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ORIGINAL ARTICLE

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Plasma pharmacokinetics and cerebrospinal fluid penetration of thioguanine in children with acute lymphoblastic leukemia: a collaborative Pediatric Oncology Branch, NCI, and Children's Cancer Group study

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Abstract *Purpose*: In preclinical studies, thioguanine (TG) has been shown to be more potent than the standard acute lymphoblastic leukemia (ALL) maintenance agent, mercaptopurine (MP), suggesting that TG may be more efficacious than MP in the treatment of childhood ALL. As part of a pilot trial in which TG was used in place of MP, we studied the plasma pharmacokinetics of oral TG and measured steady-state plasma and CSF TG concentrations during a continuous intravenous infusion (CIVI) in children with newly diagnosed standard-risk ALL. *Methods*: Nine plasma samples were collected after each patient's first 60 mg/m^2 oral TG dose during maintenance. CIVI TG (20 mg/m^2/h over 24 h) was administered during the consolidation phase of therapy, and simultaneous plasma and CSF samples were collected near the end of the infusion. TG was measured by reverse-phase HPLC with ultraviolet detection. Erythrocyte TG nucleotide (TGN) concentrations were measured 7 days after a course of CIVI TG and prior to the start of each maintenance cycle. *Results*: After oral TG ($n=35$), the mean ($\pm$SD) peak plasma concentration was 0.46 ± 0.68 μM and the AUC ranged from 0.18 to 9.5 $\mu M \cdot$ h (mean 1.5 $\mu M \cdot$ h). Mean steady-state plasma and CSF TG concentrations during CIVI ($n=33$) were 2.7 and 0.5 μM, respectively. The mean ($\pm$SD) TG clearance was 935 ± 463 ml/min per m^2. Plasma TG concentrations did not correlate with erythrocyte TGN concentrations after oral or CIVI TG. The 8-OH-TG metabolite was detected in plasma and

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CSF. *Conclusions*: TG concentrations that are cytotoxic to human leukemia cell lines can be achieved in plasma after a 60 mg/m^2 oral dose of TG and in plasma and CSF during CIVI of TG.

Key words 6-Thioguanine · 8-OH-Thioguanine · Childhood · Leukemia · Pharmacokinetics

Introduction

Over the past four decades, significant advances in the treatment of childhood acute lymphoblastic leukemia (ALL) have improved cure rates to 65% to 85%, but leukemic relapse during or shortly after the completion of maintenance therapy remains the most common cause of treatment failure. Developing new strategies to improve the efficacy of current maintenance therapy regimens is critical to further lowering relapse rates [16]. Daily oral mercaptopurine (MP) and weekly methotrexate remain the cornerstone of maintenance chemotherapy regimens, with many current treatment regimens also incorporating monthly pulses of vincristine and prednisone. The selection of MP rather than the related thiopurine, thioguanine (TG), for maintenance regimens was empirical [7] and does not have a pharmacological basis.

TG appears to have pharmacological advantages over MP for the treatment of childhood ALL. The thiopurines must be converted intracellularly to the nucleotide, thioguanylate triphosphate, which is incorporated into DNA, in order to produce a cytotoxic effect [14, 17]. Three enzymatic steps are required to convert MP to thioguanine monophosphate, whereas TG is converted to the monophosphate in a single step reaction catalyzed by hypoxanthine-guanine phosphoribosyltransferase. Additionally, in human lymphoblastic leukemia cell lines and in lymphoblasts from children with ALL, TG has been shown to be tenfold more potent than MP in vitro [2]. The IC_{50} values for the three human lymphoblastic cell lines tested ranged from 0.04 to 0.07 μM for TG. TG was also less schedule-dependent than MP in these in vitro studies. Based on these preclinical data and the results of a phase I trial of continuous intravenous infusion (CIVI) TG [10], we performed a pilot clinical trial in which CIVI and oral TG were incorporated into a multiagent chemotherapy regimen in place of MP for the treatment of children with standard-risk ALL. One rationale for incorporation of the higher dose CIVI TG regimen was to achieve cytotoxic TG concentrations in the cerebrospinal fluid (CSF).

Here we report the plasma pharmacokinetics of oral and CIVI TG, the CSF penetration of TG, and the concentration of red blood cell (RBC) TG nucleotides (TGN) in children enrolled on this pilot trial. Clinical results from this pilot study will be reported separately.

Materials and methods

Patient eligibility and protocol design

This pilot clinical trial evaluating TG in place of MP for the treatment of childhood ALL was a collaborative trial of the Pediatric Oncology Branch, NCI, and the Children's Cancer Group (CCG). Previously untreated children with standard-risk ALL as defined by the NCI consensus criteria [19] were eligible for this trial. Patients were greater than 1 year and less than 10 years of age and had a white blood cell count $< 50{,}000/\mu l$ at diagnosis. Patients with a leukemic karyotype of t(9;22) or t(4;11), an L3 morphology (Burkitt's cell leukemia), or meningeal leukemia at diagnosis were excluded from the trial. The planned treatment regimen, which was based on the best regimen from the CCG 105 study [20], is outlined in Table 1. During consolidation and interim maintenance, 480 mg/m^2 TG was administered by CIVI over 24 h (20 mg/m^2 per h) every 2 weeks for a total of six doses. A course of CIVI TG was also administered every 8 weeks during the first year of maintenance chemotherapy. The planned treatment regimen included oral TG 60 mg/m^2 per day daily during weeks 2 through 6 of each 8-week cycle during the first year of maintenance, and then daily during the second and third years of chemotherapy.

TG pharmacokinetic sampling and assay

During the first CIVI of TG, a lumbar puncture was performed at steady-state prior to the end of the infusion for CSF TG determination. A simultaneous blood sample was obtained from a site different than the site of drug infusion for the measurement of the steady-state plasma TG concentration. Blood samples were also drawn immediately prior to and 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h after the first oral dose of TG during maintenance chemotherapy. Blood samples were centrifuged and CSF and plasma were stored at –20 °C until analysis. Plasma and CSF TG concentrations were determined using a previously described reverse-phase HPLC assay [10].

The concentration of the previously reported 8-hydroxylated metabolite of TG (8-OH-TG) [11] was estimated from the TG standard curve, because there was insufficient 8-OH-TG standard available. The maximum UV absorbance of 8-OH-TG and TG are similar.

Pharmacokinetic analysis

The area under the TG concentration-time curve (AUC) for the oral dose was derived with the trapezoidal method and extrapolated to infinity. The elimination half-life was estimated by regression analysis on the terminal portion of the log-transformed plasma concentration-time curve. Plasma clearance of TG was calculated by dividing the TG dose rate (20 mg/m^2 per h) by the steady-state TG concentration in plasma during the CIVI. The CSF penetration was calculated by dividing the simultaneous steady-state concentration of TG in CSF by the steady-state concentration of TG in plasma.

The significance of the gender difference in the AUC of oral TG was evaluated with the Mann-Whitney *U*-test for comparison of unpaired means, and the relationship between patient age and the AUC of oral TG was assessed by deriving the correlation coefficient.

Intracellular thiopurines

RBC TGN concentrations were measured in each patient 7 days after CIVI TG during the consolidation phase, and prior to the start of each maintenance cycle using a previously described assay [9]. The degree of correlation between the oral TG AUC or plasma

Table 1 Planned treatment regimen

Phase	Drug	Dose	Schedule
Induction (4 weeks)	Vincristine	1.5 mg/m^2 (2 mg max dose) IV	Weekly for 4 weeks
	Asparaginase	6,000 U/m^2 IM	Mon, Wed, Fri for nine doses
	Prednisone	40 mg/m^2/day PO	Three divided doses for 28 days
	Methotrexate	According to age, IT	Days 0 and 14
Consolidation (4 weeks)	Vincristine	1.5 mg/m^2 (2 mg max dose) IV	Day 0
	Prednisone	Taper	Days 0 to 10
	Thioguanine	480 mg/m^2 CIVI	Over 24 h (20 mg/m^2/h), days 0 and 14
	Methotrexate	According to age, IT	Weekly for 4 weeks
Interim maintenance (4 weeks ×2)	Vincristine	1.5 mg/m^2 (2 mg max dose) IV	Day 0
	Prednisone	40 mg/m^2/day PO	Three divided doses for 5 days starting day 0
	Thioguanine	480 mg/m^2 CIVI	Over 24 h (20 mg/m^2/h), days 0 and 14
	Methotrexate	20 mg/m^2 PO	Weekly for 4 weeks
Delayed intensification (7 weeks)	Vincristine	1.5 mg/m^2 (2 mg max dose) IV	Days 0, 7, 14
	Asparaginase	6000 U/m^2 IM	Mon, Wed, Fri for six doses
	Dexamethasone	10 mg/m^2/day PO	Three divided doses for 21 days; taper over 7 days
	Doxorubicin	25 mg/m^2/day IV	Days 0, 7, 14
	Cytarabine	75 mg/m^2/day IV	Daily, days 29–32, 36–39
	Cyclophosphamide	1000 mg/m^2 IV	Over 1 h, day 28
	Thioguanine	60 mg/m^2/day PO	Days 28–41
	Methotrexate	According to age, IT	Day 0, 28, 35
Maintenance, year 1 (8-week cycles)	Vincristine	1.5 mg/m^2 (2 mg max dose) IV	Every 4 weeks
	Prednisone	40 mg/m^2/day PO	Three divided doses for 5 days, weeks 0, 4
	Thioguanine	480 mg/m^2 CIVI	Over 24 h (20 mg/m^2/h) starting day 0
	Thioguanine	60 mg/m^2/day PO	Daily, starting day 14, weeks 2–6
	Methotrexate	20 mg/m^2 PO	Weekly
	Methotrexate	According to age, IT	Day 0
Maintenance, years 2, 3 (12-week cycles)	Vincristine	1.5 mg/m^2 (2 mg max dose) IV	Every 4 weeks
	Prednisone	40 mg/m^2/day PO	Three divided doses for 5 days, weeks 0, 4, 8
	Thioguanine	60 mg/m^2/day PO	Daily
	Methotrexate	20 mg/m^2 PO	Weekly
	Methotrexate	According to age, IT	Day 0

Table 2 Pharmacokinetic parameters for oral TG in 35 patients (C_{max} peak plasma concentration, AUC area under the concentration-time curve, $T_{1/2}$ half-life)

	C_{max} (μM)	Time to peak (h)	AUC ($\mu M \cdot$ h)	$T_{1/2}$ (h)
Mean ± SD	0.52 ± 0.72	2.2 ± 1.3	1.5 ± 1.7	1.6[a]
Median	0.29	2.0	1.0	1.6
Range	0.07–4.0	0.50–6.0	0.18–9.5	0.8–18
Interquartile range	0.1–0.49	1.0–3.0	0.52–1.4	0.9–2.2
Coefficient of variation (%)	139	57	115	–

[a] Harmonic mean

steady-state TG concentration during CIVI and RBC TGN concentrations were analyzed using the nonparametric Spearman's rho as a test of correlation.

Results

Between January 1995 and April 1996, 58 patients, median age 3 years (range 1 to 9 years) with standard-risk ALL were enrolled on the pilot treatment trial, and pharmacokinetic samples for oral and CIVI TG were obtained from 41 patients (21 males).

Oral TG pharmacokinetics

TG and its metabolite 8-OH-TG were detected in the plasma of patients after an oral dose of TG (Fig. 1).

Pharmacokinetic parameters for oral TG are summarized in Table 2. The AUC could be extrapolated to infinity in 35 of the 41 patients (five patients had insufficient data during the terminal elimination phase to estimate the terminal $t_{1/2}$, and one patient had TG concentrations below the limit of quantitation of <0.05 μM throughout the sampling period). The TG AUC after the first 60 mg/m^2 oral dose was highly variable (Fig. 2). In the 35 patients, the $AUC_{0-\infty}$ ranged from 0.18 to 9.5 $\mu M \cdot$ h. As shown in Fig. 3, there was no significant correlation between TG $AUC_{0-\infty}$ and patients' age ($r=-0.12$; $P=0.48$), and no significant difference between $AUC_{0-\infty}$ in males vs females ($P=0.53$). The harmonic mean terminal elimination half-life of TG was 1.6 h.

The pharmacokinetics of 8-OH-TG were evaluated in a subset of 24 patients. The metabolite was quantifiable in 18 of the 24 patients. The estimated mean ($\pm$SD) peak plasma concentration of 8-OH-TG was 0.17 ± 0.09 μM, which is approximately one-third that of the peak plasma concentration of TG (0.46 ± 0.68 μM).

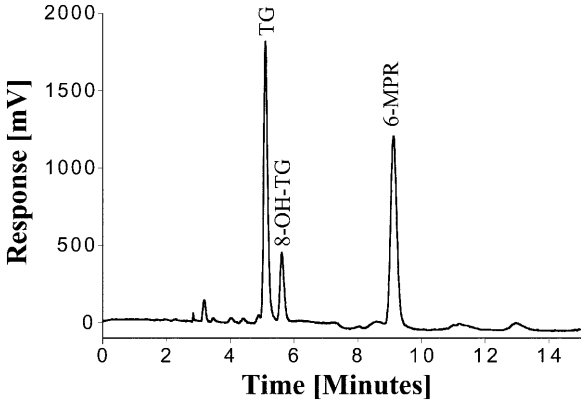

Fig. 1 Representative chromatogram from patient plasma after an oral dose of TG. Retention times are approximately 5.1 min for TG, 5.7 min for its metabolite, 8-OH-TG, and 8.9 min for the internal standard, mercaptopurine riboside (6-MPR)

CIVI TG pharmacokinetics

Samples for the determination of plasma steady-state concentrations of TG during the CIVI were collected from 33 of the patients who were enrolled on the pilot treatment trial. The mean ($\pm$SD) plasma steady-state concentration of TG was 2.7 ± 1.4 μM. Of the 33 patients, 32 had steady-state plasma concentrations of ≥ 1 μM. The mean ($\pm$SD) clearance of TG was 935 ± 463 ml/min per m^2.

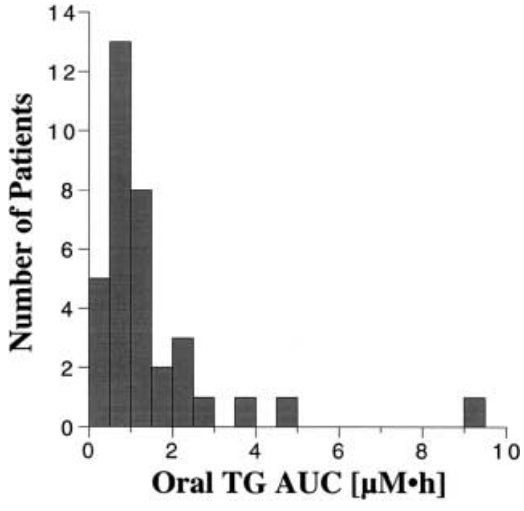

Fig. 2 Frequency distribution of plasma AUCs for 35 pediatric patients with ALL treated with 60 mg/m^2 of oral TG

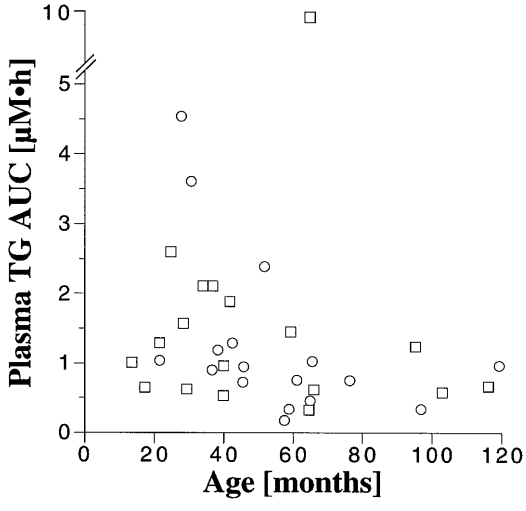

Fig. 3 The plasma AUCs of oral TG in 35 pediatric patients as a function of age and gender (❑ female, ❍ male). The variability in AUC was not explained by age-related ($r=-0.12$) or gender-related ($P=0.53$) differences in bioavailability or clearance

Table 3 CSF pharmacokinetics of TG (C_{ss} steady-state concentration)

	Plasma C_{ss} (μM) ($n=33$)	CSF C_{ss} (μM) ($n=48$)	CSF:plasma (%) ($n=32$)
Mean $\pm$ SD	2.7 ± 1.4	0.5 ± 0.5	0.18 ± 0.11
Median	2.3	0.39	0.18
Range	0.8–7.1	<0.05–2.8	<0.03–0.42
Interquartile range	1.5–3.2	0.18–0.61	0.12–0.25
Coefficient of variation (%)	52	99	58

The 8-OH-TG metabolite was detected in the plasma of 11 of a subset of 12 patients during CIVI TG. The mean (±SD) of 8-OH-TG steady-state plasma concentration, which was estimated from the TG standards, was 0.89±0.59 μ*M* and the mean (±SD) TG steady-state concentration in these 11 patients was 3.07±1.2 μ*M*.

CSF penetration

Steady-state CSF samples were collected from 48 patients, including 32 patients who had both plasma and CSF steady-state samples collected (Table 3). The mean CSF steady-state TG concentration was 0.5 μ*M* and the mean CSF:plasma ratio ($n=32$) was 18%. In a subset of 24 patients, the 8-OH-TG metabolite was detected in the CSF of 18 patients following CIVI TG, and the steady-state CSF concentration of the metabolite ranged from <0.05 to 0.27 μ*M* (mean 0.09 μ*M*).

Intracellular thiopurines

The mean (±SD) RBC TGN concentration 7 days after CIVI TG was 224±100 ng/8 × 10^8 RBC ($n=40$). RBC TGN concentrations did not correlate with steady-state plasma concentrations ($r=0.09$, Fig. 4A). The mean (±SD) RBC TGN concentration prior to maintenance cycle 2 after daily oral TG was 107.2±82 ng/8 × 10^8 RBC. RBC TGN concentrations during maintenance cycle 2 did not correlate with plasma TG AUC ($r=0.32$, Fig. 4B). In addition, there was no statistically significant correlation between RBC TGNs and C_{max} during oral dosing of TG.

Discussion

TG pharmacokinetics in children were characterized by rapid elimination (clearance >900 ml/min per m^2) during the CIVI and variable plasma drug exposure (AUC range 0.18 to 9.5 μ*M* · h) after oral dosing. This is similar to the pharmacokinetic behavior of the other thiopurine analog, MP [4, 21, 22]. With the CIVI regimen, tolerable doses of MP [1, 22] and TG achieve steady-state plasma and CSF drug concentrations and exposure durations that exceed those required to produce a cytotoxic effect in vitro against human lymphoblastic cell lines [2, 10]. For oral TG, plasma drug concentrations and exposure durations were also above the in vitro therapeutic range. The average time that the patients' plasma concentration of TG exceeded the minimal in vitro cytotoxic concentration of 0.04 μ*M* was 5.1 h (range 1 to 7.5 h), and in cell lines, exposure durations as short as 4 h were cytotoxic [2]. With oral MP, plasma concentrations and exposure durations may be subtherapeutic based on the in vitro cytotoxicity studies [2, 21].

In the other reported pharmacokinetic study of oral TG in children, five patients with ALL were evaluated after a 40 mg/m^2 oral dose of TG [13]. The median peak plasma concentration achieved was 0.1 μ*M* (range 0.045 to 0.32 μ*M*), and the median AUC_{0-6} was 0.16 μ*M* · h (range 0.15 to 0.49 μ*M* · h). The median terminal half-life was 2 h (range 0.8 to 6.2 h). The dose-dependent nature of TG pharmacokinetics [10] may explain the disproportionately higher C_{max} and AUC at a dose of 60 mg/m^2 in our study compared to the smaller study at a lower dose. Our results are also similar to those reported by Brox et al. from a study of 13 adult patients with acute myelogenous leukemia who received 100 mg/m^2 of oral TG every 12 h [6]. In that study, the maximum concentration reached following an oral dose of TG varied by 30-fold and ranged from 0.03 to 0.84 μ*M*, with a mean elimination half-life of 110 min (range 45 to 240 min).

The dose of TG used for the CIVI in the current study was based on our previous phase I trial of TG

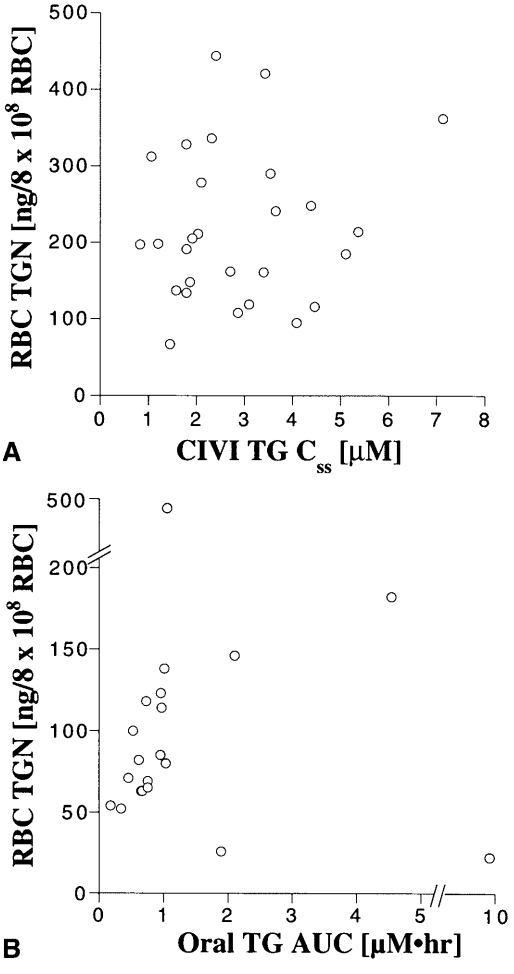

Fig. 4A,B Relationship between (**A**) TG C_{ss} during CIVI and RBC TGN concentration 7 days after the infusion ($r=0.09$, $n=27$) and (**B**) oral TG AUC and RBC TGN concentration on day 0 of the second maintenance cycle ($r=0.32$, $n=29$)

administered by CIVI in which doses were escalated until the plasma steady-state concentration exceeded the 1 μM target plasma concentration [10]. In the current study, we achieved a mean steady-state plasma concentration of 2.7 μM (range 0.83 to 7.13 μM) following a 20 mg/m^2 per h CIVI over 24 h. This is comparable to the mean steady-state plasma concentration of 4.1 μM (range 1.0 to 8.3 μM) achieved in the phase I trial.

We have previously identified the novel metabolite 8-OH-TG [11] in patients treated on the phase I CIVI TG protocol. In the current pilot trial we detected the metabolite in plasma after an oral dose of TG, and it appears to be the primary circulating metabolite under our assay conditions. The metabolite was also detected in plasma during CIVI TG, as well as in the CSF. We have previously demonstrated that TG is a substrate for aldehyde oxidase, the action of which in vitro results in formation of 8-OH-TG [11]. Oxidation of the thiopurines at the 8-position renders them inactive [8]. We speculate that the apparently low and variable bioavailability of TG observed by us and by others [6, 15] may be partly the result of first-pass metabolism to 8-OH-TG by hepatic aldehyde oxidase. The interpatient variability observed in our study following oral dosing with TG is similar to that following oral dosing with MP [21].

In this study, we did not study the intrapatient variability of TG pharmacokinetics following oral administration of drug. Experience with MP suggests that the intrapatient variability of oral thiopurines is likely to be high [4]. As RBC TGN determinations reflect repeated drug exposures over the lifespan of erythrocytes, it was not unexpected that we were unable to identify a correlation between plasma TG pharmacokinetics after a single oral dose and RBC TGN concentrations.

Central nervous system (CNS) relapse occurs in approximately one-third of the children who experience a relapse, and therefore remains an important site of relapse in childhood ALL. Current treatment regimens rely primarily on intrathecal agents for prevention of leptomeningeal recurrence, and new CNS-directed treatment strategies are needed to improve the overall success rate of ALL treatment regimens [16]. The mean steady-state TG CSF concentration was 0.5 μM during CIVI, a concentration that is approximately tenfold higher than the in vitro IC_{50} values in human lymphoblastic cell lines [2]. The CSF penetration of 18% observed in our study is similar to the estimated 25% penetration previously observed in an animal model [18]. The CSF penetration of TG is comparable to the CSF penetration of MP [3]. The tenfold greater potency of TG, however, suggests that cytotoxic concentrations of TG may also be achieved in the CSF following an oral TG dose. Although aldehyde oxidase has been observed in the CNS in animal models and may be present in humans [5, 12], it appears unlikely that CNS aldehyde oxidase contributed significantly to the metabolism of TG in the CSF, as the steady-state 8-OH-TG to TG ratio in CSF was similar to the steady-state ratio observed in plasma (0.28 and 0.25, respectively).

This pharmacokinetic study, which was part of a pilot treatment trial studying the role of TG in the treatment of ALL, provides further evidence that there may be a pharmacologic advantage for TG over MP in treating ALL. Plasma TG concentrations were in the cytotoxic range after CIVI and oral dosing, and cytotoxic concentrations were also achieved in the CSF. Based in part on the results of this pilot study, a prospective randomized trial comparing oral TG and oral MP for the treatment of pediatric patients with newly diagnosed standard-risk ALL is being performed by the Children's Cancer Group.

References

1. Adamson PC, Zimm S, Ragab AH, Balis F, Steinberg SM, Kamen BA, Vietti TJ, Gillespie A, Poplack DG (1992) A phase II trial of continuous-infusion 6-mercaptopurine for childhood leukemia. Cancer Chemother Pharmacol 30(2): 155
2. Adamson PC, Poplack DG, Balis FM (1994) The cytotoxicity of thioguanine vs mercaptopurine in acute lymphoblastic leukemia [see comments]. Leuk Res 18(11): 805
3. Balis FM, Holcenberg JS, Poplack DG (1997) General principles of chemotherapy. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology. Lippincott-Raven, Philadelphia, p 215
4. Balis FM, Holcenberg JS, Poplack DG, Ge J, Sather HN, Murphy RF, Ames MM, Waskerwitz MJ, Tubergen DG, Zimm S, Gilchrist GS, Bleyer WA (1998) Pharmacokinetics and pharmacodynamics of oral methotrexate and mercaptopurine in children with lower risk acute lymphoblastic leukemia: a joint Children's Cancer Group and Pediatric Oncology Branch study. Blood 92(10): 3569
5. Bendotti C, Prosperini E, Kurosaki M, Garattini E, Terao M (1997) Selective localization of mouse aldehyde oxidase mRNA in the choroid plexus and motor neurons. Neuroreport 8(9–10): 2343
6. Brox LW, Birkett L, Belch A (1981) Clinical pharmacology of oral thioguanine in acute myelogenous leukemia. Cancer Chemother Pharmacol 6(1): 35
7. Burchenal J, Murphy M, Ellison R, Sykes M, Tan T, Leone L, Karnofsky D, Craver L, Dargeon H, Rhoads C (1953) Clinical evaluation of a new antimetabolite, 6-mercaptopurine, in the treatment of leukemia and allied diseases. Blood 8: 965
8. Clarke DA, Elion GB, Hitchings GH, Stock CC (1958) Structure-activity relationships among purines related to 6-mercaptopurine. Cancer Res 18: 445
9. Erdmann GR, France LA, Bostrom BC, Canafax DM (1990) A reversed phase high performance liquid chromatography approach in determining total red blood cell concentrations of 6-thioguanine, 6-mercaptopurine, methylthioguanine, and methylmercaptopurine in a patient receiving thiopurine therapy. Biomed Chromatogr 4(2): 47
10. Kitchen BJ, Balis FM, Poplack DG, O'Brien M, Craig CE, Adamson PC (1997) A pediatric phase I trial and pharmacokinetic study of thioguanine administered by continuous i.v. infusion. Clin Cancer Res 3(5): 713
11. Kitchen BJ, Moser A, Lowe E, Balis FM, Widemann B, Anderson L, Strong J, Blaney SM, Berg SL, O'Brien M, Adamson PC (1999) Thioguanine administered as a continuous intravenous infusion to pediatric patients is metabolized to the novel metabolite 8-hydroxy-thioguanine. J Pharmacol Exp Ther 291(2): 870

12. Krenitsky TA, Tuttle JV, Cattau EL Jr, Wang P (1974) A comparison of the distribution and electron acceptor specificities of xanthine oxidase and aldehyde oxidase. Comp Biochem Physiol B 49(4): 687
13. Lennard L, Davies HA, Lilleyman JS (1993) Is 6-thioguanine more appropriate than 6-mercaptopurine for children with acute lymphoblastic leukaemia? Br J Cancer 68(1): 186
14. LePage GA (1960) Incorporation of 6-thioguanine into nucleic acids. Cancer Res 20: 403
15. LePage GA, Whitecar JP Jr (1971) Pharmacology of 6-thioguanine in man. Cancer Res 31: 1627
16. Margolin JF, Poplack DG (1997) Acute lymphoblastic leukemia. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology. Lippincott-Raven, Philadelphia, p 409
17. Nelson JA, Carpenter JW, Rose LM, Adamson DJ (1975) Mechanisms of action of 6-thioguanine, 6-mercaptopurine, and 8-azaguanine. Cancer Res 35(10): 2872
18. Schouten TJ, De Abreu RA, Schretlen ED, van Leeuwen MB, van Baal JM, de Vaan GA (1985) 6-Thioguanine: high-dose 2-H infusions in goats. J Cancer Res Clin Oncol 110(2): 115
19. Smith M, Arthur D, Camitta B, et al (1996) Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia [see comments]. J Clin Oncol 14(1): 18
20. Tubergen DG, Gilchrist GS, O'Brien RT, Coccia PF, Sather HN, Waskerwitz MJ, Hammond GD (1993) Improved outcome with delayed intensification for children with acute lymphoblastic leukemia and intermediate presenting features: a Children's Cancer Group phase III trial. J Clin Oncol 11(3): 527
21. Zimm S, Collins JM, Riccardi R, O'Neill D, Narang PK, Chabner B, Poplack DG (1983) Variable bioavailability of oral mercaptopurine. Is maintenance chemotherapy in acute lymphoblastic leukemia being optimally delivered? N Engl J Med 308(17): 1005
22. Zimm S, Ettinger LJ, Holcenberg JS, Kamen BA, Vietti TJ, Belasco J, Cogliano-Shutta N, Balis F, Lavi LE, Collins JM, et al (1985) Phase I and clinical pharmacological study of mercaptopurine administered as a prolonged intravenous infusion. Cancer Res 45(4): 1869