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ORIGINAL ARTICLE

Lack of effect of casopitant on the pharmacokinetics of docetaxel in patients with cancer

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Abstract
Purpose The neurokinin-1 receptor antagonist, casopitant, is a weak-to-moderate inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A) and has the potential to inhibit the metabolism of CYP3A substrates such as docetaxel.
Methods Fourteen cancer patients were enrolled in this phase 1, open-label, randomized, two-period crossover study. Intravenous (i.v.) docetaxel was coadministered with oral ondansetron and dexamethasone with (Regimen B) or without (Regimen A) 150 mg single-dose oral casopitant.
Results The geometric least-squares mean Regimen B: Regimen A ratios (90% confidence interval) for docetaxel maximum plasma concentration and area under the concentration–time curve from time 0 extrapolated to infinity were 0.97 (0.83, 1.12) and 1.06 (0.94, 1.19), respectively. Coadministration of casopitant and docetaxel was well tolerated, with adverse event profiles and absolute neutrophil count nadirs similar for both treatments.
Conclusions C_{max} and AUC of docetaxel were similar when given as monotherapy or when given in combination with casopitant. Likewise, absolute neutrophil count nadirs were similar for docetaxel alone or docetaxel with casopitant.

Keywords Casopitant · Neurokinin-1 receptor antagonist · Docetaxel · Drug interaction · CYP3A4

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Introduction

A significant number of patients undergoing treatment for cancer experience chemotherapy-induced nausea and vomiting, with a resulting deterioration in quality of life and impairment in chemotherapy treatment compliance [1, 2]. Although 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists have proven effective in reducing and preventing acute emesis, the addition of neurokinin-1 receptor antagonists provided improved protection against chemotherapy-induced nausea and vomiting, most notably in delayed emesis that occurs 2–5 days following chemotherapy, in several phase 3 trials [3–7].

Casopitant is a potent and selective neurokinin-1 receptor antagonist that has been investigated in combination with the 5-HT_3 receptor antagonist, ondansetron, and dexamethasone for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. Preclinical data in the ferret model of emesis demonstrate that casopitant significantly inhibits highly emetogenic (cisplatin) chemotherapy—induced emesis [8], and exhibited greater potency in enhancing food and water intake and reducing nausea-like symptoms in comparison with aprepitant [9], the first neurokinin-1 receptor antagonist approved for the

treatment of nausea and vomiting associated with chemotherapy [4]. Clinical trials of casopitant for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) have shown efficacy with three dosing regimens: single-dose 150 mg oral casopitant; 3-day regimens of 150 mg oral casopitant; or a 3-day regimen of 90 mg intravenous (i.v.) casopitant on day 1, followed by 50 mg oral casopitant on days 2 and 3. Two large Phase III trials demonstrated that casopitant showed a benefit versus control for overall Complete Response (0–120 h) in both MEC and HEC. Although this benefit was largely due to improvement in delayed emesis (24–120 h) in the MEC study [10], the endpoint for acute (0–24 h) as well as overall/delayed emesis was met for the HEC study [11].

Docetaxel monotherapy is classified as low on the emetogenicity scale, exhibiting up to a 30% risk of vomiting associated with its use in the absence of antiemetic prophylaxis [12, 13]. Prophylactic antiemetic regimens for docetaxel monotherapy include dexamethasone, metoclopramide or prochlorperazine on day 1 and as needed thereafter as recommended by the American Society of Clinical Oncology [13] and National Comprehensive Cancer Network [14] guidelines. However, docetaxel may be given in combination with highly or moderately emetogenic chemotherapeutic agents (e.g., cisplatin or carboplatin) that exhibit a strong component of delayed CINV, and patients may benefit from routine use of a neurokinin-1 receptor antagonist in addition to dexamethasone and a 5-HT_3 antagonist [12–15] in this setting.

Casopitant is a weak-to-moderate inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A) in vitro and in vivo [16], and docetaxel is extensively metabolized in the liver by CYP3A to inactive metabolites [17–20]. Preclinical studies have shown that potent inhibitors of CYP3A (e.g., ketoconazole, erythromycin) interfere with the metabolism of docetaxel [21]. Based on these findings, it is possible that concurrent use of CYP3A inhibitors or substrates with docetaxel could lead to an increase in the systemic exposure of docetaxel (AUC), with resulting increased docetaxel toxicity.

The NK-1 inhibitor, aprepitant is also a moderate inhibitor of CYP3A [22]. A study designed to assess the risk of drug-drug interactions associated with coadministration of aprepitant and docetaxel showed that aprepitant had no clinically significant effect on either the pharmacokinetics or toxicity of standard 3-weekly dosing (75–100 mg/m^2) of docetaxel in these patients [23]. Because the presence, extent, and clinical significance of a potential interaction between casopitant and docetaxel has not been determined, the current phase 1 study was designed to assess the pharmacokinetic parameters of docetaxel alone and in combination with casopitant, as well as to determine the safety of docetaxel monotherapy in the presence of casopitant.

Patients and methods

Patient population

Men or women ≥18 years of age with histologically confirmed malignant solid tumors who were scheduled to receive at least two courses of chemotherapy with docetaxel monotherapy as a single i.v. infusion of 20–40 mg/m^2 given over the duration of 1 h and repeated at least 7 days later were enrolled. Patients were required to have received eight or fewer prior doses of docetaxel, have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2, and have adequate hematologic and other physiologic organ function. Patients were prohibited from taking medications that are inducers or inhibitors of CYP3A4 or CYP3A5.

Exclusion criteria

Exclusion criteria included the following: pregnancy or lactation; radiation therapy to the abdomen or the pelvis in the 28 days prior to receiving, or scheduled radiation therapy to the abdomen or the pelvis in the 6 days following, first dose of study medication; receipt of docetaxel during the week prior to study day-1; known central nervous system primary or metastatic malignancy, unless successfully treated with excision or radiation and stable for at least 3 months prior to receiving first dose of study medication; active systemic infection or any poorly controlled medical condition (other than malignancy) that, in the opinion of the investigator, could confound the results of the study or pose an unwarranted risk; regular treatment with high-dose systemic corticosteroid therapy or steroid dose within 72 h prior to receiving first dose of study medication (except for docetaxel premedication) or hypersensitivity or contraindication to ondansetron or another 5-HT_3 receptor antagonist, dexamethasone, docetaxel, casopitant, or any component of the above-mentioned medications; receipt of an investigational drug within the 28 days or five half-lives (whichever was longer) prior to receiving first dose of study medication; scheduled receipt of any investigational drug during the study; gastrointestinal disease or prior surgery that would significantly affect absorption of oral medications, active peptic ulcer disease or history of peptic ulcer disease of unknown etiology, positive occult blood positive, or pepsinogen concentration below the lower limit of laboratory reference range; troponin 10% above the upper boundary of the normal range of the assay; corrected QT interval

(QTc) >480 ms; clinically significant cardiac disease that would interfere with participation in the study as determined by the investigator; inadequate venous access for pharmacokinetic sampling; and unresolved grade 2 or worse toxicity from prior therapy or known or suspected iron deficiency.

The study protocol was reviewed and approved by an institutional review board, and the study was conducted in accordance with good clinical practice guidelines. Written informed consent was obtained from each patient prior to the performance of any study-specific procedures.

Study design

Within 14 days of a screening visit, patients were randomized to receive Regimen A (docetaxel + dexamethasone + ondansetron) and Regimen B (docetaxel + casopitant + dexamethasone + ondansetron) in one of two treatment sequences (A/B or B/A). The two regimens were given during individual treatment periods at least 7 days apart. A weekly docetaxel schedule employing a lower dose of docetaxel rather than the every-3-week dose of 75 mg/m^2 was chosen to ensure that any potential increase in docetaxel exposure resulting from an interaction with casopitant would not increase the incidence of severe neutropenia. In Regimen A, patients received docetaxel (20–40 mg/m^2) by i.v. infusion and a standard prophylactic oral antiemetic regimen (8 mg oral ondansetron administered 30 min prior to the initiation of docetaxel therapy and three 8-mg oral doses of dexamethasone [at least 12 h before, 1 h before, and 12 h after docetaxel administration] starting the day before chemotherapy). In Regimen B, the patients received the same docetaxel dose and the same oral antiemetic regimen, with the addition of 150 mg single-dose oral casopitant administered 60 min prior to the initiation of docetaxel therapy, a dose and schedule of single-dose casopitant tested in phase 3 trials. The planned doses of casopitant and docetaxel could be adjusted downward to allow administration of lower doses if dose-limiting toxicities became evident. A sufficient number of patients were planned to be enrolled to ensure that at least 12 patients with evaluable docetaxel pharmacokinetic data for each treatment occasion would complete the study.

Patients were monitored for toxicity throughout the dosing period including at day 15, or 7 days after completion of dosing in the second regimen, and at 6 weeks following the completion of the second docetaxel treatment; toxicities were recorded as mild, moderate, or severe. Vital signs were obtained, routine physical examinations were performed, and ECOG performance scores were assessed at screening, prior to each docetaxel administration, and at the day 15 end-of-study visit. Vital signs were also collected within 30 min after docetaxel administration on days 1 and 8.

Study endpoints

The primary endpoint of this study was to determine the maximal observed plasma concentration (C_{max}) and area under the plasma concentration–time curve for docetaxel from time 0 extrapolated to infinity ($AUC_{[0-\infty]}$) on days 1 and 8. Secondary endpoints were as follows: (1) docetaxel terminal elimination half-life ($t½$), volume of distribution at steady state (Vd_{ss}), and systemic plasma clearance (CL) of docetaxel on days 1 and 8; (2) lowest measured absolute neutrophil count (ANC); and (3) changes in physical examination findings, blood pressure, heart rate, clinical laboratory tests, and adverse events.

Pharmacokinetic assessments

Serial venous blood samples for determination of plasma docetaxel concentrations were collected at the following time points in relation to docetaxel dosing: 0 (pre-infusion); 30 min after the start of infusion; at the end of infusion; and 0.5, 1, 2, 3, 5, 7, 9, and 24 h after the end of infusion. Blood samples were centrifuged, plasma was separated, and plasma aliquots were stored at −20°C. Plasma samples were analyzed for docetaxel using a validated analytical method based on liquid–liquid extraction, followed by high-performance liquid chromatography–tandem mass spectroscopy analysis. The lower limit of quantitation of this method for docetaxel was 0.25 ng/ml, using a 200-μl aliquot of human plasma, while the upper limit of quantitation was 500 ng/ml. The within-run precision was ≤7.6%, and the between-run precision was ≤8.1%. Accuracy was within −11.2 and +13.1% of nominal concentration. In addition, quality-control samples prepared at three different analyte concentrations and stored with study samples were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the quality-control results were to deviate from the nominal concentration by more than 15%, and at least 50% of the results from each quality-control concentration were required to be within 15% of nominal.

Pharmacokinetic analysis

Pharmacokinetic parameters were determined by noncompartmental methods using WinNonlin Pro version 4.1 (Pharsight Corporation, Mountain View, CA). Actual elapsed time from initiating docetaxel dosing was used to estimate all individual plasma docetaxel pharmacokinetic parameters. $AUC_{(0-\infty)}$ was calculated using the linear up-log down method; C_{max}, time to maximal concentration, and terminal

half-life were also determined. Systemic plasma clearance was calculated as dose (mg) divided by $AUC_{(0-\infty)}$. Volume of distribution at steady state was calculated as the product of systemic plasma clearance and mean residence time (obtained using statistical moment-analysis). Docetaxel dose-normalized (per mg) $AUC_{(0-\infty)}$ and C_{max} were also calculated.

Statistical analysis

The primary objective of the study was to determine the effect of casopitant on the pharmacokinetic parameters of docetaxel. For the primary comparison, the docetaxel pharmacokinetic parameters C_{max} and $AUC_{(0-\infty)}$ for the regimen including casopitant were compared with those for the regimen without casopitant. An analysis of variance model was employed to determine an estimate of the geometric least-squares mean ratio of the pharmacokinetic parameters with and without casopitant, along with the corresponding 90% confidence interval. The presence of an interaction effect was assessed using an estimation approach, i.e., by estimating the magnitude of any interaction together with the associated confidence interval. No formal statistical hypotheses were tested. The dependent variable in the model was the log-transformed pharmacokinetic parameter, and independent variables included a random subject effect and a fixed treatment effect.

Safety data including adverse events, electrocardiogram, vital signs, clinical chemistry, and hematology data were summarized by regimen using descriptive statistics. Absolute neutrophil count data were summarized by sequence using descriptive statistics to examine the values over the time course of the study.

Sample-size determination

A sufficient number of subjects were planned to be enrolled to ensure that at least 12 evaluable subjects would complete the study with docetaxel pharmacokinetic data for each treatment occasion. With an intrasubject coefficient of variation for docetaxel $AUC_{(0-\infty)}$ of 27.5% and a sample size of 12 evaluable subjects, it was estimated that the lower and the upper bounds of the 90% confidence interval for the ratio of the geometric means would be within 23% of the respective point estimate. Calculations were based on a symmetric two-tailed procedure on the log(e) scale.

Results

Patient population

Four centers in the United States enrolled 14 patients (12 male, 2 female), with a median age of 71.5 years (range, 55–86 years), between May 2007 and July 2008. Thirteen patients were of Caucasian/European heritage, and 1 patient was of Arabic/North African heritage. The distribution of tumor types was as follows: gastrointestinal ($n = 6$), prostate ($n = 4$), non–small cell lung cancer ($n = 2$), bladder ($n = 1$), and larynx ($n = 1$). Eleven patients (79%) completed the protocol, and 3 (21%) prematurely withdrew from the study as follows: disease progression (1 patient), pseudomonal lung infection unrelated to casopitant (1 patient), and personal reasons (1 patient, after two doses of dexamethasone in Regimen A and who did not receive casopitant, ondansetron, or docetaxel).

Pharmacokinetic data were evaluable for 12 patients who received both regimens, and safety data were available for 13 patients in Regimen B and for 14 patients in Regimen A. Irregularities noted in the pharmacokinetic profile of one patient in Regimen B suggested that the predose sample may have been taken after the docetaxel infusion had started and that the 1.0- and 1.5-h elapsed-time samples may have been transposed. Because no overall difference was seen when pharmacokinetic data were analyzed either with or without this patient, the pharmacokinetic parameter data presented exclude data from this patient.

Docetaxel pharmacokinetics

The median (35 mg/m^2) and range (20–40 mg/m^2) of docetaxel doses were identical for both Regimens A and B, and individual patients received the same dose of docetaxel during both treatment periods (i.e., no docetaxel dose reductions occurred). The median plasma docetaxel concentration–time profiles for 12 patients after both docetaxel monotherapy and docetaxel coadministered with casopitant are presented in Fig. 1. Docetaxel pharmacokinetic parameters were similar following coadministration of 150 mg single-dose oral casopitant with i.v. docetaxel when compared with docetaxel without casopitant, with

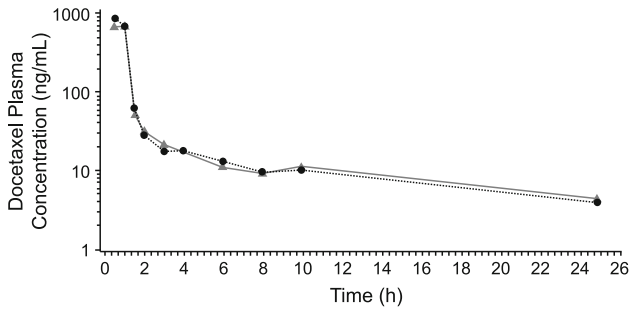

Fig. 1 Median plasma docetaxel concentration–time profiles for docetaxel without casopitant (*Regimen A*, *grey triangles*) and docetaxel with casopitant (*Regimen B*, *black circles*)

Table 1 Summary of selected docetaxel pharmacokinetic parameter estimates

Regimen[a]	No. of patients	C_{max} (ng/ml)	$AUC_{(0-\infty)}$ (ng h/ml)	DN-C_{max} (ng/ml/mg)	DN-$AUC_{(0-\infty)}$ (ng h/ml/mg)	CL (L/h)	Vd_{ss} (L)	$t½$ (h)	t^{b}_{max} (h)
A	12	916 (56.3)	1,000 (66.3)	14.3 (55.2)	15.7 (63.3)	63.6 (63.3)	376 (95.3)	12.6 (31.3)	0.98 (0.50–1.0)
B	12	884 (51.4)	1,060 (56.1)	13.8 (46.6)	16.6 (53.8)	60.2 (53.9)	324 (57.9)	12.2 (32.1)	0.98 (0.50–1.1)

Data are presented as geometric mean (%CVb)

AUC area under the concentration–time curve; *CL* systemic plasma clearance; C_{max} maximum plasma concentration; *%CVb* percent between-patient coefficient of variation; *DN* dose normalized parameters; $t½$ terminal half-life; t_{max} time to maximal plasma concentration; Vd_{ss} volume of distribution at steady state

[a] Regimen A, docetaxel without casopitant; Regimen B, docetaxel with casopitant

[b] t_{max} is presented as median and range

Table 2 Statistical comparison of pharmacokinetic parameters of docetaxel

Plasma docetaxel pharmacokinetic parameter	Geometric least-squares mean ratio [Regimen B/Regimen A][a] (90% confidence interval)
$AUC_{(0-\infty)}$, ng h/ml	1.06 (0.94, 1.19)
C_{max}, ng/ml	0.97 (0.83, 1.12)

AUC area under the concentration–time curve; C_{max} maximum plasma concentration

[a] Regimen A, docetaxel without casopitant; Regimen B, docetaxel with casopitant

geometric mean docetaxel $AUC_{(0-\infty)}$ values of 1,060 and 1,000 ng h/ml, respectively, and geometric mean docetaxel C_{max} values of 884 and 916 ng/ml, respectively (Table 1). Additionally, the results of the statistical comparison of docetaxel exposure parameters showed that coadministration of 20–40 mg/m^2 i.v. docetaxel with 150 mg single-dose oral casopitant did not produce a clinically relevant change in the $AUC_{(0-\infty)}$ or C_{max} of docetaxel (with-casopitant to without-casopitant mean ratios of 1.06 and 0.97, respectively, and 90% confidence intervals within the limits of 0.8–1.25, Table 2).

Safety

None of the planned doses of casopitant or docetaxel were adjusted downward as no dose-limiting toxicities were observed. Overall, a total of nine patients experienced 40 adverse events. Eight patients (57%) experienced 29 adverse events during Regimen A, and 5 patients (38%) reported 11 adverse events during Regimen B (Table 3). Sixteen of the 29 adverse events observed during Regimen A occurred in a single patient who experienced diarrhea, dizziness, dyspnea, fatigue, mucosal inflammation, nausea, vomiting, anorexia, cachexia, dehydration, oral candidiasis, orthostatic hypotension, pancytopenia, tachycardia (two episodes), and anemia, none of which were considered to be severe. This patient experienced no adverse events during Regimen B. Among all patients, most events were mild or moderate in intensity, with the exception of the serious adverse events described below.

Table 3 Summary of most common postdose adverse events

	Regimen A[a,b] ($n = 14$)	Regimen B[a] ($n = 13$)[c]	Total ($n = 14$)
Patients with adverse events/serious adverse events, *n*			
Clinical adverse events	8	5	9
Serious adverse events	1	3	3
Drug-related adverse events	0	2[d]	2
Most common adverse events, *n* (%)			
Asthenia	0	2 (15)	2 (14)
Headache	0	2 (15)	2 (14)
Dizziness	2 (14)	1 (8)	3 (21)
Fatigue	2 (14)	1 (8)	3 (21)
Hyperglycemia	2 (14)	0	2 (14)
Nausea	2 (14)	0	2 (14)
Vomiting	2 (14)	0	2 (14)

[a] Regimen A, docetaxel without casopitant; Regimen B, docetaxel with casopitant

[b] One patient (treatment sequence B/A) exhibited 16 adverse events, none severe, on Regimen A

[c] One patient withdrew after two doses of dexamethasone in Regimen A and did not receive ondansetron, docetaxel (or casopitant) in Regimen A, nor any study medication in Regimen B

[d] Considered related to chemotherapy but unrelated to casopitant by investigator

Three patients experienced five serious adverse events. These events were experienced by one patient (7%) undergoing treatment with Regimen A and three patients (23%) undergoing treatment with Regimen B. The serious adverse event in Regimen A was severe hiccups unrelated to study drug. The events in Regimen B consisted of moderate orbital cellulitis ($n = 1$), pseudomonal lung infection ($n = 1$), and severe asthenia and dizziness ($n = 1$). The patient who developed orbital cellulitis 39 days after the last dose of casopitant was successfully

Table 4 Summary of absolute neutrophil count (1.0×10^9 cells/l) values by treatment sequence

Regimen sequence[a]	Period	Regimen	*N*	*n*	Mean	SD	Median	Min	Max
A/B	Day 1 predose	A	8	8	5.56	3.66	4.60	1.70	13.50
	Day 8 predose	B	8	7	5.91	2.78	5.50	2.40	9.80
	Day 15	End of study	8	7	5.49	3.30	4.00	2.57	11.57
B/A	Day 1 predose	B	6	6	5.71	3.14	4.92	2.80	11.80
	Day 8 predose	A	6	6	6.52	3.24	5.60	3.30	12.80
	Day 15	End of study	6	5	5.08	3.32	6.20	1.10	9.00

Absolute neutrophil count normal range, 2–8 $\times 10^9$ cells/l

SD standard deviation

[a] Regimen A: docetaxel without casopitant; Regimen B: docetaxel with casopitant

treated with antibiotics and subsequently underwent surgery for non-serious sinusitis. The patient who developed pseudomonal lung infection 37 days after the last dose of casopitant had a prior history of pneumonia. The patient who experienced severe hiccups in Regimen A also experienced severe asthenia and dizziness in Regimen B, was withdrawn from the study, and died of progressive metastatic esophageal cancer within 1 month. None of the serious adverse events experienced by patients in Regimen B were deemed to be related to administration of casopitant.

Absolute neutrophil count values by sequence are presented in Table 4. None met the dose-limiting toxicity criterion of $\leq$1,000 neutrophils/mm^3 (1.0×10^9 cells/l). Median values for absolute neutrophil count at screening, day 1, day 8, and end of study were generally similar, and inspection of individual values by treatment sequence did not show any clinically relevant trends. Neutrophils in one patient in treatment sequence B/A shifted from 5,100 neutrophils/mm^3 at screening to 1,100 neutrophils/mm^3 at the end-of-study visit (day 15). The investigator did not consider this change to be of clinical concern. The $AUC_{(0-\infty)}$ of docetaxel for this patient was 1,245 ng h/ml during Regimen B (study population range, 504–2,870 ng h/ml) and 1,634 ng h/ml during Regimen A (study population range, 420–3,010 ng h/ml). Therefore, the docetaxel exposure was actually slightly lower in the presence of casopitant than with docetaxel monotherapy.

No clinically relevant trends were observed with respect to mean laboratory, vital sign, or electrocardiogram parameters when postdose values were compared with each patient's baseline values.

Discussion

Drug-drug interactions present a considerable challenge to prescribers, because they are associated with a high risk of patient morbidity and mortality [24]. The CYP3A enzyme plays a significant role in metabolizing many drugs, including anticancer agents such as etoposide and paclitaxel [25, 26] and is particularly important to the metabolism of docetaxel [17, 18]. A study in which docetaxel metabolites were isolated from human feces showed that CYP3A was a key route of inactivation of the parent drug [20], and additional studies have shown that total CYP3A activity is a strong predictor of docetaxel clearance [27–29].

The neurokinin-1 receptor antagonist, casopitant, has been assessed for the prevention of chemotherapy-induced nausea and vomiting. Clinical studies using probe CYP450 substrates have suggested that casopitant is a weak-to-moderate inhibitor of CYP3A [16], which potentially complicates its use in combination with agents metabolized via this enzyme pathway. Therefore, the current study sought to clarify the impact of casopitant administration on the pharmacokinetic and safety profiles of the prototypical CYP3A substrate, docetaxel. The study data showed that concomitant dosing of single-dose oral 150 mg casopitant and i.v. single-agent docetaxel resulted in no significant changes in docetaxel plasma exposure compared with that observed after administration of docetaxel in the absence of casopitant. The 90% confidence intervals for all geometric least-squares ratios were within the range of 0.8–1.25, both including and excluding the patient with the anomalous pharmacokinetic values (data not shown).

These results are concordant with a similarly designed trial of aprepitant, which is also a moderate inhibitor of CYP3A [22]. To assess the risk of drug-drug interactions associated with coadministration of aprepitant and docetaxel, a randomized, open-label, crossover study was undertaken in which the pharmacokinetics and toxicity of aprepitant were studied in 11 cancer patients receiving a single infusion of docetaxel monotherapy (60–100 mg/m^2) on two occasions, at least 3 weeks apart [23]. Patients received docetaxel alone in one treatment cycle and a 3-day regimen consisting of aprepitant 125 mg orally 1 h prior to docetaxel infusion (day 1) plus a single oral dose of aprepitant 80 mg on days 2 and 3 in the other treatment cycle. Results from this trial suggested that concomitant

administration of aprepitant had no clinically significant effect on either the pharmacokinetic parameters or toxicity of standard doses of docetaxel given every 3 weeks.

Although previous clinical studies with CYP450 probe substrates have shown that casopitant is a weak-to-moderate inhibitor of CYP3A [16], casopitant coadministration did not result in an alteration of docetaxel exposure in the current study. Casopitant pharmacokinetic parameters were not assessed in the current study. However, there is no clinical evidence that docetaxel is a significant inhibitor of CYP3A, the primary enzyme responsible for the first-pass effect and clearance of casopitant.

Coadministration of single-dose 150 mg oral casopitant (plus dexamethasone and ondansetron) with up to 40 mg/m^2 i.v. docetaxel monotherapy was well tolerated in this population of cancer patients. The five serious adverse events that occurred in the study were judged by the investigators to be unrelated to casopitant administration. Even though this population was largely Caucasian, male, and somewhat elderly, relevant differences in the clearance of docetaxel with respect to gender or race have not been seen in phase II or III population PK studies. Although there is some evidence that advanced age has been shown to correlate with docetaxel exposure, the potentially higher docetaxel exposure in the studied population would not impact the study conclusions as it was an intrapatient crossover comparison.

The use of docetaxel is associated with an increased risk of neutropenia [30, 31] which is dose and schedule dependent [32]. The current trial utilized a weekly schedule of docetaxel to help ensure that changes in docetaxel exposure would not increase rates of severe neutropenia in the event of an interaction with casopitant. Indeed, no patient developed neutropenia (absolute neutrophil count $\leq$1,000/mm^3) during the trial, and no clinically relevant trends were observed with respect to changes in absolute neutrophil counts in the presence or absence of casopitant coadministration. Importantly, given that docetaxel exhibits dose-proportional pharmacokinetics [33], no relevant pharmacokinetic interaction with single-dose oral casopitant would be predicted to occur with higher doses of docetaxel (75–100 mg/m^2) that are administered less frequently on a once every 3–4 week schedule.

In conclusion, these data demonstrate that single-dose 150 mg oral casopitant can be given safely in combination with docetaxel, dexamethasone and ondansetron, does not significantly alter intravenous docetaxel exposure, and did not result in any increased incidence of neutropenia or other adverse events.

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References

1. Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM et al (1983) On the receiving end—patient perception of the side effects of cancer chemotherapy. Eur J Cancer Clin Oncol 19:203–208
2. Osoba D, Zee B, Warr D, Kaizer L, Latreille J, Pater J (1996) Quality of life studies in chemotherapy-induced emesis. Oncology 53:92–95
3. Schmoll HJ, Aapro MS, Poli-Bigelli S, Kim HK, Park K, Jordan K et al (2006) Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Ann Oncol 17:1000–1006
4. Reddy GK, Gralla RJ, Hesketh PJ (2006) Novel neurokinin-1 antagonists as antiemetics for the treatment of chemotherapy-induced emesis. Support Cancer Ther 3:140–142
5. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, de Wit R, et al. (2003) The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the aprepitant protocol 052 study group. J Clin Oncol 21:4112–4119
6. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie Ma G, Eldridge K, Hipple A et al (2003) Addition of the neurokinin-1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 97:3090–3098
7. Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, Eisenberg PD et al (2005) Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 23:2822–2830
8. Gagnon RC, King AG (2006) Co-administration of ondansetron and casopitant mesylate, a novel NK-1 receptor antagonist, results in augmented anti-emetic activity in the ferret [abstract]. J Clin Oncol 24(18 Suppl):18608
9. King AG (2005) Comparison of anti-emetic and peri-emetic behaviors of NK-1 receptor antagonists GW679769 and aprepitant in the ferret [abstract]. Support Care Cancer 13:04–031
10. Herrstedt J, Apornwirat W, Shaharyar A, Aziz Z, Roila F, Van Belle S et al (2009) Phase III trial of casopitant, a novel neurokinin-1 receptor antagonist, for the prevention of nausea and vomiting in patients receiving moderately emetogenic chemotherapy. J Clin Oncol 27:5363–5369
11. Grunberg SM, Rolski J, Strausz J, Aziz Z, Lane S, Russo MW, et al. (2009) Efficacy and safety of casopitant mesylate, a neurokinin 1 (NK1)-receptor antagonist, in prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based highly emetogenic chemotherapy: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 10:549–558
12. Roila F, Hesketh PJ, Herrstedt J, Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (2006) Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 perugia international antiemetic consensus conference. Ann Oncol 17:20–28
13. Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM et al (2006) American society of clinical oncology

guideline for antiemetics in oncology: update 2006. J Clin Oncol 24:2932–2947
14. Ettinger DS, Bierman PJ, Bradbury B, Comish CC, Ellis G, Ignoffo RJ et al (2007) Antiemesis. J Natl Compr Canc Netw 5:12–33
15. Herrstedt J (2007) Chemotherapy-induced nausea and vomiting: ESMO clinical recommendations for prophylaxis. Ann Oncol 18(suppl 2):83–85
16. Johnson BM, Wessels D, Milleri S et al (2009) Impact of casopitant, a novel NK-1 receptor antagonist, on the pharmacokinetics of the CYP3A substrates midazolam and nifedipine [abstract]. In: Proceedings of the 100th Annual Meeting of the American Association for Cancer Research, Denver, CO. Abstract 5457, 18–22 Apr 2009
17. Marre F, Sanderink GJ, de Sousa G, Gaillard C, Martinet M, Rahmani R (1996) Hepatic biotransformation of docetaxel (Taxotere) in vitro: involvement of the CYP3A subfamily in humans. Cancer Res 56:1296–1302
18. Royer I, Monsarrat B, Sonnier M, Wright M, Cresteil T (1996) Metabolism of docetaxel by human cytochromes P450: interactions with paclitaxel and other antineoplastic drugs. Cancer Res 56:58–65
19. Clarke SJ, Rivory LP (1999) Clinical pharmacokinetics of docetaxel. Clin Pharmacokinet 36:99–114
20. Sparreboom A, Van Tellingen O, Scherrenburg EJ, Boesen JJ, Huizing MT, Nooijen WJ et al (1996) Isolation, purification and biological activity of major docetaxel metabolites from human feces. Drug Metab Dispos 24:655–658
21. Engels FK, Ten Tije AH, Baker SD et al (2004) Effect of cytochrome P450 3A4 inhibition on the pharmacokinetics of docetaxel. Clin Pharmacol Ther 75:448–454
22. Sanchez RI, Wang RW, Newton DJ et al (2004) Cytochrome P450 3A4 is the major enzyme involved in the metabolism of the substance P receptor antagonist aprepitant. Drug Metab Dispos 32:1287–1292
23. Nygren P, Hande K, Petty KJ, Fedgchin M, van Dyck K, Majumdar A et al (2005) Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients. Cancer Chemother Pharmacol 55:609–616
24. Lazarou J, Pomeranz BH, Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 279:1200–1205
25. Lin JH, Lu AYH (1998) Inhibition and induction of cytochrome P450 and the clinical implications. Clin Pharmacokinet 35:361–390
26. Parkinson A (1996) An overview of current cytochrome P450 technology for assessing the safety and efficacy of new materials. Toxicol Pathol 24:45–57
27. Yamamoto N (2000) Correlation between docetaxel clearance and estimated cytochrome P450 activity by urinary metabolite of exogenous cortisol. J Clin Oncol 18:2301–2308
28. Goh BC (2002) Explaining interindividual variability of docetaxel pharmacokinetics and pharmacodynamics in Asians through phenotyping and genotyping strategies. J Clin Oncol 20:3683–3690
29. Hirth J, Watkins PB, Strawderman M, Schott A, Bruno R, Baker LH (2000) The effect of an individual's cytochrome CYP3A4 activity on docetaxel clearance. Clin Cancer Res 6:1255–1258
30. Taxotere (docetaxel) injection concentrate [package insert]. Bridgewater, NJ: sanofi-aventis US LLC; 2008. http://www.products.sanofi-aventis.us/taxotere/taxotere.html. Accessed 6 Jan 2010
31. Bruno R, Hille D, Riva A, Vivier N, ten Bokkel Huinnink WW, van Oosterom AT et al (1998) Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 16:187–196
32. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN et al (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502–1512
33. Extra J-M, Rousseau F, Bruno R, Clavel M, Le Bail N, Marty M (1993) Phase I and pharmacokinetic study of taxotere (RP 56976; NSC 628503) given as a short intravenous infusion. Cancer Res 53:1037–1042