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Intensive chemotherapy with high doses of BCNU, etoposide, cytosine arabinoside, and melphalan (BEAM) followed by autologous bone marrow transplantation: toxicity and antitumor activity in 26 patients with poor-risk malignancies

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Summary. Twenty-six patients (median age 33 years) with poor-risk malignancies were treated with high-dose combination chemotherapy associating BCNU-etoposide-cytosine arabinoside and melphalan (BEAM) followed by autologous bone marrow transplantation (ABMT). Twenty-one patients had malignant lymphomas, three, acute lymphoblastic leukemia (ALL), and two, malignant thymomas. Eleven patients (group 1) were not in complete remission (CR) at the time of BEAM, and fifteen patients (group 2) were in CR. Hematological recovery occurred in all patients. The duration of aplasia and the non-hematological toxicities were similar in both groups. Ten of the eleven patients (group 1) evaluable for response achieved CR and one achieved partial remission (PR). Five patients relapsed, and five are in continuous CR with a short follow-up (median 8 months). Among the fifteen patients in CR at the time of BEAM (group 2), four patients relapsed and ten patients are in unmaintained continuous CR with a median follow-up of 15 months (one patient died in CR). The disease-free survival is 53%, with 29% for patients receiving BEAM while in relapse (group 1) and 65% for patients receiving BEAM while in CR (group 2). These data indicate that BEAM followed by ABMT can produce a high antitumor response with an acceptable toxicity in patients with poor-risk malignancies.

Introduction

Allogenic or autologous bone marrow transplantation (BMT) is technically feasible and is authorized for application in studies designed to test and develop new strategies of high-dose radiochemotherapy in patients with poor-risk malignancies [2, 10, 14]. Alkylating agents alone or in combination have been widely used in high-dose chemotherapy followed by BMT support: with these agents there is generally a dose-response relationship, and their main limiting factor is hematological toxicity, which is relatively easy to control by means of BMT. However, many of the different drugs that could be useful in high-dose regimens can have severe non-hematological toxicities, especially when combined together, leading to a consistent morbidity and mortality in the patients.

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We have reported, like others [9, 23, 25] that high-dose melphalan can be useful in a wide range of cancerous conditions, including various solid tumors, leukemias and lymphomas, and that its non-hematological toxicity is acceptable [24, 25, 26, 28]. In this study, we evaluated the antitumor activity and the toxicity of the association of three other different drugs given in high dosages in combination with melphalan 140 mg/m^2: BCNU + Etoposide + ara C + melphalan (BEAM). Our results in 26 patients, including 21 with malignant lymphomas, suggest that this drug combination is relatively safe and is especially efficient in the consolidation phase of patients with poor-risk malignant lymphomas.

Patients and methods

Patients

In all, 26 patients (10 females and 16 male) were treated by intensive chemotherapy with BEAM followed by autologous bone marrow transplantation (BMT). The median age was 33 years (range 3–54). There were 21 patients with malignant lymphomas, 3 with acute lymphoblastic leukemias (ALL), and 2 with malignant epithelial thymomas.

Histological subtypes were classified according to the Rappaport classification [35], and clinical staging was evaluated with reference to the Ann Arbor criteria [37]. Patient characteristics are detailed in Tables 1 and 2. Briefly, all patients had been heavily pretreated before BEAM and BMT. All had received extensive chemotherapy with a median of six different drugs (range 5–10), including anthracyclines in all patients, and 14 had received previous radiotherapy. The chemotherapy combinations received for Hodgkin's disease were MOPP, ABVD and CVPP [4]. Patients with diffuse mixed or diffuse histiocytic lymphomas had been treated with m-BACOD (13 patients) or CHOP (2 patients) [36, 40]. The patient with a Burkitt's lymphoma was treated according to the Ly.B protocol [30]. The patients with lymphoblastic lymphomas were treated according to standard adult ALL protocols [12].

Patients were divided into two groups according to their tumor status at the time of BEAM.

Group 1: The 11 patients in this group were not in CR (complete remission) at the time of BEAM: there were 2 patients with ALL in second marrow relapse; 2 patients had extensive malignant epithelial thymomas progressing

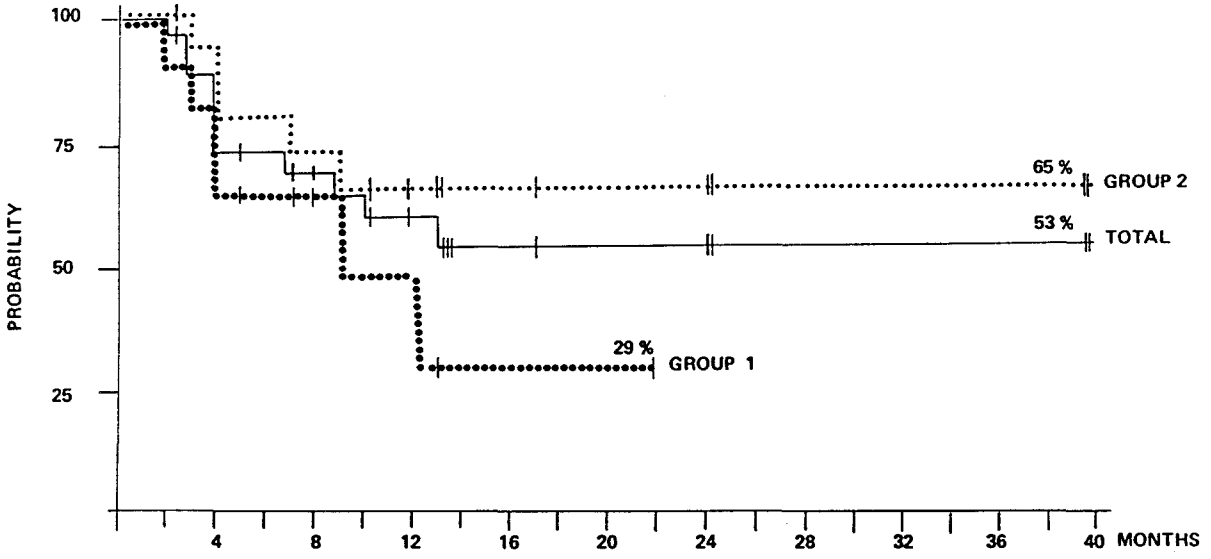

Fig. 1. Overall disease-free survival. Group 1: patients treated in relapse or progressive disease. Group 2: patients treated in complete remission

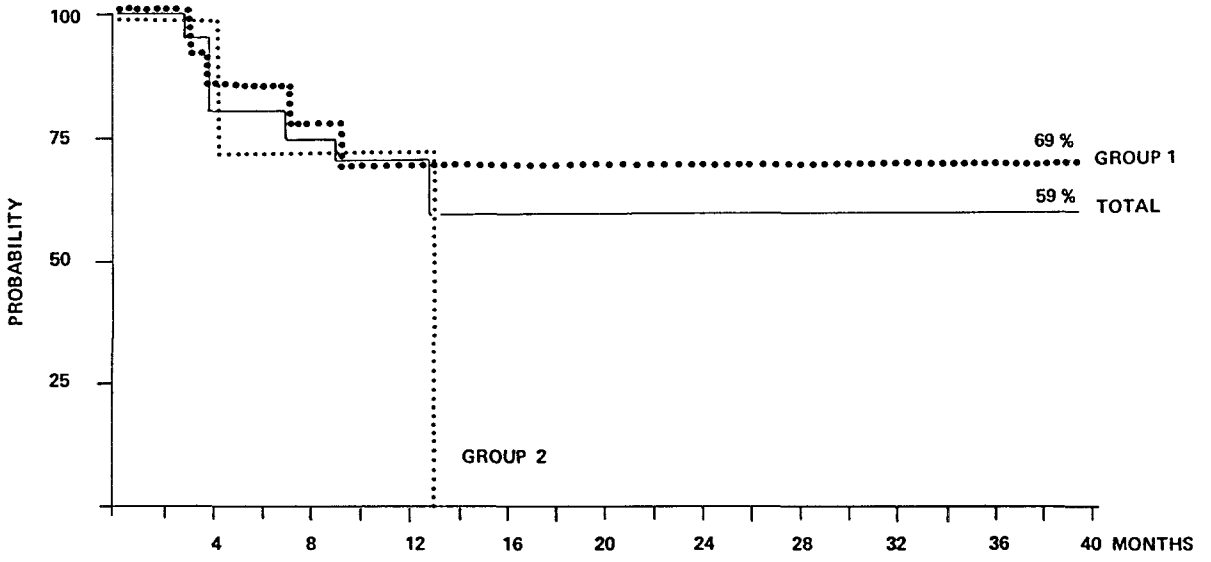

Fig. 2. Disease-free survival of patients with malignant lymphomas. Group 1: patients treated in relapse or progressive disease. Group 2: patients treated in complete remission

after radidotherapy and several chemotherapies; 7 patients had malignant lymphomas; 2 patients with Hodgkin's disease had progressive disease after failure of radiotherapy, MOPP, ABVD, and CVPP protocol; 5 patients had non-Hodgkin lymphomas (NHL); in 3, progressive disease was present after first-line and second-line chemotherapy; 2 were in relapse during first-line chemotherapy.

Group 2: The 15 patients in group 2 received BEAM while in CR. In 1, ALL was in the fourth CR after three marrow relapses; 14 had NHL; 2 adults with stage IV lymphoblastic lymphomas received BEAM for consolidation of first or second CR; 12 patients received BEAM for diffuse histiocytic lymphoma (DHL) with poor prognostic features (5 in second CR after an initial relapse during conventional therapy and 7 in first CR); 6 had advanced disease in stages III–IV (including B symptoms in 2 patients) and had previously been treated with a median of six courses of chemotherapy (range 5–9); one of these was treated with BEAM after six courses of CHOP for a stage II DHL with a large tumor mass (> 10 cm).

Methods

Conditioning regimen. The BEAM regimen is a combination of four drugs:

Bischloroethylnitrosourea (BCNU): 300 mg/m^2 by i.v. infusion over 1 h on day −6.

Cytosine arabinoside (Ara C): 100 mg/m by i.v. infusion over 1 h every 12 h on days −5, −4, −3, −2

Etoposide (VP16): 100 mg/m^2 by i.v. infusion over 1 h on days −5, −4, −3, −2

Melphalan (MPH): 140 mg/m^2 as an i.v. bolus on day −1.

Table 1. Characteristics of the patients treated during relapse or progressive disease (group 1)

Patient	Age	Sex	Diagnostic initial staging	Therapy before ABMT				Cond. regimen	Status at time of ABMT	Response duration	Status at June 1987
				Duration (months)	No. of drugs	No. of combinations	RT				
1	17	M	ALL CALLA+	44	7	4	+	BEAM 1	2nd Relapse, marrow	CR (3)	Dead at 11 months from relapse
2	4	F	ALL CALLA+	9	10	4	+	BEAM 1	2nd Relapse, marrow	CR (2)	Dead at 4 months from relapse
3	54	F	Malignant extensive thymoma	15	6	3	+	BEAM 1	PD	CR (>22)	Alive in CCR >22 months
4	54	F	DHL IV B	10	6	1	−	BEAM 1	PD, lungs	CR (>13)	Dead in CCR of 13 months from bacterial infection
5	48	M	DHL III B	7	7	2	+	BEAM 1	PD, lymph nodes	PR (4)	Dead at 8 months from relapse
6	27	F	DML II B	50	7	3	++	BEAM 2	PD, lymph nodes	CR (>13)	Alive in CCR >13 months
7	30	F	Malignant extensive thymoma	11	6	2	+	BEAM 2	PD	CR (10)	Dead at 10 months from relapse
8	8	M	Burkitt IV B	7	9	5	+	BEAM 3	PD, CNS	CR (>8)	Alive in CCR >8 months with toxic cerebral disease
9	21	M	HD IV B	109	9	4	+	BEAM 2	PD, inflammatory signs	CR (>7)	Alive in CCR >7 months
10	38	M	DHL II A	5	6	1	−	BEAM 2	PR, mediastinum	CR (4)	Alive in relapse at 6 months
11	27	F	HD IV B	72	9	3	+	BEAM 2	PD, lymph nodes, liver	CR (>5)	Alive in CCR > at 5 months

ALL, Acute lymphoblastic leukemias; DHL, diffuse histiocytic lymphoma; DML, diffuse mixed lymphoma; HD, Hodgkin's disease; RT, radiotherapy; Cond. regimen, conditioning regimen; PD, progressive disease; CR, complete response; PR, partial response; CCR, continuous complete remission

Autologous bone marrow was infused 24 h after melphalan (day 0). Patients were hydrated (3000 ml m^{-2} day^{-1}) with continuous i.v. fluids, started 6 h before treatment and continuing up to 24 h after high-dose melphalan. Thirteen patients were treated precisely according to this regimen (BEAM1). Twelve patients received the same schedule but with VP16 200 mg m^{-2} day^{-1} (BEAM2), and one patient received BEAM 2 with higher dose of BCNU: 600 mg/m^2 (BEAM3).

Bone marrow procedures. Bone marrow was harvested under sterile conditions, up to a minimum of 2×10^8 nucleated cells/kg. Harvesting was carried out within a median of 2 months (range 1–12) before grafting. At this time, the bone marrow was cytologically normal in all patients. Marrow was cryopreserved with dimethylsulfoxide (DMSO) as previously reported [17]. The frozen marrow cells were thawed rapidly in a 37° C water bath and infused through a central venous catheter. Marrow was not washed between thawing and infusion.

Cell viability after thawing was tested in all patients after storage by an in vitro colony forming assay for myeloid progenitor cells. Stepwise dilution of marrow cells was first performed [38].

The harvested marrow of 5 patients had been treated in vitro before cryopreservation: 2 patients with T lymphoblastic lymphomas had in vitro marrow purging with anti-CD5 monoclonal antibody and complement or after coupling with the A chain of Ricin (T 101 Fab Immunotoxin, Sanofi-Montpellier France) [27], and the marrow of 3 patients was treated with anti-CD10 monoclonal antibody (ALB2, Immunotech, Marseille, France) and rabbit complement as previously reported [18].

Supportive care. Each patient had a large-diameter right atrial indwelling catheter inserted upon admission. Twenty-two patients were managed in single rooms and nursed with conventional hospital isolation techniques, receiving trimethoprim sulfamethoxazole as prophylaxis against bacterial infection. Three patients were treated in laminar air flow rooms and received oral nonabsorbable antibiotics and sterile food. Febrile episodes were promptly treated with broad-spectrum antibiotics i.v. Patients received parenteral nutrition if needed (20 patients); transfusions of platelets were administered when the platelet count fell below 20.10^9/l, and red packed cells, when the hemoglobin level fell below 10 g/100 ml. All blood products except marrow were irradiated at 15 Gy.

Table 2. Characteristics of the patients treated during complete remission (group 2)

Patient	Age	Sex	Diagnostic initial staging	Sites of disease at diagnosis	Relapse	Time elapsing between		Previous therapy				Status at time of BMT	Cond. regimen	Outcome and status at June 1987
						Diag. & BMT	Last CR & BMT	No. drugs	No. combinations	No. cycles	RT			
12	43	F	LBL IV A	Marrow, med.	–	12 m	–	7	3	8	+	CR 1	BEAM 1	Alive in CCR > 40 m
13	46	M	DHL III A	LN, cavum, spleen	–	10 m	–	6	2	9	–	CR 1	BEAM 1	Relapse at 3 m Dead 12 m from relapse
14	33	M	DHL IV A	Bones	–	9 m	–	6	2	6	+	CR 1	BEAM 1	Alive in CCR > 40 m
15	54	M	DHL III B	LV	–	11 m	–	6	1	6	–	CR 1	BEAM 1	Alive in CCR > 24 m
16	23	M	DHL IV B	Intestine diffuse	Intestine	40 m	12 m	9	3	14	+	CR 2	BEAM 1	Alive in CCR > 24 m
17	50	M	DHL II A	LN (> 10 cm)	–	11 m	–	5	2	10	–	CR 1	BEAM 1	Alive in CCR > 17 m
18	3	M	ALL CALLA+	Marrow	Marrow	21 m	2 m	8	7	NE	+	CR 4	BEAM 1	Relapse (marrow) at 4 months. Dead at 6 months from relapse
19	50	F	DHL III B	LN	LN	53 m	5 m	6	3	17	+	CR 2	BEAM 1	Dead in CCR at 7 m from car accident
20	27	F	DHL IV A	Brain	Brain	6 m	2 m	8	3	6	+	CR 2	BEAM 2	Relapse (brain) 9 m Dead 9 m from relapse
21	40	M	DHL III A	LN	–	7 m	–	6	1	6	–	CR 1	BEAM 2	Alive in CCR > 13 m
22	18	M	DHL IV A	Bone, LN	LN	48 m	12 m	10	3	12	+	CR 2	BEAM 2	Alive in CCR > 13 m
23	40	M	DHL IV A	Skin, LN	–	8 m	–	6	1	6	–	CR 1	BEAM 2	Alive in CCR > 12 m
24	52	M	LBL IV B	LN, marrow	Marrow	5 m	2 m	6	2	6	–	CR 2	BEAM 2	Alive in CCR > 10 m
25	12	M	DHL IV A	Bone, LN	Bones	12 m	6 m	9	5	NE	–	CR 2	BEAM 2	Relapse (LN, bone) at 4 months Alive in PR at 6 m
26	22	F	DHL III B	LN nodes med	–	4 m	–	6	1	5	–	CR 1	BEAM 2	Alive in CCR > 2.5 m

ALL, Acute lymphoblastic leukemia; DHL, diffuse histiocytic lymphoma; LBL, lymphoblastic lymphoma; med, mediastinum; LN, lymph nodes; m, months; RT, radiotherapy; Cond. regimen, conditioning regimen; CR, complete remission; PR, partial remission; CCR, continuous complete remission

Evaluation of response and toxicity. Patient response was evaluated 1 month after autologous BMT as follows: complete response (CR) = complete disappearance of all signs related to tumor; partial response (PR) = decrease of the tumor by more than 50% at all measurable sites for at least 1 month; stable disease = no evidence of disease progression for at least 1 month.

Toxicity to the oral mucosa and gastrointestinal tract was defined as follows: mucositis was moderate if painful ulcerations were present, and severe if the pain required narcotics. Diarrhea was classed as moderate when watery stools < 1000 ml/day were passed for between 3 and 7 days or stools > 1000 ml/day fewer than 3 days, and as severe when watery stools > 1000 ml/day were passed for more than 3 days or hemorrhagic enterocolitis was present. Nausea was classed as moderate when it lasted only 1 day, and severe when it lasted more than 1 day.

Statistical methods. The Kaplan-Meier method was utilized to evaluate disease-free survival probability [20].

Table 3. Hematological recovery

	Group 1[a]	Group 2[a]	Total[a]
Infused nucleated cells/kg $\times 10^8$	1.8 (0.4–3.2)	1.6 (0.45–3.9)	1.9 (0.4–3.9)
Days to recovery of granulocytic count $>0.5 \times 10^9$/l	15 (10–27)	14 (9–>29)	15 (9–>29)
Days to recovery of platelet count $>50 \times 10^9$/l	23 (15–>120)	23 (18–>120)	25 (15–>120)

[a] Median (range)

Results

Hematological toxicity (Table 3)

Severe marrow aplasia occurred in all cases with leukocyte count $<0.1 \times 10^9$/l and platelet count $<20 \times 10^9$/l. The median number of infused marrow cells was 1.9×10^8/kg (range 0.4–3.9). Granulocytopenia $<0.5 \times 10^9$/l lasted a median of 15 days (range 9–>29) and thrombocytopenia $<50 \times 10^9$/l lasted a median of 25 days (range 15–>120).

In most patients, full hematological recovery was achieved promptly. There was no significant difference in the duration of hematological reconstitution for the patients who received transplants during CR (group 2) or during relapse (group 1).

Non-hematological toxicities

The data of the patients receiving BEAM1 or BEAM2-3 are detailed in Table 4.

Gastrointestinal toxicity was frequent: overall, significant toxicity, coded as moderate or severe, took the form of nausea in 38% of the patients, mucositis in 46% and diarrhea in 27%. These complications were not more frequent or more severe in patients receiving higher doses of chemotherapy in the conditioning regimen (BEAM2-3 versus BEAM1). Twenty-four patients developed fever during neutropenia, of unknown origin in 54% and resulting from documented bacteremias in 38%. They were febrile for a median of 3 days (range 0–12) and received antibiotics i.v for a median of 15 days (range 8–31) and amphotericin i.v. for a median of 13 days (0–45). Parenteral nutrition was needed for a median of 17 days (range 0–50), and patients were hospitalized for a median of 28 days (range 20–56). As shown in Table 4, similar supportive care was needed by the patients receiving BEAM1 and BEAM2-3.

No other significant toxicities, such as toxic renal, hepatic or cardiopulmonary effects, were noted. Central nervous system toxicity was observed in two patients: one patient (pt 20) had a brain DHL, which relapsed after conventional M-BACOD chemotherapy and 30 Gy cranial irradiation and the patient achieved a second CR after a boost irradiation of 15 Gy; she then received BEAM2 and ABMT for consolidation. The course of ABMT was not complicated until 6 months after the transplant, when the patient developed progressive apathy and cerebral deterioration. A CT scan showed only extensive post-therapeutic cerebral atrophy. A subsequent cerebral relapse occurred at 9 months leading to death.

The other patient (pt 8) received BEAM3 for a Burkitt lymphoma with central nervous system relapse resistant to high-dose Ara-C, intrathecal methotrexate and radiotherapy (18 Gy). He achieved CR after BEAM3 and is in continuous CR but has developed progressive leukoencephalopathy, presumably toxic, which started 3 months after BEAM. Despite these two severe toxicities, no patient died of the transplant procedure.

Response, relapse, and survival

Eleven patients (group 1) had measurable disease at the time of BEAM (8 had progressive disease, 3 were in relapse). All were evaluable: all had an objective response, with 10/11 achieving CR. Five relapsed within a median of 4 months. Four of these died and one (pt 10) is still alive in relapse at 6 months. One patient (pt 4) died in continuous CR (CCR) at 13 months of overwhelming pneumococcal sepsis. He was a splenectomized patient who refused to take prophylactic penicillin. Five patients are in continuous CR with a short follow-up (median 8 months: range 5–22).

Fifteen patients (group 2) were in CR at the time of BEAM. The median duration of the last CR before BEAM was 8.5 months (range 2–12). Four patients relapsed in a median of 4 months (range 3–9) in the site of the last perceptible tumor. One patient died while in CR at 7 months from a car accident.

Ten patients are in unmaintained CCR with a median follow-up of 15 months (range 2.5–36). Overall, the dis-

Table 4. Non-hematological toxicities

No. of patients with	BEAM1	BEAM2–3	Total
Moderate or severe nausea	5/13 (38%)	5/13 (38%)	10/26 (38%)
Moderate or severe mucositis	7/13 (53%)	5/13 (38%)	12/26 (46%)
Moderate or severe diarrhea	4/13 (30%)	3/13 (23%)	7/26 (27%)
Fever of unknown origin	5/13 (38%)	9/13 (70%)	14/26 (54%)
Bacteremia	8/13 (61%)	2/13 (15%)	10/26 (38%)
Days with T° >38°	3.5 (2–7)	3 (0–12)	3 (0–12)
Days with i.v. antibiotics	18 (8–31)	13 (8–31)	15 (8–31)
Days with i.v. amphotericin	13 (7–45)	9 (0–45)	13 (0–45)
Days with parenteral alimentation	16.5 (8–50)	17.5 (0–30)	17 (0–50)
Days of hospitalization	27 (23–56)	30 (20–44)	28 (20–56)

ease-free survival is 53%, with 29% for patients receiving BEAM while in relapse (group 1) and 65% for patients receiving BEAM while in CR (group 2); however this difference is not statistically significant.

Discussion

In this series of 26 patients we confirmed the clinical feasibility of the use of high-dose melphalan in combination with other drugs at high dosage, such as BCNU, Ara C, and VP16, when this regimen is followed by an autologous bone marrow rescue. This combination of drugs can be attractive for the treatment of several malignancies, e.g., acute leukemia and malignant lymphoma, in which the individual antitumor activity of each of these drugs has already been demonstrated [5, 7, 19, 22]. Most of these drugs have consistent penetration into the central nervous system, which is generally dose-dependent. Furthermore, few patients, (particularly during first-line therapy of malignant lymphomas) have been previously exposed to these drugs, even at conventional doses.

The overall toxicity of the BEAM regimen is quite acceptable, with no toxic deaths in our series even with relatively high doses of etoposide (BEAM2); the median stay in hospital was 28 days. However, severe central nervous system toxicities were observed in two patients who had previous CNS involvement that had been extensively pretreated by radiotherapy and intrathecal therapy; one of these patients had received the BEAM3 regimen with a double dose of BCNU (600 mg/m^2), which could be responsible in part for the antitumor activity and for the late toxicity. It is probable that in such patients the use of BEAM could produce CNS toxicities, which have to be considered alongside its potential advantages. In the other patients, no major early or late toxicity has been documented; this observation contrasts with that previously recorded in similar patients treated with other conditioning regimens, e.g., BACT, TACC, BAVC, CBV, UCH, Bu-Cy or Cy-TBI [1, 2, 6, 14–16, 31, 33, 34, 39, 41].

Furthermore, the overall response rate to BEAM, with 10 CR/11 patients in group 1, compares favorably with the general antitumor response to other conditioning regimens, which are probably more toxic. The high antitumor activity and the relatively low toxicity of BEAM in patients in group 1 prompted us to use this approach earlier in the course of the disease, as consolidation treatment for patients in CR (group 2). While the duration of the antitumor response was generally disappointing in group 1 patients, long-term disease-free survivals have been observed in group 2. However, in this study the difference in disease-free survival between the two groups was not statistically significant. The observation of better disease-free survival when patients receive high-dose radiochemotherapy and bone marrow transplantation for consolidation of a remission rather than as salvage treatment for resistant relapse has already been demonstrated in several malignancies, e.g., leukemias or lymphomas, both in allogeneic and in autologous BMT [11, 13, 32, 42, 43].

Our results in patients in group 2, with 65% disease-free survival for the whole group and 69% in the patients with poor-risk lymphomas, suggest that BEAM and ABMT are an efficient and safe method of consolidation for patients with such poor-risk malignancies in remission. However, these results have to be confirmed prospectively in a larger cohort of patients randomly assigned to consolidation with BEAM and ABMT or with a more conventional form of chemotherapy already known to be effective [8, 21, 36, 40]. This general strategy could be especially important in poor-risk malignant lymphomas in first CR.

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