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Phase-I–II study of high-dose melphalan and autologous marrow transplantation in adult patients with poor-risk non-Hodgkin's lymphomas

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Summary. *Eleven adult patients with poor-risk non-Hodgkin's lymphoma were treated with high-dose melphalan (140 mg/m²) or high-dose combination chemotherapy (BCNU, Ara-C, vindesine and melphalan) followed by autologous bone marrow transplantation. Six of the eight patients evaluable for response achieved complete remission and one achieved partial remission. Response duration ranged from 1.5 to 12 months (median 2 months). Prompt hematological recovery occurred in all patients. The duration of aplasia and the extrahematological toxicity were similar in both groups. High-dose melphalan alone or associated with other drugs followed by marrow infusion appears to produce a high response rate and demonstrates the potential for salvaging patients with refractory lymphoma.*

Introduction

Despite recent advances in chemotherapy of high-grade-malignancy non-Hodgkin's lymphomas [6, 12, 22, 39], the prognosis of patients who do not respond to first therapy or who relapse during treatment remains extremely poor.

Marrow transplantation has made it possible to treat such patients with more aggressive approaches using high-dose chemotherapy and/or radiotherapy [3, 11, 14, 16, 18, 30, 42].

Melphalan (L-phenyl alanine mustard), an alkylating agent, has a broad spectrum of antitumor activity, and mainly hematological toxicity. Given in high doses, whether or not combined with marrow transplantation, it has been effective in patients with refractory neoplasias, including melanomas [28], Ewing's sarcomas [8], various solid tumors [9, 21, 27, 36], multiple myelomas [29], and acute leukemias [24, 26, 29].

In this phase-I–II study we evaluated antitumor response and toxicity of high-dose melphalan alone or combined with other cytotoxic drugs and followed by autologous marrow transplantation in 11 patients with poor-risk or end-stage non-Hodgkin's lymphomas.

Patients and methods

1. Patients

All patients in this study had poor-prognosis non-Hodgkin's malignant lymphoma: chemotherapy-resistant lymphomas (7 patients had never achieved complete remission and 5 patients were in relapse resistant to all therapy), aggressive histology (4 immunoblastic lymphomas; 1 adult had Burkitt's lymphoma with central nervous system involvement). Six patients suffered from at least two of these poor-prognosis factors.

Eleven patients (7 male and 4 female) were studied and analyzed in 12 different courses; one patient (AU 27) received a second treatment and graft 4 months after the first.

Histological subtypes [10], initial staging (Ann Arbor criteria) [37], previous therapy, and status at the time of marrow transplantation are detailed in Table 1.

Methods

a) Bone marrow procedures

Harvest. Under general anesthesia bone marrow cells were taken from the anterior and posterior iliac crests of each patient and collected into sterile plastic bags containing tissue culture medium (RPMI 1640) and preservative-free heparin (dose = liquemine Roche: 50 IU/ml). The median yield of nucleated marrow cells was 2.5×10^8/kg (range: 1.6×10^8/kg to 3.4×10^8/kg). The marrow was harvested 0–4 months before the graft. At this time it was cytologically normal in all patients.

Two patients received fresh marrow graft (AU 02, AU 30). Nine received cryopreserved marrow.

Marrow transplantation with fresh marrow cells. The marrow was kept at room temperature for 24 h before transfusion.

Separation and freezing. The marrow was processed using a Haemonetics V50 cell separator equipped with a 100-ml centrifuge bowl. Marrow cells were transferred to GAMBRO bags and cryopreserved in medium containing 10% DMSO and 10% ABO compatible human plasma in liquid nitrogen, as described in detail elsewhere [17].

Thawing procedure. 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.

Colony-forming cells control. Cell viability on thawing was tested at variable intervals after storage by the in vitro colony-forming assay for myeloid progenitor cells after stepwise dilution of marrow cells [38]. CFC assays were carried

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Table 1. Patient data and response to high-dose chemotherapy

	Age/ sex	Histology[a] initial staging (disease site)	Previous therapy[b]	Duration of 1st CR (months)	Interval Δg-BMT (months)	Patient status[c] at time of marrow aspiration/ transplant	K	Response[c]	Response duration (months)	Survival (months)	Comments (relapse site)[a]
Group 1											
AU 02	60/F	Pinkus L. IV B (maxillar)	ADR, CY, VCR, 5FU, CDDP, PDN, RT	6	15	REL/ RESIST REL	60	CR	12	14	Dead from relapse (multiple subcut. nod)
AU 05	59/F	D. Im. L. IVB. (abd)	ADR, CY, VCR, PDN, RT	0	9	PR/ RESIST REL	40	NE	–	0.3	Dead from sepsis D12
AU 29	31/M	D. Large Cell L. IIB (mediast)	ADR, CY, VCR, PDN, VM26, VDS, RT	7	12	2ndCR/ 2ndCR	100	NE	2	2,5	Dead from relapse (mediast.)
AU 27	44/M	D. Im. L IVB (abd)	ADR, CY, VCR, PDN, MTX, Bleo, VDS	0	12	PR/REL	70	CR	2	10	Dead from further relapse (abd)
AU 30[d]	41/M	D. Large Cell L. IVA (cranial T.)	ADR, CY, VCR, PDN, VDS, VLB, RT	0	11	REL/ RESIST REL	70	PR	1,5	9	Dead from relapse (cranial)
Group 2											
AU 27[e]	44/M	D. Im. L. IVB (abd)	ADR, CY, VCR, PDN, MTX, Bleo, VDS, Aclacyno, 1st MPH + ABMT, RT	0	16	REL/ RESIST REL	70	CR	2	5	Dead from relapse (abd.)
AU 34	53/M	D. Im. L. IV B (meningeal, bones)	ADR, CY, VCR, PDN, MTX, CCNU, Bleo, RT	0	6	REL/ RESIST REL	100	CR	2	7+	Alive in relapse (CNS)
AU 37	25/M	Burkitt L. IV B (CNS + BM)	ADR, CY, VCR, PDN, MTX, L. asp. ARAC, 6TG, RT	0	5	PR/ PR (CNS)	90	SD	1,5	2	Dead from relapse (CNS)
AU 42	32/F	D. Hist. L. IV (mediast. + sternum)	ADR, CY, VCR, PDN, MTX, Bleo, RT	0	5	PR/PR	90	NE	–	1	Dead from pneumonia + VOD
AU 38	44/F	D. Im. L. IVB (ethm. + subcut. nod. limb)	ADR, CY, VCR, PDN, MTX, Bleo, RT	4	6	CR/REL	80	CR	4	5	Dead from further relapse (ethm.)
AU 47	26/M	Lymph. L. IIB (mediast.)	ADR, CY, VCR, PDN, MTX, L. Asp, VM26, CDDP, RT	1	7	2ndPR/ 2ndPR	100	CR	2	3+	Alive in relapse (mediast.)
AU 45	47/M	Lymph. L. IIA	ADR, CY, VCR, PDN, MTX, ARAC, 6TG, MP, RT	7	13	PR/ 2ndCR	100	NE	5+	5+	Alive and well

[a] Pinkus L, Pinkus lymphoma [35]; D. Im. L., diffuse immunoblastic lymphoma; D. Large Cell L., diffuse large cell lymphoma; D. Hist. L., diffuse histiocytic lymphoma; Lymph. L., lymphoblastic lymphoma; abd, abdominal; cranial T, cranial tumor; CNS, central nervous system; BM, bone marrow; mediast., mediastinal; ethm., ethmoidal; subcut. nod., subcutaneous nodules; VOD, veno-occlusive disease

[b] RT, radiation therapy; ADR, doxorubicin; CY, cyclophosphamide; VCR, vincristine; 5FU, 5-FU; CDDP, cisplatin; PDN, prednisone; VM 26, teniposide; VDS, vindesine; MTX, methotrexate; Bleo, bleomycin; VLB, vinblastine; Aclacyno, Aclacynomycine; MPH + ABMT, melphalan + autologous bone marrow transplant; CCNU, lomustine; L. asp., L-asparaginase; ARA C, cytosine arabinoside; 6TG, 6-thioguanine; MP, mercaptopurine

[c] REL, relapse; CR, complete response; SD, stable disease; PR, partial response; RESIST. REL, resistant relapse; NE, not evaluable

[d] Diffuse phase after 7 years of nodular lymphoma

[e] Second course of high-dose chemotherapy in this patient

out in triplicate by plating 2×10^5 nucleated cells/plate in agar medium (0.3% agar, α-MEM, and 15% fetal calf serum). For all cultures human leukocyte feeder layers were used as a source of colony-stimulating factor. Colonies of more than 50 cells were scored after 14 days incubation in a fully humidified atmosphere of 5% CO_2 and air at 37° C.

b) High-dose chemotherapy

Patients received: Group 1. High-dose melphalan alone (140 mg/m^2) was given to five patients as an IV bolus trough a central venous catheter. Patients were hydrated (3,000 ml/m^2/day) with continuous IV fluids started 6–12 h before and continued for 24 h after high-dose melphalan. Furosemide 20 mg was given IV 1 h after melphalan to induce a brisk diuresis.

Group 2. Combination chemotherapy with high-dose melphalan was given to seven patients (VAMB protocol): bischloroethyl nitrosourea (BCNU) 300 mg/m^2 IV on day 1; cytosine arabinoside (ARA-C) 200 mg/m^2 by continuous infusion on days 2, 3, 4, 5, and 6 (total = 1,000 mg/m^2; vindesine (VDS) 1.3 mg/m^2 continuous infusion on days 2, 3, 4, 5, and 6 (total = 6.5 mg/m^2); melphalan (MPH) 140 mg/m^2 IV on day 7.

One patient (AU 34) with central nervous system involvement received: BCNU 300 mg/m^2 IV on day 1; procarbazine 200 mg/m^2 IV on days 1, 2, 3, and 4 (total dose = 800 mg/m^2); VEHEM (VM 26) 200 mg/m^2 IV on days 2, 3, and 4 (total dose = 600 mg/m^2); melphalan 140 mg/m^2 IV on day 5.

Autologous bone marrow was infused 24 h (group 1) or 48 h (group 2) after IV melphalan.

c) Supportive care

Each patient had a large-diameter right atrial indwelling catheter inserted upon admission and received IV alimentation.

They were managed in single rooms with conventional hospital reverse isolation, except for patient AU 29, who was treated in a laminar air flow room.

No systematic decontamination of the gastrointestinal tract was performed; eight patients received prophylactic Bactrim and two received prophylactic granulocytes.

Febrile episodes were promptly treated with broad-spectrum IV antibiotics.

Transfusions of platelets were administered routinely when the platelet count fell below 20,000/µl and red packed cells when the hemoglobin level fell below 10 g/100 ml.

All blood products except marrow were irradiated at the dose of 15 Gy before transfusion.

d) Evaluation of response and toxicity

Patient response was evaluated 1 month after autologous bone marrow transplantation. Complete remission (CR) was defined as complete disappearance of all signs related to tumor for at least 1 month; partial response (PR) was used to define a decrease of greater than 50% in all measurable tumor for at least 1 month or disappearance for less than 1 month. Stable disease (SD) was defined as no evidence of disease progression for at least 1 month.

Toxicities to the oral mucosa and the gastrointestinal tract were defined as follows: *mucositis* was moderate if painful ulceration was present making it impossible to eat most foods; and severe if pain requiring narcotics and making eating completely impossible was present.

Severity of *diarrhea* was evaluated as follows: moderate, watery stools $\leq$ 1,000 ml/day lasting between 3 and 7 days or stools > 1.000 ml/day for less than 3 days; severe, watery stools $\geq$ 1,000 ml/day for more than 3 days or hemorrhagic enterocolitis.

Nausea was classed as mild when it lasted only 1 day and severe when it lasted more than 1 day.

Results

1) Responses

Responses are detailed in Table 1.

Twelve courses of high-dose melphalan with autologous marrow transplantation were given, and 10 patients had measurable disease at the time of intensive chemotherapy. Responses were evaluable in eight patients; two patients (AU 42 and AU 05) died early of infection. Seven of the eight evaluable patients had an objective response.

No relation was observed between the achievement of complete remission and patient status at the time of marrow collection or grafting, or pretransplant Karnofsky score.

The duration of response was short: nine of 10 patients achieved remission and relapsed after marrow transplantation within a median of 2 months (range = 1.5–12). Eight relapsed at the initial site of the tumor before marrow transplantation.

2) Hematological suppression

Hematological toxicity is detailed in Table 2. Severe marrow aplasia occurred in all cases with leukocyte counts of less than 0.1×10^9/l and platelet counts of less than 20×10^9/l. The nadir of the granulocyte counts was on day 5.5 (range: 1–11) and the nadir of the platelet count was day 7 (range: 3–11). Hematological recovery occurred after BMT in 11 evaluable patients. Granulocytopenia $\leq 0.2 \times 10^9$/l lasted from 5 to 12 days (median 8 days) and $\leq 0.5 \times 10^9$/l, from 8 to 24 days (median 14 days). Thrombocytopenia $\leq 20 \times 10^9$/l lasted from 5 to 35 days (median 17 days) and $\leq 50 \times 10^9$/l, from 13 to 52 days (median 30 days). No statistical difference was noted for aplasia between the two groups.

3) Toxicity

Toxic side-effects are detailed in Table 3. Eleven patients developed infection during aplasia: the median duration of hyperthermia > 38° C was 3 (range: 0–8) days. The number of days with IV antibiotic treatment ranged from 0 to 28 days (median 15). One patient (AU 05) died of infection by day 12. Two others developed a severe pulmonary infection with acute respiratory distress syndrome: AU 38 contracted it during staphylococcal septicemia and then improved after 7 days of ventilation; AU 42 contracted pneumococcal pneumonia on day 15 requiring assisted ventilation, but died from refractory hypoxemia. Other severe extrahematological complications were observed in the same patient (AU 42), who developed jaundice, ascitis, and biological liver failure by day 15, which could be compatible with hepatic veno-occlusive disease. Alopecia was observed in all patients. No neurological or renal toxicity occurred. Five cases of moderate or severe mucositis were observed. Four patients suffered from moderate nausea and two patients from moderate diarrhea. Anorexia occurred in all patients.

Table 2. Bone marrow graft characteristics and hematopoietic recovery

	Marrow storage	Infused nucleated cells/kg × 10^8	Infused CFC/kg × 10^4	Days with			
				Gc < 0.2 × 10^9/l	Gc < 0.5 × 10^9/l	Pl < 20 × 10^9/l	Pl < 50 × 10^9/l
Group 1							
AU 02	Room temperature	2	3	6	15	10	22
AU 05	Frozen	1.6	2.28	Not evaluable (dead in aplasia, day 12)			
AU 29	Frozen	3.4	3.4	7	–	8	5
AU 27	Frozen	1.9	6.35	8	14	17	35
AU 30	Room temperature	2.7	4.55	12	24	21	52
Group 2							
AU 27	Frozen	2.7	1.08	11	15	25	50
AU 34	Frozen	3.1	14.8	8	10	5	20
AU 37	Frozen	2.8	2.8	5	14	17	35
AU 42	Frozen	2.1	7	9	12	20	NE
AU 38	Frozen	2.8	15	10	12	35	45
AU 47	Frozen	2.2	8.8	9	15	18	22
AU 45	Frozen	2.4	11	8	14	12	20

Gc, granulocytes; Pl, platelets

Table 3. Toxic side-effects

	Infection prophylaxis	T° ≥ 38° C for (no. of days)	IV Antibiotics for (no. of days)	Mucositis[b]	Nausea	Diarrhea	Other major toxic effect
Group 1							
AU 02	Granulocytes	6	20	++	+	0	
AU 05	None	NE	NE	+	+	+	
AU 29	LAF[a]	2	6	0	+	0	Died of infection by day 12
AU 27	Granulocytes	5	19	++	++	++	
AU 30	Bactrim	1	17	0	+	0	
Group 2							
AU 27	Bactrim	8	28	+++	++	++	
AU 34	Bactrim	2	9	+	+	0	
AU 37	Bactrim	2	8	+	+	0	
AU 42	Bactrim	NE	NE	++	++	0	Pulmonary infection and toxic liver failure
AU 38	Bactrim	4	12	++	+	0	Pulmonnary infection
AU 47	Bactrim	2	8	0	++	0	
AU 45	Bactrim	0	0	+	+	0	

[a] LAF, laminar air flow room
[b] 0, none; +, mild; ++, moderate; +++, severe

The median duration of hospitalization was 28 days (range 21–38 days) for group 1 patients and 37 days (range 30–60) for group 2 patients.

Discussion

Our results show that high-dose melphalan is able to induce a high response rate in patients with multiresistant adult malignant lymphomas, with evidence of response (complete remission + partial remission) in seven of eight patients. Our two groups of patients had similar response rates: three of three when high-dose melphalan was used as single-agent chemotherapy (group 1); four of five when high-dose melphalan was used in intensive combination chemotherapy (group 2). Only a few cases of antitumor activity of high-dose melphalan in malignant lymphomas have previously been reported [9].

Thus, as in many other neoplasias [9, 28], melphalan given in high doses is active in malignant lymphomas resistant to conventional therapy.

In this population of multiresistant patients with malignant lymphomas our response and remission rate are similar to those obtained with other published high-dose chemo-radiotherapy regimens. Using autologous bone marrow grafting, Appelbaum reported with BACT a 10/14 response rate (70% CR + PR) [1]; with modified BACT[1], Hartmann obtained 11

1 Modified BACT: BCNU 200 mg/m² d1, d2, d3 CY 1,600 mg/m² every 24 h d2, d3, d4, d5 Ara-C, 100 mg/m² every 12 h d2, d3, d4, d5 6-TG, 100 mg/m² PO every 12 h d2, d3, d4, d5

CR/16 children (68%) [16]; with TACC[2], Gorin obtained 4 CR/6 (66%) [15]; with CBV or Cy-TBI, Tannir obtained 5 CR/8 (62%) [44, 45]; using Cy-TBI, Phillips recorded 23 CR/34 evaluable patients (65%) [32, 34] and Appelbaum reported 7 CR/8 patients with twin donors [3] and 14 CR/20 patients (70%) with allogenic transplantation [4]. Using the CRAB[3] regimen and allogeneic grafting O'Leary obtained CR in three cases of relapsed lymphoma [30].

This study shows that high-dose melphalan can be used in combination with other drugs known to be active agents in malignant lymphomas, such as Ara-C [13, 19, 20, 31, 43], BCNU [7, 33, 41], or vindesine [5, 23, 25, 40], without major additional toxic effects.

In our patients, extra hematological toxicites were relatively mild and not markedly different according to whether melphalan was used alone or in massive combination chemotherapy.

Hematological recovery was similar in both groups, shortened by the use of autologous marrow transplantation in all patients [2, 14].

Most of the patients relapsed after high-dose melphalan: eight of nine relapsed at the initial tumor site, demonstrating that our regimens are not completely lymphoma-ablative in such patients.

Short duration of response is relatively 'expected' in such a selection of resistant patients and has also been observed with other regimens in malignant lymphomas [1, 32] and in other malignancies [27, 29].

The feasibility and immediate antitumor activity of high-dose melphalan alone or in a combination regimen in patients with advanced adult malignant lymphomas invites us to use such a therapy at an earlier stage of the disease in selected patients known to have a poor prognosis with conventional therapy. This is the object of an ongoing cooperative study.

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2 TACC: CCNU, 200 mg/m^2 PO d2 Ara-C, 200 mg/m^2 every 12 h d2, d3, d4, d5 (7 doses) CY 45 mg/m^2/kg d1, d2, d3, d4 6-TG, 100 mg/m^2 PO every 12 h d1, d2, d3, d4 (7 doses)

3 CRAB: BCNU 200 mg/m^2 d1 CY, 50 mg/kg d1, d2, d3, d4 Ara-C, 100 mg/m^2 every 12 h d1, d2, d3, d4 (7 doses) TBI, 7.5 Gy d6

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Note added in proof: Since submission of this paper, the 2 patients who were alive in relapse AU 34 and AU 47 died at 8 and 9 month, respectively AU 45 is still alive and well at 20 month +.

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