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ORIGINAL ARTICLE

**Cheri E. Klein · Helen Kastrissios
Antonius A. Miller · Donna Hollis · Daohai Yu
Gary L. Rosner · David L. Grinblatt
Richard A. Larson · Mark J. Ratain**

Pharmacokinetics, pharmacodynamics and adherence to oral topotecan in myelodysplastic syndromes: a Cancer and Leukemia Group B study

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Abstract *Objective*: To evaluate medication adherence, pharmacokinetics and exposure versus response relationships in patients with myelodysplastic syndromes (MDS). *Methods*: Ninety adult patients with MDS received oral topotecan (1.2 mg/m^2) either once a day for 10 days or twice a day for 5 days every 21 days for up to six cycles. Dosing histories were collected using electronic monitoring devices fitted to medication vials. Topotecan plasma concentrations were measured, and exposure was determined by a sparse sampling approach and Bayesian estimation methods. Relationships between exposure and clinical response and toxicity were evaluated using logistic regression. *Results*: Overall adherence was excellent with 90% of patients taking the prescribed number of doses in cycle 1. Adherence did not differ between the two regimens. Topotecan pharmacokinetics were described using a one compartment open model with first order absorption and elimination. Pharmacokinetic parameter estimates did not differ between the once a day and twice a day dosing groups. While topotecan exposure was greater in the twice a day arm compared to the once a day arm due to drug accumulation, exposure did not correlate with clinical response. However, the probability of needing a platelet transfusion in the twice a day arm was significantly increased (by 35%) as a result of greater steady-state plasma topotecan concentrations. *Conclusions*: Adherence is high in patients with MDS receiving oral topotecan, whether the drug is prescribed once or twice daily. The optimal schedule cannot be determined from this study, as there was no evident relationship between any pharmacokinetic parameter and clinical response.

Keywords Topotecan · Myelodysplastic syndromes · Adherence · Exposure-response · Pharmacokinetics

C. E. Klein · H. Kastrissios (✉)
Department of Biopharmaceutical Sciences, The University of Illinois at Chicago, 833 South Wood Street (MC 865), Chicago, IL 60612, USA
E-mail: helenk@uic.edu
Tel.: +1-312-9960888
Fax: +1-312-9960098

A. A. Miller
Comprehensive Cancer Center, Wake Forest University, Winston-Salem, NC, USA

D. Hollis · D. Yu · G. L. Rosner
CALGB Statistical Center, Duke University, Durham, NC, USA

D. L. Grinblatt · R. A. Larson · M. J. Ratain
Section of Hematology-Oncology, Department of Medicine, Committee on Clinical Pharmacology and Pharmacogenomics, and Cancer Research Center, The University of Chicago, Chicago, IL, USA

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous disease characterized by morphologic dysplasia of one or more hematopoietic cell lines. MDS incidence increases with age, from 2 per 100,000 at age 50 to 30 per 100,000 by age 70 [1]. With the aging of the US population, more patients will be diagnosed with MDS. Patient prognosis remains poor. Survival depends on the type of MDS and ranges from an average of 5 months for high risk MDS such as refractory anemia with excess blasts in transformation (RAEBt), to 4 years for low risk MDS such as refractory anemia (RA) and RA with ringed sideroblasts (RARS) [2].

Treatment for MDS consists primarily of supportive care measures including blood transfusions, antibiotics and hematopoietic growth factors to prevent secondary complications such as infection or bleeding. Cytotoxic agents, including those showing activity against leukemia, have been explored as chemotherapy, including cytarabine, doxorubicin, and topotecan [3]. Intravenous topotecan, a topoisomerase I inhibitor, has activity in MDS. Studies to date have shown response rates of 28–66% for high risk MDS (RAEB and RAEBt) [4]. Higher response rates and a median survival time of 7–

20 months were obtained when topotecan was administered in combination with cytarabine [3, 5]. However, combination therapies require patient hospitalization with an increased risk of toxicity compared with topotecan alone.

Oral chemotherapy has advantages for protracted schedules [6], particularly in patients with risk factors for indwelling venous access devices that would otherwise be needed for continuous intravenous infusion of the drug [7]. In addition, ease of administration of oral topotecan may be advantageous in light of phase I study results indicating that prolonged dosing schedules demonstrate improved antitumor activity compared to intermittent dosing schedules [8]. Oral topotecan regimens are well-tolerated; the dose-limiting toxicity on 5-day regimens is neutropenia, while prolonged administration for 21-days results in gastrointestinal side-effects, mainly diarrhea.

In the outpatient setting, the convenience of oral drug therapy may be offset by failure to adhere to prescribed regimens, a recognized barrier to the effective management of disease [9]. Electronic monitoring has revealed substantial variability in the amount and timing of doses relative to prescribed oral dosing regimens [10]. As a result, variable adherence with prescribed drug treatment may also influence exposure to oral drug therapy and potentially impact on the effectiveness of chemotherapy in cancer patients.

Topotecan is an investigational agent in MDS. To date studies of topotecan in MDS have been limited to high risk MDS without exploring the option of chemotherapy for lower risk MDS [4]. A clinical study was conducted by the Cancer and Leukemia Group B (CALGB) to evaluate the clinical pharmacology of oral topotecan (1.2 mg/m^2) administered once a day for 10 days or twice a day for 5 days to patients with MDS. The objectives of the study were to (a) determine whether adherence to oral topotecan differed between the once- and twice-a-day regimens, (b) evaluate topotecan pharmacokinetics in elderly MDS patients and (c) examine exposure versus response relationships, including clinical response and toxicity, of oral topotecan in patients with MDS. Detailed clinical results on response, survival, and toxicity will be reported separately.

Methods

Patients

Patients with a documented diagnosis of MDS were eligible for the study. Patients were randomized to receive oral topotecan (1.2 mg/m^2), either once a day for 10 days or twice daily for 5 days every 21 days for up to six cycles. Inclusion criteria included age greater than 15 years, no prior treatment with topotecan, no prior treatment with cytotoxic agents for MDS, and normal hepatic and renal function (defined by serum aspartate transaminase (AST) values $\leq$ two times the upper limit of normal, total bilirubin $\leq$ 1.5 mg/dl, and serum creatinine $\leq$ 1.5 mg/ml). Participants signed an IRB-approved, protocol-specific informed consent.

Supply of study drug

Topotecan (0.25 mg and 1 mg capsules) was provided by Smith Kline Beecham and supplied to patients in a vial fitted with a cap containing an electronic monitoring device (EDEM, AARDEX Corp, Union City, CA, USA; 1 mg capsules only) for collection of individual dosing histories. The device consisted of a battery and a microchip that recorded every opening and closure of the cap on the vial. Patients were instructed to open the vial only to remove a dose at the time of ingestion and to only remove one dose at a time. They were further counseled to take the medication on an empty stomach, to take doses at the same time(s) each day and to space doses uniformly. Medication vials containing topotecan capsules were stored refrigerated, between 4°C and 8°C.

Adherence

In addition to the collection of electronic dosing histories, pill counts (PCs) were performed at the end of each cycle of treatment. We determined the percentage of patients that was 100% adherent based on the following definitions of adherence: the prescribed number of doses were taken, as determined by PC and electronic device (FR), all doses were taken within 2 h of the prescribed dosing interval (PI), and the correct number of doses was taken on each day of treatment (DC). Differences in adherence indices between treatment groups were evaluated using Kolmogorov–Smirnov test. A *P*-value of less than 0.05 was considered significant.

Pharmacokinetics

A sparse sampling design was utilized for pharmacokinetic data collection. Blood samples (10 ml) were collected into heparinized vials immediately prior to administration of the first dose and at the following times following the first dose administration: between 30 min and 90 min, between 120 min and 180 min, and between 210 min and 300 min. These sampling windows, rather than rigid time points, allow flexibility in the outpatient setting while allowing evaluation of population pharmacokinetics. Two additional samples were collected at any time between days 3 and 5 during the first cycle of treatment and during cycle 2 (between days 1 and 5) at anytime after dose administration. Although the timing of these two additional samples was left to the discretion and convenience of the physician and patient, the actual date and time of the last dose and date and time of the sample were recorded. Blood samples were centrifuged at 1,000 *g* and the plasma transferred to polypropylene storage

vials. Samples were stored frozen at −20°C and shipped to a central laboratory (AAM) for topotecan assay. The date and time of sample collection was recorded. The time of dose administration prior to blood sampling was recorded by the investigator and was obtained from electronic dosing histories at subsequent times.

Plasma topotecan concentrations were quantitated using a validated high performance liquid chromatography method as previously reported for another CALGB study [7]. Briefly, plasma concentrations of topotecan as the total of the lactone and carboxylate were measured. A 100 µl sample of plasma was mixed with 100 µl of methanol and 100 µl of 7% perchloric acid (v:v). After centrifugation, 50 µl of the clear supernatant was injected onto HPLC. The mobile phase consisted of 0.01 M *N*, *N*, *N*′, *N*′-tetramethyl-ethylenediamine at pH 6.0:methanol:0.1 M hexane-1-sulfonic acid sodium salt mixed at 65:25:10 by volume. The flow rate was 1.5 ml/min. Separation was achieved on a Symmetry C_{18} (3.9 mm×150 mm, 5 µm) column (Waters, Milford, MA, USA) that was maintained in a column oven at 30°C. The column effluent was monitored with a fluorescence detector set to an excitation wavelength of 361 nm and an emission wavelength of 527 nm. The HPLC assay was linear over a concentration range from 0.1 ng/ml to 10 ng/ml. The coefficients of variation for repeated analyses on the same day and between days were less than 10%. The limit of detection of topotecan in plasma was 0.1 ng/ml.

Pharmacokinetic parameters were estimated from electronic dosing histories and sparse topotecan samples using first order conditional estimation in the NONMEM program (version V) [11]. During model development, various absorption models were tested, including zero order, first order and mixed order processes. Pharmacokinetic parameters were assumed to be log normally distributed. In addition, interoccasion variability in absorption parameters was evaluated. Intersubject variability and interoccasion variability were modeled as follows:

$$P_{ik} = \overline{P} \cdot e^{(\eta_i)} \cdot e^{(\xi_{ik})} \quad (1)$$

where P_{ik} is the parameter estimate for the ith individual on the kth occasion, $\overline{P}$ is the median parameter estimate, η_i is a random intersubject effect with mean 0 and variance ω^2, and ξ_{ik} is a random interoccasion effect with mean 0 and variance ϕ^2.

The residual error model included two terms: an error term proportional to the prediction and an additive component, as follows:

$$y_{ij} = \hat{y}_{ij} \cdot (1 + \varepsilon_{1ij}) + \varepsilon_{2ij} \quad (2)$$

where y_{ij} and $\hat{y}_{ij}$ represent the jth observed and predicted concentration, respectively, for the ith subject, and ϵ_1 and ϵ_2 are the random residual errors, which are normally distributed with mean 0 and variance σ_1^2 and σ_2^2, respectively.

The final model was chosen based on model stability, −2 log likelihood (−2LL) and evaluation of diagnostic plots. The plot of observed versus predicted plasma topotecan concentration was examined for uniformity about and closeness to the line of unity, while plots of residuals and weighted residuals versus predicted concentration and time were examined for randomness about and closeness to zero.

Individual pharmacokinetic parameter estimates, including apparent clearance (clearance divided by oral bioavailability, CL/F), apparent volume of distribution (volume of distribution divided by oral bioavailability, Vc/F) and the absorption rate constant (Ka), were obtained by Bayesian estimation from the final model, using the POSTHOC function in NONMEM. Differences between treatment arms in individual pharmacokinetic parameter estimates thus obtained were compared using the Wilcoxon two-sample rank test and proportion comparisons were done using Fisher's Exact test. A *P*-value of less than 0.05 was considered significant.

Patient age, diagnosis, duration of disease, sex, race and laboratory markers for renal and hepatic function were examined as possible sources of variability in pharmacokinetic parameter estimates. Relationships between patient covariates and individual Bayesian estimates of the pharmacokinetic parameters were explored using generalized additive models (GAM) in SPLUS (StatSci, Seattle, WA, USA). The GAM allows both linear and non-linear relationships between parameters and covariates to be explored [12]. For example,

$$P_i = \overline{P} + \sum_{l=1}^{n} g_l(X_{li}) \quad (3)$$

where P_i is the parameter estimate for the ith individual, $\overline{P}$ is the median parameter estimate, X_{li} is the lth covariate for subject i and $g(.)$ is a linear or nonlinear function. Graphical analyses of each pharmacokinetic parameter versus each covariate were also examined for the possibility of nonlinear relationships. Selected covariates from the exploratory GAM and graphical analyses were further tested in NONMEM where stepwise additions ($P < 0.05$) and deletions ($P < 0.01$) determined the final model based on the change in −2LL between hierarchical models. Continuous covariates were centered around the median value and included in the model as follows,

$$P_i = \overline{P} + \theta \cdot (\mathrm{COV}_i - \overline{\mathrm{COV}}) \quad (4)$$

where θ is a parameter describing the relationship between the covariate of interest (COV) and the parameter of interest (P), $\overline{\mathrm{COV}}$ is the median value of the covariate in the population and the subscript i represents the ith individual. Categorical covariates were coded using indicator variables to allow estimation of the parameter of interest for each category.

Individual estimates of exposure were calculated from individual pharmacokinetic parameter estimates obtained from the final population pharmacokinetic model. Metrics of exposure included the average steady-state peak topotecan plasma concentration (Css,max), the average steady-state trough topotecan plasma concentration (Css,min), area under the plasma topotecan concentration versus time curve from time 0 to infinity (AUC, calculated as dose divided by apparent clearance), the average duration of time that plasma concentrations of topotecan were above 1.0 ng/ml following a single dose, and the continuous time above 1.0 ng/ml for the first cycle.

Exposure versus pharmacologic response

Pharmacologic endpoints included complete or partial response (at least 50% normalization of blood cell components and myeloblasts) and hematologic improvement (50% improvement in one or more blood cell components or platelet transfusion). Toxicities were graded for transfusion of platelets, transfusion of packed red blood cells (pRBC), platelet count, hemoglobin, absolute neutrophil count (ANC), and diarrhea, according to the Common Toxicity Criteria (version 2.0) [13].

Relationships between responses (including complete or partial response, hematologic improvement and Grade 3 or 4 toxicities) and various metrics of exposure were explored. Each response was coded as a binary variable, i.e., the response occurred or did not occur. Exposure versus response relationships were evaluated using logistic regression in SPLUS (StatSci):

$$\Pr = \frac{e^{A+Bx}}{1 + e^{A+Bx}} \quad (5)$$

where Pr is the probability of the response occurring, A is the intercept, B is the slope, and x is the metric of drug exposure. A P-value of less than 0.05 was considered significant.

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson.

Results

One hundred patients with MDS were enrolled in CALGB protocol 19803/69801 from March 1999 to May 2000. Ten patients withdrew from the study prior to receiving study medication. Of the remaining 90 patients, 44 were assigned to the once a day regimen and 46 were assigned to the twice a day regimen. Median age at study entry was 70 years (range 32–85 years). Plasma topotecan concentrations from the first treatment cycle were available for 81 patients (39 and 42 from each regimen, respectively). Samples from two individuals were lost in transit, samples for six individuals had interfering peaks, and one individual did not have blood withdrawn. Thirty-nine patients (21 and 18 from each regimen, respectively) had measurable plasma concentrations from samples collected during cycle 2. Adherence measurements were collected for 40 patients assigned to the once a day regimen and 40 patients assigned to the twice a day regimen.

Adherence to oral topotecan

Adherence measurements did not differ between the once and twice a day dosing regimens, for cycle 1 (Table 1) and over all cycles (data not shown). Overall, 90% of patients took the prescribed number of doses as recorded by the electronic monitoring device. Similar values were obtained by the PC.

The greatest variability was observed in adherence with prescribed dosing intervals with greater than 45% of patients taking their medications at dosing intervals not consistent with the prescribed dosing interval. Irregular dose administration resulted in peak and trough concentrations that were not consistent from one dose to the next and therefore differed from those expected at steady-state. Consequently, variable adherence contributed to variable topotecan plasma concentration versus time profiles in this patient population (Fig. 1).

Pharmacokinetics

A one compartment open model with first order absorption and elimination processes and an absorption lag-time of approximately 0.5 h best described topotecan plasma concentrations versus time after oral doses. Intersubject variability in topotecan absorption was large ($>100\%$). During the model development it was noted that interindividual variability in topotecan absorption increased with incorporation of data from the second cycle of treatment. Consequently, interoccasion variability was included in the absorption model. Population pharmacokinetic parameter estimates are listed in Table 2.

Individual pharmacokinetic parameter estimates for Ka, CL/F, and Vc/F did not differ significantly between patients on the once a day and twice a day dosing regimens (Table 3). Neither induction nor inhibition of

Table 1 Percent of individuals not 100% adherent during cycle one

Dosing regimen	FR	PC	PI	DC
Once a day	5.0	11.1	57.5	10.0
Twice a day	10.0	10.0	45.0	0.0

Prescribed number of doses taken according to electronic device (FR) or pill count (PC); all doses taken within 2 h of the prescribed dosing interval (PI) and correct number of doses taken on each day of treatment (DC)

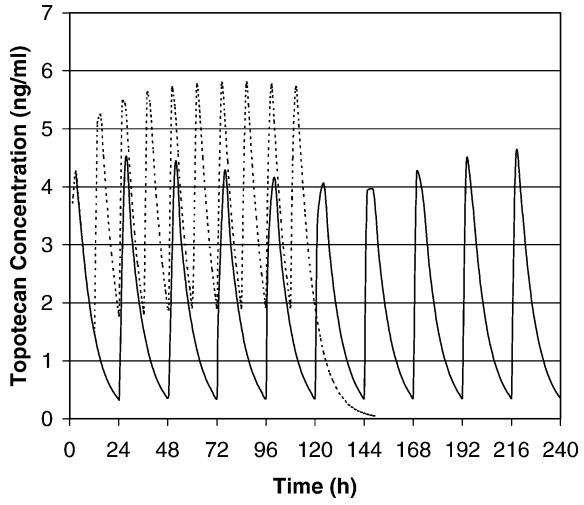

Fig. 1 Predicted topotecan plasma concentration versus time profile for once a day topotecan (2.25 mg oral dose, the dose administered to an individual with an average body surface area of 1.9 m^2; *solid line*) compared to twice a day topotecan (2.25 mg; *dotted line*)

Table 2 Pharmacokinetic parameter estimates

Parameter	Estimate	%CV[a]
Ka (h^{-1})	1.05	20.1
CL/F (l/h)	51.0	7.7
Vc/F (l)	395	9.0
Lag time (h)	0.476	7.9
K (h^{-1})	0.129	
Interindividual variability (%CV)[b]		
Ka	101.0	
CL/F	44.5	
Vc/F	44.5	
Interoccasion variability (%CV)[c]		
Ka	57.4	
Residual variability		
Proportional error (% CV)[d]	24.4	
Additive error (ng/ml)[e]	0.9	

Ka absorption rate constant, *CL/F* apparent clearance, *Vc/F* apparent volume of the central compartment, *K* elimination rate constant

[a] standard error of estimate/parameter estimate×100%

[b] $\sqrt{\omega^2} \times 100\%$(see Eq. 1)

[c] $\sqrt{\phi^2} \times 100\%$(see Eq. 1)

[d] $\sqrt{\sigma_1^2} \times 100\%$(see Eq. 2)

[e] $\sqrt{\sigma_2^2} \times 100\%$(see Eq. 2)

pharmacokinetic processes (absorption or elimination) took place with more frequent administration of topotecan. For the twice daily dosing regimen, accumulation of topotecan contributed to higher steady state minimum but not maximum concentrations compared to the once a day dosing regimen (Fig. 2). This also resulted in 28 of 42 (67%) of individuals with topotecan concentrations above 1 ng/ml for the entire dosing period in the twice a day dosing group compared to 5 of 39 (13%) in the once a day dosing group ($P < 0.0001$).

In the covariate analysis, increasing age resulted in a decrease in apparent volume of the central compartment. Apparent volume of the central compartment decreased by 3.1 l for every year greater than the median age of 70 years. Conversely, apparent volume of the central compartment increased by 3.1 l for every year of age less than 70 years.

Exposure versus pharmacologic response

Overall, 6% of patients experienced a complete or partial response while 31% displayed signs of hematologic improvement. Response rates were similar between the two dosing regimens (Table 4). In accordance, although continuous topotecan exposure greater than 1 ng/ml was more likely in the twice a day arm compared to the once a day dosing regimen, neither response (complete or partial) nor hematologic improvement correlated with metrics of topotecan exposure.

Occurrence of severe toxicities was similar between the two groups, with the exception of platelet transfusions, which was greater for patients receiving twice a day topotecan (Table 4). Accordingly, there were significant relationships between most of the metrics of systemic exposure (peak steady-state plasma topotecan concentration (Css,max; $P = 0.006$), trough steady state plasma concentration (Css,min; $P = 0.006$), continuous time above 1.0 ng/ml ($P = 0.01$) and area under the plasma concentration versus time curve from time 0 to infinity (AUC; $P = 0.03$)) and the need for a platelet transfusion. Based on these results, the estimated probability of needing a platelet transfusion was 56% for an individual with a Css,max equal to the lower quartile (3.8 ng/ml), 71% for an individual with an average Css,max (5.4 ng/ml) and 79% for an individual with a Css,max equal to the upper quartile (6.4 ng/ml). Because Css,min and the continuous time above 1 ng/ml

Table 3 Median parameter estimates for once and twice a day dosing regimens

Dosing regimen	*n*	Ka (h^{-1})	CL/F (l/h)	Vc/F (l)	Css,max (ng/ml)	Css,min (ng/ml)	AUC (ngh/ml)	Average time above 1 ng/ml (h)	Continuous time above 1 ng/ml (h)
Once a day	39	1.04	51.0	389	4.9	0.3	44.9	14.3	14
Twice a day	42	0.96	51.0	412	4.9	1.6	40.1	14.0	121
P-value[a]		0.82	0.76	0.28	0.79	< 0.0001	0.28	0.90	0.004

[a] Wilcoxon two-sample rank test

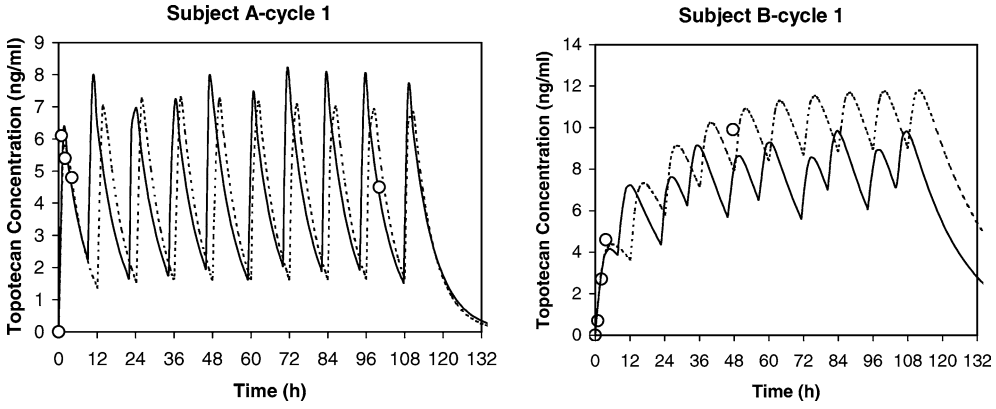

Fig. 2 Predicted topotecan plasma concentration versus time profile based on prescribed dosing regimen (*dotted line*) and based on actual dosing history, as recorded by the electronic monitoring device (*solid line*) and observed plasma concentrations (*circles*) for one subject in each treatment arm. Subject A received twice a day topotecan and subject B received once a day topotecan

Table 4 Number (percent) of patients experiencing response or toxicity (Grade 3 or 4) by dosing regimen

	Once a day ($n=39$) n(%)	Twice a day ($n=42$) n(%)
Response		
Complete and partial response	1 (3%)	4 (10%)
Hematologic improvement	11 (28%)	14 (33%)
Grade 3 or 4 toxicity		
Platelet transfusion[a]	20 (51%)	35 (83%)
Red blood cell transfusion[a]	26 (67%)	31 (74%)
Diarrhea	4 (10%)	7 (17%)
Hemoglobin	15 (38%)	24 (57%)
Absolute neutrophil count	33 (85%)	36 (86%)
Platelet count	29 (74%)	38 (90%)

[a]Significantly different between dosing regimens

were much higher on the twice a day regimen than on the once a day regimen, the need for a platelet transfusion was significantly greater for patients receiving twice a day topotecan ($P=0.003$). Thus, a typical individual receiving twice a day topotecan with an average Css,min of 1.9 ng/ml had an 88% probability of needing a platelet transfusion as compared to a patient on a once a day regimen with an average Css,min of 0.5 ng/ml whose transfusion probability was only 52%.

Discussion

With increasing availability of oral chemotherapy formulations due to increased cost-effectiveness, reduced costs of hospitalization and greater patient preference [6], patients are increasingly responsible for self-administration of chemotherapy. However, failure to adhere to the prescribed treatment regimen may be a potential limitation of oral chemotherapy. In previous studies, electronic monitoring devices have revealed surprisingly similar patterns of adherence in a wide variety of ambulatory patient populations [10]. While not infallible, the device allows evaluation of various dimensions of adherence, including the quantity, frequency and timing of doses. In cancer [14, 15], as with other diseases [10], there may be substantial variability in adherence to oral drug regimens, particularly in the timing of doses from day-to-day.

The elderly are commonly believed to demonstrate greater nonadherence with prescribed drug therapy due to physical disabilities, cognitive and memory deficits, reduced financial resources to pay for the cost of health care (including medications), and polypharmacy [16]. In the present study, adherence to two different regimens of oral topotecan in primarily elderly patients was assessed using an electronic monitoring device that records the dates and times that doses are removed from the medication container. Notably, the results of this study are not consistent with the notion of greater nonadherence with oral drug therapy in elderly patients.

Overall adherence with oral topotecan in patients with MDS was excellent. A number of factors may have contributed to greater overall adherence in this study, including self-selection bias inherent in clinical trial research. In addition to self-motivation, continued communication with the patients through repeat clinic visits, the short duration of treatment during each cycle and follow up questionnaires during each cycle of treatment may also have been factors. As with other studies of adherence with oral medications in ambulatory patient populations [10], the greatest variability occurred in interdose intervals. However, while noncompliance contributed to variability in plasma topotecan concentration versus time curves for each individual, the resultant exposure to topotecan did not correlate with pharmacologic response in patients with MDS.

After accounting for variable adherence, interindividual variability in topotecan absorption was large, varying twofold in this study population. Previously, interindividual variability in oral bioavailability from a capsule formulation was estimated to be 30% [17]. Since topotecan is absorbed more slowly in the presence of food [17], taking topotecan within 2 h of food may have contributed to both the observed magnitude of interindividual variability as well as interoccasion variability in absorption between cycles 1 and 2. Interindividual variability in apparent clearance was similar to that previously reported (approximately 40%) [18].

In elderly MDS patients, the disposition of topotecan was characterized by an absorption half-life of 0.7 h and

apparent clearance (CL/F) of 51 l/h. The estimated half-life was 5.4 h, which is approximately 30% greater than has been previously reported for patients with solid tumors (2.4–4.3 h) [17, 19–21]. A possible explanation for the longer half-life estimated in this study is the advanced age of the MDS population. The average age of the patients enrolled in this study was 70.3 years which is 10 years to 20 years older, on average, than patients with solid tumors enrolled in previous studies [8, 19, 20, 22, 23]. As renal clearance is the primary route of topotecan elimination and other studies have shown a correlation between topotecan clearance and creatinine clearance [24–26], declining kidney function with advancing age may be expected to result in reduced clearance in elderly patients [25, 27]. Although a population pharmacokinetic analysis did not detect a relationship between age and apparent clearance in this study, this is likely a consequence of the narrow range of ages in the study population, with less than 10% of patients either younger than 60 years or older than 80 years.

In a previous population pharmacokinetic study of oral and intravenous topotecan, it was suggested that topotecan clearance was reduced in patients with lower hematocrits [28] as the lactone: total topotecan plasma concentration was higher in patients with lower hematocrits resulting in a lower plasma concentration of carboxylate. In the present study, the influence of hemoglobin levels on topotecan apparent clearance was difficult to assess as all patients enrolled in this study had below normal hemoglobin levels (9.3 ± 1.4 mg/dl). Further, whereas Loos et al. [28] found that sex dependent differences in hematocrit may be related to topotecan clearance, it may not have played a role in this study since the majority of patients presented with anemia with no differences in the percentages of men and women with anemia.

Since continuous exposure to cell cycle specific agents (> 1 ng/ml for topotecan) may be more beneficial than intermittent exposure following bolus dosing [29, 30], we tested the hypothesis that greater topotecan exposure with the twice a day regimen correlated with a higher response rate. Individual metrics of topotecan exposure were estimated based on individual dosing histories and plasma topotecan concentration measurements. However, while neither response (partial or complete) nor hematologic improvement correlated with metrics of topotecan exposure, continuous topotecan exposure did result in an increased likelihood of thrombocytopenia in patients with MDS.

In this study, we combined adherence measurements with a sparse sampling design to estimate exposure to topotecan in an elderly MDS patient population. Using this approach, pharmacokinetic parameters were precisely estimated and individual estimates of systemic exposure were able to determined. Although evaluation of topotecan exposure versus efficacy and toxicity relationships did not reveal any clinically significant relationships, the approach may be utilized to explore exposure vs. response relationships for other chemotherapeutic agents, particularly during prolonged treatment cycles when adherence to the dosage regimen may be expected to be more variable.

Conflict of interest statement

No financial or personal relationships that could potentially be perceived as influencing the research described herein were identified.

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References

1. Fenaux P (1999) Myelodysplastic syndromes. In: Degos L, Linch DC, Lowenberg B (eds) Textbook of malignant haematology. Martin Dunitz, London
2. Burns CP (1999) Myelodysplastic syndromes. In: Foley JF, Vose JM, Armitage JO (eds) Current therapy in cancer. Saunders, Philadelphia, pp 374–381
3. Beran M, Estey E, OBrien S, Cortes J, Koller CA, Giles FJ et al (1999) Topotecan and cytarabine is an active combination regimen in myelodysplastic syndromes and chronic myelomonocytic leukemia. J Clin Oncol 17:2819–2830
4. Beran M, Kantarjian H, OBrien S, Koller C, Al-Bitar M, Arbuck S et al (1996) Topotecan, a topoisomerase I inhibitor, is active in the treatment of myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood 88:2473–2479
5. Beran M, Shen Y, Kantarjian H, O'Brien S, Koller CA, Giles FJ et al (2001) High-dose chemotherapy in high-risk myelodysplastic syndrome: covariate adjusted comparison of five regimens. Cancer 92:1999–2015
6. DeMario MD, Ratain MJ (1998) Oral chemotherapy: rationale and future directions. J Clin Oncol 16:2557–2567
7. Lilenbaum RC, Miller AA, Batist G, Bernard S, Hollis DR, Rosner GL et al (1998) Phase I and pharmacologic study of continuous infusion topotecan in combination with cisplatin in patients with advanced cancer: a cancer and leukemia Group B study. J Clin Oncol 16:3302–3309
8. Gerrits CJ, Burris H, Schellens JH, Eckardt JR, Planting AS, van der Burg ME et al (1998) Oral topotecan given once or twice daily for ten days: a phase I pharmacology study in adult patients with solid tumors. Clin Cancer Res 4:1153–1158
9. Cramer J, Spilker B (1991) Patient compliance in medical practice and clinical trials. Raven Press, New York
10. Kastrissios H, Blaschke TF (1997) Medication compliance as a feature in drug development. Annu Rev Pharmacol Toxicol 37:451–475
11. Beal SL, Sheiner LB (1992) NONMEM Users Guide, NONMEM Project Group. UCSF, San Francisco
12. Mandema JW, Verotta D, Sheiner LB (1992) Building population pharmacokinetic–pharmacodynamic models. I. Models for covariate effects. J Pharmacokinet Biopharm 20:511–528
13. National Cancer Institute (1998) Guidelines for reporting of adverse drug reactions. Division of Cancer Treatment, National Cancer Institute, Bethesda
14. Lee C, Nicholson P, Souhami R, Deshmukh A (1992) Patient compliance with oral chemotherapy as assessed by a novel electronic technique. J Clin Oncol 10:1007–1013
15. Waterhouse D, Calzone K, Mele C, Brenner D (1993) Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. J Clin Oncol 11:1189–1197

16. Ennis K, Reichard R (1997) Maximizing drug compliance in the elderly. Postgrad Med 102:211–224
17. Herben V, Rosing H, tenBokkel Huinink W, van Zomeren D, Batchelor D, Doyle E et al (1999) Oral topotecan: bioavailability and the effect of food co-administration. Br J Cancer 80:1380–1386
18. Loos WJ, Gelderblom HJ, Sparreboom A, Verweij J, de Jonge MJ (2000) Inter- and intrapatient variability in oral topotecan pharmacokinetics: implications for body-surface area dosage regimens. Clin Cancer Res 6:2685–2689
19. Creemers G, Gerrits C, Eckhardt J, Schellens J, Burris H, Planting A et al (1997) Phase I and pharmacologic study of oral topotecan administered twice daily for 21 days to adult patients with solid tumors. J Clin Oncol 15:1087–1093
20. Gerrits C, Burris H, Schellens J, Planting A, van den Burg M, Rodriguez G et al (1998) Five days of oral topotecan (Hycamtin) a phase I and pharmacological study in adult patients with solid tumors. Eur J Cancer 34:1030–1035
21. Gerrits CJ, Schellens JH, Burris H, Eckhardt JR, Planting AS, van der Burg ME et al (1999) A comparison of clinical pharmacodynamics of different administration schedules of oral topotecan (Hycamtin). Clin Cancer Res 5:69–75
22. Schellens J, Creemers G, Beijen J, de Boer-Dennert M, McDonald M, Davies B, Verweij J (1996) Bioavailability and pharmacokinetics of oral topotecan: a new topoisomerase I inhibitor. Br J Cancer 73:1268–1271
23. White SC, Cheesman S, Thatcher N, Anderson H, Carrington B, Hearn S et al (2000) Phase II study of oral topotecan in advanced non-small cell lung cancer. Clin Cancer Res 6:868–873
24. Montazeri A, Boucaud M, Lokiec F, Pinguet F, Culine S, Deporte-Fety R et al (2000) Population pharmacokinetics of topotecan: intraindividual variability in total drug. Cancer Chemother Pharmacol 46:375–381
25. O'Reilly S, Rowinsky EK, Slichenmyer W, Donehower RC, Forastiere AA, Ettinger DS et al (1996) Phase I and pharmacologic study of topotecan in patients with impaired renal function. J Clin Oncol 14:3062–3073
26. Léger F, Loos WJ, Fourcade J, Bugat R, Goffinet M, Mathijssen RHJ, Verweij J, Sparreboom A, Chatelut E (2004) Factors affecting pharmacokinetic variability of oral topotecan: a population analysis. Br J Cancer 90:343–347
27. Grochow LB, Rowinsky EK, Johnson R, Ludeman S, Kaufmann SH, McCabe FL et al (1992) Pharmacokinetics and pharmacodynamics of topotecan in patients with advanced cancer. Drug Metab Dispos 20:706–713
28. Loos WJ, Gelderblom HJ, Verweij J, Brouwer E, de Jonge MJ, Sparreboom A (2000) Gender-dependent pharmacokinetics of topotecan in adult patients. Anticancer Drugs 11:673–680
29. Jonsson E, Fridborg H, Csoka K, Dhar S, Sundstrom C, Nygren P, Larsson R (1997) Cytotoxic activity of topotecan in human tumour cell lines and primary cultures of human tumour cells from patients. Br J Cancer 76:211–219
30. Erickson-Miller CL, May RD, Tomaszewski J, Osborn B, Murphy MJ, Page JG, Parchment RE (1997) Different toxicity of camptothecin, topotecan, and 9-aminocamptothecin to human, canine and murine myeloid progenitors (CFU-GM) in vitro. Cancer Chemother Pharmacol 39:467–472