Cancer Chemother Pharmacol (2005) 55: 609–616
DOI 10.1007/s00280-004-0946-3

CLINICAL TRIAL REPORT

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Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients

Received: 20 August 2004 / Accepted: 28 October 2004 / Published online: 19 February 2005

Abstract *Background*: Aprepitant is a selective neurokinin-1 receptor antagonist that is effective for the prevention of nausea and vomiting caused by highly emetogenic chemotherapy. In vitro, aprepitant is a moderate inhibitor of the CYP3A4 enzyme, which is involved in the clearance of several chemotherapeutic agents. In this study we examined the potential for aprepitant to affect the pharmacokinetics and toxicity of intravenously administered docetaxel, a chemotherapeutic agent that is primarily metabolized by CYP3A4. *Methods*: A total of 11 cancer patients (4 male, 7 female, aged 50–68 years) were enrolled in this multicenter, randomized, open-label, two-period, crossover study. Patients received a single infusion of docetaxel monotherapy, 60–100 mg/m^2, on two occasions at least 3 weeks apart. During one of the cycles (treatment A), patients received docetaxel alone. During the alternate cycle (treatment B), they also received aprepitant 125 mg orally 1 h prior to docetaxel infusion (day 1), and a single oral dose of aprepitant 80 mg on days 2 and 3. The pharmacokinetic profile of docetaxel was assessed over 30 h following docetaxel infusion. Blood counts were monitored on days 1, 4, 7, and 14. *Results*: Ten patients completed the study. Concomitant administration of aprepitant did not cause any statistically or clinically significant changes in docetaxel pharmacokinetics. Values for docetaxel alone (treatment A) versus docetaxel with aprepitant (treatment B) were as follows: geometric mean AUC_{0-last} was 3.26 vs 3.17 μg h/ml ($P > 0.25$; ratio B/A 0.97); geometric mean $AUC_{0-\infty}$ 3.51 vs 3.39 μg h/ml ($P > 0.25$; ratio B/A 0.96); geometric mean C_{max} was 3.53 vs 3.37 μg/ml ($P > 0.25$; ratio B/A 0.95); and geometric mean plasma clearance was 23.3 vs 24.2 l/h/m^2 ($P > 0.25$; ratio B/A 1.04). The corresponding harmonic mean half-life values were 10.1 and 8.5 h. The two treatment regimens had similar tolerability profiles; the median absolute neutrophil count nadirs were 681/mm^3 during treatment with docetaxel alone and 975/mm^3 during aprepitant coadministration. *Conclusions*: Aprepitant had no clinically significant effect on either the pharmacokinetics or toxicity of standard doses of docetaxel in cancer patients. Aprepitant at clinically recommended doses may have a low potential to affect the pharmacokinetics of intravenous chemotherapeutic agents metabolized by CYP3A4.

Keywords Aprepitant · Docetaxel · CYP3A4 · Drug interaction · Cancer · Pharmacokinetics

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Introduction

Standard therapy for the prevention of chemotherapy-induced nausea and vomiting has typically consisted of dual treatment with a corticosteroid and a 5-hydroxytryptamine ($5HT_3$) receptor antagonist. The addition of aprepitant, a highly selective, potent, brain-penetrant NK_1 receptor antagonist, to standard antiemetic therapy consisting of a corticosteroid and a $5HT_3$ receptor antagonist, significantly improves the control of highly emetogenic chemotherapy-induced nausea and vomiting [1, 2]. The effect of aprepitant is especially robust in the

delayed phase and is maintained over multiple cycles of chemotherapy [1–3]. The recommended dose of aprepitant is 125 mg orally 1 h prior to chemotherapy (day 1) and 80 mg once daily in the morning on days 2 and 3 after chemotherapy.

In vitro studies have indicated that aprepitant does not substantially inhibit cytochrome P450 (CYP) 1A2, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP2B6 and CYP2C19, and that it moderately inhibits CYP3A4 (K_i of about 10 μM for 1′ and 4-hydroxylation of midazolam and N-demethylation of diltiazem) [4]. In vivo studies have indicated that aprepitant inhibits CYP3A4 isoenzyme activity. A study in healthy subjects using the aprepitant 125/80-mg dosing regimen over 5 days and oral midazolam as a probe substrate for CYP3A4 activity showed that aprepitant coadministration increases the area under the concentration-versus-time curve (AUC) of midazolam 2.3-fold by day 1 and 3.3-fold by day 5 [5]. The results indicated that the 5-day regimen of aprepitant is a moderate inhibitor of an orally administered CYP3A4 substrate based on the classification system proposed by Bjornsson et al. [6]. According to this classification, moderate CYP3A4 inhibition is caused by commonly used drugs such as verapamil and diltiazem. The 3-day regimen of aprepitant approved for prevention of chemotherapy-induced nausea and vomiting can also be expected to produce moderate inhibition of the metabolism of orally administered CYP3A4 substrates.

A number of chemotherapeutic agents undergo metabolic clearance in part via CYP3A4, including etoposide, vinca alkaloids, irinotecan, ifosfamide, and the taxanes docetaxel and paclitaxel. Concomitant administration with CYP3A4 inhibitors such as aprepitant could potentially decrease the metabolic clearance of these anticancer agents, resulting in increased exposure and toxicity. The clearance of docetaxel is particularly susceptible to changes in CYP3A4 activity [7]. In vitro data show that docetaxel, which is used to treat breast cancer and non-small-cell lung cancer, is metabolized primarily by CYP3A4 [7]. Moreover, studies in cancer patients, using the probe substrates erythromycin, midazolam, and cortisol, show that CYP3A4 activity is the most significant predictor of docetaxel clearance, with lower clearance and greater toxicity in patients with the lowest CYP3A4 activity [8–10]. Ketoconazole, a strong inhibitor of CYP3A4, produces a 49% decrease in docetaxel clearance, further underscoring the importance of CYP3A4 in the clearance of docetaxel [11]. The toxicity of concern would be longer and/or more severe neutropenia. Accordingly, the package circular for docetaxel (Taxotere, Aventis) recommends caution during coadministration of compounds that induce, inhibit, or are metabolized by CYP3A4 [12]. Because of its susceptibility to changes in CYP3A4 activity, docetaxel is an appropriate compound to use to determine whether aprepitant can have clinically important effects on the pharmacokinetics of an intravenous chemotherapeutic drug that undergoes CYP3A4 metabolism.

The current study was conducted to investigate the potential pharmacokinetic interaction between aprepitant and docetaxel as assessed by plasma levels of docetaxel when docetaxel is given alone and with aprepitant, and to investigate the tolerability of concomitant treatment with aprepitant and docetaxel.

Methods

Patients

The study was conducted in patients who were scheduled to receive repeated courses of monocomponent chemotherapy with docetaxel for the treatment of solid malignancy. Patients were included in the study if they had a Karnofsky score of ≥60 and a predicted life expectancy of ≥3 months. Women of childbearing potential must have had a negative urine β-hCG pregnancy test at the start of each treatment period and agreed to use contraception throughout the study. All patients gave written informed consent. Approval for the study protocol was obtained from the appropriate ethical review boards. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Exclusion criteria

Exclusion criteria included history of illness or uncontrolled disease, other than malignancy, that could confound study results or pose unwarranted risk to the patient, history of surgery within 2 weeks prior to the study, history of hypersensitivity to docetaxel or aprepitant, receipt of an investigational drug in the previous 4 weeks, and active infection. Patients were excluded for any of the following laboratory results: absolute neutrophil count $<1500/mm^3$, platelet count $<100{,}000/mm^3$, aspartate aminotransferase (AST) >1.5 times the upper limit of normal, alanine aminotransferase (ALT) >1.5 times the upper limit of normal, alkaline phosphatase >2.5 times the upper limit of normal, bilirubin >1.5 mg/dl, or creatinine >1.5 mg/dl. Patients scheduled to receive stem cell rescue therapy or chemotherapy other than docetaxel were excluded, as were those taking opiates or benzodiazepines initiated within 72 h of day 1. Systemic corticosteroid therapy was allowed as premedication for docetaxel or if the chronic dose was the equivalent of prednisone ≤ 10 mg/day, but patients were excluded if systemic corticosteroid therapy for other reasons was started within 72 h of day 1 of the study. Radiation treatment was prohibited within 2 weeks prior to and for the duration of the study. Patients were not to consume grapefruit or grapefruit juice within 1 week prior to and 1 week after the start of the study, and they were to discontinue herbal supplements at least 2 weeks prior to the start of the study.

Design

A randomized, open-label, two-period, crossover design was used with at least 3 weeks between day 1 of the two study periods. Patients received docetaxel alone (treatment A) in one period and docetaxel with aprepitant (treatment B) in the other period. The order of treatments (treatment A followed by treatment B versus treatment B followed by treatment A) was determined by a randomized, open, balanced allocation schedule. The doses of docetaxel were given according to standard treatment schedules for the tumor types included in the study, and aprepitant was given as recommended in the product circular. For treatment A, patients received a single intravenous infusion of docetaxel 60–100 mg/m^2 administered over 1 h on day 1. For treatment B, patients received the same dose of docetaxel as in treatment A (a single intravenous infusion of docetaxel 60–100 mg/m^2 administered over 1 h on day 1), plus an aprepitant regimen consisting of a single dose of aprepitant 125 mg in capsule form 1 h prior to the administration of docetaxel on day 1, and a single daily oral dose of aprepitant 80 mg in capsule form on days 2 and 3. Patients were allowed to receive standard antiemetic treatment with dexamethasone 8 mg orally twice daily on the day of and the day after docetaxel administration, and a $5HT_3$ receptor antagonist. Patients who received adjunctive antiemetic drugs were given the same doses of those drugs in each treatment period.

The study was originally designed to enroll 20 patients. However, in view of results from a preliminary analysis of the pharmacokinetic data from the first five patients indicating no interaction between aprepitant and docetaxel, enrollment was ended after 10 patients had completed the study. Physical examination and 12-lead electrocardiogram were conducted at prestudy and on day 21, i.e., in period 2 at the poststudy visit. Vital signs were examined at prestudy, on day 1 of each treatment period, and at poststudy. Fasting laboratory safety studies (blood chemistry, hematology, and urinalysis) were conducted at prestudy, poststudy, and on day 1 and day 7 of each treatment period. Additional hematology safety tests were performed on days 4, 14, and 21 of each treatment period.

Patients were monitored throughout the study for clinical adverse experiences. Clinical and laboratory adverse experiences were classified by intensity, seriousness, and drug relatedness. Because docetaxel is known to cause neutropenia [12], white blood cell (WBC) and neutrophil counts were monitored closely. For safety and to avoid confounding of the data, patients would have been discontinued from the study if they developed neutropenia in the first study period severe enough to have necessitated a reduced docetaxel dose for their next treatment cycle. Patients must have had absolute neutrophil counts $>1500/mm^3$ and platelet counts $>100{,}000/mm^3$ for docetaxel to be given in the second cycle.

Pharmacokinetic methods

Blood samples for plasma docetaxel determinations were drawn just prior to the start of the docetaxel infusion (0 h) and at 0.5, 0.92 (i.e., 55 min), 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, and 30 h after the start of the infusion. Blood was drawn into sodium heparin-containing tubes, which were immediately placed on ice and centrifuged at 0–5°C. Plasma samples were separated into cryotubes and stored at −20°C. Samples were shipped on dry ice to PPD Development (Richmond, Va.) for docetaxel assay using liquid chromatography/mass spectrometry/mass spectrometry [13]. The lower limit of quantitation of the assay was 0.01 μg/ml. For the quality control samples, the interassay precision (% coefficient of variation, CV%) ranged from 6.0 to 9.4%, and the interassay accuracy ranged from 91.6% to 100.5%.

Individual docetaxel plasma concentrations were used to estimate the docetaxel pharmacokinetic parameters AUC, maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), half-life ($t_{1/2}$), and plasma clearance. The commercial software Winnonlin version 4.1 was used to calculate these parameters. A weight of 1/y was used for fitting the terminal log-linear portion of the plasma concentration-versus-time curve to obtain the first-order terminal rate constant (λ_Z). The apparent terminal half-life was set at $\ln(2)/\lambda_Z$. The linear up/log down trapezoidal rule was used to calculate the AUC_{last} (AUC up to the last measurable concentration [C_{last}]). $AUC_{0-\infty}$ was calculated from $AUC_{last} + C_{last}/\lambda_Z$. The nominal doses of docetaxel administered and the actual sample collection times were used to estimate the parameters. The between-treatment ratios (docetaxel with aprepitant/docetaxel alone) of $AUC_{0-\infty}$, AUC_{last}, plasma clearance, and C_{max} were calculated based on these parameters.

Plasma samples were also collected for measurements of aprepitant levels in order to estimate aprepitant plasma concentrations in cancer patients and to compare the aprepitant plasma concentration profiles between the patients in the current study and 12 healthy subjects who received the aprepitant 3-day regimen in a previous study (data on file, manuscript in preparation). Samples were collected at specified time points on day 1 from immediately prior to aprepitant administration through 24 h after docetaxel administration, i.e., 25 h after aprepitant administration, and again at 24 h after the last aprepitant dose that was given on day 3. Samples were analyzed by Merck Research Laboratories (West Point, Pa.). Aprepitant was extracted from plasma using a liquid–liquid extraction method, and liquid chromatography-tandem mass spectrometry was used for detection and quantitation [14]. The lower limit of quantitation was 10 ng/ml. For the standard samples, the intraday precision (CV%) ranged from 1.1% to 5.7% and accuracy ranged from 96% to 103%.

The individual plasma aprepitant levels were used to estimate the pharmacokinetic parameters of aprepitant (AUC_{0-24h}, C_{max}, and T_{max} on day 1, and C_{24h} after the

day-3 dose of aprepitant). Because the plasma sample was collected at 25 h, and not at 24 h, after aprepitant on day 1, the C_{24h} for day 1 was first estimated using linear interpolation. The linear trapezoidal rule was then used to calculate the $AUC_{0–24h}$ to allow comparisons with the historical data. The C_{max} and T_{max} were obtained by inspection. The actual sampling times were used to calculate AUC.

Statistical methods

The primary hypothesis was that coadministration of aprepitant would not increase the plasma concentration of docetaxel to a clinically meaningful degree, i.e., the ratio of the geometric mean $AUC_{0–last}$ for docetaxel with aprepitant/docetaxel alone would be <1.5. To address this hypothesis, the individual $AUC_{0–last}$ data for docetaxel were natural log transformed and evaluated with an analysis of variance (ANOVA) model appropriate for a two-period, two-treatment, two-treatment-sequence, crossover design. The model contained the following factors: the between-subject factors of treatment sequence (carryover effect) and subject-within-treatment-sequence (between-subject error), and the within-subject factors of treatment, period, and within-subject error. The carryover effect was tested at $\alpha = 0.10$ and evaluated graphically. A two-sided 90% confidence interval (CI) (equivalent to a one-sided upper 95% confidence limit) for the true mean between-treatment difference in ln-$AUC_{0\text{-last}}$ was calculated using the mean square error (MSE) derived from the ANOVA model and referencing a *t*-distribution. These limits were exponentiated to obtain the corresponding 90% CI for the true ratio (docetaxel with aprepitant/docetaxel alone). $AUC_{0–\infty}$, C_{max}, and plasma clearance of docetaxel were analyzed using the same ANOVA methodology described above for $AUC_{0–last}$. Descriptive statistics were provided by treatment for T_{max} and half-life. The pharmacokinetics of aprepitant in cancer patients were evaluated by graphically comparing day-1 $AUC_{0–24h}$ and C_{max} and day-3 C_{24h} of aprepitant in the present study with day-1 $AUC_{0–24h}$ and C_{max} and day-3 C_{24h} from a previous study with 12 healthy subjects (data on file, manuscript in preparation).

Summary statistics were provided for WBC count, absolute neutrophil count, and platelet count percent change from baseline. Percent change from baseline for each individual on each day was calculated as $100\times[(\text{day i}/\text{day 1})-1]$, where i = 4, 7, 14. Hodges-Lehmann estimation was used to obtain an estimate of median percent change from baseline by treatment on each day. A distribution-free 95% CI (due to Tukey) for the true median, based on the Wilcoxon signed ranks test, was also calculated.

A Hodges-Lehmann estimate [15] of the median between-treatment difference (docetaxel with aprepitant minus docetaxel alone) in percent change from baseline was also calculated, as was a distribution-free 95% CI (due to Moses) [15] for the true median, based on the Wilcoxon rank sum test. For this analysis, the treatment effect was evaluated by comparing the individual period differences (period 2−period 1) between the two treatment sequence groups as outlined by Jones and Kenward [16].

An exact confidence interval could not be calculated for day 4 due to the small sample sizes in the two treatment sequence groups ($n = 2$ and 6). Therefore, the minimum and maximum difference in period differences between the two sequence groups is given instead.

Nadir absolute neutrophil count was also identified for each patient by treatment as the minimum of the day-4, day-7, and day-14 values. Nadir percent change from baseline was then calculated, and the data were initially analyzed with the ANOVA methodology described previously. The residuals showed evidence of non-normality; therefore, the distribution-free analyses described above were applied to nadir percent change.

Because one patient received pegfilgrastim as prophylaxis for neutropenia in his first treatment cycle, the safety analyses for neutrophils described above were done both with and without this patient.

No adjustments were made for multiplicity because there was only one primary hypothesis.

Determination of sample size and power

The original power statement was based on a sample size of 20 patients. For a two-period, two-treatment, two-treatment-sequence, crossover study with 20 subjects (10 subjects per sequence), there would be a probability of 0.80 that the observed limit of a one-sided upper 95% CI for the geometric mean $AUC_{0–last}$ ratio (docetaxel with aprepitant/docetaxel alone) would be <1.5, assuming that the true variation was similar to that observed in a previous study (MSE 0.2401) [17] and the true ratio was 1.

A preliminary analysis of pharmacokinetic data from the first five patients who completed this study revealed no significant pharmacokinetic interaction. Assuming a true within-subject variance for AUC similar to the MSE obtained from the analysis of the first five subjects, MSE 0.0136 (natural log-scale), with ten subjects completing the study there would be 0.99 probability that the observed limit of a one-sided upper 95% CI for the geometric mean $AUC_{0\text{-last}}$ ratio (docetaxel with aprepitant/docetaxel alone) would be <1.5, assuming that the true ratio is 1. Therefore enrollment was ended after ten patients had completed the study.

Results

Patients

Of 11 patients randomized, 10 (3 male, 7 female, age 50–68 years) completed the study. One patient was

discontinued from the study on day 2 of his first treatment cycle (docetaxel with aprepitant) because of slightly unstable liver function at screening and a concomitant medication taken during the treatment cycle (modafinil) that could have confounded interpretation of pharmacokinetic data. This patient was excluded from the analysis of pharmacokinetics, WBC, absolute neutrophil count, and platelet count. Cancer diagnoses included six women with breast cancer, one woman and one man with lung cancer, and two men with prostate cancer. The dose of docetaxel ranged from 71 to 100 mg/m^2.

Docetaxel pharmacokinetics

Figure 1 shows mean plasma concentrations of docetaxel administered alone (treatment A) and with aprepitant (treatment B). Figure 2 shows individual docetaxel $AUC_{0-\infty}$ values of docetaxel administered alone and with aprepitant. Table 1 summarizes the plasma pharmacokinetic parameters of docetaxel administered with and without aprepitant. The ratio of the geometric mean AUC_{0-last} of docetaxel plus aprepitant (3.17 μg h/ml) to the geometric mean AUC_{0-last} of docetaxel alone (3.26 μg h/ml) was 0.97 (90% CI 0.86, 1.10). There were no significant sequence effects or period effects for AUC_{0-last}, $AUC_{0-\infty}$, C_{max}, and plasma clearance of docetaxel. The median T_{max} of docetaxel was 0.71 h when docetaxel was given alone and 0.92 h when given with aprepitant, and the corresponding values for the harmonic mean half-lives were 10.1 and 8.5 h.

Aprepitant pharmacokinetics

An exploratory analysis was conducted to compare the pharmacokinetics of aprepitant in cancer patients with the pharmacokinetics in healthy subjects from a previous study. In the cancer patients and the healthy subjects, respectively, on day 1, the geometric mean

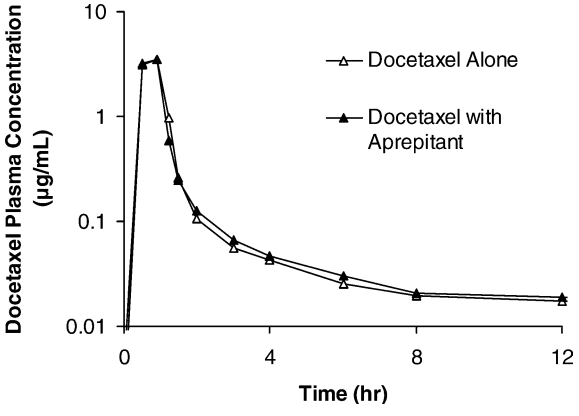

Fig. 1 Mean plasma concentration profiles of docetaxel administered alone (treatment A) and with aprepitant (treatment B)

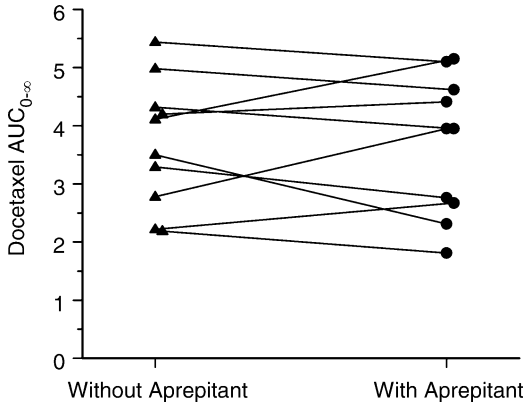

Fig. 2 Individual docetaxel $AUC_{0-\infty}$ values during treatment with docetaxel alone (treatment A) and docetaxel with aprepitant (treatment B)

AUC_{0-24h} values were 25.7 and 19.5 μg h/ml, the geometric mean C_{max} values were 1900 and 1539 ng/ml, and the geometric mean T_{max} values were 3 and 4 h. On day 3, in the cancer patients and the healthy subjects, the geometric mean C_{24h} values were 356 and 613 ng/ml, respectively.

Safety

The safety and tolerability analysis was conducted on all 11 patients enrolled, 10 of whom reported at least one clinical adverse experience. Table 2 summarizes the adverse experiences. There were 74 adverse experiences, including one that was serious. Of the 73 nonserious clinical adverse experiences, 30 were rated by the investigators as mild in intensity, 38 as moderate, and 5 as severe. The most common nonserious clinical adverse experiences were fatigue (eight occurrences in 6 of 11 patients, 55%), nausea (eight occurrences in 6 of 11 patients, 55%), and diarrhea (seven occurrences in 5 of 11 patients, 45%). The drug-related clinical adverse experiences that occurred were fatigue and asthenia in one patient during treatment A (docetaxel alone). No patients were discontinued from the study due to clinical or laboratory adverse experiences, and no patients died during the study.

One 55-year-old man developed a serious clinical adverse experience of febrile neutropenia requiring hospitalization after he received docetaxel 155 mg (75 mg/m^2) in the treatment cycle consisting of docetaxel alone (treatment A). His absolute neutrophil count had decreased to 340/mm^3 11 days after he received docetaxel. The neutropenia resolved and the patient recovered without sequelae.

Nine of the 11 patients developed a total of 45 nonserious laboratory adverse experiences. All of these patients had decreased total WBC and/or neutrophil counts, as would be expected based on the known effects of docetaxel treatment. One patient had decreased hemoglobin and lymphocyte counts that were not

Table 1 Pharmacokinetic variables for docetaxel given with and without aprepitant

Pharmacokinetic variable	Geometric mean[a]			90% CI of ratio	*P* value[b]	MSE[c]
	Docetaxel alone (A)	Docetaxel with aprepitant (B)	Ratio (B/A)			
AUC_{0-last} (μg h/ml)	3.26	3.17	0.97	0.86, 1.10	> 0.250	0.021
$AUC_{0-\infty}$ (μg h/ml)	3.51	3.39	0.96	0.84, 1.10	> 0.250	0.025
C_{max} (μg/ml)	3.53	3.37	0.95	0.84, 1.09	> 0.250	0.023
Plasma clearance ($L/h/m^2$)	23.3	24.2	1.04	0.91, 1.18	> 0.250	0.025
T^d_{max} (h)	0.71	0.92				
Half-life[e] (h)	10.1	8.5				

AUC: area under the concentration-versus-time curve
C_{max}: maximum plasma concentration
T_{max}: time to C_{max}
[a]Based on least squares estimate from ANOVA performed on natural log-transformed values
[b]Corresponds to null hypothesis of zero between-treatment difference versus two-sided alternative
[c]Mean square error on the natural log scale
[d]Values are medians
[e]Values are harmonic means

Table 2 Summary of clinical adverse experiences

	Docetaxel alone (treatment A), $n = 10$	Docetaxel with aprepitant (treatment B), $n = 11$	Total[a], $n = 11$
Patients with clinical adverse experiences (*n*)	8	10	10
Patients with serious clinical adverse experiences (*n*)	1	0	1
Patients with drug-related clinical adverse experiences (*n*)	1	0	1
Most common nonserious clinical adverse experiences [*n* (% of patients)]			
Fatigue	4 (40)	4 (36)	6 (55)
Nausea	3 (30)	4 (36)	6 (55)
Diarrhea	3 (30)	3 (27)	5 (45)

[a]Totals are based on numbers of patients who had the adverse experience

considered drug-related. Of six drug-related laboratory adverse experiences, five occurred in a single patient and involved increased AST and ALT values during both treatment cycles, in addition to increased blood urea associated with treatment A (docetaxel alone).

It was of special interest to evaluate how aprepitant might affect hematologic parameters including WBC and absolute neutrophil counts, as well as platelet counts, when given concurrently with docetaxel. Table 3 provides absolute neutrophil count data. Grade 3 or 4

Table 3 Absolute neutrophil counts during treatment with docetaxel alone (treatment A) and docetaxel with aprepitant (treatment B)

Day	Absolute neutrophil count (median, cells/mm^3)			Percent change[b] from baseline[c] (95% CI)[d]		Difference[c] (B−A) (95% CI)[e]
	Docetaxel alone	Docetaxel with aprepitant	Docetaxel alone (A)	Docetaxel with aprepitant (B)		
All patients who completed	1	4400 ($n = 10$)	4791 ($n = 10$)			
	4	3450 ($n = 10$)	5000 ($n = 9$)	−29.1 (−42.1, −14.4)	24.5 (−22.9, 109.9)	43.7 (6.6, 161.2)
	7	681 ($n = 10$)	975 ($n = 10$)	−81.3 (−91.9, −69.3)	−75.8 (−89.0, −63.0)	6.5 (−4.1, 16.6)
	14	1146 ($n = 10$)	1550 ($n = 10$)	−67.3 (−86.6, 15.4)	−56.2 (−82.2, −25.5)	1.9 (−77.7, 27.8)
Excludin patient 20[a]	1	4200 ($n = 9$)	4700 ($n = 9$)			
	4	3400 ($n = 9$)	4700 ($n = 8$)	−29.1 (−47.7, −9.9)	14.1 (−33.3, 56.9)	33.4 (4.8, 55.4)[f]
	7	700 ($n = 9$)	849 ($n = 9$)	−80.2 (−92.5, −64.9)	−77.4 (−91.1, −63.6)	3.3 (−9.5, 14.9)
	14	891 ($n = 9$)	1500 ($n = 9$)	−67.2 (−86.9, 22.1)	−60.8 (−84.3, −27.5)	−5.1 (−79.1, 22.9)

[a]This patient received pegfilgrastim as prophylaxis for neutropenia in his first treatment cycle
[b]Percent change = 100×[(day i/day 1)−1], where i = 4, 7, 14
[c]Hodges-Lehmann estimate
[d]Distribution-free CI based on the Wilcoxon signed ranks test (Tukey)
[e]Distribution-free CI based on the Wilcoxon rank sum test (Moses)
[f]Observed minimum and maximum difference; due to small sample sizes, exact CI could not be calculated

neutropenia occurred in six patients during treatment with docetaxel alone and in five patients during treatment with docetaxel plus aprepitant. An exploratory analysis showed that hematologic parameters displayed the expected toxic effects of docetaxel, which were not different when docetaxel was coadministered with aprepitant and, thus, were consistent with the lack of effect of aprepitant on docetaxel pharmacokinetics.

Discussion

Studies with midazolam as a probe of CYP3A4 activity indicate that aprepitant moderately inhibits the clearance of orally administered CYP3A4 substrates [5] and weakly inhibits the clearance of intravenously administered CYP3A4 substrates [18]. Because aprepitant may be administered with a variety of chemotherapeutic agents that may undergo CYP3A4 metabolism, it was important to characterize the potential effects of aprepitant on such an agent. In this study we examined whether concomitant administration of aprepitant would affect the pharmacokinetics and toxicity of docetaxel, an intravenously administered chemotherapeutic agent that is predominantly metabolized by CYP3A4 [7]. In cancer patients, docetaxel clearance correlated well with CYP3A4 activity, which was assessed using the probe substrates erythromycin, midazolam, and cortisol [8–10]. Recently, a population pharmacokinetic study conducted in cancer patients also showed that CYP3A4 activity correlates with the clearance of docetaxel [19], and a pharmacokinetic study in cancer patients receiving docetaxel and ketoconazole (a specific, strong inhibitor of CYP3A4) further defined the importance of CYP3A4 in docetaxel clearance [11]. Docetaxel was an appropriate agent to use in the present study because among chemotherapeutic agents it is especially sensitive to changes in CYP3A4 activity.

In this study, cancer patients received an approved dose of docetaxel (60–100 mg/m^2) with and without aprepitant given as the 3-day regimen approved for use (125 mg on day 1 and 80 mg/day on days 2 and 3). The aprepitant regimen had no clinically important or statistically significant effects on any of the pharmacokinetic parameters of docetaxel (AUC, C_{max}, plasma clearance, time to C_{max}, and half-life). The geometric mean $AUC_{0-\infty}$ for docetaxel with aprepitant (treatment B) was nearly the same as that for docetaxel alone (treatment A), resulting in a ratio of treatment B to treatment A of 0.96 with a 90% CI of 0.84–1.10 for the true AUC ratio. (The corresponding AUC_{0-last} ratio was 0.97 with a 90% CI of 0.86–1.10.) A clinically meaningful increase in docetaxel AUC was defined as an upper bound of the confidence interval of ≥1.5 for the geometric mean AUC_{0-last} ratio. Thus, the results show that concomitant aprepitant caused no clinically important increase in the docetaxel AUC because the upper limit of the 90% CI for the true geometric mean AUC_{0-last} ratio (and $AUC_{0-\infty}$ ratio) was < 1.5. Aprepitant pharmacokinetics were similar between cancer patients in this study and healthy subjects from a previous study. Therefore, the lack of effect of aprepitant on the pharmacokinetics of docetaxel cannot be attributed to insufficient exposure to aprepitant because, in these cancer patients, plasma aprepitant concentrations were similar to or even slightly higher than concentrations observed in healthy subjects. The findings suggest that aprepitant may not necessarily increase the plasma levels or otherwise alter the pharmacokinetics of other intravenous chemotherapeutic drugs that are also CYP3A4 substrates.

The overall patterns of adverse experiences and neutropenia were similar between the two treatment cycles. Because the toxicity of docetaxel is largely a function of plasma concentration of docetaxel, the similarity between the treatment cycles is consistent with the finding that aprepitant had no meaningful effect on docetaxel plasma concentration [12, 20].

Although this was a small study ($n = 10$) in cancer patients, based on a within-subject variance of 0.0136 for log-scale AUC_{0-last}, and assuming that the true AUC treatment ratio (docetaxel with aprepitant/docetaxel alone) was 1.0, this sample size was anticipated to provide greater than 99% power to show that the true AUC ratio was less than 1.5. The observed within-subject variance for the ten subjects was somewhat larger than that used in the power calculation (0.021); therefore, the actual power would have been somewhat less than anticipated. Still, the point estimate for the AUC ratio was close to 1.0 (0.97), and the 90% CI was relatively narrow (0.86–1.10), supporting the hypothesis of no clinically meaningful effect of aprepitant on docetaxel AUC.

In conclusion, aprepitant taken by cancer patients at doses of 125 mg on day 1 and 80 mg/day on days 2 and 3 had no effect on the pharmacokinetics of docetaxel administered intravenously at doses of 60–100 mg/m^2 on day 1. Aprepitant was generally well tolerated when given with docetaxel and produced plasma aprepitant levels similar to those observed in healthy subjects. The results of this study suggest that aprepitant has a low potential to affect the pharmacokinetics of intravenous chemotherapeutic agents metabolized by CYP3A4.

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