Cancer Chemother Pharmacol (1995) 37: 155–160

ORIGINAL ARTICLE

Donna Przepiorka · Timothy Madden · Cindy Ippoliti
Zeev Estrov · Meletios Dimopoulos

Dosing of ThioTEPA for myeloablative therapy

Received: 10 June 1994/Accepted: 15 January 1995

Abstract High-dose thioTEPA is used frequently in myeloablative regimens for marrow transplantation, but the need for dose adjustments in obese patients has not been explored. We determined the pharmacokinetics of thioTEPA and its metabolite TEPA during first-dose infusion of thioTEPA 150–250 mg/m^2 given daily for 3 days in combination with busulfan and cyclophosphamide, and evaluated the results for correlations with toxicity and dosing strategies. The study included 15 adults undergoing marrow transplantation for hematologic malignancies. Plasma samples were obtained at various times over a 24-h period, and concentrations of thioTEPA and TEPA were measured by gas chromatography. At 22–24 h after initiation of a 4-h infusion, the mean ± SE plasma concentration of thioTEPA was 124 ± 63 ng/ml, while that of TEPA was 235 ± 69 ng/ml. For CFU-GM and BFU-E growth in vitro, the IC_{50}s of thioTEPA were 83 ng/ml and 16 ng/ml, respectively, and the IC_{50}s of TEPA were 141 ng/ml and 47 ng/ml, respectively. Using a two-compartment model, the mean thioTEPA Vc was 47.4 ± 4.7 l/m^2, $t_{1/2}\alpha$ 19 ± 5 min, $t_{1/2}\beta$ 3.7 ± 0.5 h, and plasma clearance 302 ± 21 ml/min per m^2. The mean AUCs were 6.9–16.2 mg h/l for thioTEPA and 8.9–21.2 mg h/l for TEPA, while the mean peak concentrations were 0.95–2.08 μg/ml for thioTEPA and 0.88–1.90 μg/ml for TEPA. There was a significant association of grades 2–4 maximum regimen-related toxicity (RRT) with TEPA peak > 1.75 μg/ml and with combined thioTEPA and TEPA AUC > 30 mg h/l (5/6 vs 0/9, $P = 0.01$ for both comparisons), suggesting that drug exposure was an important determinant of toxicity and, potentially, efficacy. ThioTEPA Vc correlated best with adjusted body weight ($r = 0.74$, $P = 0.0015$). In an evaluation of 74 adults receiving thioTEPA 750 mg/m^2 in combination with busulfan and cyclophosphamide, the maximum RRT for patients at ideal weight was significantly greater than that for obese patients dosed on ideal weight (mean RRT grade 1.7 vs 1.0, $P = 0.004$) but did not differ from the maximum RRT for obese adults dosed on actual or adjusted weights. We recommend that for obese patients thioTEPA be dosed on adjusted body weight. Measurements at time-points after 24 h are needed to determine when thioTEPA and TEPA concentrations are below myelosuppressive levels and safe for marrow infusion.

Key words ThioTEPA · bone marrow transplantation · pharmacokinetics

Supported in part by a grant from the American Cyanamid Corporation

D. Przepiorka (✉) · C. Ippolite · M. Dimopoulos
Department of Hematology, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA

T. Madden
Department of Experimental Pediatrics, University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

Z. Estrov
Departmental of Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

Introduction

N, *N'*, *N''*-Triethylenethiophosphoramide (thioTEPA) is a polyfunctional alkylating agent with a long reputation for activity in the treatment of solid tumors and hematologic malignancies [3, 17]. In single-dose phase I studies, the maximal tolerated dose (MTD) of thioTEPA has been shown to be 65 mg/m^2, and myelosuppression is the dose-limiting toxicity [14, 24]. With fractionation of the dose over 3–4 days and with hematopoietic stem cell support, the MTD of thioTEPA is 900 mg/m^2 as a single agent [32] and 500–750 mg/m^2 when used in combinations [9, 29–31], and dose escalation is associated with an improvement in response rates for patients with refractory disease. The activity of thioTEPA in a broad range of tumors

and its lack of toxicities that overlap with other alkylating agents has led to its frequent use in high-dose regimens.

In vivo thioTEPA undergoes oxidative desulfuration to TEPA, an active metabolite [21], and the conversion to TEPA may be saturable [14, 15, 24]. Since cumulative urinary alkylating activity exceeds the sum of measurable thioTEPA and TEPA concentrations [5, 13], it is likely that other active metabolites are formed, but these have not yet been identified. Over a broad range of doses in adults, thioTEPA has been reported to have a $t_{1/2}\beta$ of 1.3–5.2 h, a clearance of 10–28 l/h per m^2, and a volume of distribution (Vc) of 27–65 l/m^2 [1, 5, 10, 12, 13, 15, 16, 24, 25]. Using conventional doses of thioTEPA, the half-life ($t_{1/2}$) of TEPA is 4.9–17.6 h [10, 13, 24, 25], but TEPA kinetics have not been reported for patients on high-dose regimens.

When using chemotherapeutic agents at the limit of nonhematologic toxicity, there is a substantial risk for adverse outcome. This underscores the need for accurate dosing. Obesity has been identified as one factor that may complicate drug dosing [6]. Little has been published on the need for dose adjustments when using chemotherapeutic agents in obese patients [18, 27, 33], and no information is available for thioTEPA. We determined the pharmacokinetics of thioTEPA and its metabolite TEPA during first-dose infusion of a 3-day schedule in a high-dose combination regimen and evaluated these results for correlations with toxicity and dosing strategy.

Materials and methods

Patients and treatment

The pharmacokinetics study included 15 adults from a phase I protocol. All patients had advanced hematologic malignancies and were undergoing autologous or allogeneic marrow transplantation (Table 1). The preparative regimens consisted of thioTEPA 150–250 mg/m^2 i.v. daily for 3 days, busulfan 1 mg/kg orally every 6 h for 10 or 12 doses, and cyclophosphamide 60 mg/kg i.v. daily for 2 days. Details of the clinical studies have been described previously [8, 29, 30]. The protocol was approved by the Surveillance Committee of the M.D. Anderson Cancer Center, and written informed consent was obtained from each patient.

Eight patients in the pharmacokinetics study were more than 10% above ideal body weight, and six of these were more than 20% above ideal body weight. The dose of thioTEPA administered was based on the body surface area (BSA) calculated from ideal weight where BSA (m^2) = [height (m) × weight (kg)/3600]$^{1/2}$ [20], and ideal weight (kg) = (0.9)[height (cm) − 152] + 50 (or + 45.5 for females) [7]. ThioTEPA supplied as a powder was reconstituted to 10 mg/ml in normal saline, and the calculated dose was infused intravenously by pump over 4 h.

For the evaluation of the effects of dosing basis on regimen-related toxicity (RRT), data were obtained from a toxicity database for all patients treated with thioTEPA 250 mg/m^2 i.v. daily for 3 days, busulfan 1 mg/kg orally every 6 h for ten doses, and cyclophosphamide 60 mg/kg i.v. daily for 2 or 3 days as described previously [28]. For patients more than 20% above ideal body weight, busulfan was dosed on ideal weight and cyclophosphamide on adjusted weight. Adjusted body weight was calculated as ideal weight + 0.4(actual weight − ideal weight) [23].

Table 1 Patient characteristics

Number of patients	15
Males/females	11/4
Median age (years)	33.5
Range	16–54
Performance status	
0	5
1	9
2	1
Prior therapy	
Chemotherapy	7
Radiation	0
Both	8
Diagnosis	
Leukemia	8
Lymphoma	7
Transplant type	
Autologous	7
Allogeneic	8

Toxicity grading

Early RRT was graded according to the criteria of Bearman et al. [4]. In this system, grade 1 toxicity is reversible without treatment, grade 2 is not life threatening but requires treatment, grade 3 requires life-support intervention, and grade 4 is fatal. RRT in each organ system was scored as the highest grade achieved in that organ system through day 28, except that deaths occurring after day 28 as a result of RRT occurring before day 28 were also scored as grade 4. Adverse events that could be attributed to infection (culture proven), bleeding, or other medications were not scored as RRT. The maximum toxicity was the highest grade recorded in any individual organ system.

In vitro colony inhibition assays

ThioTEPA (Lederle Laboratories, Pearl River, N.Y.) or TEPA (obtained from Dr. G. Sosnovsky, University of Wisconsin, Madison, Wis.) was added at concentrations of 50–500 ng/ml at initiation of cultures of 2×10^5 low-density marrow cells in 0.8% methylcellulose with Iscove's modified Dulbecco's medium (GIBCO, Grand Island, N.Y.), 30% fetal calf serum, 10 ng/ml recombinant sargramostim or 15 ng/ml interleukin-3, 50 ng/ml stem cell factor (Immunex Corp., Seattle, Wash.), and 1.0 U/ml human erythropoietin (British Columbia Research Institute, Vancouver, B.C.). Duplicate cultures at each concentration were incubated for 14 days at 37°C in humidified air containing 5% CO_2. Aggregates of more than 500 hemoglobinized cells or with three or more erythroid subcolonies were identified as burst-forming units-erythroid (BFU-E). Clusters of 40 or more granulocytes, macrophages, or both were identified as colony-forming units-granulocyte-macrophage (CFU-GM). The numbers of BFU-E and CFU-GM were ascertained for cultures with (experimental) and without (control) added drug, and the percent inhibition was calculated as 100 × (control − experimental)/control. The results were fitted to a logarithmic curve (True Epistat V4.01, Epistat Services, Richardson, Tx.), and the equation was used to calculate the concentration that provided 50% inhibition (IC_{50}).

Sample collection and analysis

Heparinized blood samples were obtained before and at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h from the start of the first infusion of

thioTEPA. Plasma was separated by centrifugation and stored at − 20°C until analyzed. For analysis of thioTEPA, a 250-µl aliquot of plasma was extracted with 750 µl ethyl acetate, separated by centrifugation, evaporated to dryness under nitrogen and reconstituted in 100 µl ethyl acetate. For analysis of TEPA, 250 µl plasma was extracted with chloroform, centrifuged and separated. The chloroform layer was assayed directly. Samples were analyzed on Hewlett Packard Model 5890 gas chromatograph equipped with a nitrogen phosphorus detector using hydrogen at a flow rate of 3.5 ml/min and a detector temperature of 250°C. Separation was achieved with a 1.8 m × 2 mm glass column containing OV225 on 100/120 mesh Supelcoport using helium as the carrier at a flow rate of 30 ml/min [19]. The injector and oven temperatures were set at 180°C and 230°C, respectively, and the detector power at 30 pA. A standard curve was generated daily using 0.05–50 µg/ml of each analyte, and the accuracy of the curve was determined using two independent controls. Sample concentrations of thioTEPA and TEPA were determined by comparing the peak height of the sample with that of the external standards. Using this technique, the within-day and between-day coefficients of variation were less than 5%.

Pharmacokinetics and statistics

Initial parameter estimates were obtained by curve-stripping techniques. A two-compartment model with zero-order input and first-order elimination was fitted (PCNONLIN V3.0, Statistical Consultants, Lexington, Ky.) to obtain disposition parameters for thioTEPA. The area under the concentration × time curve (AUC) was calculated by the trapezoidal rule, and the clearance was calculated as dose/AUC.

Mean values are reported ± 1 SE. Correlations between measures of drug exposure and toxicity were assessed by Fisher's exact test with correction for multiple comparisons. Spearman's rank correlation coefficient was calculated to determine the best concordance between Vc and BSA. Student's *t*-test was used to determine differences in maximum RRT grade between groups dosed differently.

Results

Pharmacokinetic studies were done for five patients at each of three dose levels of thioTEPA. The mean thioTEPA Vc was 47.4 ± 4.7 l/m^2, $t_{1/2}\alpha$ 19 ± 5 min, $t_{1/2}\beta$ 3.7 ± 0.5 h, plasma clearance 302 ± 21 ml/min per m^2, and TEPA AUC:thioTEPA AUC ratio 1.4 ± 0.1. The Vc, terminal half-life, clearance of thioTEPA, and TEPA AUC:thioTEPA AUC did not vary significantly between dose levels. The AUCs and peak concentrations of both thioTEPA and TEPA were lowest at the first dose level but did not differ between the second and third dose levels (Table 2).

ThioTEPA plasma concentrations fell quickly following completion of the 4-h infusion, but TEPA plasma concentrations remained relatively high (Fig. 1). At 22–24 h after initiation of the infusion, the mean plasma concentration of thioTEPA was 124 ± 63 ng/ml, while that of TEPA was 235 ± 69 ng/ml. For CFU-GM and BFU-E growth in vitro, the IC_{50}s were 83 ng/ml and 16 ng/ml, respectively, for thioTEPA, and the IC_{50}s were 141 ng/ml and 47 ng/ml, respectively, for TEPA (Fig. 2). Thus, for a proportion of the patients, the plasma concentrations of thioTEPA and TEPA at 24 h were still well above the IC_{50}s for hematopoietic colony growth in vitro.

Table 2 Drug exposure. Values are means ± SE

	ThioTEPA dose (mg/m^2)		
	150	200	250
Number of patients	5	5	5
AUC (mg h/l)			
ThioTEPA	6.9 ± 1.1	16.2 ± 2.6	12.2 ± 1.0
TEPA	8.9 ± 1.9	21.2 ± 3.0	18.2 ± 2.0
Combined	15.9 ± 2.8	37.4 ± 5.0	30.4 ± 2.7
Peak (mg/l)			
ThioTEPA	0.95 ± 0.11	1.99 ± 0.21	2.08 ± 0.13
TEPA	0.88 ± 0.14	1.90 ± 0.24	1.88 ± 0.15

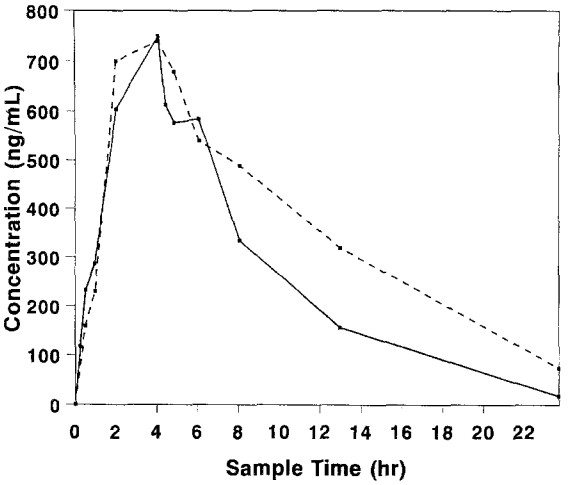

Fig. 1 Plasma concentrations of thioTEPA (*solid line*) and TEPA (*dashed line*) during and after a 4-h intravenous infusion of 150 mg/m^2 thioTEPA

ThioTEPA was not detectable on the day of marrow infusion (6 days from the last dose of thioTEPA) in any patient tested, but two patients still had measurable levels of TEPA in plasma samples (84 and 125 ng/ml, respectively). One expired on day 21 posttransplant without evidence of engraftment, and the other was transfusion-independent but persistently pancytopenic at 1 year posttransplant.

Correlations between toxicity and measures of drug exposure were evaluated. Five patients developed grades 2–4 RRT, and this occurred only in the mucosal, hepatic and central nervous systems. There was no correlation between grades 2–4 RRT in an individual organ system and any of the parameters of drug exposure. However, there was a significant association of grades 2–4 maximum RRT with TEPA peak > 1.75 µg/ml and with combined thioTEPA and TEPA AUC > 30 mg h/l (5/6 vs 0/9, $P = 0.01$ for both comparisons).

Correlations were evaluated between thioTEPA Vc and BSA calculated from ideal, real, and adjusted

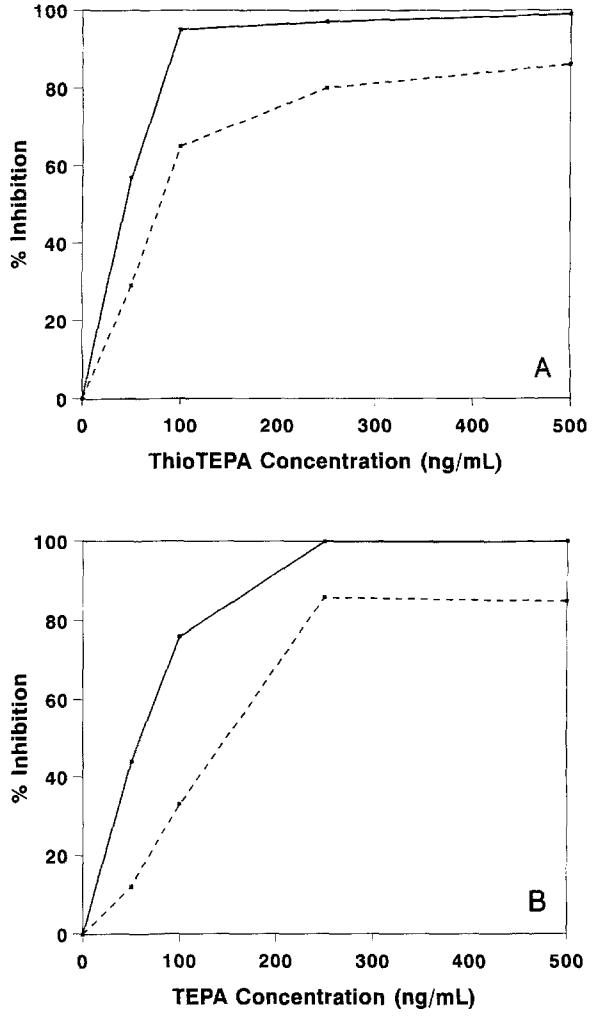

Fig. 2A B Inhibition of BFU-E (*solid line*) and CFU-GM (*dashed line*) in vitro by thioTEPA (**A**) and TEPA (**B**)

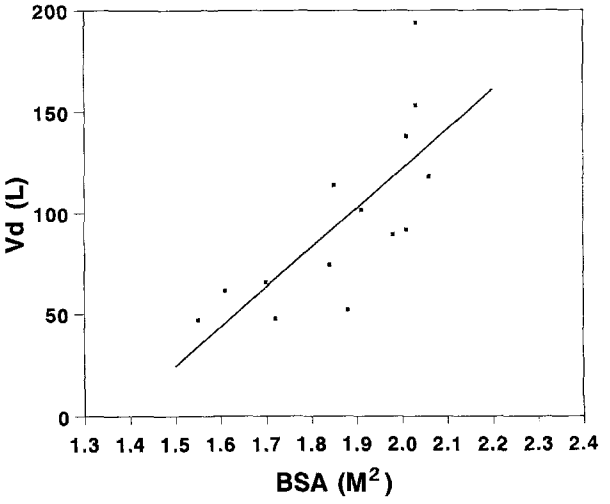

Fig. 3 Correlation between volume of distribution and adjusted body surface area (BSA). The point for one patient with a BSA of 2.7 m^2 is off the graph

weights. Vc correlated best with adjusted body weight (Fig. 3). The correlation coefficients were 0.63 ($P = 0.01$), 0.68 ($P = 0.005$), and 0.74 ($P = 0.0015$), respectively. For 74 adults receiving three doses of thioTEPA at 250 mg/m^2 in combination with busulfan and cyclophosphamide [28], maximum RRT for patients at ideal weight was significantly greater than that for obese patients dosed on ideal weight (Table 3) but did not differ from maximum RRT for obese adults dosed on actual or adjusted weight.

Discussion

The results in these patients demonstrate that the pharmacokinetic disposition parameters of thioTEPA when used at a high dose are similar to those obtained when using conventional doses of thioTEPA [1, 5, 10, 12, 13, 15, 16, 24, 25]. Toxicity in our patients correlated with measures of drug and/or metabolite exposure, suggesting that inaccurate dosing would have major clinical implications. A review of toxicities revealed that RRT was significantly decreased in obese patients receiving thioTEPA at doses based on ideal body weight, while there was no significant difference in mean maximum RRT between lean patients dosed on real body weight and obese patients based on actual or on adjusted body weight. However, the number of patients studied may be too small to determine if actual or adjusted body weight provided better uniformity in RRT. Since thioTEPA Vc correlated best with adjusted body weight, we recommend the use of adjusted body weight for dosing thioTEPA for obese patients until more information is available to support the use of actual body weight.

Others have reported that following conventional dose thioTEPA, myelosuppression correlates with thioTEPA AUC and clearance but not with TEPA

Table 3 Effect of dosing method on maximum toxicity (patients receiving thioTEPA 750 mg/m^2, busulfan 10 mg/kg and cyclophosphamide 120–150 mg/kg as described in reference 28). Values are means ± SE (*RRT* regimen-related toxicity)

Actual weight	Basis of dosing	Number of patients	Maximum RRT
Ideal	Actual weight	49	1.7 ± 0.1
Greater than ideal	Actual weight	6	1.3 ± 0.3[a]
Greater than ideal	Adjusted weight	6	1.2 ± 0.4[b]
Greater than ideal	Ideal weight	13	1.0 ± 0.2[c]

[a] $P = 0.15$ vs first group
[b] $P = 0.08$ vs first group
[c] $P = 0.004$ vs first group

disposition parameters [10, 24]. With the use of high-dose thioTEPA and marrow support, Antman et al. [2] have reported that toxicity correlates with thioTEPA AUC, but TEPA pharmacokinetics were not evaluated. Nonhematopoietic toxicity in our patients after high-dose thioTEPA correlated with the sum of the AUCs for thioTEPA and TEPA, a measure of total exposure to alkylating agents. This suggests that the combined AUCs may be useful as a basis for an adjusted-dose approach when using high-dose thioTEPA.

However, it should be noted that RRT in our patients reflects the effects of all agents used in the regimen. Thus, although correlations between RRT and thioTEPA pharmacokinetic parameters were noted, these may actually be surrogates for differences in overall drug handling rather than for thioTEPA alone. While definite conventions for busulfan and cyclophosphamide dose adjustments have been promulgated within the transplant field, an extensive literature to support these conventions does not exist.

Some studies have suggested that metabolism of thioTEPA may be capacity-limited [14, 24, 25], while others have not [1, 5]. Oxidation of thioTEPA to TEPA by P450 isozymes IIB1, IIC11, and IIC6 has been associated with a suicide-type inactivation of these metabolizing enzymes [21, 22]. This inactivation has proven to be both time- and concentration-dependent, resulting in considerable loss of metabolic capacity ($> 50\%$) [21]. An evaluation of thioTEPA plasma clearance when high doses were used has demonstrated that clearances are significantly lower for patients receiving 450–900 mg/m^2 in comparison with those for patients receiving 300–450 mg/m^2 (117 vs 226 ml/min per m^2, $P < 0.001$) [26]. We report an even higher mean thioTEPA clearance (302 ml/min per m^2) when using the lower dose range of 150–250 mg/m^2. Linear regression of all doses (150–900 mg/m^2) demonstrated a significant negative correlation ($P < 0.001$) [26] and supports the suggestions that metabolic clearance of thioTEPA is saturable at high dose levels.

Although the limited sampling prohibited our ability to fully evaluate the disposition of TEPA, the concentration-time curves are consistent with a slower clearance of this metabolite in comparison with that of the parent compound. At 18–20 h after infusion, plasma TEPA concentrations were still well above the IC_{50} for human hematopoietic colony growth in vitro. Since metabolism of thioTEPA is associated with inactivation of the hepatic P450 enzymes involved [21], repeated doses might be expected to result in even further delay in drug and/or metabolite clearance as well as alter metabolism of other agents administered subsequently in a combination regimen. At low dose levels, no change in clearance or AUC could be detected between the first and third daily doses [11], but it is not known if this will remain true when repeated high doses of thioTEPA are administered. Alternatively, the preclinical studies may not be fully applicable in humans. It was noteworthy that two patients still had detectable TEPA 6 days after the last dose of drug, and both had problems with engraftment.

While its broad spectrum of antitumor activity makes thioTEPA a useful agent for high-dose regimens, the optimal dosing strategy is not clear. Our results support the use of adjusted body weight over ideal weight for dosing thioTEPA in obese patients, but additional studies of long-term clearance of thioTEPA and TEPA after repeated high-dose treatment with thioTEPA will be required to design dose schedules that do not induce adverse drug interactions and do not impair engraftment.

References

1. 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
2. Antman K, Eder JP, Elias A, Ayash L, Shea TC, Weissman L, Critchlow J, Schryber SM, Begg C, Teicher BA, Schnipper LE, Frei E (1990) High-dose thiotepa alone and in combination regimens with bone marrow support. Semin Oncol 17 [Suppl 3]: 33
3. Bateman JC (1955) Chemotherapy of solid tumors with triethylene thiophosphoramide. N Engl J Med 252: 879
4. Bearman SI, Appelbaum FR, Buckner CD, Petersen FB, Fisher LD, Clift RA, Thomas ED (1988) Regimen-related toxicity in patients undergoing bone marrow transplantation. J Clin Oncol 6: 1562
5. Cohen BE, Egorin MJ, Kohlhepp EA, Aisner J, Gutierrez PL (1986) Human plasma pharmacokinetics and urinary excretion of thiotepa and its metabolites. Cancer Treat Rep 70: 859
6. Cox J, Penn N, Masood M, Hancock AK, Parker D (1987) Drug overdose – a hidden hazard of obesity. J R Soc Med 80: 87
7. Devine BJ (1974) Gentamicin therapy. Drug Intell Clin Pharmacol 8: 650
8. Dimopoulos MA, Alexanian R, Przepiorka D, Hester J, Andersson B, Giralt S, Mehra S, Van Besien K, Delasalle KB, Reading C, Deisseroth AB, Champlin RE (1993) Thiotepa, busulfan and cyclophosphamide: A new preparative regimen for autologous marrow or peripheral blood stem cells transplantation in high risk multiple myeloma. Blood 82: 2324
9. Eder JP, Elias A, Shea TC, Schryber SM, Teicher BA, Hunt M, Burke J, Siegel R, Schnipper LE, Frei E, Antman K (1990) A Phase I-II study of cyclophosphamide, thiotepa and carboplatin with autologous bone marrow transplantation in solid tumor patients. J Clin Oncol 8: 1239
10. Hagen B (1991) Pharmacokinetics of thio-TEPA and TEPA in the conventional dose-range and its correlation to myelosuppressive effects. Cancer Chemother Pharmacol 27: 373
11. Hagen B, Walseth F, Walstad RA, Iversen T, Nilsen OG (1987) Single and repeated dose pharmacokinetics of thio-TEPA in patients treated for ovarian carcinoma. Cancer Chemother Pharmacol 19:143
12. Hagen B, Walstad RA, Nilsen OG (1988) Pharmacokinetics of thio-TEPA at two different doses. Cancer Chemother Pharmacol 22: 356
13. Hagen B, Neverdal G, Walstad RA, Nilsen OG (1990) Long-term pharmacokinetics of thio-TEPA, TEPA and total alkylating activity following i.v. bolus administration of thio-TEPA in ovarian cancer patients. Cancer Chemother Pharmacol 25: 257
14. Heideman RL, Cole DE, Balis F, Sato J, Reaman GH, Packer RJ, Singher LJ, Ettinger LJ, Gillespie A, Sam J, Poplack D

(1989) Phase I and pharmacokinetic evaluation of thiotepa in the cerebrospinal fluid and plasma of pediatric patients: Evidence for dose-dependent plasma clearance of thiotepa. Cancer Res 49: 736
15. 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
16. Lazarus H, Reed M, Spitzer T, Rabaa M, Blumer J (1987) High-dose IV thiotepa and cryopreserved autologous bone marrow transplantation for therapy of refractory cancer. Cancer Treat Rep 71: 789
17. Leonard BJ, Israels MCG, Wilkinson JF (1956) Treatment of Hodgkin's granuloma, chronic lymphatic leukemia, polycythemia vera and other reticuloses with triethylene-thiophosphoramide. Lancet i: 1017
18. Lind MJ, Margison JM, Cerny T, Thatcher N, Wilkinson PM (1989) Prolongation of ifosfamide elimination half-life in obese patients due to altered drug distribution. Cancer Chemother Pharmacol 25: 139
19. McDermott BJ, Double JA, Bibby MC, Wilman DEV, Loadman PM, Turner RL (1985) Gas chromatographic analysis of triethylenethiophosphoramide and triethylenephosphoramide in biological specimens. J Chromatogr Biomed Appl 338: 335
20. Mosteller RD (1987) Simplified calculation of body-surface area. New Engl J Med 317: 1098
21. Ng S-F, 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
22. Ng S-F, Waxman DJ (1991) N, N′, N″-Triethylenethiophosphoramide (thio-TEPA) oxygenation by constitutive hepatic P450 enzymes and modulation of drug metabolism and clearance in vivo by P450-inducing agents. Cancer Res 51: 2340
23. Notari RE (1987) Biopharmaceuticals and clinical pharmacokinetics. Marcel Dekker, New York Basel, p. 380
24. 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
25. O'Dwyer PJ, LaCreta FP, Schilder R, Nash S, McAleer C, Miller LL, Hudes GR, Ozols RF (1992) Phase I trial of thiotepa in combination with recombinant human granulocyte-macrophage colony-stimulating factor. J Clin Oncol 10: 1352
26. Petros WP, Madden T, Gupton C, Egorin MJ, Fangmeier J, Peters WP (1994) Dose-related clearance of thiotepa in patients receiving high-dose chemotherapy and autologous bone marrow transplantation. Pharmacotherapy 14: 361
27. Powis G, Reece P, Ahmann DL, Ingle JN (1987) Effect of body weight on the pharmacokinetics of cyclophosphamide in breast cancer patients. Cancer Chemother Pharmacol 20: 219
28. Przepiorka D, Dimopoulos M, Smith T, Ippoliti C, Diener K, Luna M, Alexanian R, Champlin RE (1994) Thiotepa, busulfan and cyclophosphamide as a preparative regimen for marrow transplantation: Risk factors for early regimen-related toxicities. Ann Hematol 68: 183
29. Przepiorka D, Ippoliti C, Giralt S, van Besien K, Mehra R, Deisseroth AB, Andersson B, Luna M, Cork A, Lee M, Estey E, Andreeff M, Champlin R (1994) A phase I-II study of high-dose thiotepa, busulfan and cyclophosphamide as a preparative regimen for allogeneic marrow transplantation. Bone Marrow Transplant 14: 449
30. Przepiorka D, Nath R, Ippoliti C, Mehra R, Hagemeister F, Diener K, Dimopoulos M, Giralt S, Khouri I, Samuels B, van Besien K, Andersson B, Deisseroth AB, Luna M, Cabanillas F, Champlin R (1995) A phase I-II study of high-dose thiotepa, busulfan and cyclophosphamide as a transplant regimen for malignant lymphoma. Leuk Lymphoma (in press)
31. Williams SF, Bitran JD, Kaminer L, Westbrook C, Jacobs R, Ashenhurst J, Robin E, Purl S, Beschorner J, Schroeder C, Golomb HM (1987) A phase I-II study of bialkylator chemotherapy, high-dose thiotepa, and cyclophosphamide with autologous bone marrow reinfusion in patients with advanced cancer. J Clin Oncol 5: 260
32. Wolff SN, Herzig RH, Fay JW, LeMaistre CF, Brown RA, Frei-Lahr D, Stranjord S, Giannone L, Coccia P, Weick JL, Rothman SA, Krupp KR, Lowder J, Bolwell B, Herzig GP (1990) High-dose N, N′, N″-triethylenethiophosphoramide (thiotepa) with autologous bone marrow transplantation: phase I studies. Semin Oncol 17 (Suppl 3): 2
33. Zuccaro P, Guandalini S, Pacifici R, Pichini S, Di Martino L, Guiducci M, Guiliani M, Di Tullio MT, Pettoello-Mantovani M (1991) Fat body mass and pharmacokinetics of 6-mercaptopurine in children with acute lymphoblastic leukemia. Ther Drug Monitor 13: 37