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Toxicity of weekly oral topotecan in relation to dosage for gynecologic malignancies: a phase I study

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Abstract

The aim of this study was to determine the dose of weekly oral topotecan that allows safe administration and to evaluate the pharmacokinetics of this dose in patients with recurrent gynecologic malignancies. The first cohort of patients received oral topotecan 6 mg/week administered orally on days 1, 8, and 15 of a 28-day regimen. A standard 3 + 3 dose-escalating phase design was used for dose levels II–V (8, 10, 12 and 14 mg/week). Toxicity was scored according to the Common Terminology Criteria for Adverse Events. Cumulative toxicity was summarized in the 6–12 mg/week combined cohort and 14 mg/week cohort separately. Pharmacokinetic samples were obtained for day 1, cycle 1 only in the expansion cohort (dose level V). Twenty-five patients received a total of 88 cycles of therapy. Hematologic toxicities of grade 3 (6–12 mg dose) were neutropenia (25%) and anemia (8.3%). Gastrointestinal toxicities of grade 3 were diarrhea (16.7%) and obstruction (8.3%, disease-related). Grade 3 or 4 (14 mg/week) hematologic toxicities consisted of neutropenia (38.5%), platelets (15.4%), anemia (15.4%), infection with neutropenia (7.7%), and thrombosis (7.7%). Gastrointestinal toxicities of grade 3 were diarrhea (7.7%), obstruction (7.7%), and vomiting (7.7%). One patient died secondary to neutropenic sepsis. One patient (4%; 95% confidence interval: 2.1, 22.3) showed a partial response and five patients (20%; 95% confidence interval: 7.6, 41.3) had stable disease. An oral topotecan dose of 14 mg/week for 3 consecutive weeks out of 4 is mostly associated with acceptable toxicities and may be considered for use in future single-agent phase II trials.

Keywords

chemotherapy; gynecologic malignancies; oral topotecan; ovarian cancer; pharmacokinetics; phase I trial

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Conflicts of interest

Deborah Smith is employed by GlaxoSmithKline, LLC as a kineticist and performed the pharmacokinetic analysis for this study. There are no conflicts of interest for other authors.

Introduction

Ovarian cancer is the most lethal and endometrial cancer is the most frequent gynecological malignancy. In 2011, over 15 460 women will die from ovarian cancer, and the incidence of endometrial cancer is expected to increase with the obesity epidemic [1]. The incidence of ovarian cancer is predicted to increase because of an aging society. Topotecan is a common agent used as second-line therapy for recurrent ovarian, endometrial, and cervical cancers [2–4]. Patients prefer oral to intravenous chemotherapy and oncologists are becoming more cognizant of patient preferences related to quality of life [5,6].

Recently, oral topotecan has been explored for convenient dosing [7–12]. Second-line oral topotecan was administered at 2.3 mg/m² for 5 days every 21 days, yielding an overall response rate of 21.6% in ovarian cancer, comparable with previous intravenous studies [9]. Grade 4 neutropenia was less frequent with oral therapy. Low-dose drug administration at higher frequency has gained favor over high-dose intermittent schedules [13–15].

Previously, topotecan has been dosed on a body surface area (BSA) to individualize the dose and decrease the interpatient variability. Studies have shown that dosing on a BSA basis has little effect on decreasing variability in oral topotecan exposure [16]. The mean bioavailability of oral topotecan is 40%, with a range of 23–66% [7,8]. Topotecan is a substrate for the efflux transporters P-glycoprotein (ABCB1) and breast cancer-resistant protein (BCRP, ABCG2). The variability in oral topotecan absorption is largely because of BCRP-mediated efflux in the intestinal epithelium. Dosing on either a milligram basis (flat dose) or with BSA does not decrease this variability as absorption is influenced in part by efflux transporters known to differ between patients. In addition, a flat dose may facilitate dosing with decreased medication errors.

The aims of this study included establishing the dose of weekly oral topotecan and determining the safety and tolerability of this regimen in gynecologic malignancies. In addition, pharmacokinetic data were assessed in an expanded cohort.

Methods

This was a dose-escalation study with a standard 3 + 3 design. The first cohort of patients received topotecan at a starting dose of 6 mg/week (dose level I) administered orally on days 1, 8, and 15 of a 28-day regimen. Three patients were enrolled at each subsequent dose level up to dose level V (14 mg/week, dosing increased by 2 mg/week/level). If one patient out of three experienced a dose-limiting toxicity (DLT), an additional three patients were enrolled at that dose level; DLTs were based only on cycle 1. Pharmacokinetic samples were obtained for 10 additional patients on day 1, cycle 1 in the expansion cohort, after assessment of the highest dose level. Institutional review board approval from University Hospitals Case Medical Center was obtained, and all patients signed informed consent before participation.

Eligibility criteria

Patients with histologically confirmed recurrent gynecologic malignancy receiving three or fewer prior chemotherapy regimens and prior radiation limited to less than 25% of the bone marrow with at least 3 weeks since any prior treatment were eligible. Adequate bone marrow, renal, hepatic and intestinal function, and a Karnofsky's performance status of 60% or more were required. Patients with borderline or low malignant potential tumors and those who had received treatment with cytotoxic chemotherapy within 21 days or any investigational drug within 28 days or other concurrent treatments for cancer were not included. Patients who had received prior treatment with topotecan or other camptothecin analogs were excluded. Patients were not allowed to take medications that inhibit or induce P-glycoprotein or BCRP transporters during the trial as changes in these transporters can alter the absorption of oral topotecan. In addition, patients with chronic gastrointestinal conditions, septicemia, severe infection, acute hepatitis, or concurrent severe medical problems were excluded.

Treatment plan

Oral topotecan (GlaxoSmithKline, Collegeville, Pennsylvania, USA) was initiated at 6 mg/week for dose level I on days 1, 8, and 15 of a 28-day regimen. The drug was supplied as 1.0 mg capsules. All nursing education was standardized and patients were instructed to bring in their medication containers and pill calendar at each visit to assess compliance. For the first cycle in all patients, oral topotecan was administered in the clinic and patients were observed for a minimum of 30min. Treatment was provided on an outpatient basis, and patients were instructed to take the study drug with an 8 oz glass of water at the same time each day and to remain in a sitting position for 30min. No antiemetic premedication was given before the first dose of cycle 1. Patients were provided antiemetic medications after the first dose as needed.

Sampling collection and processing and pharmacokinetic analysis

Samples were obtained from 10 patients at the highest dose tested (14 mg). On day 1 of course 1, oral topotecan was administered with 240 ml (8 oz) of water after an overnight fast. Patients were restricted to water for 1 h before and after dosing. Following the 2-h pharmacokinetic blood sample, patients could have a light meal and could eat as they wished after the 4-h sample. Whole-blood samples (3 ml) were collected in heparinized tubes on day 1, course 1, at before the dose and 0.5, 1, 1.5, 2, 4, 6, 8, 10–12, and 24 h after the dose. Samples were processed and the resulting plasma samples were assayed for total topotecan concentrations using a validated assay [17].

Adverse event monitoring

Patients were monitored weekly with phone calls and monthly at clinic visits for overall and specific topotecan-related toxicities using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [18]. Adverse events, such as hematologic and gastrointestinal toxicities, were managed by modification of dose or dosing delays and adjustments. Patients delayed were evaluated weekly until adequate

hematological and nonhematological parameters were obtained. If delays of more than 2 weeks occurred, patients were excluded from the trial.

Dose-limiting toxicity

DLT included any of the following acute toxicities occurring within 30 days of cycle 1: grade 4 neutropenia [absolute neutrophil count (ANC) < 500/mm³] greater than 7 days or associated with fever and requiring antibiotics, thrombocytopenia (platelets < 25 000/mm³), grade 3–4 thrombocytopenia (platelets < 50 000/mm³) in the setting of bleeding requiring platelet transfusion, patients delayed for more than 2 weeks, and omission of dose because of the patient not meeting hematologic dosing parameters during two out of three weekly doses.

Treatment modifications

The weekly therapy parameters were obtained on days 8 and 15 and therapy was omitted if hemoglobin was less than 9.0 g/dl, ANC was less than 1000/mm³, or platelet count was less than 50 000. Patients who did not have adequate counts within 2 weeks received a one-level dose reduction in all subsequent cycles for dose level II or higher. Patients reduced remained at that dose level for subsequent cycles. Patients did not receive prophylactic growth factors [filgrastim (G-CSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] or thrombopoietic agents; however, growth factors could be used for the management of febrile neutropenia/sepsis and patients could receive erythropoietin or blood transfusions for management of anemia. For the first occurrence of febrile neutropenia and/or documented grade 4 neutropenia (ANC < 500/mm³) persisting more than 7 days, chemotherapy was reduced one dose level. Patients with grade 4 thrombocytopenia (platelets < 25 000/mm³) were reduced one dose level. Patients missing two out of three doses were reduced one level for the subsequent cycle.

Dose reductions because of nonhematologic toxicity were considered as follows: renal toxicity of grade 2 or above and grade 3 or higher elevations in liver function tests resulted in a one-level dose reduction and delay in subsequent therapy for a maximum of 2 weeks until the patient recovered to grade 1. Gastrointestinal toxicities were managed without dose modification. Persistent (greater than 24 h) grade 3 or higher toxicity despite medical management was reduced one dose level and delayed for a maximum of 2 weeks until recovered to grade 1. Missed doses could be taken within 24 h, provided the hematological parameters were met.

Evaluation criteria

Patients receiving at least one dose of drug were evaluated for adverse effects. The Response Evaluation Criteria in Solid Tumors (RECIST) was used to assess response after cycles 3 and 6 (if applicable) [19].

Statistical considerations

The dose-escalation phase used a standard 3 + 3 phase 1 design. Doses were escalated to the next planned dose if zero of three or one of six patients experienced significant toxicity. Toxicities and dose reductions from all courses were recorded to provide an assessment of

cumulative toxicity. The baseline patient demographics and clinical characteristics were compared between the combined 6–12 mg/week cohort and the combined 14 mg/week cohort by the Mann–Whitney nonparametric test or χ^2 -tests. The frequencies of the highest-grade toxicities were determined in the combined 6–12 and 14 mg/week groups.

The total topotecan plasma concentration and the actual sample time relative to the dose data were analyzed using standard noncompartmental methods with WinNonlin Professional Edition Version 5.2 (Pharsight Corporation, Cary, North Carolina, USA). Pharmacokinetic parameters were the maximum observed concentration ($C_{\max}$), time at which $C_{\max}$ occurred ($T_{\max}$), terminal half-life ($t_{1/2}$), and area under the concentration curve from 0 to last quantifiable time point [$AUC_{(0-t)}$] and extrapolated to infinity [$AUC_{(0-N)}$]. Pharmacokinetic parameter values were reported as the geometric mean (% coefficient of variation), except for $T_{\max}$, which is reported as median (minimum – maximum).

Results

Twenty-six patients were enrolled from March 2009 to October 2010. One patient was could not be evaluated because of clinical progression after 1 week. Twelve patients were entered on dose levels I–IV (6, 8, 10, 12 mg/week) and 13 on dose level V (14 mg/week) and the expanded cohort. No significant differences in the patient characteristics between the two groups were found (Table 1). The majority of patients were White (88%), treated for recurrent ovarian/peritoneal disease (64%), and had stage III/IV disease (80%). Overall, 72% had received two or more prior chemotherapy regimens (median 2.0) and 16% radiation therapy.

Dose-escalation phase: dose modifications and toxicity

6 mg/week—There were no first-cycle DLTs. Two patients received three cycles of treatment. One patient received eight cycles. No dose modifications were required.

8 mg/week—There were no first-cycle DLTs. Two patients received six cycles of treatment and one patient received three cycles. No dose modifications occurred.

10 mg/week—There were no first-cycle DLTs. The first patient received four cycles. Subsequent patients received two and six cycles and no dose modifications were required.

12 mg/week—There were no first-cycle DLTs. Two patients received three cycles and one patient received two cycles. No dose modifications were required.

14 mg/week—The safety and tolerability data from this level were combined with the expansion cohort for reporting purposes.

The overall worst-grade toxicities (for all cycles) for the combined 6–12 mg/week cohort are presented in Table 2. Hematologic toxicities of grade 3 were neutropenia (25%) and anemia (8.3%). Gastrointestinal toxicities of grade 3 were diarrhea (16.7%) and obstruction (8.3%, disease-related). Seven (4.8%) doses of drug were held because of anemia in five patients,

neutropenia in one patient, and a grade 2 creatinine in one patient. Three patients (25%) declined further treatment because of grade 1/2 fatigue.

Expanded cohort phase (14 mg/week): dose modifications and toxicity

As no DLTs occurred in the first three patients, this level was expanded to include an additional 10 patients (total $n = 13$). One patient received six cycles, six patients received three cycles, two patients received two cycles, and two patients received one cycle at 14 mg/week. One significant toxicity occurred during the first cycle (grade 4 platelets and grade 4 neutropenia). An additional significant toxicity occurred during cycle 2 (grade 5 neutropenic sepsis), resulting in death. This patient, age 67 years, had recurrent ovarian cancer and had received three previous treatment regimens (two cytotoxic and one biologic) and no previous radiation therapy.

Three patients required dose modifications because of treatment delays. Thirteen (11.1%) doses of drug were held because of anemia in eight patients, neutropenia in seven, and thrombocytopenia in two. One patient had pancytopenia and two had decreased ANC.

The overall worst-grade toxicities (for all cycles) for the 14 mg/week cohort are presented in Table 3. Grade 4 toxicities included neutropenia (15.4%), infection with neutropenia (7.7%), and thrombosis (7.7%). Hematologic toxicities of grade 3 were neutropenia (23.1%), platelets (15.4%), and anemia (15.4%). Gastrointestinal toxicities of grade 3 were diarrhea (7.7%), obstruction (7.7%), and vomiting (7.7%).

Six of 13 (46.2%) patients in the 14 mg cohort and four of 12 (33.3%) in the 6–12 mg cohort had at least one grade 3 or 4 hematologic toxicity ($P = 0.688$). For gastrointestinal toxicities, two of 13 (15.4%) in the 14 mg cohort and three of 12 (25%) in the 6–12 mg cohort had at least one grade 3 event ($P = 0.645$).

Pharmacokinetics: expanded cohort phase

The total topotecan pharmacokinetic parameters are summarized in Table 4; the mean (range) concentration–time data are presented in Fig. 1. The terminal $t_{1/2}$ values for all patient profiles were determined using either three or four data points. Percentages of extrapolated $AUC_{(0-N)}$ were generally less than 5% and were less than 11% in all cases. The median T_{max} was 3.0 h (1.5 to 4.0 h). Following absorption, plasma total topotecan concentrations decreased in a biexponential manner with an average $t_{1/2}$ of 5.1 h.

Response/progression

One patient (4%; 95% confidence interval: 2.1, 22.3) who received 6 mg/week and had squamous vulvar cancer showed a partial response. Five patients (20%; 95% confidence interval: 46.4, 84.3) had stable disease and 17 (68%) had disease progression. Disease status was unknown in two patients (8%) secondary to a death because of neutropenic sepsis and transfer to hospice in a second patient. Six patients (24%) received six or more cycles of therapy, four of 12 (33.3%) patients in the 6–12 mg/week cohort and two of 13 (15.4%) in the 14 mg/week cohort. Patients who received six or more cycles ranged in age from 57 to 92 years, and had recurrent ovarian cancer (three), vulvar (one), endometrial (one), or

cervical cancer. In these women, previous chemotherapeutic regimens ranged from one to three, and two patients had received previous radiation therapy. There were no apparent similarities in the demographic and clinical characteristics among this subgroup of women.

Discussion

Intravenous topotecan is a standard second-line chemotherapeutic treatment for gynecologic malignancies, with response rates ranging from 12 to 33% [4,9,15]. Challenges to dispensing chemotherapy include transportation. Most patients do not transport themselves to chemotherapy visits, with the need to rely on family and friends. An opportunity to overcome such a barrier may be provided by oral antineoplastic agents [5]. As topotecan is frequently used for recurrent gynecologic oncology patients, it is a natural transition to improve patient access by developing the oral route.

The starting dose used in this study of 6 mg/week oral topotecan was chosen as it is similar to previous intravenous weekly studies (4 mg/m²) on the basis of BSA of 1.6 m². A weekly dosing strategy was used as previous studies have revealed decreased myelosuppression with weekly versus daily dosing [15]. In addition, metronomic dosing has become more favored [13]. A recent study showed that the marketed formulation can be administered to patients with solid tumors in the fed or the fasted state, with similar systemic exposures [11]. The most common adverse events in this study were because of myelosuppression, which is consistent for oral or intravenous topotecan [2,9]. The most frequent nonhematologic toxicities included diarrhea, obstruction, and vomiting [9,12]. However, toxicity increased as the weekly dose increased and not all patients could complete the planned six cycles of therapy. One patient who was receiving 14 mg/week after the second cycle of therapy died. The patient received the first cycle without DLT. After the second cycle, she was admitted for neutropenic fever and died shortly after.

Following oral absorption, plasma total topotecan concentrations decreased in a biexponential manner with a mean $t_{1/2}$ of 5.1 h. Moderate intersubject variability was observed, with % coefficient of variation of the $C_{\max}$ and $AUC_{(0-N)}$ values of 62 and 57%, respectively. This variability is higher than that reported previously for oral administration [8,11,20], likely because of one patient, whose $C_{\max}$ and $AUC_{(0-N)}$ values were 1.5-fold and 2.0-fold higher, respectively, than the next highest values. The coefficients of variation without this patient's $C_{\max}$ and $AUC_{(0-N)}$ values were 47 and 32%, respectively, similar to those reported previously [8,11,20]. These higher values occurred in the patient who died secondary to neutropenic fever.

The reason for the high exposure in this patient is unknown, but as the $T_{\max}$ and $t_{1/2}$ values were similar to those in other patients, it is likely because of increased absorption. Topotecan is a known substrate for ABCG2 (BCRP) and ABCB1 (P-glycoprotein) transporters, with ABCG2 being the more important of the two [21]. Although the reason for the increased bioavailability is unknown, inhibition of ABCG2 and/or a genetic variant resulting in decreased ABCG2 expression or activity are possibilities. Concomitant medication use was documented; however, it is possible that this patient may have been

taking something that we were unaware of. She was pretreated in a similar manner as the other patients.

In the presence of elacridar, an inhibitor of both transporters, topotecan's apparent oral bioavailability increased from 40 to 97%, and the total topotecan $C_{\max}$ and $AUC_{(0-N)}$ values increased on average 2.8-fold and 2.4-fold, respectively [21]. In addition to elacridar, a number of medications, endogenous substances, and flavonoids are known substrates or inhibitors of ABCG2 [22]. Known variants (421C > A and 34G > A) of ABCG2 have been identified that affect the function and/or the expression of its encoded protein [23–26]. The approximate allele frequency in Whites for 421C > A and 34G > A is 11 and 10%, respectively [27]. In a study comparing the pharmacokinetics in patients who were heterozygous for 421C > A ($n = 2$) versus wild type ($n = 10$), topotecan lactone oral bioavailability was increased 1.34-fold in heterozygous compared with wild-type patients [26].

On a weekly schedule, the recommended intravenous topotecan dose is 4 mg/m² [17]. The highest oral dose administered on a weekly schedule in this study was 14 mg (B7.7 mg/m²). Consistent with the previously reported oral bioavailability of topotecan, the $C_{\max}$ and AUC values were higher after an intravenous administration of 4 mg/m² than after an oral administration of 14 mg; however, by 2–3 h after the administration of topotecan (start of infusion or oral administration), the mean plasma total topotecan concentrations were comparable after two doses/routes of administration [17]. In a similar manner, after an oral or an intravenous administration of the respective recommended doses for the five-daily-doses schedule (1.5 mg/m² intravenous and 2.3 mg/m² oral), higher $C_{\max}$ and AUC values were found with intravenous administration; however, by 2–3 h after administration, the plasma total topotecan concentrations were comparable after the two doses/routes of administration [8]. During ~90% of the dosing interval, the plasma total topotecan concentrations were similar at the recommended oral and intravenous doses for both the weekly and the daily dose schedules.

Despite dose escalation to 14 mg/week, a maximum tolerated dose was not defined. After increasing to 14 mg/week, the decision was made not to continue dose escalation because of concerns related to increased overall toxicity and in particular gastrointestinal toxicity because of the number of pills patients would be required to ingest.

An oral topotecan dose of 14 mg/week for 3 consecutive weeks out of 4 is mostly associated with acceptable toxicities. The pharmacokinetic behavior of total topotecan at an oral dose of 14 mg was similar to that observed in other studies. On a dose-normalized basis, the values of $C_{\max}$ and $AUC_{(0-N)}$ for total topotecan were similar to those observed in the previous studies [8,11,20,21]. The elimination $t_{1/2}$ was similar to that in previous studies following oral and intravenous administration [11,17]. We documented tolerance to a weekly oral schedule by most patients under study, and phase II studies including quality-of-life assessments with this schedule are warranted.

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Fig. 1.
Mean ($\pm$ range) total topotecan plasma concentration versus time on linear and log scales (mean only).

Table 1

Patient demographics and clinical characteristics

	Overall (n= 25)	Dose- escalation phase, 6–12 mg/ week (n= 12)	Expanded cohort, 14 mg/week (n= 13)	P value*
Age, median (range) (years)	59.0 (38–92)	64.0 (38–92)	58.0 (39–77)	0.205
Race				0.729
White	22 (88%)	10	12	
African-American	2 (8%)	1	1	
Pacific Islander	1 (4%)	1	–	
Site of disease				0.550
Ovarian/peritoneal	16 (64%)	8	8	
Uterine/endometrial	7 (28%)	3	4	
Cervix	1 (4%)	–	1	
Vulvar	1 (4%)	1	–	
Stage				0.464
I	3 (12%)	2	1	
II	2 (8%)	–	2	
III	15 (60%)	7	8	
IV	5 (20%)	3	2	
Karnofsky's performance status				0.250
70–80%	7 (28%)	2	5	
90%	9 (36%)	6	3	
100%	9 (36%)	4	5	
Insurance status				0.315
Medicare	6 (24%)	2	4	
Medicare/private	5 (20%)	4	1	
Private	14 (56%)	6	8	
Tumor grade				0.480
I	1 (4%)	1	–	
II	2 (8%)	–	2	
III	22 (88%)	11	11	
Prior chemotherapy regimens				0.304
None	1 (4%)	–	1	
1	6 (24%)	2	4	
2	12 (48%)	8	4	
3	6 (24%)	2	4	
Prior radiation treatment	4 (16%)	2	2	0.999

* Mann-Whitney nonparametric test or χ^2 -test.

Table 2Highest-grade toxicity (for all cycles) by category for dose levels I–IV (6–12 mg/week $n = 12$)

Adverse event	Grade				
	1	2	3	4	5
Anemia	2 (16.7)	9 (75)	1 (8.3)	–	–
Neutrophils, ANC	2 (16.7)	1 (8.3)	3 (25)	–	–
Platelets	5 (41.7)	1 (8.3)	–	–	–
Constipation	4 (33.3)	–	–	–	–
Diarrhea	3 (25)	1 (8.3)	2 (16.7)	–	–
Nausea	8 (66.7)	2 (16.7)	–	–	–
Vomiting	1 (8.3)	–	–	–	–
Heartburn	2 (16.7)	–	–	–	–
GI obstruction	–	–	1 (8.3)	–	–
GI bleeding	1 (8.3)	–	–	–	–
Allergy	1 (8.3)	–	–	–	–
Fatigue	8 (66.7)	2 (16.7)	–	–	–
Dermatology/skin	4 (33.3)	2 (16.7)	–	–	–
Hemorrhage/bleeding	1 (8.3)	–	–	–	–
Infection	–	1 (8.3)	–	–	–
Lymphatics	1 (8.3)	–	–	–	–
Neurology	1 (8.3)	–	–	–	–
Metabolic	1 (8.3)	1 (8.3)	–	–	–
Pain	5 (41.7)	–	–	–	–
Pulmonary/respiratory	2 (16.7)	–	–	–	–

Number (%) of patients listed.

ANC, absolute neutrophil count; GI, gastrointestinal.

Table 3Highest-grade toxicity (for all cycles) by category for dose level V and expanded cohort (14 mg/week, $n = 13$)

Adverse event	Grade				
	1	2	3	4	5
Anemia	1 (7.7)	8 (61.5)	2 (15.4)	–	–
Neutrophils, ANC	–	3 (23.1)	3 (23.1)	2 (15.4)	–
Platelets	6 (46.2)	2 (15.4)	2 (15.4)	–	–
Constipation	2 (15.4)	–	–	–	–
Diarrhea	4 (30.8)	–	1 (7.7)	–	–
Nausea	9 (69.2)	–	–	–	–
Vomiting	3 (23.1)	1 (7.7)	1 (7.7)	–	–
Constitutional	6 (46.1)	4 (30.8)	1 (7.7)	–	–
Dermatology/skin	1 (7.7)	1 (7.7)	–	–	–
Infection	–	–	–	–	1 (7.7)
Lymphatics	1 (7.7)	–	1 (7.7)	–	–
Neurology	3 (23.1)	–	–	–	–
Metabolic	1 (7.7)	2 (15.4)	1 (7.7)	–	–
Ocular	1 (7.7)	–	–	–	–
Pain	4 (30.8)	2 (15.4)	–	–	–
Pulmonary/respiratory	2 (15.4)	–	–	–	–
Vascular	–	–	–	1 (7.7)	–

Number (%) of patients listed.

ANC, absolute neutrophil count.

Table 4

Pharmacokinetic parameters for 14 mg/week

Pharmacokinetic parameter ^a	Geometric mean (% coefficient of variation)
$C_{\max}$ (ng/ml)	43.3 (62%)
$T_{\max}$ ^b (h)	3.0 (1.5–4.0)
AUC _(0–t) (ng h/ml)	307 (55%)
AUC _(0–∞) (ng h/ml)	323 (57%)
$t_{1/2}$ (h)	5.1 (24%)

^a Pharmacokinetic parameters are the maximum concentration ($C_{\max}$), time to maximum concentration ($T_{\max}$), area under the plasma concentration–time curve to the last quantifiable concentration [AUC_(0–t), $t = 24$ h] and to infinity [AUC_(0–∞)], and half-life ($t_{1/2}$).

^b $T_{\max}$ values presented as median and range.