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High-dose combination cyclophosphamide, cisplatin, and melphalan with autologous bone marrow support*

A clinical and pharmacologic study

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Summary. A total of 23 patients were treated at five dose escalations with high-dose combination cyclophosphamide, cisplatin, and melphalan with autologous bone marrow support. The maximum tolerated doses of cyclophosphamide, cisplatin, and melphalan were 5,625, 180, and 80 mg/m^2, respectively. The dose-limiting toxicity was cardiac toxicity. Objective tumor regression occurred in 14 of 18 evaluable cases, with a median duration of 3.5 months. Pharmacokinetic evaluation of melphalan in 20 patients revealed a dose-related increase in maximum plasma concentration (C_{max}) and area under the curve (AUC). Perturbation of the melphalan plasma half-life and AUC, associated with severe toxicity, resulted when renal insufficiency occurred. The results suggest that high-dose combination cyclophosphamide, cisplatin, and melphalan produces frequent, rapid responses in breast cancer, melanoma, and sarcoma, although with significant extramedullary toxicity. The pharmacokinetics suggest that modification of the treatment schedule may result in a reduction of treatment-related toxicity.

Introduction

Alkylating agents have demonstrated broad clinical activity in a variety of human neoplasms and a steep dose-response relationship for both therapeutic and toxic effects. Furthermore, in human and animal experimental systems, selected alkylating agents demonstrate non-cross-resistance with other alkylating agents as well as other classes of drugs [16, 17]. Clinical studies have revealed that at escalated doses with autologous bone marrow support, the toxicities associated with selected individual alkylating agents differ [10]. These differences offer the possibility of combining several agents at maximally tolerated doses. In previous studies we have found that nearly full transplant doses of cyclophosphamide, cisplatin, and carmustine could be used in combination [14] and that the addition of melphalan produced excessive renal and gastrointestinal toxicity [13]. The appearance of nephrotoxicity was unexpected from single-agent trials, suggesting an interactive toxicity among components of the combination used. Clinical trials have implicated nitrosoureas in the production of renal toxicity [9], although the use of high-dose combination carmustine and melphalan with autologous bone marrow support did not result in renal toxicity [11].

To explore the effects of altering an individual agent in a high-dose combination regimen and to develop a high-dose combination with targeted activity toward breast cancer and melanoma, we evaluated the toxicology, pharmacology, and therapeutic effect of high-dose cyclophosphamide, cisplatin, and escalating doses of melphalan with autologous bone marrow support in patients with advanced resistant malignancies.

Methods

Patient population. Patients with metastatic cancer and sarcoma underwent an initial evaluation, including history and physical exam, histopathologic review, chest X-ray, pulmonary function tests, ECG, cardiac radionuclide-gated blood pool scanning, creatinine clearance, computerized axial tomography of the brain, bone scan, and bilateral posterior iliac crest bone-marrow aspirates and biopsies. Patients with CNS, bone or bone marrow metastases were excluded, as well as those with significant renal (creatinine >1.5 mg/dl; creatinine clearance <60 cc/min), hepatic (bilirubin ≥ 2.0 mg/dl; SGOT >2 times normal), pulmonary FEV_1, FVC, or DLCO $<65\%$ of the predicted values), or cardiac dysfunction (ejection fraction $<45\%$ or decreasing with exercise). Patient characteristics including prior therapy for metastatic disease are summarized in Table 1. The median age was 38 years (range, 15–54 years). Informed consent was obtained from all patients, and the protocol was approved by the Duke University Institutional Review Board and the Cancer Therapy Evaluation Program, National Cancer Institute.

Bone marrow harvest and storage. With the patient under general anesthesia, bone marrow was aspirated from the posterior iliac crests using modified 12-gauge Rosenthal aspiration needles and anticoagulated with preservative-free heparin. A buffy-coat concentrate of the marrow was obtained using a Cobe 2991 blood cell washer. A mean of 1.96×10^8 nucleated cells/kg were suspended in 10% dimethylsulfoxide (DMSO) and 20% autologous plasma, cryopreserved at $-1°$ C/min, and stored in vapor-phase liquid nitrogen.

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Table 1. Patient characteristics and treatment response

Dose level	UPN	Diagnosis	Age	Prior therapy	Chemotherapy given (mg/m²)				Rate of tumor regression −log (dV/dt)
					CPA dose	cDDP dose	L-Pam dose	Clinical response/outcome	
1	2	Breast cancer	36	CMF	5625	165	40	CR, 88 days; died of disease day 306	0.13
	5	Breast cancer	37	CMF/CAF/VBL/A CI	5625	165	40	NE, died therapy-related toxicity, sepsis day 20	–
	9	Melanoma	39	None	5625	165	40	PR, 114 days; died of disease day 301	0.07
2	16	Breast cancer	29	CMF, A, XRT	5625	180	40	CR, 54 days; died of sepsis day 54	0.14
	17	Melanoma	38	Immunotherapy	5625	180	40	CR, alive NED > 642 days	0.02
	21	Melanoma	40	Immunotherapy	5625	180	40	PR, 75 days; died of disease day 108	
3	31	Melanoma	40	None	5625	180	80	PR, 129 days; died of disease day 274	
	33	Osteogenic sarcoma	28	A, MTX, cDDP	5625	180	80	PR, 125 days; died of disease day 390	
	34	Melanoma	30	Surgery	5625	180	80	NR, alive with disease > 537 days	0.00
	50	Breast cancer	35	CAF, CMF	5625	180	80	PR, 152 days; died of disease day 332	0.07
	79	Breast cancer	44	XRT, CMFVP, cDDP/VP16	5625	120	80	NE, died renal failure, sepsis day 40	–
	86	Synovial sarcoma	26	CAM × 3	5625	180	80	PR, 148 days; died of disease day 204	0.05
	87	Neuroblastoma	22	Surgery, CA	5625	180	80	PR, 100 days; alive with disease > 150 days	0.03
	89	Gastric cancer	51	FAMito, cDDP/VP16	5625	180	80	NE, died *Candida* sepsis day 17	–
	97	Melanoma	32	BOLD, XRT	5625	180	80	PR, 60 days, alive with disease > 140 days	
	98	Melanoma	42	Immunotherapy	5625	180	80	NE, died CNS bleed into metastases day 11	
	104	Synovial sarcoma	15	XRT, VdAC, cDDP/VP16, DTIC	5625	180	80	PR, > 95 days	0.005
4	41	Gastric cancer	54	None	5625	180	120	NE, died acute cardiac failure day -1	–
	49	Melanoma	41	None	5625	180	120	NR, died of disease day 132	–
	53	Melanoma	38	None	5625	180	120	PR, 85 days; died of disease day 110	0.21
	58	Breast cancer	35	XRT, CMF, CAFVP	5625	180	120	PR, 108 days; died of disease day 125	0.11
5	64	Melanoma	45	None	5625	180	150	NR, died of disease day 252	–
	66	Melanoma	43	Immunotherapy, XRT	5625	180	150	NR, died of disease day 101	–

Abbreviations: A, doxorubicin; *CPA,* cyclophosphamide; *cDDP,* cisplatin; *L-Pam,* melphalan, phenylalanine mustard; *F,* 5-fluorouracil; *XRT,* radiation therapy; *A CI,* continuous infusion adriamycin; *M,* methotrexate; *DTIC,* dacarbazine; *V,* vincristine; *P,* prednisone; *Mito,* mitomycin C; *BOLD,* bleomycin, vincristine, lomustine, dacarbazine; *dA,* dactinomycin; *CNS,* central nervous system

Treatment protocol. All patients had a double- or triple-lumen right atrial catheter placed for venous access, and treatment was carried out in a private room with access via reverse isolation. Patients were provided a low bacterial, low fungal content diet. The schedule for drug administration is shown in Fig. 1.

Cyclophosphamide was given in a 1-h infusion on days -6 to -4. Cisplatin was given in a 72-h continuous i.v. infusion on days -6 through -3. Melphalan was given on day -4 in a 1-h infusion through unique patient number (UPN) 41 and as a 2-h infusion thereafter; it was given at four dose levels, with at least two patients at each dose level. The doses of cisplatin and cyclophosphamide were those determined to be maximally tolerated in prior studies, and the schedules selected were comparable to those in our previously reported experience [10, 14, 15]. Continuous-infu-

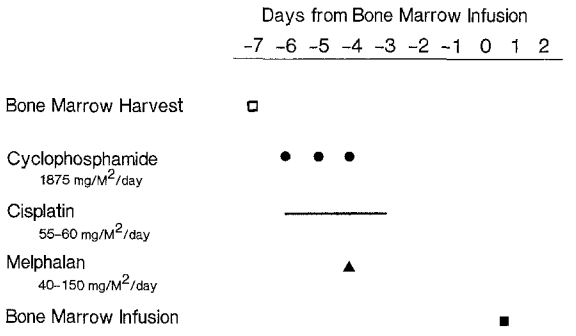

Fig. 1. Protocol for drug administration and bone marrow infusion, following therapy. Cyclophosphamide was given in 1-h infusions equally divided on each of the first 3 days of treatment. Cisplatin was given as a continuous i.v. infusion over 24 h on each of the first 3 days of treatment. Melphalan was given as an i.v. infusion and escalated as a single drug. Doses for all agents are given in Table 1. Bone marrow reinfusion was carried out at the end of day 0

sion perphenazine or metaclopromide, benadryl, and lorazepam were used as antiemetics. After UPN 64, perphenazine was no longer used because of associated high-grade heart block occurring in three patients, two of whom required temporary pacemaker placement [6]. Bladder irrigation using saline containing neomycin (80 mg/l) and polymyxin B (400,000 IU/l) was carried out until 24 h after the last dose of cyclophosphamide.

Bone marrow infusion and supportive care. On the 3rd day following the completion of chemotherapy, the bone marrow was thawed rapidly at 37° C at the patient's bedside and rapidly infused without further treatment. All blood products given were irradiated with 1500 cGy, and RBCs were transfused to maintain a hematocrit >42%. Single-donor, irradiated leukocyte-poor platelets, human leukocyte antigen (HLA)-matched if appropriate, were given to maintain a count $>20{,}000/mm^3$.

Full staging evaluations were carried out before study entry and at the time of hospital discharge. Serial determinations of tumor size were done by caliper measurement of skin and lymph node areas and those of pulmonary disease, by chest radiograph. Complete (CRs) and partial responses (PRs) required 100% and 50%–99% reduction in the product of perpendicular diameters of measurable lesions, respectively. Patients dying of toxicity before day 30 were considered not evaluable for response.

Pharmacokinetics. Blood samples (7 ml) were obtained from a peripheral heparin lock and collected in iced tubes containing 100 IU heparin; they were taken just prior to the start of melphalan infusion and at 15-min intervals throughout the infusion. Beginning at the end of the infusion, samples were collected at 5-min intervals until 75 min, and then at 2, 4, and 6 h after completion of the infusion. Plasma was separated by centrifugation at 4° C and stored at −70° C until analysis.

Melphalan plasma levels were determined by a modification of an HPLC technique based on the method of Flora et al. [5]. Plasma (0.5 ml) was deproteinized with perchloric acid (22 µl) after the addition of dansyl-proline (50 µg/ml) as an internal standard. After centrifugation (1000 g, 10 min) and filtration (0.22 µm, Millipore, Waltham, Mass), HPLC chromatography was carried out by injecting 40 µl filtrate on a 150×4.6 mm reverse-phase C18-µBondapack column (Waters Associates, Milton, Mass). Isocratic elution was done using 25:75 acetonitrile: 2% acetic acid, with UV detection at 254 nm. Quantitation was carried out by the construction of a standard curve of the ratio of peak area of melphalan to internal standard vs the known concentrations of standard plasma samples run simultaneously with the unknown samples. Pharmacokinetic modeling was done using a nonlinear regression computer program (PCNonlin, Statistical Consultants, Lexington, Ky), assuming a one-compartment model for melphalan disposition with continuous i.v. infusion.

Results

In all, 23 patients received combination chemotherapy with cyclophosphamide, cisplatin, and melphalan at five dose escalations (Table 1). The maximum tolerated doses for this combination and schedule were 5625, 180, and 80 mg/m^2, respectively.

Acute toxicity

All patients experienced moderately severe nausea and vomiting during chemotherapy. Two patients (UPN 5 and 66) developed third-degree heart block associated with episodes of nausea and vomiting requiring temporary transvenous pacemaker placement in one patient (UPN 66); these episodes were attributed to perphenazine administration [6]. Acute cardiac failure occurred in one patient, resulting in death on day -1; postmortem examination revealed a diffuse hemorrhagic myocarditis similar to that observed with cyclophosphamide alone [18, 19] or in combination [3, 7]. One patient experienced an acute deterioration of mental status resulting from a large cerebral hemorrhage within 48 h of completing chemotherapy and died on day +11. Postmortem examination revealed hemorrhage into one of multiple metastatic melanoma lesions that had not been detected by pretreatment computerized axial tomography of the brain.

Myelosuppression

The duration and extent of myelosuppression was not dose-related. The median time to recovery of leukocytes (WBC >1000/µl) was 17.1 ± 6.5 days, with the median time to platelet transfusion independence being 21 days. Patients required an average of 21.5 platelet transfusions (range, 3–66). There were four episodes of hemorrhage: two into previously unsuspected CNS metastatic melanoma lesions; one pulmonary hemorrhage; and one clinically unsuspected, small subdural hematoma detected during evaluation of a confusional state. Two patients (UPN 53 and 59) required a second infusion of bone marrow to develop sustained marrow function; one had been heavily pretreated with cisplatin and developed acute renal failure during treatment, and the other lost marrow function after treatment with trimethoprim-sulfamethoxazole for a pulmonary infiltrate. Both patients recovered with supportive care.

Infection

Fever above 38.3° C developed in all treated patients. In all, 21 culture-proven infections developed in 13 patients during myelosuppression, including three cases of *Candi-*

da septicemia and two of pneumonia (one *Aspergillus* and one *Herpes simplex*), based on culture and lung biopsy showing multinucleate giant cells. As shown in Table 2, there were 11 cases of bacteremia, including *Pseudomonas aeruginosa, Staphylococcus epidermidis, Enterococcus,* and *Streptococcus viridans.* Four patients developed *H. simplex* infections, all of which responded to treatment with acyclovir.

Cardiac toxicity

Symptomatic volume overload that occurred in nine patients during therapy was managed by diuresis. Decreased electrocardiac R-wave voltage of >25% in leads I, II, and AVF was seen in 19 of 23 (82%) evaluable patients. Echocardiographic evidence of pericardial effusion was found in five patients (21%); it resulted in hemodynamic compromise requiring pericardiocentesis in two. Serial left ventricular ejection fractions (LV EF) were evaluated by multigated radionuclide angiography in 17 patients. Six patients (35%) developed reductions in LV EF of >10% during therapy; two of these returned to normal limits. Two of the remaining four patients died, one of hemorrhagic myocarditis and the other, of *Candida* sepsis with evidence of intramyocardial hemorrhage and fungus; the third and fourth patients were discharged with symptomatic and asymptomatic cardiomyopathies, respectively. Clinically significant hypertension did not occur, in contrast to our previous experience with high-dose combination cyclophosphamide, cisplatin, and carmustine [10, 14].

Table 2. Major and life-threatening toxicity (deaths) by dose level

Dose level	1	2	3	4	5	Total
Patients (*n*) treated	3	3	11	4	2	23
Total deaths	1	1	3	1	0	4
Toxicity:						
Cardiac						
EKG voltage decrease	2	2	9	4	2	19
LV EF decrease	0	1	2	2	1	6
Pericardial effusion	0	0	2	2	1	5
Cardiomyopathy	0	0	1	0	1	2
Hemorrhagic myocarditis	0	0	1	1 (1)	0	2
Hemorrhage						
Gastrointestinal	0	0	0	0	0	0
CNS	0	1	1 (1)	1	0	3
Pulmonary	0	0	0	1	0	1
Infection						
Bacterial sepsis	1	3 (1)	6	0	1	11
Fungal						
Candida	1 (1)	1	1 (1)	0	0	3
Aspergillus	0	0	1 (1)	0	0	1
Viral						
H. simplex	1	1	1	1	0	4
H. zoster	0	1	0	0	0	1
Cytomegalovirus	0	0	0	0	1	1
Hepatic						
Bilirubin >5 mg/dl	1	2	6	3	1	13
Bilirubin >10 mg/dl	0	1	2	1	1	5
Toxic hepatitis	1	1	1	0	0	3
Gastrointestinal						
Stomatitis	0	0	1	1	0	2
Diarrhea >1.5 l/day	0	0	0	0	1	1
Renal						
Creatinine 1.5–3 mg/dl	1	1	5	2	1	10
Creatinine >3.0 mg/dl	0	0	2	1	0	3
Proteinuria >2.0 g/24 h	3	0	4	3	2	12
Other						
Disorientation	0	0	1	0	1	2
Pleural effusions	1	0	1	0	0	2
Pulmonary emboli	0	0	0	1 (1)	0	1
Erythematous rash	1	1	2	1	1	6
Vocal cord edema	0	0	1	1	0	2

Abbreviations: EKG, electrocardiogram; *LV EF,* left ventricular ejection fraction; *CNS,* central nervous system. Dose levels are defined in Table 1; deaths may have more than one cause

Hepatic toxicity

Nine patients (39%) developed elevations in SGOT >60 IU during the 1st week following therapy; eight (88%) of these subsequently developed serum bilirubin elevations to >5 mg/dl during their courses. Of the 14 patients who did not show early SGOT elevations, 5 (35%) developed bilirubin elevations to >5 mg/dl and 5, bilirubin elevations to >10 mg/dl. Despite the frequency of hyperbilirubinemia, transaminase elevations to >150 IU occurred in only five patients and were not correlated with increased bilirubin. Pathologic examination of three patients revealed centrilobular necrosis; veno-occlusive disease was not documented in any patient. Hepatic toxicity was felt to be a major contributor to death in two patients.

Renal toxicity

An early rise in serum creatinine to >1.5 mg/dl was seen in 10 of 23 patients (43%), with 4 of 23 patients developing creatinine elevations >3.0 mg/dl. Two patients developed acute renal failure during chemotherapy; one had previously undergone extensive therapy with cisplatin and had a pretreatment creatinine clearance of 61 cc/min, and the other had no predisposing factors; both patients had a delayed plasma clearance of melphalan and died of therapy-related toxicity. Asymptomatic proteinuria >2.0 g/24 h was observed in 13 (56%) patients; it was maximal 1 week following therapy and resolved by the time of hospital discharge in all patients. Protein electrophoresis revealed that the predominant urinary protein was albumin.

Gastrointestinal toxicity

All patients experienced mild to moderate nausea and vomiting during therapy. Mucositis severe enough to prevent oral intake occurred in only two patients, and diarrhea lasting more than 2 days with fluid loss exceeding 1500 ml/day occurred in one.

Other toxicities

An erythematous macular rash developed at the time of initial leukocyte return in six patients (26%); it flared and then generally resolved over 72–96 h without specific therapy or alteration of medication. Biopsy of the rash revealed nonspecific lymphocytic infiltration of the dermis. Severe hoarseness and aphonia resulting from vocal cord edema occurred in two patients 10–20 days after marrow infusion and resolved without specific therapy. Disorientation developed in two patients during periods of significant metabolic abnormalities that cleared slowly after complete correction of the serum chemistries.

Table 3. Pharmacokinetics of high-dose melphalan in combination with CPA and cisplatin

Melphalan dose (mg/m^2)	No.	AUC (μg min/ml)	$t_{1/2}$ (min)	C_{max} (μg/ml)
40	5	50.2±14.7	20.5±8.9	0.07±0.23
80	9	120.5±52.0	30.5±9.7	1.21±0.46
120	3	188.5±11.7	29.9±3.7	1.46±0.06
150	2	199.4± 5.7	24.7±3.6	1.59±0.01
All	19	121.1±63.6	27.1±9.3	1.16±0.45

Abbreviations: No., number patient treatment courses analyzed; *AUC*, area under the curve; $t_{1/2}$, half-life; C_{max}, maximum plasma concentration reached. All derived pharmacokinetic values are expressed ± SD

Melphalan pharmacokinetics

Plasma melphalan levels in 20 patients were assayed using HPLC reverse-phase chromatography. Table 3 shows the derived mean pharmacokinetic values for the four dose levels of melphalan. The composite plasma half-life measured for all patients was 27.1 min. Plasma AUC values increased linearly (r = 0.72) with the dose (Fig. 2), as did C_{max} (r = 0.89). Two patients developed acute renal failure and displayed a prolonged melphalan plasma half-life, which in one case could not be estimated with the plasma samples obtained; the latter patient died 4 days later of hemorrhagic myocarditis.

Antitumor effect

In all, 18 treatment courses were evaluable for response; the data are summarized in Table 1. Of the 18 patients, all have relapsed or died except 2 (1 with melanoma at 23+ months and 1 with sarcoma at 4+ months). Excluding early deaths, 14 of 18 patients (78%) showed objective clinical evidence of response to therapy. Despite extensive previous treatment, all of the evaluable patients with breast cancer responded to therapy. Three patients with large-volume, drug-resistant sarcomas responded to this high-dose melphalan-containing regimen. In general, the duration of response in these patients with resistant disease was short (median, 3.5 months; range, 2−23+), as was survival (median, 7.9 months; range, 2−23+). The rate of tumor volume regression (-log dV/dt) [10] calculated from serial caliper measurements of tumors ranged from 0.07 to 0.14 for patients with breast cancer and from 0.02 to 0.21 for patients with melanoma. The observed responses were rapid, with maximal tumor regression attained by day 45 after therapy in all cases except one patient with synovial sarcoma (UPN 104).

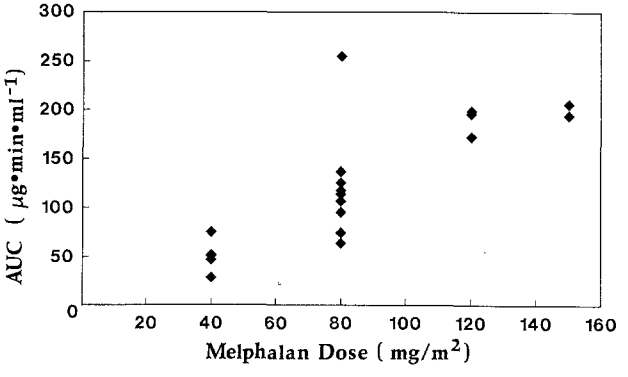

Fig. 2. Relationship of the plasma melphalan area under the curve (AUC) to the melphalan dose in mg/m^2. Points represent the AUC estimated from melphalan plasma levels for individual patients treated at the various dose escalations

Discussion

This trial was undertaken to determine the effect of modifying a single drug in a treatment program using a high-dose combination of alkylating agents. We have previously reported a phase I trial of cyclophosphamide, cisplatin, and carmustine [10]; the present trial explores the effects of substituting melphalan for carmustine. The results demonstrate that this high-dose combination of cyclophosphamide, cisplatin and melphalan with autologous bone marrow support produces frequent and rapid responses, with dose escalation limited primarily by cardiotoxicity. We estimated the maximum tolerated doses of cyclophosphamide, cisplatin, and melphalan to be 5625, 180, and 80 mg/m^2, respectively, when used as described in this report. At this dose level, toxicity either was not dose-related (infectious complications, hemorrhage into CNS tumors) or was reversible with standard clinical management. However, above this dose level, toxicity was generally more severe and difficult to manage. The limited number of patients studied complicates a more precise definition of the maximum tolerated dose. Evaluation of the role of the marrow autograft in shortening the period of myelosuppression was not undertaken in this study.

The development of cardiotoxicity may reflect an overlapping toxicity of melphalan with cyclophosphamide, both bis-chloroethylamines. Cardiotoxicity has been reported with cyclophosphamide used at high doses alone [19] or in combination [3, 7]. However, the dose used in this study was 75% of the cyclophosphamide dose generally associated with cardiotoxicity. Even in high-dose studies with bone marrow support, melphalan has not been associated with cardiotoxicity as a single agent [4, 12]. In previous studies, we did not observe cardiotoxicity with comparable doses in using the combination of cyclophosphamide, cisplatin, and carmustine [10, 14]. The frequency of reductions in EKG R-wave voltage and the left ventricular ejection fraction and of the development of pericardial effusions and hemorrhagic myocarditis suggests that myocardial injury is common with this combination of agents. However, as with cyclophosphamide alone, a component of the injury appears to be reversible, since EKG voltage and left ventricular ejection fractions frequently returned to baseline following therapy. The cardiotoxicity tended to be more severe at higher melphalan doses, although manifestations occurred at all dose levels. Manifestations of cardiac injury occurred as commonly in patients who had previously undergone anthracycline therapy as in those who had received no prior therapy.

Massive proteinuria (>2 g/24 h) was an unexpected toxicity commonly encountered in this trial; it was transient and unassociated with other manifestations of renal injury, resolving in all cases by the time of discharge from the hospital. Reductions in glomerular filtration rate were less common with this combination than those previously encountered with cyclophosphamide, cisplatin, and carmustine [10, 14]. The data reported in this trial suggest that

the severe nephrotoxicity encountered previously [14] with the combination of cyclophosphamide, cisplatin, carmustine, and melphalan may reflect overlapping toxicity at both the tubule and glomerulus. The removal of a tubular nephrotoxic component (carmustine) may be responsible for the reduced tubular toxicity of the regimen reported here. Although transient glomerular toxicity was frequent, it appeared to be of little clinical significance. Hepatic toxicity manifesting as isolated hyperbilirubinemia also occurred frequently but generally resolved without specific clinical intervention. Veno-occlusive disease was not observed. The nature of the toxicities encountered by the substitution of melphalan for carmustine suggests that the dose-limiting toxicities of high-dose combination chemotherapy are not easily predictable from single-agent studies [6].

The pharmacologic behavior of melphalan in this combination was similar to that previously observed when it was given as a single agent [1, 8, 20]. The AUC and maximal plasma concentration were linearly related to the dose and generally appeared unaffected by the other drugs in the combination. However, in two cases in which patients developed renal failure during treatment, the plasma elimination of melphalan was delayed and was associated with significant extramedullary toxicity. Plasma clearance of melphalan has previously been demonstrated to be dependent on renal function [2]. These data suggest that because cisplatin may induce renal dysfunction and alter melphalan clearance, the latter might more safely be given prior to cisplatin administration. The plasma half-life of melphalan in the present study was shorter (27.1 min) than that reported previously (50, 78, and 108 min), which may be due to simultaneous aggressive saline diuresis (3 l/m^2 per day) and furosemide used to prevent complications due to cyclophosphamide and cisplatin or to other factors. Forced diuresis has been shown to shorten the mean plasma clearance of melphalan in children but not adults [20].

In the present study of patients with malignant diseases refractory to standard therapy, the frequency of objective response (78%) was gratifying, although the duration of unmaintained remission was a median of 3.5 months, with only one response in excess of 1 year. Responses of breast cancer patients were frequent and rapid, with two of four evaluable patients achieving a complete response; responses of melanoma patients were generally partial and of short duration, although one patient remains free of disease after almost 2 years.

The occurrence of major organ toxicity at doses of melphalan substantially less than that achievable by melphalan alone suggests that our ability to modify therapeutic regimens by drug substitution may be limited [15]. Nevertheless, therapeutic responses to high-dose therapy are rapid and often substantial, even in patients who have previously received substantial chemotherapy. However, in this patient population the duration of remission was limited, suggesting either that the disease bulk was too great or that the tumors had intrinsic resistance that could not be overcome by dose-intensified therapy. The role of high-dose therapy with autologous marrow support should most appropriately be critically evaluated in early disease settings, and a formal definition of the therapeutic response to high-dose therapy alone as well as in combination with induction chemotherapy is essential.

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