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ORIGINAL ARTICLE

The effect of aprepitant and race on the pharmacokinetics of cyclophosphamide in breast cancer patients

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Abstract
Purpose The prodrug cyclophosphamide is metabolized by cytochrome P450(CYP)2B6 to the active metabolite, 4-hydroxycyclophosphamide (4-OH), and by CYP3A4/5 to toxic chloracetaldehyde and 2-dechloroethylcyclophosphamide (DCE). Since aprepitant is a moderate inhibitor of CYP3A4, the study was designed to determine whether its concurrent use alters the pharmacokinetics (PK) of cyclophosphamide. In addition, we sought to determine the effect of race and pharmacogenomics on cyclophosphamide PK.
Methods Eighteen patients with localized breast cancer were randomized in this double-blinded cross-over study to receive aprepitant or placebo in addition to cyclophosphamide 600 mg/m^2 and doxorubicin 60 mg/m^2. Blood samples were collected for both PK analysis of cyclophosphamide and metabolites and pharmacogenomic analysis. Single nucleotide polymorphisms genotyped were CYP3A4*1B, CYP3A5*3, and CYP2B6*6.
Results The geometric mean area under concentration–time curve (AUC_{0-t} μg/mL h) for cyclophosphamide was 282 following aprepitant and 230 following placebo (ratio 1.23; 90% CI 1.13, 1.33). 4-OH AUC_{0-t} (μg/mL h) was 6.80 following aprepitant and 6.96 following placebo (ratio 0.98; 90% CI 0.88, 1.08). DCE AUC_{0-t} (μg/mL h) was 6.76 following aprepitant and 9.37 following placebo (ratio 0.72; 90% CI 0.64, 0.81). Genotype analysis was confounded by race. Race was a significant predictor of DCE $\ln AUC_{0-t}$ ($P = 0.0169$) as African Americans had approximately a 2-fold higher DCE AUC than Caucasians.
Conclusions Aprepitant altered the exposure of cyclophosphamide and DCE but not the active 4-OH metabolite, making it unlikely that aprepitant would change the clinical efficacy of cyclophosphamide. African Americans were also found to have altered PK compared with Caucasian patients.

Keywords Aprepitant · Cyclophosphamide · Pharmacokinetics · Pharmacogenomics

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Introduction

Aprepitant is a substance P/neurokinin receptor antagonist used to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV). The American Society of Clinical Oncology (ASCO) CINV guidelines recommend the addition of aprepitant to dexamethasone and a serotonin antagonist for highly emetogenic chemotherapy regimens. Aprepitant is also recommended for moderately emetogenic regimens that include doxorubicin and cyclophosphamide (AC) therapy [1]. This recommendation was based upon the efficacy of aprepitant in 866 patients receiving moderately emetogenic chemotherapy (99% of whom received AC). A complete response was defined as no vomiting and no use of rescue antiemetic medications. Overall complete response was higher with the aprepitant-containing regimen than with the standard antiemetic regimen of ondansetron and dexamethasone (50.8% vs. 42.5%, $P = 0.015$). Additionally, a higher percentage of patients receiving aprepitant reported no vomiting (75.7% vs. 58.7%, $P < 0.001$) [2].

Aprepitant undergoes extensive hepatic metabolism, primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C19. The terminal half-life ranges from approximately 9 to 13 h. In addition to being a substrate for CYP3A4, aprepitant is also initially a moderate inhibitor of CYP3A4. Paradoxically, induction develops after greater than 14 consecutive days of dosing [3]. The FDA approved dosing regimen for oral aprepitant is 125 mg on day 1 and 80 mg on days 2 and 3 following chemotherapy; thus, the inhibitory effects are of considerable clinical concern.

Aprepitant's moderate inhibition of CYP3A4 was documented in 16 healthy volunteers using oral midazolam as a probe. Aprepitant was dosed at 125 mg orally on day 1 followed by 80 mg orally on days 2–5. The area under the concentration–time curve (AUC) of midazolam was increased by 2.3-fold on day 1 and 3.3-fold on day 5. Additionally, the midazolam C_{max} and half-life were also increased on day 1 (1.5-fold and by 1.7 h, respectively) and day 5 (1.9-fold and 3.3 h) [4]. Coadministration of aprepitant with oral dexamethasone, a CYP3A4 substrate and commonly used antiemetic with aprepitant, increased the dexamethasone AUC 2.2-fold on days 1–5. The dexamethasone was dosed at 20 mg on day 1 and 8 mg on days 2 through 5, and the aprepitant was dosed identically to the previous study [5].

Cyclophosphamide (CPA) is an antineoplastic alkylating agent used as treatment for a variety of malignancies including breast cancer. The most common toxicities occurring in >10% of patients include myelosuppression, nausea, vomiting and alopecia. Less common side effects include hemorrhagic cystitis, cardiac toxicity, and rare neurotoxicity and nephrotoxicity [6]. CPA is a prodrug that must be converted to the active metabolite, 4-hydroxycyclophosphamide (4-OH), via hydroxylation. The majority of this metabolism occurs in the liver by the cytochrome P-450 enzyme system. CYP2B6 has been shown to play the largest role in CPA activation, accounting for 48–57% of the hydroxylation, while CYP2C9 and CYP3A4 have been shown to account for 15–17 and 12–18%, respectively [7, 8]. CPA can also undergo *N*-dechloroethylation cleavage to chloroacetylaldehyde (the metabolite responsible for neurotoxicity and nephrotoxicity) and dechlorethylcyclophosphamide (DCE). Although only about 10% of CPA is converted to DCE, CYP3A4 is responsible for ≥95% of this conversion [9]. It is hypothesized that differences in CYP2B6 and CYP3A4 expression may influence CPA efficacy and/or toxicity. Both enzymes have shown significant variability between individuals. CYP3A4 has demonstrated 20-fold interpatient variability, while CYP2B6 has been reported to vary 20-fold to 250-fold [10–13]. For individuals with low CYP2B6 activity, CYP3A4 becomes more important for CPA activation.

Breast cancer patients receiving AC are at high risk for experiencing chemotherapy-induced nausea and vomiting. Thus, due to the metabolic profile of aprepitant, the potential for a drug–drug interaction exists when it is given concurrently with CPA. This interaction has been investigated in the stem cell transplant setting with two trials demonstrating no significant change in the exposure of 4-OH [14, 15]. However, the potential for interaction in the breast cancer setting was assessed given the curable nature of the population who would be receiving aprepitant with CPA and the lower dose of CPA used, which may result in an altered PK profile. The primary objective of this study was to determine the effects of aprepitant on CPA, 4-OH and DCE pharmacokinetics (PK) as measured by the plasma AUCs.

Patients and methods

Patient selection

Patients (men and women) from the University of North Carolina Breast Cancer Clinic were identified by the primary treating medical oncologist and were screened for enrollment if they were at least 18 years of age and scheduled to receive a CPA-containing regimen for the treatment for breast cancer. Eligible patients also had to have a life expectancy of at least 2 months and adequate hematologic, renal, and hepatic function as defined by an absolute neutrophil count ≥1,500 /uL, hemoglobin ≥9.0 mg/dL, platelets ≥100×10^9 /L, aspartate aminotransferase (AST) ≤ twice the upper limit of normal, alanine aminotransferase (ALT) ≤ twice the upper limit of normal, and a serum creatinine ≤1.5 mg/dL.

Patients were excluded if they were unable to provide written informed consent, were pregnant or lactating, and had a contraindication to aprepitant or whose dose of CPA changed between cycle 1 and cycle 2. Patients were also excluded if they were taking concurrent medications or herbal products known to be CYP3A4 substrates, inhibitors, and/or inducers, with the exception of the dexamethasone contained as part of the standard antiemetic regimen or if they had been on a stable dose of a substrate for at least 3 months prior to study entry and remained on the same dose during the entire study. Women of childbearing potential must have had a negative blood β-hCG pregnancy test prior to the first study cycle. All patients gave written informed consent, and the study was approved by the University of North Carolina Office of Human Research Ethics.

Study design and treatments

A randomized, double-blind, placebo-controlled, cross-over design was utilized. All patients received AC therapy consisting of doxorubicin 60 mg/m^2 given as a slow intravenous push followed by CPA 600 mg/m^2 given intravenously over 30 min. Prior to the first cycle of AC, patients were randomized to receive either treatment with aprepitant on cycle 1 followed by treatment with matching placebo on cycle 2 or the reverse sequence. The treatment sequence was determined by a randomized, balanced allocation schedule blocked in groups of four patients. Treatment with aprepitant consisted of 125 mg orally on day 1 and 80 mg orally on days 2 and 3. One hour after the aprepitant or placebo dose, and following the infusion of doxorubicin, patients received the CPA infusion.

In addition to either aprepitant or placebo, antiemetic medications (ondansetron 24 mg orally and dexamethasone 12 mg orally) were given on the day of treatment 30 min prior to both cycles on day 1. Dexamethasone 8 mg orally was continued on the morning of days 2 and 3. Rescue medication was permitted following AC and included lorazepam 1 mg orally given every 4 h as needed and prochlorperazine 10 mg orally given every 6 h as needed. Each patient was given a diary to record dates and times; scheduled medications were taken, any use of rescue antiemetic therapy, and any adverse effects thought due to antiemetic therapy.

Pharmacokinetic methods

Whole blood samples for plasma CPA, 4-OH, and DCE were collected prior to CPA treatment, immediately following the end of infusion and at 0.5, 1, 3, 6, 8, 12, 16, 20, and 24 h after the CPA infusion. This same sampling schedule was repeated for cycle 2 of CPA. Blood was drawn into EDTA-containing tubes, which were immediately placed on ice. Samples for CPA and DCE were centrifuged at 1,200$\times g$ at 4°C for 5–10 min, and plasma was aliquoted into cryotubes and stored at −80°C until analysis. Because of the reactivity of the 4-OH (closed form) and aldophosphamide (open form) metabolites of CPA, whole blood for 4-OH analysis was immediately added to a solution of a hydroxylamine-based derivatizing agent consisting of O-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine-HCl (PFBHA). CPA, 4-OH, and DCE were measured at Duke Cancer Institute Clinical Pharmacology Lab using an internally validated liquid chromatography/tandem mass spectrometry (LC–MS/MS) method based on previously published works [16, 17]. Quality control acceptance criteria were 85% accuracy at all levels except 80% at lower limit of quantification (LLOQ = 200, 4, and 16 ng/mL for CP, 2deCP, and 4-OH-CP, respectively).

Plasma concentrations of CPA, 4-OH, DCE were used to estimate pharmacokinetic parameters using WinNonlin (Pharsight Co., Mountain View, CA). A non-compartmental model was used to fit the concentration–time data. The PK profiles for each subject were determined, including the following parameters: AUC_{0-t}, $AUC_{0-\infty}$, time to maximum concentration (t_{max}), maximum concentration (C_{max}), clearance, and half-life ($t_{1/2}$). It should be noted that AUC_{0-t} are the only AUC parameters reported for 4-OH and DCE metabolites, as these metabolites did not reach a log-linear terminal phase, thus not allowing for the calculation of $AUC_{0-\infty}$. The actual doses of CPA and sample collection times were used to estimate the parameters. Patients served as their own pharmacokinetic (PK) controls in the analysis.

Pharmacogenomic analysis

Whole blood from all 18 patients was collected for pharmacogenomic (PG) analysis. DNA from all patients was extracted from whole blood using a QIAcube (QIAGEN, MD, USA) with the QIAamp DNA Mini Kit (QIAGEN). Extracted DNA was used to perform PCR. PCR primers were designed using PSQ HS 96 SNP software (QIAGEN) and carried out using 1 ng of genomic DNA, 0.005 nmol of each primer, and 1X AmpliTaq Gold PCR Master Mix (Applied Biosystems, CA, USA) or HotStar Taq DNA polymerase (0.5 units) (QIAGEN) (as specified by the references) in a 20 μL reaction [18, 19]. Annealing temperatures of 54, 65, 54, and 56°C were used for *CYP3A4*1B* (rs2740574), *CYP3A5*3* (rs776746), *CYP2B6 516* (rs3745274), and *CYP2B6 785* (rs2279343), respectively. Pyrosequencing was conducted as previously described [20].

Statistical analysis

The primary objective of this study was to evaluate the effect of aprepitant on the metabolism of CPA and 4-OH in

breast cancer patients receiving a chemotherapy regimen containing CPA. Sample size estimates were based upon the following considerations. Interindividual variability in CPA clearance was 37% (in placebo cycle and the same variance in the aprepitant cycle), with 21% interoccasional variability between cycles 1 and 2 [21]. The latter value was assumed for paired calculations. With a sample size of 18, the study should have more than 80% power to detect a 30% difference in CPA AUC between the 2 treatment periods. All AUC, C_{max}, and clearance data were natural log-transformed and evaluated with a repeated measures analysis of variance (ANOVA), mixed effect model for a two-period, two-treatment, two-sequence ($2 \times 2 \times 2$) cross-over design. A two-sided 90% confidence interval (CI) was used to calculate between-treatment differences expressed as geometric mean ratios (hereafter referred to as ratios). ANOVA was calculated using WinNonlin Software version 5.2.1 (Pharsight Corp., Mountain View, CA). Period and sequence effects were also considered statistically significant and reported only if the P value was <0.05. Descriptive statistics were reported for all t_{max} (medians and ranges) and $t_{1/2}$ (means and standard deviations) data. Assessment of outliers also was performed by plotting the difference of predicted log-AUC per subject and confirmed by using the "2-sigma rule" in statistical process control [22].

Descriptive statistics including geometric means and 95% CIs were separately used to report comparisons between races in the CPA + placebo group. An ANCOVA analysis was used when comparing between-race differences in metabolic formation using lnCPA AUC_{0-t} as a covariate.

Results

Patient characteristics

A total of 19 patients were enrolled in the study. The patients were predominantly female (1 male, 18 females) and ranged in age from 38 to 77 years. One-third of patients were African American ($n = 6$) with the remaining two-thirds being Caucasian ($n = 12$). One patient withdrew from the study prior to cycle 2 for personal reasons. This patient was excluded from PK analysis. Based on AUC data, one patient arguably qualified as an outlier. However, a sensitivity analysis with the outlier either included or removed yielded the same results. Therefore, all 18 patients were included in the analyses. The demographic/clinical characteristics of the 18 patients in whom PK data were evaluated are listed in Table 1.

Table 1 Patient characteristics

Characteristics	Number of patients
Patients enrolled	18
Gender	
Male	1
Female	17
Median age (range)	55 (38–77)
Race/Ethnicity	
Caucasian	12
African American	6
Genotype (Caucasians)	
CYP2B6*6 (516 or 785)	
GG	7
GT, TT	5, 0
CYP3A4*1B	
*1A/*1A	10
*1B/*1A, *1B/*1B	2, 0
CYP3A5*3	
*3/*3	9
*1/*3, *1/*1	3, 0
CYP3A4/5*2[a]	2
Genotype (African Americans)	
CYP2B6*6 (516 or 785)	
GG	2
GT, TT	3, 1
CYP3A4*1B	
*1A/*1A	1
*1B/*1A, *1B/*1B	4, 1
CYP3A5*3	
*3/*3	0
*1/*3, *1/*1	4, 2
CYP3A4/5*2[a]	5
Chemotherapy regimen	
Dose dense AC + T	12
AC every 3 weeks	4
AC + TH	1
T + Dose dense AC	1

AC, doxorubicin and cyclophosphamide; *T,* paclitaxel; *TH,* paclitaxel and trastuzumab

[a] Denotes at least one variant CYP3A4 and one CYP3A5 allele

Cyclophosphamide pharmacokinetics

Summary PK parameter estimates for CPA, DCE, and 4-OH administered with and without aprepitant are presented in Table 2. Spaghetti plots illustrate the change in AUC_{0-t} from CPA + placebo to CPA + aprepitant for individual subjects (Fig. 1).

Table 2 Summary PK parameters of CPA and metabolites DCE and 4-OH from 18 evaluable patients

CPA or metabolite	Placebo + CPA (Treatment A)	Aprepitant + CPA (Treatment B)	Ratio (B/A)	90% CI
CPA				
$AUC_{0-\infty}$ (ug/mL h)	247	317	1.28	1.17–1.40
AUC_{0-t} (ug/mL h)	230	282	1.23	1.13–1.33
CL (L/h)	4.83	3.77	0.78	0.71–0.86
C_{max} (ug/mL)	31.1	30.8	0.99	0.92–1.06
$T_{1/2}$ (h)[a]	6.07 (SD 1.93)	7.29 (SD 1.73)	NA	NA
T_{max} (h)[b]	0.5 (0.5–1.0)	0.5 (0.5–1.0)	NA	NA
4-OH				
AUC_{0-t} (ug/mL h)	6.96	6.80	0.98	0.88–1.08
C_{max} (ug/mL)	0.96	0.67	0.70	0.55–0.87
T_{max} (h)[b]	0.5 (0.5–0.65)	0.5 (0.5–3.5)	NA	NA
DCE				
AUC_{0-t} (ug/mL h)	9.37	6.76	0.72	0.64–0.81
C_{max} (ug/mL)	0.51	0.36	0.71	0.62–0.78
T_{max} (h)[b]	8.55 (6.5–20.5)	12.5 (3.5–20.5)	NA	NA

Aprepitant or placebo was given orally at a dose of 125 mg day 1 and 80 mg on days 2 and 3. Cyclophosphamide was given at an IV dose of 600 mg/m^2 for both treatments

$AUC_{0-\infty}$, area under the concentration–time curve extrapolated to infinity; AUC_{0-t}, area under the concentration–time curve to the last measureable concentration (24 h post-CPA infusion); C_{max}, maximum concentration; $T_{1/2}$, half-life; T_{max} , time to maximum concentration; *NA*, not applicable

[a] $T_{1/2}$ is reported as mean (standard deviation, SD)

[b] T_{max} is reported as median (range)

CPA coadministration with aprepitant resulted in a 28% (90% CI, 17–40%) increase in the mean $AUC_{0-\infty}$ compared with placebo (reference treatment). The ratio of mean AUC_{0-t} of CPA + aprepitant (282 μg/mL h) to CPA + placebo (230 μg/mL h) was 1.23 (90% CI, 1.13–1.33), similar to $AUC_{0-\infty}$, since only 7% of the AUC was extrapolated to infinity. The intrasubject variability in CPA $AUC_{0-\infty}$ and AUC_{0-t} was 16 and 14%, respectively, somewhat smaller than that used in sample size projections.

The mean clearance significantly decreased, from 4.9 L/h (CPA alone) to 3.8 L/h after CPA was administered with aprepitant (ratio: 0.78; 90% CI, 0.71–0.86). There were small but statistically significant period effects for $AUC_{0-\infty}$ ($P = 0.0347$), AUC_{0-t} ($P = 0.0415$), and CPA CL ($P = 0.0353$) with period 2 values somewhat lower. Small but similar period 2 findings also were found for 4-OH ($P = 0.0143$) and DCE ($P = 0.0342$) C_{max}. During placebo, a significant direct correlation was shown between lnCPA $AUC_{(0-t)}$ and lnDCE AUC_{0-t} ($r^2 = 0.45$, $P < 0.01$) but not ln4-OH AUC_{0-t}.

4-OH metabolite pharmacokinetics

Despite higher CPA after aprepitant administration, there were no differences in 4-OH AUC_{0-t} whether coadministered with aprepitant or placebo. The ratio of mean AUC_{0-t} of 4-OH + aprepitant (6.96 μg/mL h) to CPA + placebo (6.80 μg/mL h) was 0.98 (90% CI, 0.88–1.08). Mean C_{max} was reduced by 33% when coadministered with aprepitant compared with placebo. The ratio of mean C_{max} of 4-OH + aprepitant (0.67 μg/mL) to mean C_{max} of 4-OH + placebo (0.96 μg/mL) was 0.70 (90% CI, 0.55–0.87).

2-dechloroethyl metabolite pharmacokinetics

The mean DCE AUC_{0-t} was reduced by 28% after CPA was coadministered with aprepitant versus given with placebo. The ratio of mean C_{max} of DCE given with placebo (0.51 μg/mL) to the mean C_{max} of DCE given with aprepitant (0.36 μg/mL) was 0.72 (90% CI, 0.64–0.81). The median T_{max} increased 45% after CPA coadministration with aprepitant (12.5 h) compared with placebo (8.6 h).

Pharmacokinetics, race, and genotype

When comparing race and genotype data with PK, only the placebo arm was used in the analysis. As all African Americans had at least two variant alleles, genotype analysis was confounded by race (Table 2). Although African

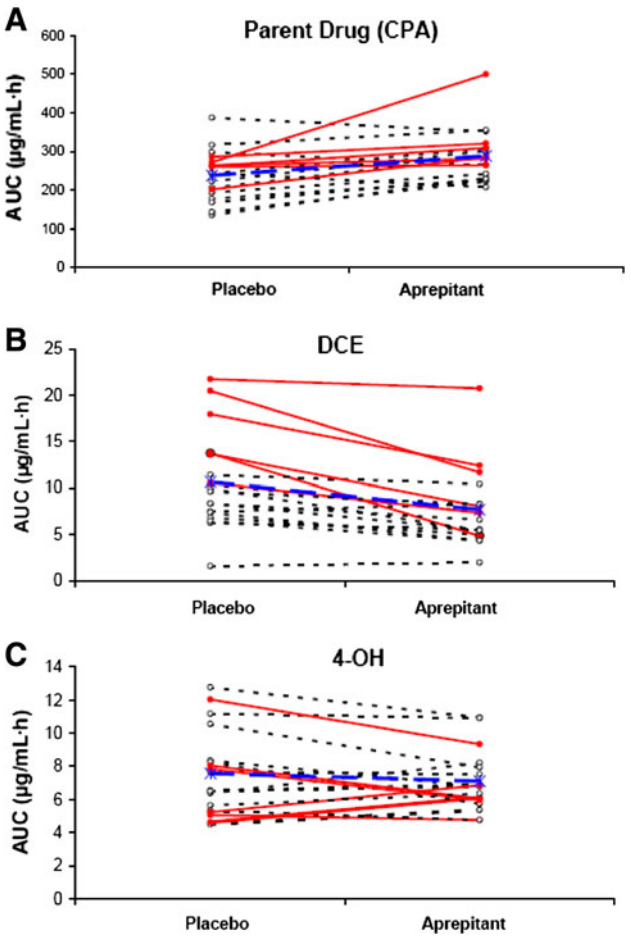

Fig. 1 Plot of AUC_{0-t} for **a** parent drug CPA following placebo and aprepitant; **b** AUC_{0-t} for DCE following placebo and aprepitant; and **c** AUC_{0-t} for 4-OH for placebo and aprepitant. Mean change is represented by the *thick*, *scored line* with star connectors; African Americans, *solid lines* and *filled-circles;* and Caucasians, *dotted lines* with *open-circles*

Americans had altered PK of parent and both metabolites when compared to Caucasians, only lnDCE AUC_{0-t}, (but not 4-OH), was significantly higher in African Americans after controlling for lnCPA AUC_{0-t} ($P = 0.0169$) (Table 3).

Toxicity

There were no serious aprepitant-related toxicities reported. Non-serious toxicity included 3 patients who developed hiccups after aprepitant administration, which is consistent with product labeling. The assessment of neutropenia frequency following treatment with AC was initially intended; however, confounding factors such as differences in AC frequency (every 2 compared to every 3 weeks) and the sporadic use of pegfilgrastim prevented this analysis from being useful.

Table 3 Geometric mean AUC (95% CI) of cyclophosphamide and metabolites by race

Cyclophosphamide or metabolite	African Americans ($n = 6$)	Caucasians ($n = 12$)
CPA	256	217
AUC_{0-t} (ug/mL h)	(225–291)	(177–267)
4-OH	6.58	7.16
AUC_{0-t} (ug/mL h)	(4.51–9.59)	(5.96–8.61)
DCE	15.1	7.38
AUC_{0-t} (ug/mL h)	(10.7–21.3)	(5.24–10.4)

AUC_{0-t} area under the concentration–time curve to the last measureable concentration (24 h post-CPA infusion); *CI,* confidence level

Discussion

The purpose of this study was to determine the effects of aprepitant on the PK of the parent drug CPA and the metabolites 4-OH and DCE in breast cancer patients receiving chemotherapy with AC. The exposure of both CPA and the metabolite DCE were altered when aprepitant was concurrently administered with CPA. Concomitant use of aprepitant with CPA resulted in a significant increase in exposure of the parent drug but no change in C_{max} or t_{max}. This increased parent (prodrug) exposure was seen in conjunction with a significant decrease in DCE AUC and C_{max}, and an increase in DCE t_{max} when aprepitant was administered with CPA. A reasonable explanation for the increased parent drug and decreased DCE metabolite is moderate inhibition of CYP3A4 by aprepitant. CYP3A4 accounts for greater than 95% of the conversion of CPA to DCE [7–9]. The metabolic fate of the additional parent drug is unclear from this study due to limited metabolite assessment. The pharmacokinetic–pharmacodynamic relationship of CPA is not fully understood [23].

Importantly, the exposure (i.e., AUC_{0-t}) of the active 4-OH metabolite did not change significantly with the addition of aprepitant, although there was a significant reduction in 4-OH C_{max} when CPA was given concurrently with aprepitant. This lack of alteration would be expected based upon the finding that the majority of CPA conversion (48–57%) to 4-OH occurs by CYP2B6, which has not be shown to be affected by aprepitant [3, 7–9]. Measures of total drug exposure (AUC) have traditionally been utilized to determine comparative efficacy with cyclophosphamide [24]. Assuming this is true, there should be no loss of CPA-intended cytotoxicity with the addition of aprepitant.

The PK interaction between aprepitant and CPA was previously assessed by De Jonge et al., using a population PK model in 6 patients receiving a regimen containing high-dose CPA (1,500 mg/m^2/day × 4 days). The authors reported a 7% increase in exposure of parent CPA and 5%

decrease in the exposure of 4-OH in the presence of aprepitant with most patients also experiencing a lower C_{max}. [14] Similarly, another study involving 22 patients receiving concurrent therapy with aprepitant and cyclophosphamide 60 mg/kg every 24 h for 2 doses prior to stem cell transplant also did not demonstrate a change in CPA or 4-OH exposure [15]. However, it is noteworthy that both studies utilized much higher CPA doses compared to those utilized in the current trial, which may explain the differences in the metabolite fate of the parent drug. Nevertheless, even their difference in 4-OH exposure was small and likely of minor clinical significance.

In this small study, a finding of racial difference in cyclophosphamide PK is intriguing and hypothesis generating. African Americans have significantly higher DCE concentrations, but not 4-OH, compared to Caucasians, even after adjusting for greater CPA exposure. More DCE formation may be due to genetic polymorphisms as all studied African Americans carried variant alleles in at least two genotypes of CYP3A4, CYP3A5, and/or CYP2B6. Several other studies have observed that African Americans have altered PK of many CYP3A4/5 substrates including cyclosporine, triazolam, and methylprednisolone [25–28]. In patients receiving combination chemotherapy containing fluorouracil, epirubicin, and cyclophosphamide (FEC), slightly higher incidence of grade 2 or higher non-hematologic toxicity was seen in African Americans (75%) than in Caucasians (64%), although a slightly higher incidence of hematologic toxicity was seen in Caucasians (36%) than African Americans (25%) [29]. In pediatric patients with acute lymphocytic leukemia receiving 200 mg/m^2 of cyclophosphamide, hemorrhagic cystitis was found to be twice as frequent in African-American children ($16\%, n = 5$) than in Caucasian children ($7\%, n = 20$) [30]. It does appear that African Americans exhibit an altered toxicity profile, which may be explained by altered PK possibly secondary to pharmacogenetic polymorphisms of drug-metabolizing enzymes involved with CPA metabolism. Although, higher DCE suggests a greater risk of CPA toxicity by chloracetaldehyde, both the race/pharmacogenomic and CPA correlation findings should be interpreted with caution, since the current study was designed to address the drug–drug interaction effect of aprepitant and CPA and the subsequent analysis was exploratory in nature and in a small study population.

In conclusion, oral aprepitant (125 mg on day 1 and 80 mg on days 2 and 3) resulted in lower peak concentrations, but no significant change in exposure of the 4-OH active metabolite of CPA when administered prior to CPA (600 mg/m^2) in patients with breast cancer. Changes seen in the exposure of the parent drug and DCE metabolite are unlikely to affect efficacy of the drug. Genetic polymorphisms in drug-metabolizing enzymes involved in the metabolism of CPA may also partially explain interpatient PK differences between patients of different races. A large, adequately powered, clinical study designed with appropriate stratification to address effects of race and genetics on CPA PK is needed to further explore these findings.

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