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ORIGINAL ARTICLE

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Pharmacokinetic interaction between ondansetron and cyclophosphamide during high-dose chemotherapy for breast cancer

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Abstract *Purpose*: Both ondansetron and cyclophosphamide are thought to be metabolized by hepatic microsomal processes. The purpose of this study was to evaluate the potential pharmacokinetic interactions between ondansetron and high-dose alkylating agent chemotherapy. *Methods*: A total of 54 breast cancer patients receiving high-dose cyclophosphamide, cisplatin and carmustine were treated prospectively in four sequential cohorts. Cohorts I and II received continuous infusions of both ondansetron and prochlorperazine, and cohorts III and IV received a continuous infusion of ondansetron alone at the same doses. All patients received lorazepam every 4 h. A group of 75 matched historical controls had received a continuous infusion of prochlorperazine with lorazepam. Pharmacokinetic monitoring of each drug used in the high-dose chemotherapy regimen was conducted. *Results*: Median AUCs of cyclophosphamide in patients receiving ondansetron (73.6 mg/ml · min) were lower than those of the control patients (88.3 mg/ml · min, $n = 75$, $P = 0.0004$), but the median cisplatin AUC was approximately 10% higher and no difference in the disposition of carmustine was demonstrated. Patients treated with ondansetron displayed a higher frequency of headaches than the controls. The frequency of achieving complete emetic control was greater in the ondansetron + prochlorperazine groups compared to the ondansetron alone groups and was greater in both these groups than in the prochlorperazine alone group on the first day of therapy only. *Conclusion*: Ondansetron altered the systemic exposure to cyclophosphamide when these agents were administered concomitantly. Ondansetron did not substantially improve overall emetic control when used alone but may improve control in combination with prochlorperazine. Future randomized studies are needed to delineate the effect of ondansetron on the disposition of the active cyclophosphamide metabolites so that clinical implications can be addressed.

Key words Ondansetron · Cyclophosphamide · Pharmacokinetics · Bone marrow transplant

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Introduction

Despite the fact that high-dose combination chemotherapy with hematopoietic cellular support is an increasingly common approach to treating metastatic or high-risk stage II/III breast cancer [17], relatively little is known regarding the effects of ancillary medications on the clearance of high-dose chemotherapy. These regimens typically employ alkylating agents at myeloablative doses which are at or near major organ dose-limiting toxicities. Cyclophosphamide, one of the most commonly used agents, is associated with cardiac toxicity when given in the bone marrow transplantation setting in doses of up to 200 mg/kg [24]. The cardiac toxicity has a wide spectrum which varies between fatal hemorrhagic myocarditis to cardiac arrhythmias, congestive heart failure and pericardial effusions. There is evidence that increased clearance of cyclophosphamide (potentially faster conversion to the active metabolite) is associated with a higher incidence of cardiac toxicity as manifested by symptomatic congestive heart failure [2, 21]. Carmustine and cyclophosphamide have also been associated with pulmonary toxicity occurring 4 to 8 weeks after bone marrow transplantation [14, 22].

Drugs with a suspected potential to alter the pharmacokinetics of certain antineoplastic drugs are often excluded from use in clinical trials or prescribed in carefully controlled circumstances (e.g. corticosteriods, multidrug resistance modifiers). However, combinations of antiemetic agents are utilized to manage the nausea and vomiting associated with these high-dose chemotherapy regimens despite the paucity of data concerning potential interactions with hepatically metabolized drugs. Ondansetron is a serotonin antagonist which has gained rapid acceptance and is widely employed to prevent chemotherapy-induced emesis [9, 12]. This agent is metabolized via hepatic microsomal enzymes, but the potential for pharmacokinetic interaction with high-dose chemotherapy has not been examined.

Cyclophosphamide is of particular concern when administered at high-doses with these agents owing to the risk of life-threatening cardiac toxicity and its disposition profile. Cyclophosphamide is metabolized by hepatic mixed-function oxidases to forms which are transported intracellularly and these spontaneously degrade to molecules which are thought to account for most of this drug's cytotoxicity [7]. High-dose cyclophosphamide induces hepatic microsomal enzymes within 24 h of exposure, resulting in increased clearance of parent compound and increased formation of cytotoxic metabolites [16]. Combinations of ondansetron with conventional cyclophosphamide-containing regimens have not resulted in an altered toxicity profile, but the potential pharmacokinetic and pharmacodynamic interactions of these two agents in the high-dose setting warrant investigation, and this was the objective of this trial.

Materials and methods

Patient eligibility

Breast cancer patients receiving high-dose combination cyclophosphamide, continuous infusion cisplatin, and carmustine with autologous hematopoietic cellular support were eligible for this study. Prior to high-dose chemotherapy, stage IV patients received a doxorubicin-based induction regimen for two to four cycles (doxorubicin, fluorouracil and methotrexate; AFM) and high-risk stage II/III patients received four cycles of adjuvant doxorubicin and fluorouracil. Patients were required to have normal organ functions (creatinine clearance >60 ml/min, liver function tests values less than twice normal, normal electrocardiogram and left venticular ejection fraction $>50\%$) and to sign written informed consent. The protocol was approved by the institutional review board for ethical research. Patients were excluded if they were pregnant, had a documented allergy to any study drug, or were receiving any of the following medications within 2 weeks of high-dose chemotherapy: corticosteroids, phenytoin, phenobarbital, $histamine_2$ antagonists, or any parenteral antibiotic.

Treatment plan and assessment

This was an open-label, prospective study. The high-dose chemotherapy regimen consisted of 3 days of cyclophosphamide (1875 mg/m^2 per day) and continuous infusion cisplatin (55 mg/m^2 per day) followed by carmustine (600 mg/m^2) on the 4th day. The details of this regimen have been described elsewhere [18]. Patients were sequentially enrolled into one of four study cohorts segregated based on the type of antiemetic and its dose, as shown in Fig. 1. The antiemetic regimen began 30 min prior to the start of chemotherapy on day −6 and continued throughout the 4 days of chemotherapy until 18 h after completion of carmustine. Those in cohorts I and II received diphenhydramine 25 mg i.v. every 6 h during the prochlorperazine infusion. All patients received lorazepam 1 mg/m^2 iv every 4 h throughout the study period, except those who became excessively somnolent in whom the dosage was decreased by 50%. All patients were placed on central cardiac monitors throughout the 4 days of chemotherapy and daily EKGs were performed prior to each daily administration of chemotherapy. Physical examination, complete blood count with differential, and chemistry panel for serum creatinine, BUN, glucose, potassium, chloride, sodium, bicarbonate, magnesium and phosphorus were performed daily. Liver function tests were done prior to chemotherapy and every 4 days thereafter. Patient weight, fluid intake and output, and vital signs were recorded daily.

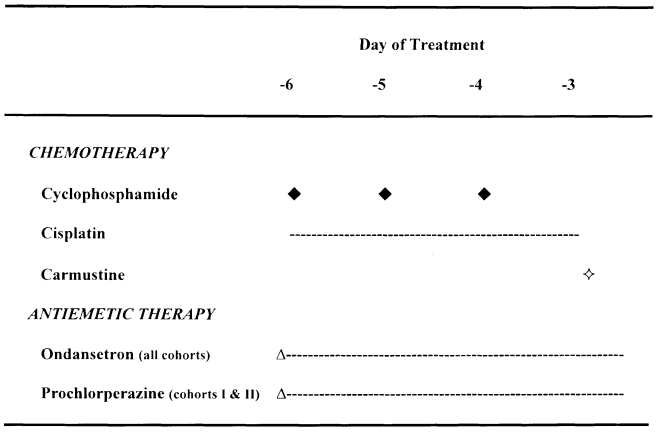

Fig. 1 Antiemetic dosage: Cohorts I and III – ondansetron 4.5 mg/m^2 loading dose followed by 0.6 mg/m^2 per h continuous infusion; cohorts II and IV – ondansetron 9.0 mg/m^2 loading dose followed by 1.2 mg/m^2 per hour continuous infusion; Cohorts I and II – concurrent prochlorperazine 6 mg/m^2 loading dose followed by 1.5 mg/m^2 per h continuous infusion. All patients received lorazepam 1 mg/m^2 intravenously every 4 h

Emetic control was assessed by recording the number of emetic episodes per day on the nursing flow sheet. Nurses evaluated potential antiemetic toxicities every 12 h, including: cardiac (chest pain, arrhythmias, or EKG changes), dizziness, extrapyramidal side effects (akasthesias, dystonia), excess sedation, headache, hallucinations, bad dreams, gastrointestinal effects (abdominal pain, diarrhea), visual disturbances, and allergic reactions. Patient satisfaction was informally evaluated by the nursing staff as part of the toxicity evaluation process. All patient comments and complaints were documented on the study flow sheets.

Data from the patients on this study were compared with those obtained from historical controls used to estimate the appropriate sample size, as described in the statistical section. All of the subsequently described pharmacokinetic sampling and analytic methods were also consistent between the groups. The historical control patients had metastatic breast cancer which had been treated with multicycle induction therapy (doxorubicin, fluorouracil, and methotrexate) followed by exactly the same high-dose combination chemotherapy with prochlorperazine and lorazepam for emetic control. No other ancillary drugs were given during the administration of high-dose chemotherapy. These patients also met the same organ function criteria for treatment as the study patients.

Determination of cyclophosphamide concentrations

Samples were drawn at 0 h (preinfusion), 1/2 h (mid-infusion), 1 h (end of infusion) and at 11/2, 2, 3, 5, 7, 9, 12, 17, and 21 h after the

start of the infusion on each day of cyclophosphamide administration. Approximately 5 ml of blood was collected into heparinized tubes for each time-point using a lumen separate from the point of infusion. Plasma was obtained by refrigerated centrifugation at 900 *g* for 10 min. Samples were stored at −20°C for 24–48 h then analyzed for both protocol-treated patients and historical controls.

Standards and quality control samples were prepared from neat chemical (Sigma Chemical Company, St. Louis, Mo.) and diluted with single donor plasma to yield concentrations ranging up to 100 μl/ml. The extraction of cyclophosphamide from plasma samples was initiated by adding 1 ml of a 25.0 μg/ml ifosfamide (Bristol-Myers Squibb, Princeton, N.J.) internal standard solution to 1.0 ml of plasma. The mixture was then loaded onto a Supelclean LC-Si solid-phase extraction column (Supelco, Bellefonte, Pa.) and eluted with 1 ml acetonitrile. All solvents used in the assays reported here were HPLC grade. The eluants were blown dry with nitrogen and resuspended in 300 μl methanol.

Samples were analyzed using a previously published method with modification [3]. Briefly, 25 μl of eluates was injected onto an HPLC system consisting of a 3.9 × 150 mm Waters NovaPak C_{18} analytic column (4 μm particle size; Millipore Corporation, Milford, Mass.). The mobile phase (15% acetonitrile 85% monobasic sodium phosphate) was delivered isocratically at a rate of 1.3 ml/min. The Waters Associates HPLC system (Milford, Mass.) consisted of a Model 510 pump, a refrigerated WISP Model 710B autosampler and a Model 490 programmable multiwavelength detector set at 200 nm. The system was interfaced to a personal computer using Maxima 820 software. The lower limit of cyclophosphamide quantitation for this assay was 1 μg/ml. Interassay and intraassay variabilities were 7% and 5%, respectively.

Determination of cisplatin concentrations

Blood samples were collected in heparinized tubes at 8:00 a.m. (every 24 h during infusion) on days −5, −4 and −3 of treatment and immediately placed on ice for transport to the laboratory. The samples were centrifuged at 900 *g* for 10 min at 4°C within 30 min of collection. Plasma was promptly removed and placed in an Amicon Centrifree micropartition device (molecular weight cut off 30 *kDa*; Amicon, Beverly, Mass.) and spun at 2000 *g* for 30 min at 4 °C. The ultrafiltrates were stored at −70 °C and analyzed within 1 week for both protocol-treated patients and historical controls.

Standards and quality control samples were prepared from platinum atomic absorption standard solution (Sigma Chemical Company, St. Louis, Mo.). A stock solution made in 0.9% NaCl was used to prepare a series of standard solutions ranging from 50 ng/ml to 300 ng/ml. Plasma ultrafiltrates, quality control samples and standards were analyzed for platinum content by our previously published graphite furnace atomic absorption spectrophotometry assay with modification using automated sample delivery (Perkin-Elmer, Models 2380, HGA 400 and AS40, Norwalk, CT) [19]. Aliquots of 25 μl were dispensed into a pyrolytically coated graphite tube and the platinum was detected at a wavelength of 265.9 nm using a slit width of 0.7 mm. The furnace program consisted of three drying steps followed by charring at 1100°C, and atomization at 2700°C. The data were collected and analyzed using a Perkin-Elmer Nelson integrator. The lower limit of platinum quantitation for this assay was 50 ng/ml. Interassay and intraassay variabilities were 1% and 2%, respectively.

Determination of carmustine concentrations

Samples were collected at 0 (preinfusion), 60, 120 (end of infusion), 130, 140, 150, 165, 180, and 210 min after the start of the infusion into 10 ml heparinized tubes containing 3 ml 25 μg/ml 5,5-diphenylhydantoin (the internal standard; Sigma Chemical Company, St. Louis, Mo.) in ethyl acetate. Precisely 3 ml of whole blood were added to each tube at the designated sample time followed by inversion and refrigeration. The cellular components were separated by refrigerated centrifugation at 900 *g* for 10 min within 24–48 h of sample collection for both controls and protocol-treated patients, then a 1-ml aliquot of the supernatant was transferred to a glass tube.

Standards ranging up to 10 μg/ml and quality control samples were prepared by addition of diluted pharmaceutical grade carmustine (Bristol-Myers Squibb Company, Princeton, NJ) to whole blood (American Red Cross, Durham, NC) using sampling tubes as described above. The ethyl acetate supernatants from samples and standards were concentrated by evaporation under nitrogen and subsequently reconstituted with 300 μl methanol.

Carmustine concentrations were determined by a previously published method with modification [14]. Briefly, 25-μl aliquots of the eluates were injected onto an HPLC system consisting of a 25.0 cm × 4.6 mm Supelcosil LC-18-DB column (5 μm particle size; Supelco, Bellefonte, Pa). The mobile phase (55% methanol:45% purified water) was delivered isocratically at a rate of 1.6 ml/min. The Waters Associates HPLC system consisted of a Model 510 pump, a refrigerated Model 712 WISP autosampler and a Lambda Max Model 481 LC spectrophotometer set at a wavelength of 237 nm. The system was interfaced using Maxima 820 software. The lower limit of carmustine quantitation for this assay was 0.5 μg/ml. Interassay and intraassay variabilities were 4% and 10%, respectively.

Pharmacokinetic modeling and statistics

Selection of the appropriate pharmacokinetic models and initial parameter estimations were performed by curve stripping techniques (RSTRIP V.4.03, MicroMath, Salt Lake City, Utah). Subsequent evaluations of individual data sets were conducted by weighted nonlinear least-squares regression using a one- or two-compartment model each with zero-order input and a first-order elimination process for carmustine and cyclophosphamide, respectively (PCNONLIN V.4.2, ClinTrials, Apex, NC). AUC data were derived from the pharmacokinetic parameter estimates. For cyclophosphamide, the AUC for each dose was estimated independently owing to metabolic induction, thus the values reported here reflect the addition of all three AUCs for each patient. The overall clearance and AUC values for cisplatin were determined by noncompartmental methods.

The sample size determination was based on the assumption that the overall AUC over 3 days of cyclophosphamide administration correlates with drug-induced toxicity. A sample size of 15 patients per cohort provided 80% power to detect a change in mean AUC of about 0.8 standard deviations from the historical mean of 92 mg/ml · min. Two sided statistical analyses were conducted using the Wilcoxon test for paired analyses and the Mann-Whitney *U*-test for non-paired group comparisons.

Results

A total of 58 patients were registered on the study as verified by the Duke Cancer Center Protocol Office, and 54 were evaluable. One patient was never transplanted and three patients requested removal from the study within the first 24 h because of anxiety and poor emetic control. Table 1 shows the patient demographics and treatment assignments for the 53 women and 1 man evaluated in this trial. No patients received cyclophosphamide as part of their standard chemotherapy regimen which was administered in the 2 to 4 months prior to admission for high-dose chemotherapy. Patient cohorts I and II (ondansetron plus prochlorperazine) and patient cohorts III and IV (ondansetron alone) were combined for the presentation of results.

Table 1 Patient demographics and treatment assignment

Treatment cohort	*N*	Median age (years) (range)	Stage and diagnosis (*N*)
I & II ondansetron + prochlorperazine	30	43 (26–57)	Stage II breast cancer (6) Stage IV breast cancer (24)
III & IV ondansetron alone	24	42 (27–58)	Stage II breast cancer (4) Stage IV breast cancer (20)
Prochlorperazine historical controls	75	41 (27–56)	Stage IV breast cancer (75)

Table 2 Summary of systemic exposure to chemotherapy

Drug	*N*	Study group		Historic controls			
		Median	Interquartile range	*N*	Median	Interquartile range	*P*-value[a]
Cyclophosphamide AUC (mg/ml · min)	47	73.6	66.7–83.1	75	88.3	75.9–103	< 0.0001
Carmustine AUC (μg/ml · min)	46	501	351–916	58	564	458–709	0.49
Cisplatin AUC (mg/ml · min)	45	0.80	0.70–1.00	63	0.73	0.63–0.85	0.043

[a]Mann-Whitney test

Pharmacokinetics

The overall systemic exposure, as measured by the chemotherapy AUCs, was highly variable between patients, as anticipated. AUCs varied over a 3.2-, 10.7- and 5.2-fold range for cyclophosphamide, carmustine and cisplatin, respectively. Interquartile AUC ranges are displayed in Table 2. The median AUC for carmustine was not substantially altered by concurrent exposure to ondansetron compared to the historical control patients; but, the former group demonstrated a median cisplatin AUC which was approximately 10% above that found in the controls (Table 2). The plasma clearance of cyclophosphamide increased by approximately twofold over the 3 days of drug administration, resulting in lower parent drug AUC with subsequent doses. This occurred in both controls and ondansetron-treated patients (Fig. 2) but was more obvious in the latter group. The median AUC of cyclophosphamide was substantially less in the study patients receiving ondansetron alone or ondansetron plus prochlorperazine (76.0 mg/ml · min and 70.8 mg/ml · min, respectively; 73.6 mg/ml · min, all study groups combined) when compared with the 75 historical control patients (88.3 mg/ml · min). Overall, a statistically significant 17% increase in the clearance of cyclophosphamide parent compound was noted in the presence of continuous infusion ondansetron (Table 2).

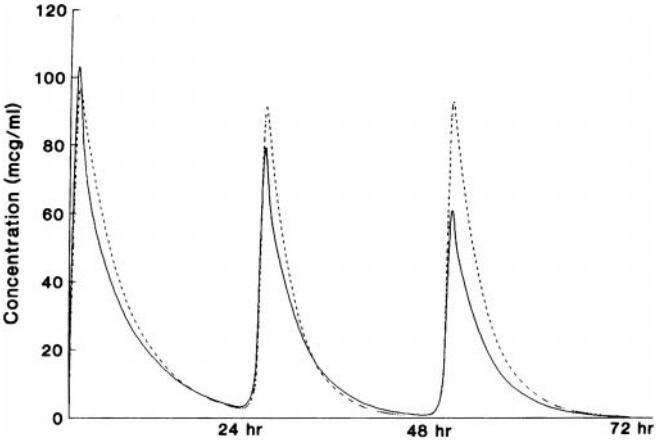

Fig. 2 Disposition of cyclophosphamide following each of three daily 1 h infusions (1875 mg/m^2 per day) in the patient experiencing the median AUC of those treated with ondansetron (*solid line*) and the patient with the median AUC of the control group

Toxicity and response

Cardiac arrhythmias or evidence of heart failure are reported for the 30-day period following bone marrow transplant, and hepatic toxicities, excluding acute stem cell infusion effects, are reported for the same 30-day period, whereas renal toxicity is evaluated only until 5 days after stem cell reinfusions to avoid the confounding effect of nephrotoxic antibiotics which were used more often posttransplant in the historical control patients. The renal toxic effects of cisplatin in this regimen are typically seen within 1 to 2 days following completion of chemotherapy. Transient elevations of total bilirubin to levels greater than 2 mg/dl associated with progenitor cell infusions were common, but no life-threatening hepatic toxicity occurred on the study (Table 3). Renal toxicity, defined as an elevated serum creatinine to greater than 1.5 mg/dl, was not increased in the study patients as compared with the controls. An increased risk of cardiac toxicity was also not detected, as only 3% of patients receiving ondansetron and prochlorperazine experienced at least a 25% decline in left ventricular ejection fraction as measured by MUGA compared with 9% of control patients. No cardiac arrhythmias, other

Table 3 Pharmacodynamic effects of ondansetron on organ toxicities. Organ toxicities were defined as follows: hepatic – total bilirubin >2.0 mg/dl before 30 days posttransplant excluding transient elevations associated with stem cell reinfusions; renal – serum creatinine >1.5 mg/dl between day of treatment −6 and +5; cardiac – greater than 25% decline in baseline ejection fraction or arrhythmias

Treatment cohort	Hepatic	Renal	Cardiac
Study group	20%	7%	2%
Prochlorperazine controls	28%	4%	9%

than transient tachycardia during high-dose chemotherapy, or hemorrhagic myocarditis occurred during the study period.

Of the 54 patients on this study, 39 were evaluable for tumor response. Of 28 patients with a partial response to induction therapy, 13 were converted to a complete response (46%) by the high-dose chemotherapy. The overall response rate following bone marrow transplantation was 97% (51% CR, 46% PR).

Antiemetic efficacy

This study was not designed to compare the antiemetic efficacy of the four regimens. However, there are limited data for serotonin antagonist-containing combination regimens in cancer patients receiving multiple days of high-dose chemotherapy. Table 4 shows the observed results along with the percentage of historical control patients achieving complete emetic control with prochlorperazine and lorazepam alone. The combination of ondansetron and prochlorperazine offered complete emetic protection to all study patients on the first day of chemotherapy. The emetic control declined each day thereafter, with essentially no benefit associated with ondansetron use during carmustine administration on the last day. There was no evidence of a dose-response benefit with the higher dose of ondansetron. The lack of sedation resulting from elimination of prochlorperazine from the regimen had a negative impact on efficacy and patient satisfaction during antiemetic therapy. Five patients assigned to the ondansetron alone cohorts requested removal from study owing to poor emetic control and cited lack of sedation as a source of dissatisfaction with the regimen.

There were no unexpected side effects associated with ondansetron use in these patients. Mild to moderate headaches were reported by 24% of all study patients and were attributed to the use of ondansetron. Other side effects included blurred vision (13%), strange dreams (5.5%), diarrhea (13%), dizziness (9%), visual hallucinations (3.6%), and hiccups (3.6%) which were seen across all study groups and are commonly associated with lorazepam and the high-dose chemotherapy. Three patients receiving the prochlorperazine plus ondansetron regimen were excessively sedated and the lorazepam dosage was reduced.

Discussion

Concurrent administration of chemotherapy with other ancillary support drugs, including antiemetic medications, is frequently necessary with high-dose regimens, yet little information is available on potential interactions between the various classes of drugs. Relatively minor alterations in the disposition of chemotherapeutic agents may be clinically important in this setting owing to a potential for saturable drug clearance and/or distribution with high-doses, in addition to the obviously lower therapeutic index with such drug administration strategies [13].

The primary goal of this study was to evaluate the influence of ondansetron on the pharmacokinetic disposition of cyclophosphamide. We found a statistically significant 17% median reduction in the systemic exposure to parent cyclophosphamide in patients receiving ondansetron with or without prochlorperazine compared to a group of matched control patients who did not receive ondansetron. Therefore, concurrent ondansetron treatment was associated with an increase in the systemic clearance of parent cyclophosphamide compared to patients being treated with prochlorperazine alone. This effect was more obvious as therapy progressed (Fig. 2).

More than 95% of ondansetron is metabolized by the body primarily via oxidation at the 8-position [20]. Studies conducted in vitro have suggested that the cytochrome P450 isoenzymes CYP1A2, CYP2D6 and the CYP3A subfamily are involved in ondansetron hydroxylation [8, 10]. However, we are not aware of any data which indicate that ondansetron can influence the metabolism of other drugs. The primary P450 enzymes responsible for cyclophosphamide activation are thought to be CYP2B as well as the more abundant 3A4 and 3A5 [5, 25]. The analytic methodology used in the present trial was only capable of measuring the parent prodrug compound, but recent studies by us and others have correlated accelerated clearance (reduced AUC) of this entity with increased toxicity in the high-dose setting

Table 4 Percentage of patients with complete emetic control. Of 24 patients in the ondansetron alone group, 5 requested removal from study after day of treatment −5 because poor emetic control

Treatment cohort		Day of treatment			
		−6	−5	−4	−3
I & II	Ondansetron + prochlorperazine	100	90	41	14
III & IV	Ondansetron alone	74	22	0	4
	Prochlorperazine controls	10	63	48	25

[2, 21]. Thus one would anticipate that drugs which accelerate parent cyclophosphamide clearance, such as ondansetron, may increase the exposure of the patient to activated drug resulting in possibly more efficacy and/or toxicity. No such alteration in efficacy or toxicity was observed in the relatively small patient population reported here. Toxicities were not increased in grade or frequency, and response rates were consistent with expected responses for patients with metastatic breast cancer treated with this regimen, although the power to detect such differences was low.

Effects on duration of response are not yet known. Cyclophosphamide clearance may be influenced by several factors which were controlled for in the present trial including dose, administration rate and concomitant drug therapy. This drug can induce its own metabolism and recent findings have demonstrated that administration of cyclophosphamide in higher daily doses than those used in our trial can result in nonlinear parent drug disposition [6]. Both of these characteristics are consistent with a high potential for perturbation in metabolic clearance by enzyme-altering drugs.

The precise mechanism of the ondansetron-cyclophosphamide drug interaction could be clarified with evaluations of the 4-hydroxycyclophosphamide/aldophamide intermediates which are thought to be produced by hepatic P450 metabolism and responsible for providing an intracellular product from which active alkylating species can be derived. A clinically feasible analytic method for conduct of such a study has been recently described [1].

The results of our prospective study are strikingly similar to those of a retrospective evaluation conducted at the University of Colorado which utilized exactly the same high-dose chemotherapy regimen [4]. That study found a mean parent cyclophosphamide AUC of 76.7 mg/ml · min in 23 patients treated with ondansetron compared with 90.7 mg/ml · min in 129 receiving prochlorperazine ($P = 0.001$).

Neither our study nor that of the Colorado group showed differences in the pharmacokinetics of carmustine when administered with ondansetron. While phenobarbital pretreatment has been demonstrated to lessen its activity and increase cyclophosphamide systemic clearance in a rat model [15], the primary mechanism of carmustine clearance from human blood is thought to occur via spontaneous hydrolysis at physiologic pH. Thus, the lack of an apparent effect of ondansetron on carmustine disposition is not surprising.

The Colorado study did show lower systemic exposure to cisplatin in patients treated with ondansetron. We saw a borderline difference in cisplatin disposition in the current study, but the trend was in the opposite direction, i.e. the ondansetron-treated patients had a slightly higher platinum exposure. Differences in analytic methods may account for this discrepancy. However, the physiologic mechanism of platinum clearance when it is administered by this schedule is most likely related to interaction with proteins and perhaps some relatively minor renal component. One would not anticipate an interaction with ondansetron and cisplatin based on physiologic principles.

Antiemetic efficacy and toxicity were secondary endpoints of this study. These results are reported because several observations were made that may contribute to the design of improved antiemetic protocols for patients receiving multiple-day regimens of highly emetogenic chemotherapy. The current literature is focused on evaluation of emetic control during standard cisplatin-based or cyclophosphamide-based chemotherapy regimens and thus provides inadequate data upon which to base antiemetic therapy for bone marrow transplant patients. Our observation that ondansetron, at either dose level, offered excellent antiemetic control on day 1 of cisplatin and cyclophosphamide chemotherapy is consistent with previous findings [23]. The loss of complete emetic control with multiple-day regimens has also been described elsewhere, although, the reason for this breakthrough nausea and vomiting is unclear [11]. The particularly disappointing antiemetic efficacy noted on the 4th day of therapy with administration of carmustine may have been a consequence of the delayed emetic effects of the previously infused cisplatin as well as the acute, highly emetogenic effect of carmustine. High-dose carmustine is classically associated with severe retching and vomiting for 2 to 4 h immediately following administration. The role of serotonin release in the pathophysiology of carmustine emesis has not been established and serotonin antagonists have not been evaluated for efficacy with this agent.

After completion of this study we began administering ondansetron (10 mg i.v. infusion) only on the last day of chemotherapy (30 min prior to carmustine) and have observed improved emetic control compared with the results presented in this study (45% complete control). These patients received the original prochlorperazine plus lorazepam regimen throughout the 4 days of chemotherapy. This observation supports the hypothesis that tachyphylaxis occurs with multiple-day ondansetron administration. Our results further support the need for controlled clinical trials to address the unique challenge of providing efficacious antiemetic therapy for patients receiving multiple-day high-dose chemotherapy with blood or marrow stem cell support.

This study exemplifies the necessity of systematically evaluating new ancillary drugs for their influence on the disposition of high-dose chemotherapeutic regimens, particularly those normally exhibiting a higher frequency of acute toxicity.

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