Cancer Chemother Pharmacol (1983) 10:109–111

Cancer Chemotherapy and Pharmacology

High-Dose Melphalan and Autologous Bone Marrow Transplant for Relapsed Acute Leukaemia

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Summary. *Seven patients with relapsed acute leukaemia were treated with high-dose melphalan (HDM) followed by the infusion of autologous cryopreserved remission marrow. Toxicy was minimal and all seven patients had a complete response. Four patients are still in unmaintained remission at 14, 13, 10, and 3 months, the first two having received a second course of HDM to consolidate the result. The role of HDM as a form of intensification therapy for patients with acute myeloid leukaemia in first remission should be investigated.*

Introduction

Despite the recent advances in the treatment of acute leukemia, the prognosis for patients who experience relapse remains extremely poor. This population of patients has often been treated with active new agents such as 5-azacytidine, m-AMSA, VP-16213 and high-dose cytarabine [4, 7, 9, 10]. The highest reported response rates for such treatments have been in the range of 30%–40%, and much lower rates have often been reported. Several investigators [1, 3] have proposed and have recently attempted a different approach, which consists in the administration of high-dose chemotherapy, with or without total-body irradiation, followed by the infusion of the patients's marrow, obtained and cryopreserved during remission. Results obtained with this approach compare favorably with the best results of conventional therapy for relapsed AL. Remission marrow is capable of engraftment after cryopreservation and remissions, usually of short duration, can be achieved in 40%–70% of patients. High-dose melphalan followed by autologous or pseudosyngenic marrow transplantation has been reported to be feasible and to yield a high tumor response index in patients with melanoma [6] and relapsed leukemia [5].

We report here our clinical experience and preliminary results obtained with high-dose melphalan (HDM) followed by autologous cryopreserved remission marrow in the treatment of relapsed AL.

Patients and Methods

Seven patients (Table 1) with relapsed acute leukaemia were studied. Six had acute myeloid leukaemia (AML) and one had acute lymphoblastic leukaemia (ALL). All except one (patient AU01) had bone marrow aspirated during the first remission. Three patients (AU06, AU16, AU23) were treated in their first relapse and four in their second relapse. The median age was 38 years (range 3–66).

Bone Marrow Collection, Processing, Storage, and Infusion. 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. The median yield of nucleated marrow cells was 1.64×10^8/kg (range $0.5–4.2 \times 10^8$/kg). The marrow was processed using a Haemonetics 30 cell separator equipped with a 100-ml centrifuge bowl. Marrow cells were transferred to GAMBRO bags and then cryopreserved in medium containing 10% DMSO and 10% ABO-compatible human plasma in liquid nitrogen, as described in detail elsewhere [2].

The frozen marrow cells were thawed rapidly in a 37° C waterbath and infused through a central venous catheter, 12–24 h after HDM. Marrow was not washed between thawing and infusion.

Table 1. Patient data, and response to HDM

Patient	Sex/age	Diagnosis[a]	Complete response duration (months)	Survival (months)
AU01	M/47	AML (M3) 2nd relapse	$2^1/_2$	4
AU04	F/38	AML (M3) 2nd relapse	$1^1/_2$	17+[b]
AU06	M/46	AML (M3) 1st relapse	16+	16+
AU14	M/25	ALL (L1) 2nd relapse	9	10
AU16	F/42	AML (M2) 1st relapse	5	5
BE01	M/3	AML (M2) 2nd relapse	13+	13+
AU23	F/66	AML (M1) 1st relapse	6+	6+

[a] FAB classification
[b] Patient AU04 relapsed 6 weeks after HDM; a further remission was obtained with daunorubicin, cytarabine, and thioguanine and consolidated with a 2nd course of HDM

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CFC-c Assay. Cell viability on thawing was tested at variable intervals after storage by the in vitro colony forming assay for myeloid progenitor cells after a stepwise dilution of marrow cells [8]. CFC-c assays were carried 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 placental conditioned medium was 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.

Conditioning Treatment Before Transplantation. Melphalan was given as an IV bolus through a central venous catheter previously inserted. Six patients received 140 mg/m^2 and one, 240 mg/m^2. All were well hydrated with continuous IV fluids started 6–12 h before and continued for 24 h after HDM. Furosemide 20 mg was given IV 1 h after melphalan to induce a brisk diuresis.

Supportive Care. All patients had large-diameter right atrial catheters inserted upon admission and some received IV alimentation. One patient was treated in an LAF room and received prophylactic non-absorbable antibiotics. Six patients were treated in single rooms with reverse-barrier nursing and received prophylactic granulocytes.

Febrile episodes were promptly treated with broad-spectrum IV antibiotics. Platelet transfusions and red cell concentrates were given when indicated. All blood products were irradiated with 1500 rad prior to transfusion.

Results

Toxicity

Non-hematopoietic toxicities were mainly related to the gastrointestinal tract, with mild to moderate nausea occurring in all patients and moderate mucositis in two. Four patients developed fever during neutropenia and three had documented bacterial infections. No other significant toxicity such as renal, hepatic, cardiopulmonary, or neurologic effects, was observed. Alopecia occurred in all patients.

Table 2. Bone marrow graft characteristics and hematopoietic recovery

Patient	Nucleated marrow cells infused $\times 10^8$/kg	CFC-c infused $\times 10^4$/kg	Granulocytes (days) $\times 10^9$/l $< 0.2 < 1$	Platelets (days) $\times 10^9$/l $< 20 < 50$
AU01	0.5	0.25	17	8
			37	58
AU04	0.6	0.35	7	14
			22	19
AU06	1.3	2.6	7	–
			18	18
AU14	1	0.1	10	4
			14	20
AU16	0.87	0.01	10	16
			35	28
BE01	4.2	–	11	–
			32	–
AU23	1.8	0.36	6	90
			90	–

Anti-Leukaemic Effect

All seven patients had a complete response with bone marrow cleared of leukemic cells and absence of leukemia for more than 1 month. Evidence of engraftment, documented by bone marrow aspiration 10 days after transplantation, was seen in all patients. Details of individual haematopoietic recovery are summarized in Table 2.

Four patients (AU04, AU06, BE01, and AU23) are still alive and in remission at 17+, 16+, 13+ and 6+ months. Three patients have died, two of recurrent leukemia (AU01 and AU14) and one of infection (AU16). A second course of HDM, again in conjunction with autologous marrow rescue, was given as a form of remission consolidation to four patients (AU04, AU06, AU14, AU16). The first two are still alive in unmaintaine complete remission. The last two died 7 and 3 months after the second treatment, of recurrent leukemia and infection, respectively.

Discussion

Although the number of patients reported here is small, some valid conclusions can be drawn from this study: it confirms that in acute leukemia, a disease usually refractory to low-dose melphalan, massive doses of this drug are significantly active, as previously reported in relapsed patients after allogenic marrow transplantation [5]. The usefulness of marrow rescue after melphalan 140 mg/m^2 has been previously demonstrated in patients with melanoma receiving or not receiving autologous marrow transplants [6]. We have also been able to confirm something that others have already reported [1, 3]: cryopreserved remission marrow is capable of engraftment and subsequent hematopoietic reconstitution. With three patients in complete remission at 17+, 16+, and 13+ months this approach is certainly gratifying, but it is unlikely to be more than palliative. In fact, the successful outcome of autologous BMT in AL will depend on the complete eradication of residual leukaemia prior to transplantation and the elimination of all leukemic cells from the graft. None of these was attempted in our patients.

Better results will probably be obtained if HDM is given as a form of early and/or late intensification therapy for patients with AML in first remission, and further studies are now in progress to assess its activity in this application.

Acknowledgement. M. M. Abecasis was supported by a grand from the Leukaemia Research Fund (UK).

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Received October 13, 1982/Accepted November 23, 1982