with the apparent reduction of G4 episodes to 7% compared with 18% reported for BEAM.[41,42] A favorable trend for FEAM can be also envisaged for chemotherapy-induced nausea and vomiting, and diarrhea, because no G4 toxic episodes were recorded in our cohort, leading to overall G3/G4 rates of 15 and 7%, respectively. Other large series of patients conditioned with BEAM have reported that the incidence of G3/G4 chemotherapy-induced nausea and vomiting, and diarrhea ranges from 15–20 to 22–25%, respectively.[1–4,28,29] FEAM was also associated a very low rate of renal (1%) and hepatic (2%) G2 adverse events. This confirms data from preclinical studies in which Laquerriere *et al*.[33] compared the hepatic tolerability of FTM to BCNU and CCNU. In that *in vitro* study in rat hepatocytes, it was shown that FTM was not directly hepatotoxic, and produced only modest and reversible changes in the biochemical functions of liver cells, in contrast to other nitrosoureas that caused substantial disturbances in cell cycle progression.[33] Accordingly, no veno-occlusive liver disease episodes occurred in our cohort of patients.

Considering pulmonary adverse events, we observed no G3/G4 toxicity, and only a single G2 episode of slight thickening of the interlobular septa in a symptomatic patient with microbiologically documented Klebsiella and Pseudomonas aeruginosa infection. The episode resolved on targeted antibiotic therapy, thus minimizing its qualification as a typical drug-induced non-infectious

pulmonary complication (NIPC).[5] In addition, there was one transient episode of G1 exertion dyspnea and a G1 larynx edema. Both events quickly resolved without steroid therapy. The median time to development of non-infectious pulmonary complications in patients conditioned with carmustine-based regimes was 90 days post-ASCT (range 52–289), with later episodes occurring within the year.[5] Although the delayed occurrence of non-infectious pulmonary complications in some patients cannot yet be excluded, the present data suggest that the FEAM regime is not associated with a significant risk of moderate-to-severe pulmonary complications.

The relatively short follow-up of our study does not allow any conclusions in terms of survival or the long-term efficacy of FEAM conditioning. However, it is noteworthy that the regimen achieved CRs in chemoresistant cases, converted a pre-transplantation PR status into CR in several patients, and that, at a median follow-up of 13 months (range 1–23 months), 56 patients (80%) achieving CR after transplantation were alive and disease free. Interestingly, none of the four patients with documented central nervous system involvement before ASCT showed, at the longest follow-up of 17 months, any disease progression at the level of the central nervous system, which is consistent with the active passage of FTM through the blood-brain barrier. Three of these patients are in continuous CR, one died of causes unrelated to lymphoma.

Considering the limits of the study design, we have shown that substitution of the less toxic FTM for BCNU within the BEAM conditioning regimen is both feasible and safe. The FEAM regimen was associated with hemopoietic recovery times comparable to carmustine-containing regimes, and was devoid of unexpected adverse events. It also showed a very favorable acute toxicity profile with regards to mucositis and hepatic, renal, and pulmonary complications. Although a longer follow-up is needed to evaluate the clinical efficacy and long-term safety, these promising results may also prompt a randomized comparison of FEAM vs standard carmustine-based regimens.

Conflict of interest

Dr Tania Perrone is an employee of Italfarmaco S.p.A., Italy. All other authors have no financial or other conflict to declare.

Acknowledgements

We thank the following physicians who participated in the study: Rosella Matera, Ospedale Vito Fazi, Lecce, Potito Rosario Scalzulli, Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Paolo Di Carlo, Ospedale Civile, Pescara. This work was supported in part by a grant to A Pinto from Ministero della Salute, Ricerca Finalizzata FSN, IRCCS, Rome, Italy.

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