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A phase I/II study of high-dose cyclophosphamide, cisplatin, and thioTEPA followed by autologous bone marrow and granulocyte colony-stimulating factor-primed peripheral-blood progenitor cells in patients with advanced malignancies

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Abstract The purpose of the present study was to determine the maximally tolerated dose of thioTEPA given with fixed high-dose cyclophosphamide (CPA) and cisplatin (cDDP) followed by autologous bone marrow (ABM) with or without granulocyte colony-stimulating factor (G-CSF)-primed peripheral-blood progenitor cells (PBPCs) in patients with advanced malignancies. Patients were required to have histologically documented malignancies and adequate renal, hepatic, pulmonary, and cardiac function. CPA was given at 1,875 mg/m^2 per day as a 1-h i.v. infusion for 3 consecutive days, and cDDP was given at 55 mg/m^2 per day as a 24-h continuous i.v. infusion over 3 days concurrently with CPA. ThioTEPA was given once as a 1-h i.v. infusion (300–900 mg/m^2) either following (the first 13 patients) or prior to CPA and cDDP. In all, 31 patients received PBPCs. A total of 46 patients were treated. There were 6 deaths among the 15 patients who did not receive PBPCs (13 received thioTEPA following CPA and cDDP). Among the other 31 patients who received PBPCs (all of whom also received thioTEPA prior to CPA and cDDP), there were 4 deaths, all involving patients with refractory ovarian carcinoma. The main toxicities were mucositis, esophagitis, hepatotoxicity, and nephrotoxicity. The median time required to achieve an absolute neutrophil count of 500 μl was 10 days (range, 9–12 days) for those who received PBPCs and 15 days (range, 15–34 days) for those who did not receive PBPCs. Altogether, 47% of the major organ toxicities (grades 3 and 4 renal, hepatic, and cardiac toxicities) occurred among the 15 patients who did not receive PBPCs, although these patients received thioTEPA at the lowest 2 dose levels. There were 3 complete responses and 22 partial responses among 35 evaluable patients (overall response rate, 71%), with the median duration of response being 3.5 months (range, 2–17 months). The maximally tolerated dose of thioTEPA was 600 mg/m^2 given as a 1-h i.v. infusion on the day prior to CPA and cDDP administration. The combination of high-dose CPA, cDDP, and thioTEPA is a well-tolerated regimen when thioTEPA is given prior to CPA and cDDP and when the combination also includes PBPCs in addition to ABM. This regimen is active in a variety of malignancies.

Key words Bone marrow transplantation · Phase I/II trial · Chemotherapy

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Introduction

Alkylating agents are among the most commonly used drugs in high-dose regimens, followed by autologous cellular support [1–11]. This is based on the observation that alkylating agents have a steep dose-response curve both in vitro and in vivo [1, 2]. Although

myelosuppression is a common side effect of all alkylating agents, the non-hematologic toxicities induced by these drugs are often nonoverlapping [3–11]. The non-hematopoietic dose-limiting toxicities include mucositis and hepatotoxicity for melphalan [4], mucositis and neurotoxicity for thioTEPA [5], hepatic and pulmonary toxicities for carmustine (BCNU) [6], cardiotoxicity for cyclophosphamide [7–9], and renal and neurologic toxicity for ifosfamide [6]. One of the first high-dose combinations of alkylating agents to be tested comprised cyclophosphamide, cisplatin, and BCNU [7]. This is the most commonly used combination in most of our high-dose protocols at Duke University Medical Center. In 1986, another combination of cyclophosphamide, cisplatin, and thioTEPA was investigated in an attempt to decrease the morbidity and mortality associated with the combination of cyclophosphamide, cisplatin, and BCNU. ThioTEPA was substituted for BCNU to decrease the incidence of interstitial lung disease [17] and because of the synergism between cisplatin and cyclophosphamide or thioTEPA that had been shown in vitro [12]. A lack of cross-resistance among these agents had also been demonstrated [13].

Oxidative desulfuration of thioTEPA by hepatocytes results in the production of TEPA, an active alkylating metabolite. Studies conducted in rodents have demonstrated that this process produces a suicide inactivation of P-450 enzymes [14]. These data produce concern because they imply that clinical administration of high doses of thioTEPA may yield saturable drug clearance and, hence, exaggerated toxicity.

Cyclophosphamide and cisplatin were given at doses that had been studied by us in a previous trial and found to produce acceptable toxicity [7–9]. ThioTEPA was added in escalating doses to evaluate the safety and toxicity profile of this combination. The maximally tolerated dose of thioTEPA was defined as 600 mg/m^2 given i.v. over 1 h 1 day prior to the start of cyclophosphamide administration at 1,875 mg/m^2 per day as a 1-h i.v. infusion on 3 consecutive days and of cisplatin at 55 mg/m^2 per day as a 24-h continuous i.v. infusion over 3 days concurrently with cyclophosphamide.

Patients and methods

Patient selection

Patients were eligible when they had histologically confirmed malignant tumors for which established curative or palliative treatment modalities were unavailable. Other eligibility criteria included adequate hepatic (serum levels of bilirubin and liver transaminases amounting to less than 2 times the upper limit of the normal range), renal (serum creatinine levels of less than 1.2 mg% and creatinine clearance equal to or greater than 60 ml/min), pulmonary (the forced vital capacity, forced expiratory volume in 1 s, and diffusing capacity of the lung for carbon monoxide being greater than 60% of the predicted values), and cardiac (ejection fraction equal to or greater than 45%) function; normal peripheral blood counts at the time of bone marrow harvest; a negative computed tomography (CT) scan of the head for active metastatic parenchymal disease; bilateral posterior iliac-crest bone-marrow aspirations and biopsies showing no evidence of cancer; and the absence of human immunodeficiency virus antibody and hepatitis B antigen as well as active infection at the time of bone marrow harvest. All patients had to have a Karnofsky performance status greater than 70%. Informed consent was obtained from all patients, and the study was approved by the Duke University Institutional Review Board.

Treatment program

The high-dose chemotherapy program included cyclophosphamide given at 1,875 mg/m^2 per day (for a total dose of 5,625 mg/m^2) as a 1-h i.v. infusion on 3 successive days [days -6, -5, and -4 from the day of bone marrow infusion (day $+1$)] and cisplatin given at 55 mg/m^2 per day (for a total dose of 165 mg/m^2) as a 72-h continuous i.v. infusion (days -6, -5, and -4). ThioTEPA was given as a 1-h i.v. infusion in escalated doses, as shown in Table 1, on either day -4 (first 13 patients) or day -7.

Patients were transfused with PRBC to maintain a hematocrit greater than 42% until leukocyte recovery. Aggressive i.v. hydration and continuous bladder irrigations were utilized for prevention of renal and bladder toxicity as previously described [20].

Cellular support

Bone marrow

As described elsewhere [8], all patients underwent bone marrow harvesting from the posterior iliac crest while under general or regional anesthesia. Bone marrow was thawed rapidly at 37°C in a water bath and infused over 10 min without further processing through the central venous catheter on day $+1$.

Peripheral-blood progenitor cells

In addition to bone marrow, 31 patients received granulocyte colony-stimulating factor (G-CSF)-primed peripheral-blood progenitor cells (PBPCs; patients entered between 1991 and 1994). G-CSF (Filgrastin; Amgen, Inc., Thousand Oaks, Calif.) was given at a dose of 5 μg/kg per day for 8 days by s.c. injection, and the PBPCs were

Table 1 Dose-escalation schedule for high-dose cyclophosphamide, cisplatin, and thioTEPA

Agent (mg/m^2)	Dose level				
	1	2	3	4	5
Cyclophosphamide[a]	5,625	5,625	5,625	5,625	5,625
Cisplatin[b]	165	165	165	165	165
ThioTEPA[c]	300	450	600	750	900

[a] Infused i.v. over 60 min on days -6, -5, and -4 (day $+1$ is the day of bone marrow infusion)
[b] Given over 24 h as a continuous i.v. infusion on days -6, -5, and -4
[c] Infused i.v. over 60 min, either on day -4 (in 13 patients) or on day -7 (in 33 patients)

harvested via leukapheresis on days 6, 8, and 9. One-third of the available G-CSF-primed PBPCs were given on the day of the bone marrow infusion (day + 1) and for 2 days prior to that (days − 1 and 0).

G-CSF administration

After high-dose chemotherapy the i.v. administration of G-CSF at a dose of 16 μg/kg per day over 4 h was begun on the 1st day of PBPC infusion (day − 1) among patients who had PBPCs harvested. G-CSF was discontinued when the absolute neutrophil count (ANC) was greater than 2,500/μl on 3 consecutive days.

Supportive care

Single-donor platelets were given to maintain a platelet count greater than 25,000/μl, if possible. Daily cultures were performed for bacterial and fungal infection if a patient's temperature was greater than 38.3°C and was not associated with blood products or amphotericin B administration.

Sample collection and pharmacokinetic methodology

Concentrations of thioTEPA were determined from plasma samples collected prior to the infusion and at the following times in relation to the onset of infusion: 0.5, 1.0, 1.2, 1.3, 1.5, 2, 2.5, 3, 5, 9, and 13 h. ThioTEPA was analyzed by published chromatographic methods following storage at − 70°C [15, 16].

A two-compartment model with zero-order input and first-order elimination was fit to the individual time-concentration data sets using weighted nonlinear least-squares regression, although some data sets were best described by one- or three-compartment models ($n = 2$ and 1, respectively). The area under the concentration-time curve (AUC) was calculated by trapezoidal methods with extrapolation to infinity using the residual concentration and terminal elimination rate constant. Linear regression and the Mann-Whitney test were used for pharmacodynamic and pharmacokinetic comparisons at different doses.

Evaluation of response to therapy and toxicity

Response to therapy

Standard response criteria were used [7]. Patients who died early of toxicity (within 60 days from the day of bone marrow infusion) were considered inevaluable for response. In patients with bone disease, response was evaluated on the basis of measurable disease as long as there was no progression in the preexisting bony lesions. Response duration and overall survival were determined for all patients as of October 1994 from day + 1 (day of bone marrow infusion) to disease progression or death, respectively. The time to hematologic reconstitution was measured from the day of bone marrow infusion (day + 1) to the recovery of an ANC equal to or greater than 500/μl with transfusion independence for platelets (equal to or greater than 25,000/μl).

Toxicity

Toxic effects were evaluated according to the Cancer and Leukemia Group B (CALGB) classification; the toxicity grade reflects the most severe degree or the most abnormal laboratory value encountered during the evaluated period.

Results

Patients' characteristics

A total of 46 patients were treated on this trial between March 1986 and August 1994. The characteristics of the patients are shown in Table 2.

Toxicity

Hematologic toxicity

One patient was inevaluable for myeloid engraftment due to death on day − 2 secondary to acute hemorrhagic myopericarditis. Eight of the nine patients dying early who were evaluable for platelet engraftment never fully engrafted their platelets prior to their death (days + 21, + 25, + 30, + 30, + 33, + 33, + 34, and + 52). All of these patients died secondary to

Table 2 Characteristics of treated patients

	Number	%
Number of patients treated	46	100
M/F	6/40	13/87
Age (years):		
Median	41	
Range	25–58	
Prior therapy:		
Chemoterapy	29	63
Chemotherapy and radiation	9[a]	20
Surgery and/or radiation	3	6
Only prior adjuvant chemotherapy	3	6
Immunotherapy	2	4
Chemotherapeutic regimens in the metastatic setting[b]:		
1	17	37
2	12	26
3 or more	9	20
Histology:		
Breast	25	54
Ovary	15	33
Melanoma	4	9
Colon	2	4
Predominant site of metastases[c]:		
Visceral	44	96
Soft tissue[d]	2	4

[a] 2 patients received ^{32}P i.p.
[b] 11 patients received in addition 1 or 2 chemotherapeutic regimens in the adjuvant setting
[c] 6 patients had bone involvement in addition to other measurable sites
[d] Lymph nodes and chest wall, each in 1 patient

Table 3 Peripheral blood cell recovery after high-dose cyclophosphamide, cisplatin, and thioTEPA (*NA* Not applicable)

Dose level	Number of patients		Median number of days to achieve ANC > 500 mm^3 (range)[a]	Median number of platelet transfusions (range)
	Total	Those who received PBPCS		
1	9	0	17 (15–34)	22 (15–110)
2	17	11	11 (9–30)[b]	17 (6–105)
3	15	15	11 (9–12)	26 (8–78)
4	3	3	9 (9–12)	27 (33–79)
5	2	2	NA (10, 11)	28 (11, 45)

[a] Day + 1 is the day of bone marrow infusion
[b] Patients who did not receive PBPCs recovered their ANC of 500/mm^3 or more cells in 13–30 days, whereas those who received G-CSF-primed PBPCs recovered their ANC of 500/mm^3 or more cells in 9–11 days

multiorgan failure with or without systemic infection. As a result, delayed platelet engraftment could have been secondary to the ongoing systemic process(es). Four patients required reinfusion of backup bone marrow on days + 22, + 25, + 79, and + 23 and engrafted their platelets after 11, 46, 15, and 4 days from the day of reinfusion, respectively. The median number of days required to achieve an ANC greater than or equal to 500/μl and the number of platelet transfusions given are shown in Table 3 by dose level. The first 15 patients (all the 9 patients treated on level 1 and 6 of the 17 patients treated on level 2) did not receive G-CSF-primed PBPCs and, as a result, the median numbers of days needed to achieve an ANC greater than or equal to 500/μl were 17 or 18 days on level 1 and 9, 10, or 11 days on levels 2–5. In fact, all patients treated on levels 3–5 who received PBPCs engrafted their neutrophils between days 9 and 12.

Other toxicities

There were ten early deaths during the study. On day − 2, one patient died secondary to acute hemorrhagic myopericarditis. This complication has been associated with high-dose cyclophosphamide [17]. Autopsy revealed severe biventricular dilation with bleeding into the myocardium. Electron microscopy revealed interstitial hemorrhage, and the mitochondria were swollen with cristae disruption. This patient was inevaluable with regard to toxicities of the gastrointestinal tract because she died prior to the onset of such toxicities. All of the other nine patients died secondary to multiorgan failure with or without systemic infection.

Almost all patients had mild to moderate degrees of nausea and/or vomiting, which were controlled by different regimens that were in use at the time patients were admitted to the unit. Most patients had mild to moderate diarrhea, which was controlled by commonly used agents, although one patient required treatment with octreotide. In all, 26 patients (58%) developed grade 3 or 4 stomatitis and/or esophagitis, requiring either narcotics to eat or total parenteral nutrition (Table 4). This toxicity was seen across all levels. Eight patients developed grade 3 or 4 nephrotoxicity and four required hemodialysis. Three of the eight patients concomitantly developed veno-occlusive disease of the liver, and all three of these patients died. Four patients who required hemodialysis were among the patients treated on dose levels 1 and 2 who did not receive G-CSF-primed PBPCs. Of 18 patients who developed hepatotoxicity, 13 were treated on dose levels 1 and 2. Three patients developed cardiotoxicity, which consisted of severe congestive heart failure, supraventricular tachycardia, and hemorrhagic myopericarditis in 1 patient each. Five patients developed grade 3 or 4 neurotoxicity, which mainly manifested as decreased sensorium and disorientation. One patient developed seizures, but that occurred in the setting of acute renal failure.

Infection

All patients developed fever during either the chemotherapy or the period of bone marrow aplasia. In all, 22 patients had positive blood and/or urine cultures, 15 had positive blood cultures (4 with gram-positive cocci, 4 with gram-negative rods, 4 with both gram-positive cocci and gram-negative rods, and 3 with fungi), and 9 had positive urine cultures (4 with enterococci, 2 with gram-negative rods, and 3 with candida). In addition, one patient was suspected to have developed pneumonia and required mechanical intubation for several days.

Pharmacokinetic analysis

The pharmacokinetics of thioTEPA were evaluated in 37 patients as summarized in Table 5. The systemic clearance varied widely over a 7-fold range [coefficient of variation (CV), 50%], yielding overlapping

Table 4 Nonhematologic toxicities encountered following high-dose cyclophosphamide, cisplatin, and thioTEPA (*ED* Early deaths)

Dose level (*n*)	ED[a]	Type and number of patients with grades 3 and 4 toxicity[b]				
		Mucosal	Renal	Hepatic	Cardiac	Neurological
1 (9)	3	2	3	6	2	1
2 (17)	4	11	2	7	0	2
3 (15)	3	8	2	2	0	1
4 (3)	0	3	1	2	0	0
5 (2)	0	2	0	1	1	1
All (46)	10	26	8[c]	18[d]	3[e]	5

[a] 5 of the 7 deaths occurred among patients entered on levels 1 and 2 when thioTEPA was given on day −4 (following cyclophosphamide and cisplatin) and among patients who did not receive G-CSF-primed PBPCs

[b] CALGB grading scale

[c] 4 patients required hemodialysis, of whom 3 developed veno-occlusive disease of the liver and died and 1 recovered

[d] 6 patients developed veno-occlusive disease of the liver and died, of whom 3 required hemodialysis

[e] 1 patient developed congestive heart failure and another patient developed recurrent supraventricular tachycardia; both required and responded to treatment. The third patient developed acute hemorrhagic myopericarditis and died

Table 5 ThioTEPA mean (SD) pharmacokinetic parameters

	n	Systemic clearance ($ml\,min^{-1}\,m^{-2}$)	AUC ($\mu g\,ml^{-1}\,min$)	C_{max} ($\mu g/ml$)
ThioTEPA on day −4	13	245 (126)		
ThioTEPA on day −7	24	175 (76)		
ThioTEPA dose level:				
1	7	185 (104)	2,183 (1,121)	16.3 (10.5)
2	16	244 (102)	2,097 (678)	9.1 (2.5)
3	9	179 (93)	4,114 (1,953)	16.0 (7.5)
4	3	111 (24)	6,984 (1,590)	22.8 (9.4)
5	2	126 (14)	7,166 (808)	18.5 (0.7)
All patients	37	200 (100)		

thioTEPA systemic exposure (AUC) across dosing groups (Fig. 1A). The mean clearance value was higher in those receiving thioTEPA on day −3 as compared with those treated on day −7; however, this difference did not achieve statistical significance ($P = 0.115$; Table 5). Patients receiving the two highest dose levels (700 and 900 mg/m^2) displayed substantially lower median clearance as compared with those treated at 300 and 450 mg/m^2 (116 versus 198/$ml\,min^{-1}\,m^{-2}$, $P = 0.014$; Fig. 1B).

We evaluated the relationship between thioTEPA systemic exposure and the subsequent development of severe mucositis for those dose levels that exclusively used PBPCs (i.e., levels 3–5). These data demonstrate a stronger correlation between mucositis and the AUC ($r^2 = 0.41$, $P = 0.018$) than between mucositis and the dose ($r^2 = 0.19$, $P = 0.129$).

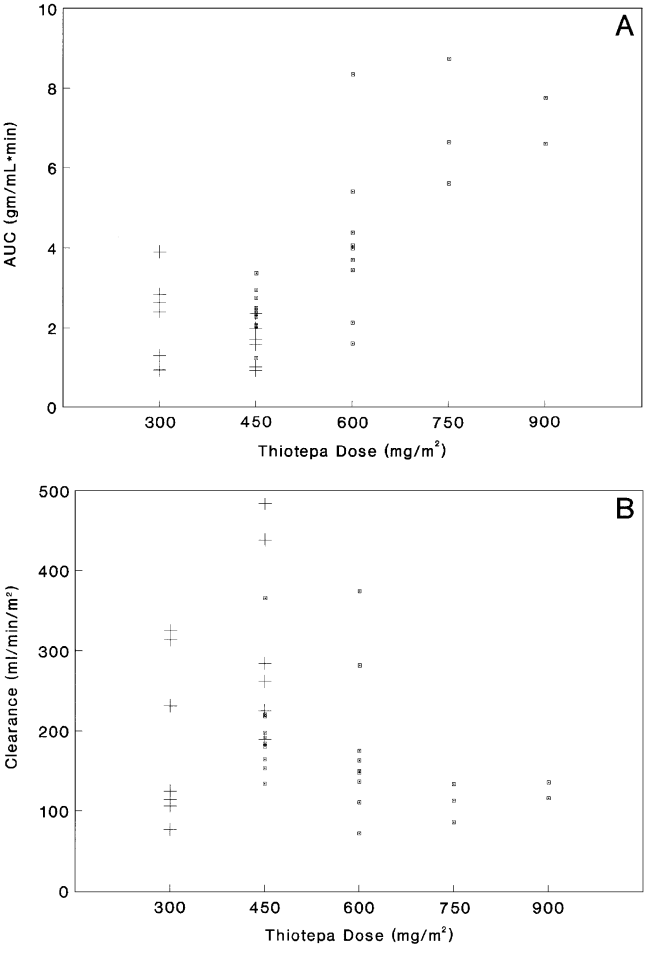

Fig. 1A, B ThioTEPA systemic exposure as determined according to **A** AUC and **B** clearance for individual patients. *Crosses* represent patients receiving the drug on day −4; *boxes* show data from infusions given on day −7

The patient with the second highest thioTEPA clearance on day −7 was receiving concurrent treatment with phenobarbital and primidone for a seizure disorder. As compared with over 100 control patients not receiving anticonvulsant therapy, her cyclophosphamide systemic clearance values were also substantially elevated on each of the 3 days (days −6, −5, and −4) .

Response

Restaging studies and physical examinations were performed (1) 6 weeks after the administration of high-dose cyclophosphamide, cisplatin, and thioTEPA, (2) every 6 weeks for 6 months, (3) every 12 weeks for 6 months, (4) every 6 months for 1 year, and then (5) yearly. Of the 46 patients, 35 were evaluable for response (10 early deaths occurred within 60 days of administration of the high-dose regimen and 1 patient had ovarian cancer documented by laparotomy despite negative CT scans). The responses observed by tumor type and dose level are shown in Table 6. There were 3 complete responses (CRs) and 22 partial responses (PRs), for an overall response rate of 71%. Responses were seen in all tumor types and at all dose levels. The median response duration was 3.5 months (range, 2–17 months). However, all patients have suffered relapses.

Discussion

The goal of this phase I/II trial was to determine the maximally tolerated dose of a combination of cyclophosphamide, cisplatin, and thioTEPA given with autologous bone marrow support in patients with refractory malignancies. This regimen was associated with 22% mortality. However, 6 of the 10 deaths occurred among the first 15 patients (entered between 1986 and 1989), who received only bone marrow support without G-CSF-primed PBPCs (mortality, 40%). Of these 15 patients, 13 received thioTEPA on the day following cyclophosphamide and cisplatin administration (day −4). The unanticipated mortality encountered at these doses and the possibility of a pharmacokinetic interaction led us to alter the administration sequence by giving thioTEPA on the day prior to cyclophosphamide and cisplatin dosing (day −7) in the remaining 33 patients (entered between 1990 and 1994). Both alterations in the kinetics of thioTEPA and cisplatin and our not giving G-CSF-primed PBPCs could have contributed to the very high mortality seen among the first 15 patients treated during this study, although they received thioTEPA at the two lowest dose levels.

The other 4 deaths occurred among the remaining 31 patients who received G-CSF-primed PBPCs in addition to bone marrow and who received thioTEPA on day −7 (mortality rate, 13%). All four of these deaths occurred among patients with ovarian carcinoma, who had been heavily pretreated and whose disease was thus refractory to standard therapy (all had received four or more chemotherapeutic regimens prior to the high-dose chemotherapy). Therefore, infusing thioTEPA prior to cyclophosphamide and cisplatin, giving G-CSF-primed PBPCs in addition to bone marrow, and not treating heavily pretreated patients with refractory disease may decrease the mortality and morbidity of this high-dose regimen. ThioTEPA was given at a dose of 600 mg/m^2, which is 20 times the usual dose given without cellular support (a dose escalation higher than that used for cyclophosphamide and cisplatin).

All patients experienced severe bone marrow suppression. The addition of G-CSF-primed PBPCs shortened the duration of neutropenia from a median of 17.5 (range, 15–34) and 11 (range, 9–30) days for patients entered on dose levels 1 and 2, respectively, to a median of 9–11 days for all patients entered on dose levels 3–5 and achieving myeloid engraftment between days 9 and 12. The shorter period of neutropenia with the addition of PBPCs was observed among patients who received higher doses of thioTEPA. Dose escalation in this study was continued beyond the 450-mg/m^2 dose of thioTEPA because in early 1990, evidence was accumulating with regard to the attenuation of the morbidity and mortality of high-dose chemotherapy with autologous bone marrow

Table 6 Tumor responses recorded after high-dose cyclophosphamide, cisplatin, and thioTEPA by tumor type (*ED* Early death—before day + 60, *NE* not evaluable, *CR* complete response, *PR* partial response, *NR* no response, *PD* progressive disease, *RR* response rate)

Diagnosis	Patients (*n*)	Response						RR (%)	Median duration of response (months)[a]
		ED	NE	CR	PR	NR	PD		
Breast	25	4	0	3	12	4	2	71	4 (2.5–17)
Ovary	15	5	1	0	6	3	0	67	4 (2.5–6)
Melanoma	4	1	0	0	2	1	0	67	3.5 (3, 4)
Colon	2	0	0	0	2	0	0	100	2.5 (2, 3)
Total	46	10	1	3	22	8	2	71	3.3 (2–17)

[a] Unmaintained response; range given in parentheses

support achieved by the addition of G-CSF-primed PBPCs. Severe thrombocytopenia was observed at all dose levels, with the median engraftment period being 16–27 days.

The most common nonhematopoietic and dose-limiting toxicity observed was gastrointestinal. In all, 58% of the patients had grade 3 or 4 mucositis/esophagitis, requiring either narcotics to eat or parenteral nutrition; all 5 patients entered on dose levels 4 and 5 had either grade 3 or 4 mucositis/esophagitis. The hepatorenal toxicities observed during this trial occurred mainly among patients who did not receive G-CSF-primed PBPCs [18–20].

We found that the systemic clearance of parent thioTEPA was lower in patients receiving higher doses of drug. This implies that clearance is a potentially saturable process, and one may thus anticipate larger than expected increments in systemic exposure for an incremental increase in dose. Pharmacokinetics studies of thioTEPA given by short-term infusion in adult patients have been reported for doses significantly lower than those used in the present investigation. Previous studies reveal conflicting results regarding the association between dose and drug clearance in that some investigators have noted that clearance may be saturable at higher doses [21, 22]; however, the average clearance noted in our study ($200\ ml\ min^{-1}\ m^{-2}$) is even lower than these previous reports.

In the only published pharmacokinetics study we are aware of that evaluated patients given similar total doses (180–900 mg/m^2), the drug was infused continuously over 4 days in conjunction with cyclophosphamide. Thus, the amounts given per day are between those described in the low-dose studies mentioned above and those given in our high-dose study [23]. A comparison of these thioTEPA clearance values with our data reveal higher rates of clearance for the continuous-infusion regimen. Clinical studies of thioTEPA that use dose ranges similar to the higher levels evaluated in our study should proceed with caution because unexpectedly high systemic exposure may become evident on dose escalation or, potentially, in patients with organ dysfunction. Alteration of the thioTEPA administration sequence did not result in a statistically significant change in elimination of the parent drug; however, a trend was noted for higher clearance of the parent drug when it was given following cyclophosphamide (day -4). These data are in agreement with the continuous-infusion data described above, which note induction of thioTEPA clearance the drug is given with cyclophosphamide.

Our study did not investigate the theoretical, albeit potentially important, interaction of inhibition of renal excretion of the active metabolite TEPA by cisplatin. It appears from the pharmacokinetic and pharmacodynamic correlation that knowledge of thioTEPA disposition could identify patients who would subsequently develop severe mucositis at the maximally tolerated dose. This concept should be tested prospectively in a phase II setting. One patient on this trial was receiving anticonvulsant therapy concurrently with thioTEPA and demonstrated high clearance of both thioTEPA and cyclophosphamide. This case provides an important illustration of the point that noncytotoxic drugs that are used in bone-marrow transplant patients may have profound influences on cytotoxic drug exposure. Similar results have recently been reported by Rodman et al. [24] for high-dose etoposide and concurrent anticonvulsant therapy.

Of the 34 evaluable patients, 71% had either a CR or a PR. Responses were brief, most probably due to the observation that the majority of patients entered onto this study had been heavily pretreated and their disease was thus refractory to standard chemotherapy. Responses were seen at all dose levels. The efficacy and toxicity of this combination should be tested in a group of patients with less prior treatment and bulky disease.

We conclude that cyclophosphamide, cisplatin, and thioTEPA can be combined at the doses determined in this study. The maximally tolerated dose of thioTEPA was defined as 600 mg/m^2 given i.v. over 1 h on the day prior to the administration of cyclophosphamide at 1,875 mg/m^2 per day as a 1-h i.v. infusion on 3 consecutive days and of cisplatin at 55 mg/m^2 per day as a 24-h continuous i.v. infusion over 3 days concurrently with cyclophosphamide. ThioTEPA is a drug that can be given with a significant dose intensity in comparison with standard doses. ThioTEPA should be given prior to cyclophosphamide and cisplatin. In addition, giving G-CSF-primed PBPCs attenuates some of the side effects associated with high-dose chemotherapy. Toxicity to the bone marrow and gastrointestinal tract are the major side effects. Other side effects included toxicities related to the heart, kidneys, liver, and central nervous system. The efficacy of this combination should be better defined in a phase II trial.

References

1. Schabel FM Jr (1978) Fundamentals in cancer chemotherapy: introduction. Antibiot Chemother 23: 1
2. Schabel FM Jr, Griswold DP Jr, Corbett TH, Laster WR Jr (1984) Increasing therapeutic response rates to anticancer drugs by applying principles of pharmacology. Cancer 54 [Suppl 6]: 1160
3. Frei E III, Cucchi CA, Rosowsky A, Tantravahi R, Bernal S, Ervin TJ, Ruprecht RM, Haseltine WA (1985) Alkylating agent resistance: in vitro studies with human cell lines. Proc Natl Acad Sci USA 82: 2158
4. Lazarus HM, Herzig RH, Wolff SN, Phillips GL, Sptizer TR, Fay JW, Herzig GP (1985) Treatment of metastatic melanoma with intensive melphalan and autologous bone marrow transplantation. Cancer Treat Rep 69: 473
5. Myers SE, Williams SF (1993) Role of high-dose chemotherapy and autologous stem cell support in treatment of breast cancer. Hematol Oncol Clin North Am 7: 631
6. Phillips GL, Wolff SN, Fay JW, Herzig RH, Lazarus HM, Schold C, Herzig GP (1986) Intensive 1,3-bis-(2-chloroethyl)-

1-nitrosourea (BCNU) monochemotherapy and autologous marrow transplantation for malignant glioma. J Clin Oncol 4: 639
7. Peters WP, Eder JP, Henner WD, Schryber S, Wilmore D, Finberg R, Schoenfeld D, Bast R, Gargone B, Antman K, Anderson J, Anderson K, Kruskall MS, Schnipper L, Frei E III (1986) High dose combination alkylating agents with autologous bone marrow support: a phase I trial. J Clin Oncol 4: 646
8. Peters WP, Shpall EJ, Jones RB, Olsen GA, Bast RC, Gockerman JP, Moore JO (1988) High dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. J Clin Oncol 6: 1368
9. Peters WP, Stuart A, Klotman M, Gilbert C, Jones RB, Shpall EJ, Gockerman J, Bast RC Jr, Moore JO (1989) High dose combination cyclophosphamide, cisplatin and melphalan with autologous bone marrow support. A clinical and pharmacologic study. Cancer Chemother Pharmacol 23: 377
10. Jones RB, Shpall EJ, Ross M, Coniglio D, Affronti ML, Peters WP (1990) High-dose carboplatin, cyclophosphamide, and BCNU with autologous bone marrow support: excessive hepatic toxicity. Cancer Chemother Pharmacol 26: 155
11. Antman K, Ayash L, Elias A, Wheeler C, Hunt M, Eder JP, Teicher BA, Critchlow J, Bibbo J, Schnipper LE, Frei E III (1992) A phase II study of high-dose cyclophosphamide, thioTEPA, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. J Clin Oncol 10: 102
12. Lidor YJ, Shpall EJ, Peters WP, Bast RC Jr (1991) Synergistic cytotoxicity of different alkylating agents for epithethial ovarian cancer. Int J Cancer 49: 704
13. Schabel FM Jr, Skipper HE, Trader MW, Laster WR Jr, Griswold DP Jr, Corbett JH (1983) Establishment of cross-resistance profiles for new agents. Cancer Treat Rep 67: 905
14. Ng SF, Waxman DJ (1990) Biotransformation of *N*, *N*′, *N*″-triethylenethiophosphoramide: oxidative desulfuration to yield *N*, *N*′, *N*″-triethylenephosphoramide associated with suicide inactivation of a phenobarbital-inducible hepatic P-450 monooxygenase. Cancer Res 50: 464
15. Tinsley PW, O'Dwyer PJ, LaCreta FP (1989) High performance liquid chromatographic analysis of *N*, *N*′, *N*″-triethylenethiophosphoramide in human plasma. J Chromatogr 495: 318
16. Egorin MJ, Cohen BE, Kohlhepp EA, Gutierrez PL (1985) Gas-liquid chromatographic analysis of *N*, *N*′, *N*″-triethylene thiophosphoramide and *N*, *N*′, *N*″-triethylene phosphoramide in biological samples. J Chromatogr 343: 196
17. Panella TJ, Peters WP, White JG, Hannun YA, Greenberg CS (1990) Platelets acquire a secretion defect after high-dose chemotherapy. Cancer 65: 1711
18. Peters WP, Rosner G, Ross M, Vredenburgh J, Meisenberg B, Gilbert C, Kurtzberg J (1993) Comparative effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) on priming peripheral blood progenitor cells for use with autologous bone marrow after high-dose chemotherapy. Blood 81: 1709
19. Peters WP (1991) High-dose chemotherapy and autologous bone marrow support for breast cancer. In: Devita VT, Hellman S, Rosenberg SA (eds) Important advances in oncology. J.B. Lippincott, Philadelphia, p 135
20. Peters WP, Ross M, Vredenburgh JJ, Meisenberg B, Marks LB, Winer E, Kurtzberg J, Bast RC Jr, Jones R, Shpall E, Wu K, Rosner G, Gilbert C, Mathias B, Congilio D, Petros W, Henderson IC, Norton L, Weiss RB, Budman D, Hurd D (1993) High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. J Clin Oncol 11: 1132
21. O'Dwyer PJ, LaCreta F, Engstrom PF, Peter R, Tartaglia L, Cole D, Litwin S, DeVito J, Poplack D, DeLap RJ, Comis RL (1991) Phase I/pharmacokinetic reevaluation of thioTEPA. Cancer Res 51: 3171
22. Ackland SP, Choi KE, Ratain MJ, Egorin MJ, Williams SF, Sinkule JA, Bitran JD (1988) Human plasma pharmacokinetics of thioTEPA following administration of high-dose thiotepa and cyclophosphamide. J Clin Oncol 6: 1192
23. Henner WD, Shea TC, Furlong EA, Flaherty MD, Eder JP, Elias A, Begg C, Antman K (1987) Pharmacokinetics of continuous-infusion high-dose thiotepa. Cancer Treat Rep 71: 1043
24. Rodman JH, Murry DJ, Madden T, Santana VM (1994) Altered etoposide pharmacokinetics and time to engraftment in pediatric patients undergoing autologous bone marrow transplantation. J Clin Oncol 12: 2390