Cancer Chemother Pharmacol (1991) 27: 373–378

034457049100023H

Cancer Chemotherapy and Pharmacology

Pharmacokinetics of thio-TEPA and TEPA in the conventional dose-range and its correlation to myelosuppressive effects*

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Received 20 November 1989/Accepted 7 November 1990

Summary. A total of 13 patients with ovarian cancer were studied during the initial two courses of i.v. thio-TEPA treatment they underwent after primary surgery. Following an increase in the dose from 60 to 80 mg for the second course, no sign of saturation of thio-TEPA elimination processes or of formation of the metabolite TEPA occurred, indicating dose-independent pharmacokinetics. Myelosuppression after courses was registered by serial measurements of platelets and leukocytes. The time to platelet nadir was quite uniformly 3 weeks and tended to be longer than that of leukocytes, which averaged 2 weeks but showed greater interindividual variation. Linear regression analyses of pharmacokinetic parameters versus myelosuppression revealed statistically significant correlations between thio-TEPA pharmacokinetics and the percentage of reductions in leukocytes and platelets at their mean nadirs. In contrast, no such correlation could be demonstrated for TEPA despite its greater exposure to the body in terms of AUC. We advocate further investigation of this pharmacokinetic-pharmacodynamic relationship so as to establish individualized dosing of thio-TEPA.

Introduction

Several studies on the human pharmacokinetics of the alkylating agent thio-TEPA have been published [1, 6, 8, 12–16, 19, 20]. However, the results are conflicting as regards the effect of the dose on the pharmacokinetics of this drug. Some authors have claimed that thio-TEPA displays dose-independent pharmacokinetics whereas others have reported dose dependency [1, 13, 15, 16, 19]. The oxydative desulphuration of thio-TEPA to TEPA has also recently been shown to occur in humans [6, 21], as has been known for years in various other species [4, 7, 22]. TEPA, which possesses cytotoxic activity, appears in the blood shortly after the administration of thio-TEPA and persists there longer than does the parent drug. Hepatic cytochrome P-450-mediated metabolism of thio-TEPA, with retention of its alkylating activity [10], has been reported in preliminary form [24]. The knowledge of the pharmacokinetics of TEPA, however, remains limited. The immediate side effects of thio-TEPA are remarkably rare, which makes this drug convenient in terms of patient tolerability. Myelosuppression represents the dose-limiting toxicity and may be severe and unpredictable [2, 17, 18].

The aims of the present study were to study further the pharmacokinetics of thio-TEPA and TEPA, with emphasis on their relationship to the dose increment, to perform systematic registration of changes in haematologic parameters during thio-TEPA treatment, and, finally, to establish possible correlations between the drug's pharmacodynamic (myelosuppressive effects) and pharmacokinetic parameters.

Materials and methods

Patients. Patients with ovarian cancer who had been allocated to single-drug thio-TEPA treatment according to the current treatment plan at the Department of Gynecology and Obstetrics of the Regional Hospital, Trondheim, were included in the study. A total of 13 patients were enrolled and studied during their initial two courses of chemotherapy. Their median age was 73 years (range, 45–84 years). The thio-TEPA treatment was given after staging/debulking surgery. No subject had received other chemotherapy prior to the thio-TEPA treatment. The patients' characteristics are given in Table 1. All subjects had advanced disease (FIGO stage III). All had normal serum bilirubin levels; in one case, serum creatinine levels were elevated due to chronic renal disease, but the remaining 12 patients had normal values.

Treatment. thio-TEPA (Lederle Laboratories) was dissolved in sterile water (1 mg/ml) and given by a short-term (<5 min) i.v. infusion. Single-dose courses were given at 4-week intervals. The beginning dose was 60 mg and it was increased to 80 mg for the second course. No dose correction for body surface or weight was made.

* The work described in this paper was supported by grants from the Cancer Fund at the Regional Hospital (Trondheim) and the Norwegian Cancer Society (Oslo). During this work the author was a research fellow for the Norwegian Cancer Society

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Table 1. Patients' characteristics

Median age	73 (range, 45–84) years
Mean body surface	1.6 (range 1.4–1.9) m^2
FIGO stage	III ($n = 13$)
WHO performance status:	0 ($n = 2$) 1 ($n = 3$) 2 ($n = 6$) 3 ($n = 2$)
Serum creatinine	98 (range 56–314) µmol/l
Serum bilirubin	7 (range, 3–13) µmol/l

Pharmacokinetics. Blood samples for analysis of thio-TEPA and TEPA concentrations were taken from a Venflon cannula in the forearm opposite to the drug-infusion site before treatment and at 5, 10, 20 and 30 min as well as at 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 h after drug administration. Serum was separated by centrifugation (1,100 *g* for 10 min) after coagulation for 20 min and then stored at –20° C until analysis. Model-independent pharmacokinetic parameters were calculated. The elimination rate constant (K_e) for thio-TEPA and TEPA was calculated by least-squares regression from the terminal linear slope of the individual semilogarithmic serum concentration-time plots; the calculation for TEPA was performed from the point at which its concentration equalled or exceeded 10 times that of thio-TEPA. The elimination half-life was derived from the equation $t_{1/2} = \ln 2/K_e$.

The area under the serum concentration-time curve (AUC) was calculated from zero to infinity using the trapezoidal rule:

$$AUC = \sum_{i=0}^{n-1} (t_{i+1} - t_i) \frac{C_{i+1} + C_i}{2} + \frac{C_n}{Ke},$$

where C_i represents the serum concentration measured at time t_i and C_n denotes the last measured serum concentration at time t_n. The total body clearance (Cl_t) for thio-TEPA was calculated from the equation $Cl_t = D/AUC$, where D is the delivered i. v. dose. Thio-TEPA and TEPA were assayed by gas chromatography as previously described [11, 14].

Myelosuppression. Myelosuppression was registered by serial measurements of platelet and leukocyte counts in peripheral blood. Measurements were performed weekly during the 8-week period covering the two courses under study.

Statistics. Differences between groups of observations were evaluated statistically by the Wilcoxon rank-sum test. The correlation between pharmacokinetic parameters and myelosuppression was investigated by linear regression including the calculation of Pearson correlation coefficients (r) and the significance of r towards zero. The analyses were performed using the statistical programme StatWorks (Cricket Software Inc.) on an Apple Macintosh computer.

Results

Pharmacokinetics

The serum concentration vs time curves for thio-TEPA and TEPA at thio-TEPA doses of 60 and 80 mg are shown in Fig. 1. The corresponding pharmacokinetic parameters are summarised in Table 2. The peak concentration (C_{max}) and AUC for thio-TEPA showed a dose-proportional increase, and the elimination half-life and total body clearance were not significantly different at the two dose levels, reflecting dose-independent pharmacokinetics. No sign of saturation of the metabolic conversion of thio-TEPA to TEPA was observed following an increase in the dose, as reflected by the unchanged ratios $AUC_{thio\text{-}TEPA}/AUC_{TEPA}$ and $C_{max\text{-}thio\text{-}TEPA}/C_{maxTEPA}$. No significant difference in the elimination half-life of TEPA between the two dose levels was observed.

Myelosuppression

The time course of leukocyte and platelet counts after the initial two courses of thio-TEPA treatment are given in Fig. 2 A. The average time to nadir was 3 weeks for platelets and 2 weeks for leukocytes during both courses under study. The time to leukocyte nadir showed greater interpatient variability than did the value for platelets. At 4 weeks after the courses, however, the nadir of both parameters had been passed in the great majority of patients; after 4 weeks, platelet nadirs were observed only on three occasions and leukocyte nadirs, on two occasions.

One women experienced severe myelosuppression; the time courses for her leukocyte and platelet counts are given in Fig. 2B. After the second course she developed grave pancytopenia (leukocytes, $0.5 \times 10^9/mm^3$; platelets, $13 \times 10^9/mm^3$; hemoglobin, 6.5 g/dl) complicated by suppurative parotitis. No bleeding complication occurred

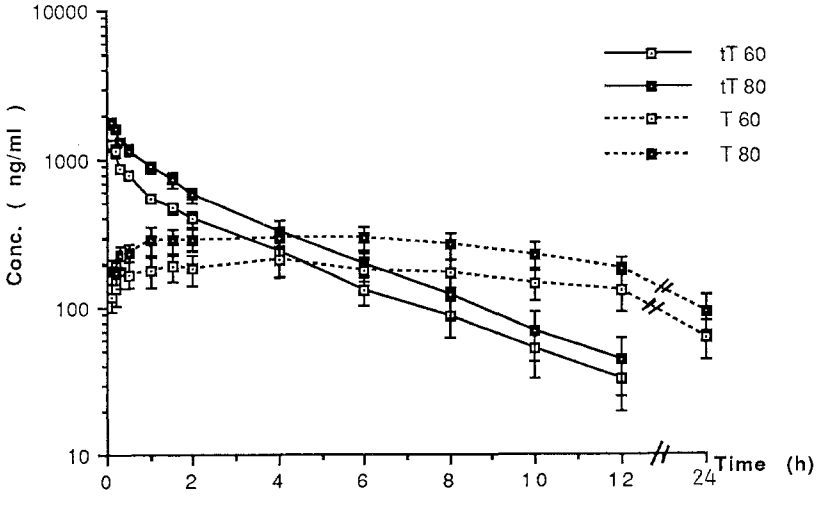

Fig. 1. Serum concentration-time curves for thio-TEPA (*tT*) and TEPA (*T*) after short-term i. v. infusions of thio-TEPA in 13 patients at doses of 60 and 80 mg. Points and bars represent the mean ± SEM

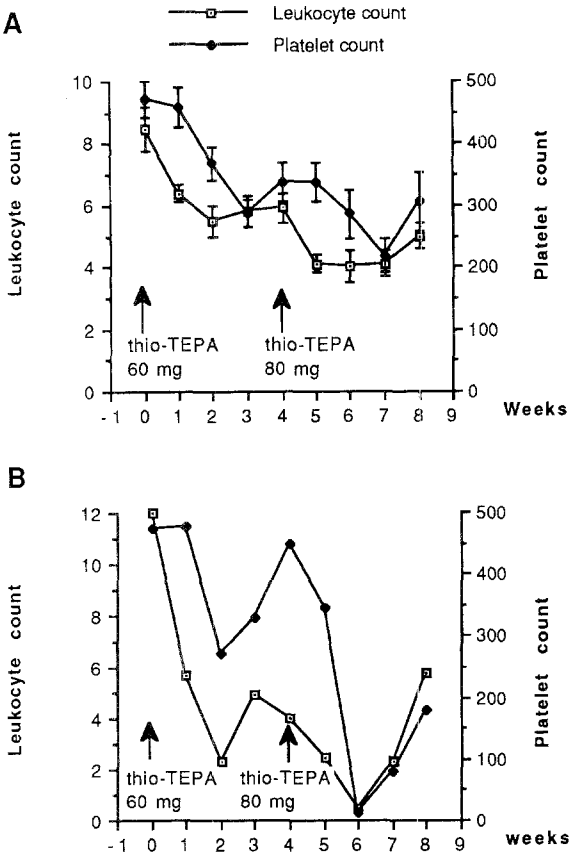

Fig. 2 A, B. The time course of platelet and leukocyte counts following the initial 2 courses of thio-TEPA treatment **A** in all 13 patients and **B** in one patient with severe myelosuppression. Points and bars in **A** represent the mean ± SEM

except cutaneous petechiae. The patient was given blood and platelet infusions and antibiotics and recovered within 2 weeks. The time to platelet nadir in this subject was 2 weeks for both courses, in contrast to all other patients, who showed values of at least 3 weeks. Due to an obvious tumour response after two courses, her treatment was continued at reduced doses. After 10 weeks a clinically complete response was achieved, which lasted for 5 months. Further severe myelotoxicity was not observed.

Apart from myelosuppression, side effects were limited to transient nausea and vomiting observed in two patients on the day of drug administration, in both cases after the 80-mg dose. No alopecia, allergy, CNS toxicity or urotoxicity was observed.

Correlation of pharmacokinetics and pharmacodynamics

To overcome the great variability in pretreatment values for platelet and leucocyte counts, the percentage of reduction in these parameters was used instead of absolute nadir values in the correlation analyses [9]:

$$\% \text{ reduction} = \frac{(\text{pre-course value} - \text{nadir value}) \times 100}{\text{pre-course value}} .$$

Statistically significant correlations were encountered only when reductions at the average times of nadir (i.e. 2 weeks for leukocytes and 3 weeks for platelets) were used instead of individual points of nadir. Pearson correlation coefficients between reductions in platelet and leukocyte counts and the various pharmacokinetic parameters of thio-TEPA and TEPA are given in Table 3. During the initial course, in which a dose of 60 mg was given, only the leukocyte reduction was significantly correlated to the AUC and elimination half-life for thio-TEPA. During the second course (dose, 80 mg), the percentage of reduction in both leukocytes and platelets were positively correlated to the elimination half-life and AUC for thio-TEPA. In addition, the reduction in platelets was inversely correlated to the total body clearance of this drug. Although substantial exposure to TEPA in terms of the AUC was observed, no significant correlations were demonstrated between myelosuppression and the AUC, C_{max} or elimination half-life values for TEPA; neither was the sum of AUCs for thio-TEPA and TEPA in individual patients significantly correlated to the degree of myelosuppression. Plots of the AUC

Table 2. Pharmacokinetic parameters for thio-TEPA and TEPA at the two dose levels of thio-TEPA

	thio-TEPA			TEPA		
	60 mg	80 mg	*P*-value	60 mg	80 mg	*P*-value
C_{max} (ng/ml)	1,331 ±119	1,828 ±135	0.002	273 ±46	353 ±62	0.002
$t_{1/2\,B}$ (h)	2.44 ± 0.26	2.29 ± 0.29	0.09	17.6 ± 3.6	15.7 ± 2.7	0.48
AUC (ng h ml^{-1})	2,832 ±412	4,127 ±668	0.004	4.789 ± 1,022	7,452 ± 1,667	0.004
Cl_t (ml/min)	446 ± 63	419 ± 56	0.11			
$\frac{C_{max\ thio\text{-}TEPA}}{C_{max\ TEPA}}$	8.6 ± 1.6 (60 mg)			7.3 ± 1.3 (80 mg)		0.211
$\frac{AUC_{thio\text{-}TEPA}}{AUC_{TEPA}}$	0.9 ± 0.2 (60 mg)			0.9 ± 0.2 (80 mg)		0.380

Values represent means ± SEM

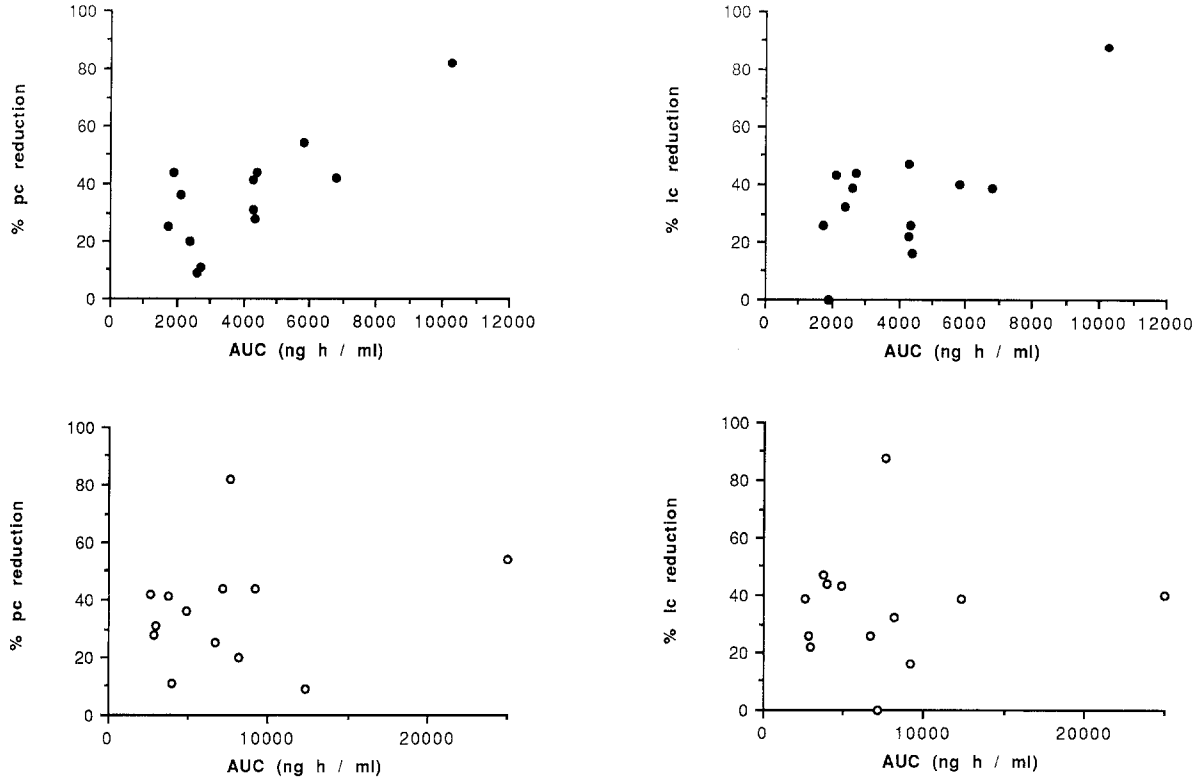

Fig. 3. The relationships between the percentage of reduction in platelets (*pc*) and leukocytes (*lc*) and the AUCs for thio-TEPA (●) and TEPA (○) during the 2nd course of treatment. Reductions in platelets after 3 weeks and reductions in leukocytes after 2 weeks are shown

Table 3. Pearson correlation coefficients between the percentage of reduction in platelets and leukocytes and the different pharmacokinetic parameters for thio-TEPA and TEPA

	thio-TEPA			TEPA		
	$t_{1/2B}$	AUC	Cl_t	C_{max}	$t_{1/2B}$	AUC
Platelet reduction (%):						
60 mg	0.22	0.46	0.52	0.39	0.28	0.13
	(0.488)	(0.123)	(0.081)	(0.170)	(0.380)	(0.679)
80 mg	0.73*	0.79*	–0.56*	0.34	0.18	0.21
	(0.005)	(0.001)	(0.049)	(0.180)	(0.558)	(0.484)
Leukocyte reduction (%):						
60 mg	0.82*	0.58*	–0.36	0.04	0.39	0.24
	(0.001)	(0.040)	(0.173)	(0.876)	(0.160)	(0.423)
80 mg	0.83*	0.68*	–0.50	0.11	0.06	0.08
	(<0.001)	(0.010)	(0.080)	(0.726)	(0.853)	(0.806)

Numbers in parentheses represent the *P*-values
* Statistical significance below the 5% level

vs myelosuppression data for thio-TEPA and TEPA during the second course are given in Fig. 3.

Discussion

As compared with phase I studies using dose escalations over a wide range, the dose increase in the present study from 60 to 80 mg thio-TEPA was relatively minor and could represent a limitation of the study's ability to predict dose-independent pharmacokinetics. On the other hand, pharmacokinetics at these two doses were studied in the same patients, thereby reducing the possibility of interindividual variation [12]. This design was also used in our previous study of thio-TEPA pharmacokinetics at doses of 20 and 30 mg [13]. The AUC/dose ratios at 20- and 30-mg doses were 55 ± 8 and 60 ± 10, respectively, which were not significantly different from the values of 47 ± 7 and

52 ± 8 for 60- and 80-mg doses in the present study. Thus, dose-independent pharmacokinetics are indicated for thio-TEPA over a wide conventional dose range.

Dose independency has also been confirmed in two studies of high-dose thio-TEPA treatment with autologous bone marrow transplantation (ABMT). Doses were escalated in ranges of 1.8–7 mg/kg [1] and 135–1,215 mg/m^2 [19], respectively, with no evidence of saturation of thio-TEPA clearance being observed. In contrast, another high-dose study using dose escalation in the range of 180–900 mg/m^2 indicated saturation of thio-TEPA clearance with increasing dose [16]. Recently, a study in pediatric patients has reported steadily declining total clearance of thio-TEPA and saturation of the formation of TEPA at doses increasing from 25 to 75 mg/m^2 [15]. This dose range includes the doses used in the present study, which represented equivalent doses of 37.6 ± 3.1 and 50.1 ± 4.1 mg/m^2.

This important disagreement between our results and those of the pediatric study may have several explanations. First, the capacity for metabolism of thio-TEPA in children may be different from that in adults and may lead to saturation in children at lower concentrations. Second, the children comprising the study population may have been susceptible to diverging thio-TEPA pharmacokinetics due to the combination of advanced, refractory disease and heavy pretreatment with other forms of chemotherapy and radiation. However, we also believe that the study design was suboptimal, as only 3–5 patients were studied at each dose level. Interindividual variance alone could have been responsible for the data that were interpreted as showing evidence of dose-dependent pharmacokinetics. Although great interindividual variation existed, the mean AUC for TEPA in the present study increased proportionally with increases from the 60- to the 80-mg dose. The same applied to the C_{max} value obtained for TEPA. Thus, we did not observe any sign of saturation of TEPA formation following an increase in the thio-TEPA dose, which supports our finding of dose-independent pharmacokinetics.

The occurrence of leukocyte nadirs before platelet nadirs was reported in one early clinical study [3] and, more recently, in an additional clinical study [20] and in an experimental study in rats [23]. However, this phenomenon was not described in the above-cited pediatric study, in which nadirs for both granulocytes and platelets were reported on day 17 [15]. Our finding of a more uniform time to nadir for platelets than for leukocytes would be expected because platelets originate from the bone marrow alone, whereas the leukocytes in peripheral blood originate from both the bone marrow and the lymphoproliferative system. A more precise study design would therefore have involved measurement of the different WBC constituents instead of the total number of leukocytes.

The study of pharmacokinetic - pharmacodynamic relationships was restricted to myelosuppression because a systematic evaluation of therapeutic response would have been hampered by different intentions for the use of chemotherapy among patients (curative, adjuvant, palliative). More convincing correlation between pharmacokinetics and pharmacodynamics during the second as compared with the first course would be expected, merely because of the increased dose. In addition, the high levels of platelets and leukocytes prior to the first course (Fig. 2A) may reflect increased bone marrow activity due to the surgical trauma, as most patients underwent surgery ~2 weeks before the start of chemotherapy. The subsequent fall in platelets and leukocytes may reflect a normalization of bone marrow activity following surgery, interfering with chemotherapy-induced myelosuppression.

In contrast to our findings for the parent drug, no significant correlation could be demonstrated between any available pharmacokinetic parameter of the metabolite TEPA and its pharmacodynamics in terms of myelosuppression, despite the much greater interindividual variation noted in the exposure of patients to TEPA as opposed to the parent drug. The most obvius interpretation of these data would be that in the clinical situation the cytotoxicity of TEPA is lower than that of thio-TEPA. Although the mean AUC value for TEPA exceeded that for thio-TEPA, its peak concentration reached <20% of that of the parent drug. If a threshold concentration for the cytotoxic effect of TEPA exists, it may be that this value was not exceeded. On the other hand, it could be that factors not reflected by the current pharmacokinetic parameters are determinants for the cytotoxic effect of TEPA, e.g. distribution, serum protein binding and cellular uptake. Available clinical pharmacological data on TEPA are limited and conflicting. The findings of the present study oppose the proposition that thio-TEPA should act as a pro-drug for TEPA [6]. Further studies of TEPA are needed to clarify its role in the total metabolism of thio-TEPA and its contribution to the cytotoxic effect.

The current description of the pharmacokinetic-pharmacodynamic relationship for thio-TEPA that was obtained by linear regression no doubt represents a simplification of the issue. More sophisticated mathemathical models such as those proposed for carboplatin [5, 9] are probably needed for the construction of predictive models for individualized dosing. However, the present data represent the first attempt to describe this relationship during treatment with conventional doses of thio-TEPA and should encourage further investigation in future studies. A limited sampling strategy for the prediction of the AUC for the drug has been proposed [1].

No significant divergence of thio-TEPA pharmacokinetics was found in the only patient with reduced renal function. However, the subject who developed pancytopenia exhibited pharmacokinetic parameters during both courses of thio-TEPA that were clearly divergent from those of the other patients. Elimination half-lives were 5.18 and 5.49 h during the 1st and 2nd courses, respectively, as compared with 95% confidence intervals of 1.23–3.19 and 1.09–2.97 h, respectively, in the remaining 12 patients. Renal and hepatic functions were normal and no concomitant medication was given. The body surface was 1.6 m^2, which is equal to the mean, showing that this patient was not given proportionally larger doses than the rest of our subjects. One could speculate that the delayed clearance of thio-TEPA in this case was a result of its impaired conversion to TEPA; however, the ratios of $AUC_{thio\text{-}TEPA}/AUC_{TEPA}$ were 1.2 and 1.4 at the 60- and 80-mg doses, respectively, which is not significantly different from the mean

ratio of 0.9 found at both dose levels. Thus, although no specific background for an alteration in the pharmacokinetics of thio-TEPA can be offered, the latter provides an explanation for the unexpected myelosuppression observed in this patient.

In conclusion, this study further indicates dose-independent pharmacokinetics for thio-TEPA. The time to platelet nadir was quite uniformly 3 weeks and was usually longer than the time to leukocyte nadir, which was more variable. These data indicate that 4 weeks would be the advisable interval between courses in patients treated with single i.v. bolus injections of thio-TEPA. The demonstration of significant correlations between the pharmacokinetics of the parent drug and its effects on the bone marrow should encourage efforts to develop pharmacokinetically guided strategies for dose individualization in future studies.

Acknowledgements. The author would like to thank O. G. Nilsen for his advice and encouragement during the preparation of this paper. The excellent technical assistance of G. Neverdal is also greatly appreciated.

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