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High-Dose Melphalan and Total Body Irradiation with Bone Marrow Transplantation for Refractory Malignancies

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Abstract—*We investigated if high dose melphalan and total body irradiation could be administered to adult patients with acceptable toxicity. Nineteen adult patients with relapsed disease,* 15 *of them having hematologic malignancies, were treated with high-dose melphalan* (100 mg/m^2–140 mg/m^2) *divided over* 2 *consecutive days followed by a rest period of* 4 days *before receiving total body irradiation,* 850 rad *administered in five fractionated doses over* 3 days. *Subsequently* 11 *patients received autologous, seven allogeneic and one syngeneic, bone marrow transplantation. All patients had severe myelosuppression and the major extramedullary toxicity was mucositis. There were three early deaths, two related to septicemia and one to graft-versus-host disease with associated cytomegalovirus pneumonitis. All patients were heavily pretreated, and* 16 *were demonstrating progressive disease on alternative salvage therapies at the time of bone marrow transplantation. Two of the* 16 *evaluable patients* (12.5%) *achieved complete remissions, and* 10 (63%) *achieved partial remissions for a total response rate of* 75%. *One patient is a long-term disease-free survivor* (*over* 1 yr). *An occasional patient may be cured by this approach. The combination of melphalan, an alternative alkylating agent to cyclophosphamide and total body irradiation are associated with moderate gastrointestinal toxicity in heavily pretreated adult patients. The combination warrants further investigation in a less heavily pretreated population to determine more accurately the complete response rate.*

INTRODUCTION

THERE ARE now many studies of high-dose chemotherapy, with and without total body irradiation (TBI) utilizing allogeneic or autologous bone marrow support in nonleukemic disorders. Increased response rates have been reported for patients with a number of different tumors, and a small number of neuroblastoma and lymphoma patients in relapse are probably cured by this approach [1–12]. The alkylating agent used most often in studies incorporating total body irradiation (TBI) has been cyclophosphamide. However, a number of relapsing patients have been continuously exposed to cyclophosphamide, and the possibility exists that there is a cyclophosphamide resistance in their tumors that decreases the drug's efficacy at escalated doses.

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Melphalan, administered at high doses ranging from 140 mg/m^2 to 220 mg/m^2, has shown a broad range of activity across multiple tumor types and has also shown activity in tumors resistant to high-dose cyclophosphamide [13–20]. High-dose melphalan, therefore, is an obvious choice as an alternative alkylating agent to cyclophosphamide in combination with TBI. A small number of pediatric patients have received melphalan–TBI combinations, but as yet no reports have been published on the toxicity of this program in adults [11, 12].

Obviously, the tolerance to bone marrow transplantation procedures is lower in adults than children, and the toxicity and mortality are much higher. We initiated a study in adults of high-dose melphalan at 100–140 mg/m^2 followed by fractionated TBI at slightly lesser doses than usual, 850 rad to reduce potentially lethal gastrointestinal toxicity. Our initial goal was to determine if this combination of intravenous melphalan and TBI at less than maximum doses was associated with acceptable toxicity in previously treated adult pa-

tients. Complete response rates were anticipated to be low because of the multiple prior therapies these patients had received. We report here our initial experience, including the toxicity and response rate, in a group of heavily pretreated adult patients with relapsed disease often progressing on a conventional salvage regimen.

MATERIALS AND METHODS

Patient eligibility

To be eligible for the study, a patient had to have histologic proof of cancer and either be in partial remission (PR) but judged to have a high potential for inevitable progression or have chemotherapy-resistant disease in relapse. The patient's life expectancy had to be at least 12 wk and his performance status two or less (Zubrod's scale). The cardiac ejection fraction had to be greater than 0.5 measured by technicium scan. Patients with compromised pulmonary function were excluded before bone marrow transplantation by evaluating their forced expiratory volume at 1 sec (FEV^1), vital capacity, and diffusion capacity. Patients were excluded if FEV^1 or vital capacity was less than 70% of predicted and the diffusion capacity less than 30% of predicted. Level of bilirubin had to be less than 2 and creatinine less than 2.5. In keeping with institutional policy, all patients signed an informed-consent form indicating their awareness of the investigational nature of the study.

Administration of chemotherapy and infused marrow

On days 1 and 2, patients received intravenous melphalan; the dose for 17 patients was 70 mg/m^2 on each day and for two patients, 50 mg/m^2 on each day, for a total dose of 140 mg/m^2 or 100 mg/m^2. Just before they began chemotherapy on day 1, their levels of serum electrolytes, blood urea nitrogen, and creatinine were determined. Patients then received 1 liter of 0.9 N saline 3–4 hr before the melphalan. Melphalan was administered in its own diluent into a rapidly flowing intravenous catheter over 15–30 min. After the melphalan infusion, hydration was continued with 5% dextrose and water (D-5W), 0.45 N saline, and supplemental potassium at a rate of 125 ml/hr for a total of 8 hr. On the morning of days 2 and 3 the levels of electrolytes, blood urea nitrogen, and creatinine were reassayed. After chemotherapy, patients had a 4-day rest period before TBI. In murine studies, this rest period is associated with reduced gastrointestinal toxicity [21].

TBI in five fractions, each of 170 rad midplane, was then administered over 3 days, using a sagittaire 25 meV linear accelerator. Patients were treated supine, to two lateral fields at a treatment distance of 3.5–4 m. The midplane dose rate was approx. 15 rad/min. This resulted in exposure times of approx. 13–14 min for each treatment. Bone marrow previously collected, cryopreserved if autologous, and thawed was infused after the last radiation dose. The details of marrow collection and cryopreservation have been described previously [22]. One half hour prior to the bone marrow infusion, 50 mg of benadryl and 500 mg of sodium methylprednisolone were administered intravenously to prevent reactions.

Supportive care

Patients were nursed in isolation in a sterile laminar flow room when available. They began taking prophylactic antibiotics after the necessary cultures had been obtained and entered the isolation room 2 days after beginning sterile food and prophylactic oral antibiotics. For autologous transplantation patient received Bactrim Metronidazole and Ketoconazole and for allogeneic transplantation, Gentamycin, Nystatin, and Vancomycin. During periods of infection, the prophylactic antibiotics were temporarily discontinued and patients received the appropriate systemic antibiotics and, in some instances, white blood cell transfusions. All blood products administered within 3 months after the bone marrow infusion were irradiated with 2500 rad in order to avoid graft-versus-host disease (GVHD). Total parental nutrition was administered to patients with persistent anorexia and weight loss.

Graft-versus-host prophylaxis

Prophylactic treatment varied during the period of the study. One regimen consisted of steroids during the first week after bone marrow transplantation followed by oral methotrexate for the first 100 days post-transplantation. In the latter part of this study we administered cyclosporin, initially intravenously, and then orally, at doses intended to achieve serum levels of approx. 200 ugm/ml. Treatment of established GVH reaction included high-dose corticosteroids.

Criteria for response and toxicity

All tumor measurements were recorded. Complete remission (CR) was defined as disappearance of all clinical evidence of tumor for a minimum of 4 weeks. The patient had to be free of all symptoms. Partial remission (PR) was defined as a 50% or greater decrease in the product of the diameters of all measured lesions with no simultaneous increase in the size of other lesions or appearance of new lesions.

RESULTS

Prior therapy

Nineteen patients were treated. The median age was 27. The diagnosis and performance status of each are presented in Table 1. Fifteen of these 19 patients had hematologic neoplasms. Tables 2, 3, and 4 list the prior therapy, response to that prior therapy, and behaviour of the disease up to the time of transplantation. Three of four patients with solid tumors, six of eight with other hematologic malignancies, and all seven with diffuse large cell lymphoma were demonstrating progressive disease despite chemotherapy prior to transplantation. Most patients had received three prior combination chemotherapy regimens plus or minus radiation therapy before they were considered for transplantation.

Response

Table 5 documents response. Of the 19 patients, 16 were evaluable for response. Two (12.5%) had CRs and 10 (63%) had PRs, for a total response rate of 75%. Of the four remaining patients, only

Table 1. Patient characteristics

Number		19
Age, median (range)		27 (21–56)
Sex M : F		12 : 7
Performance status		0 : 1 1 : 10 2 : 8
Diagnosis	Choriocarcinoma of testis	1
	Teratocarcinoma of testis	1
	Neuroblastoma	2
	Burkitt's lymphoma	1
	Non-Burkitt undifferentiated lymphoma	1
	Lymphoblastic lymphoma	1
	NPDL*	2
	Hodgkins disease	1
	Myeloma	2
	DLCL†	7

* Nodular poorly differentiated lymphoma.

† Diffuse large cell lymphoma. One patient had transformed from a cutaneous T-cell lymphoma and one from a NPDL.

Table 2. Patients with nonhematologic tumors: prior therapy and response

Patient No.	Diagnosis	Prior therapy	Response	Relapse on/off therapy	Progressive disease at transplantation
1.	Choriocarcinoma, Testis	Velban, bleomycin C-DDP (VBP)	PR	On	
		AMSA	Prog	On	Yes
		VP-16 & C-DDP	Prog	On	
2.	Teratocarcinoma, Testis	VBP	PR	On	
		CYT, Actinomycin, C-DDP	Prog	On	Yes
		CYT & ADR	Prog	On	
3.	Neuroblastoma	CYVADIC	PR	Off	
		CYT & C-DPP, local XRT	Stable	On	Yes
		VP-16	Prog	On	
4.	Neuroblastoma	CYVADIC	PR		No

C-DDP = *Cis-* Diamminedichloroplatinum
AMSA = Acridinyl anisidide, methanesulfon-m-anisidide, 4'-(9-acridinylamino)
VP-16 = Etoposide
VBP = Velban, bleomycin, *cis*-platinum
CYT = Cyclophosphamide
ADR = Adriaycin
CYVADIC = Cyclophosphamide, vincristine, adriamycin, darcarbazine

Table 3. Prior therapy and response of patients with hematologic malignancies excluding diffuse large cell lymphoma

Patient No.	Diagnosis	Prior therapy	Response	Relapse on/off therapy*	Progressive disease at transplantation
1.	Burkitt Lymphoma	VAD	PR	On	
		M-COAP	CR	On	No
		CYT Adria Prednisolone	CR		
2.	Lymphoblastic Lymphoma	M-COAP	PR		
		IMVP-16	PR		Yes
		HOAP BLEO	Prog	On	
3.	Lymphoblastic Lymphoma	M-COP	Prog	On	
		ADOAP	Prog	On	Yes
		HD ARA-C + Decadron	≤ PR	On	
4.	NPDL	Chlorambucil	PR	On	
		BACOP	Prog	On	No
		CCNU, CYT, VCR, VP-16	≤ PR		
5.	NPDL	CHOP BLEO	PR	On	
		Local XRT	CR	Off	Yes
		CHOP	PR	On	
6.	Hodgkins	MOPP	CR	Off	
		BCAV	CR	Off	Yes
		CBV + Autologous marrow	PR	Off	
7.	Myeloma	VCR, CYT, L-PAM, Prednisone Adria S/C ARA-C, Lower Body XRT	PR	On	Yes
		VAD	CR	On	
8.	Myeloma	VCAD-VAD	≤ PR	On	
		C-DDP	Prog	On	Yes
		High-Dose Melphalan	≤ PR	On	

VAD, vincristine, Adriamycin, high-dose decadron; M-COAP, methotrexate, cyclophosphamide, cytosine, arabinoside, prednisone; IMVP-16, ifosphamide, methotrexate, VP-16 (etoposide); HOAP BLEO, hydroxydaunorubicin, Oncovin, cytosine, arabinoside, prednisone, bleomycin; HD ARA-C, high-dose cytosine, arabinoside; BACOP, bleomycin, Adriamycin, cyclophosphamide, Oncovin, prednisolone, bleomycin; CHOP BLEO, cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisolone, bleomycin; XRT, X-irradiation, BCAV, bleomycin, CCNU, Adriamycin, vinblastine; CBV, cyclophosphamide, BCNU, VP-16 (Etoposide); S/C ARA-C, subcutaneous arabinoside; L-PAM, melphalan; CCNU, lomustine.

two showed evidence of minor regression. The median response duration has been short, 2.5 months. The two CR patients are alive and disease-free at this writing at 19+ and 7+ months. One patient who died from early sepsis, and another who was thought to be only a PR clinically but died from GVHD at 4 months had no disease at autopsy.

Hematological toxicity

Three early deaths occurred in the study, two were related to septicemia and one to early graft-versus-host disease with associated cytomegalovirus pneumonitis. We performed a total of 11 autologous bone marrow transplants (ABMT), seven allogeneic transplants, and one syngeneic transplant. In the autologous transplants, the median and range of times to reach 0.1, 0.5, and 1×10^3 granulocytes/mm^3 were 14 (11–31), 23 (11–60+), and 36 (40–60+) days, respectively. The median and range to reach 20, 50, and 100×10^5 platelets were 26 (13–128+), 26 (14+–128+), and 46 (14–

Table 4. Patients with diffuse large cell lymphomas: prior therapy and response

Patient No.	Prior therapy	Response	Relapse on/off therapy	Progressive disease at transplantation
1.	CHOP-BLEO	CR	On	
	MIME	PR	On	Yes
2.	CHOP-BLEO	PR	Off	
	ADOAP	NR	On	Yes
	CHOP-BLEO	CR	On	
3.	CHOP-BLEO/CMED	PR	On	Yes
4.	Local XRT*	CR	Off	
	CHOP-VP-16 XRT	PR	Off	Yes
	Tropical nitogen mustard local XRT	Prog		
5.	M-COP/HOAP-BLEO	CR	Off	
	MOP	PR	On	Yes
	MIME	CR	On	
6.	CHOP & upper mantal XRT	CR	On	Yes
7.	MOPP & Mediastinal XRT	Prog	On	
	CHOP-BLEO	Prog	On	Yes
	ABVD	Prog	On	
	High-dose MTX	Prog	On	

CHOP-BLEO, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone, bleomycin; MIME, methyl-GAG, isophosphamide, methotrexate, etoposide; ADOAP, Adriamycin, Oncovin, cytosine, arabinoside, prednisone; XRT, X-irradiation; VP-16, etoposide; M-COP, methotrexate, cyclophosphamide, Oncovin, prednisone; MOP methotrexate, Oncovin, prednisone; MOPP, nitrogen mustard, Oncovin, procarbazine, prednisone; ABVD, Adriamycin, bleomycin, vinblastine, dacarbazine.

128+) days, respectively; however, two patients have not totally recovered a normal platelet level after 100 days of follow-up, despite granulocyte recovery to greater than $1 \times 10^3/mm^3$. In the limited number of allogeneic transplants evaluable, the median recovery time to 0.1, 0.5 and $1 \times 10^3/mm^3$ granulocytes was shorter, 19, 20 and 25 days, respectively. The average recovery to 20 and $50 \times 10^5/mm^3$ platelets was similar, 25 days. All allogenic transplants showed signs of engraftment, despite the lower-than-usual radiation dose used in this study.

The most frequent infections were bacterial. Seven episodes of pneumonia or septicemia and one perirectal infection. Three patients developed viral infections, two cases of herpes simplex and one cytomegalovirus pneumonitis. There was also one episode of candida septicemia and a fatal aspergillus septicemia associated with GVHD. Another two patients had fevers of undiagnosed origin.

Other toxicities

Eighteen of the 19 patients showed evidence of stomatitis, seven severe and three life threatening. Sixteen patients (84%) experienced mild nausea and vomiting, 15 patients (79%) mild to moderate diarrhoea, and one patient severe diarrhoea. Nine of the patients (47%) experienced mild changes in liver function tests and five experienced severe changes; these were related to either infectious episodes or graft-versus-host disease. There was no treatment-related renal toxicity with changes in renal function occurring only during infectious episodes. No cardiac toxicity developed; pulmonary changes were related only to graft-versus-host disease or viral infection.

DISCUSSION

We have described here the first experiences with high-dose melphalan and fractionated TBI in an adult population. Melphalan is an obvious choice as an alternative alkylating agent to high-dose cyclophosphamide to combine with TBI. Melphalan at doses of 140 mg/m^2–220 mg/m^2 has shown activity across a broad number of tumor types including melanoma, Ewing's sarcoma, neuroblastoma, leukemia, and gastrointestinal cancer [13–20]. Promising activity in association with TBI and, in some instances, with other chemotherapy agents has been reported in pediatric

Table 5. Response to melphalan and total body irradiation

Response	Response duration	Survival (months)	Nature of transplantation	Cause of death
Solid tumors				
NR	–	1	Auto	Disease
≤ PR	1	3	Auto	Sepsis
PR	5	8	Allog	Disease
PR	9	13	Auto	Disease
Hematologic malignancies				
Inevaluable	–	0.5	Allog	Sepsis
≤ PR	1	2	Allog	Disease
NR	–	6	Allog	Disease
PR (no disease at autopsy)	4	4	Allog	GVH Fungi
PR	3	12+	Ident. Twin	–
Inevaluable	–	1	Allog	GVH, Interst Pneumonitis
PR	2	2	Auto	Infection
PR	1.5	2	Allog	GVH CMV Pneumonia Sepsis
Large cell lymphoma				
CR	19+	19+	Auto	–
*CR	7+	7+	Auto	–
†PR	1.5	2.5	Auto	Disease
†PR	6	6+	Auto	–
Inevaluable (no disease at autopsy)	–	1	Auto	Sepsis
PR	2	2.5	Auto	Disease
PR	1	1	Auto	Infection

NR, no response; PR, partial response; CR, complete recovery.
*Patient developed abnormal circulating cells and marrow involvement after storage and at time of relapse.
†Difficult to determine response between CR and PR. One patient with normal physical and routine radiological abnormalities but residual computerized axial tomography scan abnormalities. One patient with a difficult to interpret chest X-ray.
Patients are listed in identical order as in the previous three tables.

patients with neuroblastoma [11–12]. High-dose melphalan has also been active in patients with either neuroblastoma or myeloma (Barlogie, B., unpublished observations) previously exposed to high-dose cyclophosphamide, suggesting an absence of cross-resistance [20]. It is also more appealing than alternative alkylating agents such as busulphan, which has the potential for pulmonary and hepatic toxicity [23, 24].

The most important extramedullary toxicity was severe mucositis requiring analgesic therapy and preventing oral intake. This occurred in seven of the 19 patients, but its severity could be over estimated because of the intensive prior therapy of this patient group. We hope that, in a less heavily treated population, the melphalan dose could be further escalated to the usual single agent doses of 180 mg/m^2. However, there have been unreported cases of veno-occlusive disease in children treated with melphalan 180 mg/m^2 and TBI. Despite less than maximum doses of both melphalan and TBI, all six patients receiving allogeneic transplants showed engraftment. We did not perform studies to show mixed chimerism.

The potential response rate is hard to evaluate because of the exceptionally chemotherapy-resistant nature of the tumors treated. We should emphasize that only two of the patients transplanted and evaluable for response did not have disease that was progressive on alternate therapy at the time of transplantation. Progressive disease whilst on chemotherapy has proved to be a most important prognostic aspect for a durable response in patients with lymphoma who have relapsed and will probably apply to other diseases as well. Nevertheless, two patients with large cell lymphoma whose disease was progressing on alternate therapy at the time of transplantation are alive and disease-free at 19 and 7 months post-transplantation. Two further patients who died had no evidence of disease at autopsy. Because many patients with large cell lymphoma have been

previously exposed to combination programs containing cyclophosphamide, we believe that melphalan plus TBI should be considered for patients with relapsed large cell lymphoma. Our future plans are to (1) cautiously investigate whether the dosage of melphalan in combination with TBI can be further escalated, and (2) most importantly, whether this program has high therapeutic efficacy for large cell lymphoma at first relapse. At this time we believe that answering these questions is more valuable than continuing melphalan-TBI studies in patients whose tumors are progressing on other salvage therapies.

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