Association of High-dose Cyclophosphamide, Cisplatin, and Carmustine Pharmacokinetics with Survival, Toxicity, and Dosing Weight in Patients with Primary Breast Cancer\textsuperscript{1}

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ABSTRACT

This report investigates relationships between the pharmacokinetics and pharmacodynamics of high-dose alkylators used for the treatment of primary breast cancer.

Eighty-five women with primary breast cancer involving ≥10 lymph nodes received four cycles of standard-dose chemotherapy followed by a high-dose regimen consisting of: cyclophosphamide (1875 mg/m\textsuperscript{2} once daily × 3), cisplatin (165 mg/m\textsuperscript{2} given over 72 h), carmustine (600 mg/m\textsuperscript{2}), and stem cell transplantation. Dosages were attenuated in patients whose body weight exceeded their calculated ideal weight by >20%. Pharmacokinetics of the high-dose chemotherapeutic agents were evaluated in each patient by collection and analysis of serial blood samples.

Area under the concentration time curve (AUC) for cyclophosphamide and carmustine was highly variable (>10-fold inter-patient range) with coefficients of variation >50%, in contrast to cisplatin exposures (2-fold range; coefficient of variation 12%). The dosing method for overweight patients resulted in significantly lower systemic exposure to cisplatin (\(P = 0.035\)). The parent cyclophosphamide clearance on the 1st day of administration was significantly higher in patients who experienced acute cardiac toxicity (\(n = 5; P = 0.011\)), whereas carmustine disposition was not found to be different in those developing pulmonary toxicity (\(n = 25; P = 0.96\)).

Kaplan-Meier analysis (median follow-up of 5.9 years) demonstrated that patients with lower cyclophosphamide AUC (faster parent drug clearance to potentially cytotoxic compounds) survived longer (\(P = 0.031\)).

Inter-individual differences in the pharmacokinetic disposition of high-dose chemotherapy may explain variability in both response and toxicity. Prospective strategies, which attempt to individualize AUC, should be evaluated in this setting.

INTRODUCTION

Utilization of high-dose chemotherapy with hematopoietic stem cell support has resulted in improvement in the treatment of malignancies such as some lymphomas and leukemias (1–3). However, inter-patient variability in the pharmacokinetic disposition of the agents used in the high-dose regimens may result in observable differences in outcome (4). Such variability is of particular concern in the transplant setting because the chemotherapy ablative regimens use doses 4–10 times those tolerated without hematopoietic support and have a higher frequency of life-threatening toxicity (5). In addition, preclinical data from cell culture experiments suggest that the concentrations achieved with high-dose alkylator regimens lie in a steep portion of the dose-response curve (6–8). Despite these concerns, relatively few studies of high dose chemotherapy pharmacokinetics are found in published literature.

We have reported previously the clinical results of a Phase II study using high-dose alkylators and autologous hematopoietic stem cell support in 85 women with high-risk, primary breast cancer (9). The Kaplan-Meier curves for overall survival appeared very stable by the 6-year median follow-up time for these patients. Thus, we felt that this would be a reasonable time to analyze the association between the systemic chemotherapy exposure achieved by a patient and her likelihood for survival. We also describe other relationships between toxicity, individual dose calculations, and pharmacokinetics of the high-dose alkylators used in these patients.

PATIENTS AND METHODS

Treatment Plan and Assessment. All 85 patients who were treated at Duke University Medical Center on the Phase II protocol mentioned above also consented to have pharmacokinetic blood draws obtained during the high-dose chemotherapy regimen. Demographic and clinical information regarding the patients is presented in Table 1. The high-dose regimen consisted of 3 days of cyclophosphamide (1875 mg/m\textsuperscript{2} i.v. given over 60 min each day) and cisplatin (165 mg/m\textsuperscript{2} as a 72-h continuous i.v. infusion concurrent with cyclophosphamide),
Table 1  Patient demographics and clinical data for this study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n or Median value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of evaluable patients</td>
<td>85</td>
</tr>
<tr>
<td>Age</td>
<td>38 yrs</td>
</tr>
<tr>
<td>Race (Caucasian/African-American/Hispanic)</td>
<td>80/4/1</td>
</tr>
<tr>
<td>Actual body surface area</td>
<td>1.73 m²</td>
</tr>
<tr>
<td>Adjusted (dosing) body surface area</td>
<td>1.72 m²</td>
</tr>
<tr>
<td>Number of patients &gt;20% ideal weight</td>
<td>25</td>
</tr>
<tr>
<td>Antiemetics during chemotherapy</td>
<td>Prochlorperazine 58</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>27</td>
</tr>
<tr>
<td>Transplant-related toxicities</td>
<td>Cardiac 7 (8%)</td>
</tr>
<tr>
<td></td>
<td>Renal 18 (21%)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary 26 (31%)</td>
</tr>
<tr>
<td></td>
<td>Hepatic 10 (12%)</td>
</tr>
</tbody>
</table>

The actual body weight was used to calculate the adjusted body surface area except in situations where the actual weight was >120% of the ideal weight. In the latter cases, an “adjusted” body weight was used by averaging the body surface area obtained from the ideal weight and the actual weight. The “adjusted (dosing) body surface area” shown in this table is a median value used for prescribing the high-dose chemotherapy.

followed by carmustine (600 mg/m² i.v. given over 2 h) on the 4th day. The details of such and associated clinical results have been described previously (9). The dose of chemotherapy for an individual patient was calculated from the actual body weight, unless the actual weight was >120% of the ideal weight. In the latter cases, an “adjusted” body weight was used by averaging the BSA obtained from the ideal weight and the actual weight. Ideal body weight was determined from NY Life Insurance actuarial tables, which use height and body frame size, as determined by wrist circumference. Concurrent antiemetic therapy included continuous i.v. infusion of either prochlorperazine or metoclopramide, with the addition of lorazepam. All patients were placed on central cardiac monitors throughout the 4 days of chemotherapy, and electrocardiograms were performed before each daily administration of chemotherapy. Physical examination, complete blood count with differential, and a chemistry profile panel for serum creatinine, blood urea nitrogen, glucose, potassium, chloride, sodium, bicarbonate, magnesium, and phosphorus were performed daily. Liver function tests were done before chemotherapy and every 4 days thereafter. Patient weight, fluid intake and output, and vital signs were recorded daily.

Patients were divided into groups based on the occurrence of transplant-related toxicities using the following criteria. Pulmonary toxicity was defined by the sudden onset of progressive exertional dyspnea accompanied by a reduced diffusing capacity for carbon monoxide on pulmonary function testing, as described previously (9). Acute cardiac toxicity was identified by symptomatic chest pain and electrocardiogram evidence of ST depression. Nephrotoxicity was defined by serum creatinine values > 1.4 mg/dl (Cancer and Leukemia Group B grade 1). Patients were identified as experiencing hepatic toxicity if they met the criteria for veno-occlusive disease, as defined by McDonald et al. (10).

Determination of Cyclophosphamide Concentrations.
Samples were drawn at 0 h (preinfusion), ½ h (mid-infusion), 1 h (end of infusion), and at 1½, 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 were 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 and then analyzed.

Standards and quality control samples were prepared from neat chemical (Sigma Chemical Co., St. Louis, MO) and diluted with single donor plasma to yield concentrations ranging ≤100 μl/ml. The extraction of cyclophosphamide from plasma samples was initiated by adding 1 ml of a 25 μg/ml ifosfamide (Bristol-Myers Squibb, Princeton, NJ) internal standard solution to 1 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 of acetonitrile. All solvents used in the assays reported here were HPLC7 grade. The eluants were blown dry with nitrogen and re-eluted in 300 μl of methanol.

Samples were analyzed by modification of a method published previously (11). Briefly, 25 μl of the eluates were injected onto an HPLC system consisting of a 3.9 × 150-mm Waters NovaPak C₁₈ analytic column (4 μm of particle size; Millipore, Milford, MA). 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, MA) 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 inter-assay, and intra-assay variabilities were 7 and 5%, respectively.

Determination of Cisplatin Concentrations. Blood samples were collected in heparinized tubes every 24 h during the cisplatin continuous infusion. The samples were centrifuged at 900 G for 10 min at 4°C, and the plasma was stored at −70°C for later analysis.

Standards and quality control samples were prepared from platinum atomic absorption standard solution (Sigma Chemical Co.). A stock solution was prepared in 0.9% saline. Fresh, single donor plasma (American Red Cross, Durham, NC) was used to make the final dilutions for plasma standards of 200-1500 ng/ml. Plasma samples and standards were diluted 1:3.5 with 5%, respectively.

Blood samples were collected in heparinized tubes every 24 h during the cisplatin continuous infusion. The samples were centrifuged at 900 G for 10 min at 4°C, and the plasma was stored at −70°C for later analysis.

Standards and quality control samples were prepared from platinum atomic absorption standard solution (Sigma Chemical Co.). A stock solution was prepared in 0.9% saline. Fresh, single donor plasma (American Red Cross, Durham, NC) was used to make the final dilutions for plasma standards of 200-1500 ng/ml. Plasma samples and standards were diluted 1:3.5 with 0.25% Triton X 100 (Sigma Chemical Co.) before injection. Patient samples, controls, and standards were analyzed for platinum content by a modification of our previously published graphite-furnace atomic absorption spectrophotometry assay using automated sample delivery (models 2380, HGA 400, and AS40; Perkin-Elmer, Norwalk, CT; Ref. 12). Aliquots (25 ml) 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 a 1100°C char and a 2700°C atomization. The data were collected and analyzed using a Perkin-Elmer Nelson integrator. The lower limit of platinum quantitation for this

7The abbreviations used are: HPLC, high-performance liquid chromatography; AUC, area under the concentration time curve.
assay was 200 ng/ml. Samples with concentrations appearing to exceed the standard curve were diluted in donor plasma and reanalyzed. Inter-assay and intra-assay variabilities were 3.7 and 4.2%, 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 of heparinized tubes containing 3 ml of a 25 μg/ml 5,5 diphenylhydantoin (the internal standard; Sigma Chemical Co.) solution 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 and a 1-ml aliquot of the supernatant was transferred to a glass tube.

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

Carmustine concentrations were determined by modification of a method published previously (5). Briefly, 25-μl aliquots of the eluates were injected onto an HPLC system consisting of a 25 cm × 4.6-mm Supelcosil LC-18-DB column (5-μm particle size; Supelco). 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 inter-assay, and intra-assay variability was 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, UT). 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. The AUC for each dose of cyclophosphamide was estimated independently; thus, the “total AUC” values reported here reflect the addition of all three AUCs for each patient.

Pharmacokinetic/pharmacodynamic correlations were conducted on segregated data sets using the Kruskal-Wallis test. Ten patients experiencing high-dose, chemotherapy-related mortality were intended to be excluded from the pharmacokinetics: survival analyses because high systemic exposure could theoretically send the curve in the opposite directions in the case of toxic death versus extended disease-free survival. Pharmacokinetic-survival assessments were conducted by segregation of patients based on the median systemic exposure to each high-dose alkylator via Kaplan-Meier plots and the Log-rank test (13).

RESULTS

Examples of high-dose chemotherapy disposition in a patient closest to the median level of systemic exposure for all three drugs are displayed in Fig. 1. Parent levels of cyclophosphamide declined within a patient on each repeat dose, consistent with autoinduction of its metabolism. Plasma platinum concentrations increased over the course of the 72-h cisplatin infusion. This is most likely an accumulation of activated platinum species bound to plasma proteins and small sulfhydryl molecules. Wide inter-patient variability in the systemic clearances of both carmustine and parent cyclophosphamide was observed, compared with a relatively tight range of variation in cisplatin disposition (Table 2).

Fig. 1. Cyclophosphamide, cisplatin, and carmustine plasma concentration data for a patient who displayed AUC values closest to the median for each drug. All concentrations are expressed in units of μg/ml.
Cyclophosphamide systemic clearance increased by a median of 2-fold within patients over the 3 days of drug administration (Table 2). This effect was rapid and relatively consistent, occurring in all but 1 patient. There was some evidence for an association between a patient’s cyclophosphamide AUC or systemic exposure and outcome on the first dose compared with the last dose, as shown in Fig. 2.

Table 3 displays the systemic chemotherapy exposures found in those patients whose weight was >120% of their ideal weight and, thus, were given attenuated doses (as described in “Patients and Methods”) compared with the others on this study who weighed <120% of their ideal weight. The data suggest that this approach to dose attenuation is under-treating the obese individuals in the case of cisplatin and also possibly cyclophosphamide. Simulation of the systemic platinum exposure, which would have been achieved if the obese patients were dosed on their actual weight, negates the statistical difference in these groups (assuming there is a linear relationship between the dose and systemic exposure). It is difficult to make conclusions for the cyclophosphamide and Carmustine data because of the wide degree of inter-patient variability in the clearance of these two agents and, thus, lack of power of such comparisons.

Associations between transplant regimen-related toxicities and the systemic exposure of the chemotherapy agent(s) suspected to be implicated in such are shown in Table 4. Patients with acute cardiac toxicity (occurring, by definition, on the last day of high-dose chemotherapy) displayed substantially faster parent cyclophosphamide systemic clearance values during the 1st day of drug administration. No other relationships were found to be statistically different in patients exhibiting toxicity.

Fourteen patients treated on this protocol have relapsed with breast cancer after high-dose therapy by the 6-year median follow-up time. Alkylator systemic exposures for the 10 patients who died of regimen-induced toxicity were not substantially different for cyclophosphamide or cisplatin; however, there was a trend toward higher Carmustine levels. Nevertheless, we censored these individuals out of the efficacy analysis, as was our original intention. Evaluation of the remaining 75 patients based on the median chemotherapy exposures yielded a significant relationship between cyclophosphamide AUC and overall survival, as shown in Fig. 3. Those with parent drug AUC values, which were below the median, had a higher chance of survival. We believe these data indicate that the parent drug is being converted to the activated 4-hydroxycyclophosphamide metabolite quicker and/or more efficiently in these individuals. Similar relationships were not found when patients were segregated by either the Carmustine or cisplatin exposures.

**DISCUSSION**

Perhaps the first published clinical example of a clear association between inter-patient differences in chemotherapy pharmacokinetic disposition and anticancer response was provided by Evans et al. (14). Their data demonstrated a correlation between the systemic exposure to repetitive high doses of methotrexate and disease-free survival in children with acute lymphocytic leukemia.

Inter-patient variability in drug disposition should be most evident and important when the majority of malignant cells are thought to be chemotherapy sensitive, and there is a good chance for a prolonged overall disease-free survival in the population. We felt that such was the case in the treatment of high-risk primary breast cancer with adjuvant high-dose chemotherapy and, thus, undertook this study to primarily focus on investigation of associations between alkylating agent systemic exposure and outcome.

A prolonged overall disease-free survival, while obviously desirable, makes a correlation of variations in systemic chemotherapy exposure with efficacy rather difficult because of the duration of follow-up necessary before conducting these investigations. We chose to first evaluate pharmacokinetic-efficacy correlates at the 6-year median follow-up time because the relapse rate had stabilized by then. These investigations revealed a correlation between parent cyclophosphamide AUC (but not that of Carmustine or cisplatin) and overall survival (Fig. 3).

Randomized studies that used single doses of cyclophosphamide per cycle of standard chemotherapy have demonstrated conflicting results as to the relationship between dose and efficacy (15, 16). Comparison of these data with those obtained on the current study is difficult because of the multiple dose nature of the high-dose regimen and, thus, the potential for auto-induction of metabolic activation, as discussed below. Perhaps more importantly, combination of cyclophosphamide with glutathione-depleting alkylators, such as cisplatin and Carmustine, may exaggerate its clinical effects in the high-dose setting. The concentration of glutathione in tumor cells has been shown to correlate with the degree of resistance to cyclophosphamide metabolites (17).

Cyclophosphamide requires metabolic activation via conversion to a 4-hydroxylated species for clinical activity. We believe our data demonstrate that faster rates of conversion (i.e., lower parent drug levels) result in increased exposure to the intermediate metabolite, 4-OH cyclophosphamide, and this ultimately provides more intracellular exposure to the active phosphoramide mustard species. This mode of reasoning is consistent with data published by other investigators who, by using similar doses and without concurrent influence of metabolic inhibitors, such as thiopeta, were able to correlate the exposure of parent drug to that of the 4-OH metabolite (18, 19). It is

<table>
<thead>
<tr>
<th>Drug</th>
<th>Systemic exposure</th>
<th>Systemic clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1</td>
<td>32.1 (67)</td>
<td>58.3 (39)</td>
</tr>
<tr>
<td>Dose 2</td>
<td>19.7 (66)</td>
<td>95.2 (51)</td>
</tr>
<tr>
<td>Dose 3</td>
<td>17.8 (54)</td>
<td>105.5 (50)</td>
</tr>
<tr>
<td>Total AUC</td>
<td>69.6 (59)</td>
<td>NA</td>
</tr>
<tr>
<td>Dose 3/dose 1</td>
<td>0.50 (31)</td>
<td>2.00 (36)</td>
</tr>
<tr>
<td>Cisplatin (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h Concentration</td>
<td>864 (26)</td>
<td>NA</td>
</tr>
<tr>
<td>48-h Concentration</td>
<td>1738 (16)</td>
<td></td>
</tr>
<tr>
<td>72-h Concentration</td>
<td>2301 (12)</td>
<td></td>
</tr>
<tr>
<td>Carmustine</td>
<td>599 (145)</td>
<td>1002 (49)</td>
</tr>
</tbody>
</table>

* Units for this parameter are ml/min/m².
* NA, not applicable.

\[a\] AUC data are presented for cyclophosphamide and Carmustine in units of mg/ml × min and µg/ml × min, respectively.

\[b\] Units for this parameter are ml/min/m².
important to realize that doses slightly higher than those used in our study (or when cyclophosphamide is given with metabolic inhibitors) may not display such a relationship because of saturation of metabolic pathways (19).

Ayash et al. (20) also investigated the relationship between parent cyclophosphamide disposition, toxicity, and efficacy in 19 women with metastatic breast cancer who were receiving high-dose cyclophosphamide, thiotepa, and carboplatin. Patients who experienced cardiac toxicity displayed a significantly faster parent cyclophosphamide clearance (low AUC) and had a longer duration of response, consistent with our data. Similar associations between nonhematological toxicity and cyclophosphamide AUC were found by investigators at the University of Colorado using the same cyclophosphamide/cisplatin/carmustine regimen studied here (21). Importantly, our study shows that the parent cyclophosphamide clearance on the first of the three doses may allow for early identification of patients who will experience acute cardiac toxicity during the stress of carmustine administration (Table 4). More recently developed analytic methods allow for clinical measurement of the active 4-OH metabolite of cyclophosphamide (22). Future studies should compare the utility of parent versus metabolite exposures as predictors of patient effects.

The potential for cyclophosphamide to induce its own metabolism has been described previously (23–25); however, the degree of change we have seen in parent drug clearance over the 3-day course indicates a potential for very high active metabolite formation on the final infusion. An intriguing comparison may be found between these data and those found with the more widely used high-dose cyclophosphamide-thiotepa regimen. The latter calls for the administration of a similar total dose of cyclophosphamide to the cyclophosphamide/cisplatin/carmustine regimen; however, it is given over 96 h as a continuous infusion concurrent with thio-tepa (26). The ratio of the

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**Table 3** Median systemic exposure to chemotherapy in patients who were >120% of their ideal body weight (“obese”) compared with others, indicating the potential influence of the formula used to calculate chemotherapy doses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obese</th>
<th>Nonobese</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>25</td>
<td>60</td>
<td>0.055</td>
</tr>
<tr>
<td>Total cyclophosphamide AUC (mg/ml × min)</td>
<td>63.9</td>
<td>73.4</td>
<td></td>
</tr>
<tr>
<td>Cisplatin 72-h concentration (ng/ml)</td>
<td>2240</td>
<td>2349</td>
<td>0.035</td>
</tr>
<tr>
<td>Carmustine AUC (µg/ml × min)</td>
<td>642</td>
<td>579</td>
<td>0.824</td>
</tr>
</tbody>
</table>

**Table 4** Associations between chemotherapy median pharmacokinetic parameters and post-transplant organ toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Pharmacokinetic parameter</th>
<th>Nontoxic patients</th>
<th>Toxic patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Total cyclophosphamide AUC</td>
<td>76.3</td>
<td>55.6</td>
<td>0.094</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide dose 1 clearance</td>
<td>49.0</td>
<td>79.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Renal</td>
<td>24-h Cisplatin concentration (ng/ml)</td>
<td>857</td>
<td>936</td>
<td>0.229</td>
</tr>
<tr>
<td></td>
<td>72-h Cisplatin concentration (ng/ml)</td>
<td>2295</td>
<td>2374</td>
<td>0.431</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Carmustine AUC</td>
<td>599</td>
<td>595</td>
<td>0.963</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Total cyclophosphamide AUC</td>
<td>70.1</td>
<td>63.4</td>
<td>0.645</td>
</tr>
<tr>
<td></td>
<td>Carmustine AUC</td>
<td>599</td>
<td>482</td>
<td>0.927</td>
</tr>
</tbody>
</table>

* AUC data are presented for cyclophosphamide and carmustine in units of mg/ml × min and µg/ml × min, respectively.
A direct association between systemic exposure to carmustine and post-transplant pulmonary toxicity was demonstrated by investigators at the University of Colorado Bone Marrow Transplant Program (28). We have not found this correlation in the patients treated on this trial (Table 4) or in another series, which we published recently (29). Patients who had very high systemic exposures to carmustine on the latter trial did have a higher frequency of pulmonary toxicity; however, there was no difference in the median exposures when subjects were segregated based on toxicity. Reasons for the discrepancy between Duke and Colorado analyses may be related to slight differences in the infusion duration between the centers and/or differences in the definition/identification of pulmonary toxicity.

Previous evaluations of cisplatin pharmacokinetics by our group during the cyclophosphamide/cisplatin/carmustine regimen and by others have demonstrated associations between systemic platinum exposure and subsequent nephrotoxicity (30–33). The 21% of patients in the current trial with post-transplant nephrotoxicity displayed a slightly higher median systemic platinum exposure; however, this difference was not statistically significant, perhaps attributable to the low frequency of toxicity.

The pharmacokinetic disposition of various drugs, including some antineoplastics, has been evaluated in obese patients (34–36). These studies imply that the systemic clearance of highly extracted drugs may be enhanced, whereas data are also available, which describe reduced clearance for other agents (37). Most institutional dosing policies for “obese” individuals have not been derived from actual pharmacokinetic or toxicity studies, and it is doubtful that one policy will provide accurate dosing for every drug. Retrospective evaluation of clinical studies, in which the doses of combination chemotherapy (including cyclophosphamide) were determined based on actual patient weight, has not demonstrated increased toxicity (38, 39). Such associations may not hold true in the situation of high-dose chemotherapy where the therapeutic index and drug disposition characteristics can be dramatically different (5).

Similar to many other bone marrow transplant programs, we have a systematic approach to attenuation of chemotherapy doses in patients who are “significantly” above their ideal weight. Utilization of such a strategy was justified in the earlier days of transplantation because of the relatively high frequency of treatment-related toxicity. Contemporary changes in post-transplant ancillary therapies, particularly the use of colony-stimulating factor-primed peripheral blood progenitor cells, have been associated with a surprising reduction in toxicity (40). Thus, the concern for potentially overdosing obese patients if their total body weight is used in the calculation of doses may not be as worrisome today. Regardless of this, we feel that the data presented here do not support such dose attenuation. Given the associations we found with drug levels and response, this practice may even reduce efficacy. It is important to realize that no patients on this study were morbidly obese, i.e., greater than two to three times their ideal weight. It may make sense to arbitrarily attenuate doses in such individuals, but there is little actual data to support this practice. Fortunately, such obese patients are exceedingly rare in our population; thus, collaborations between major centers and cooperative groups treating high numbers of patients should look at this issue prospectively.

Evans et al. (41) have published subsequently the fol-
low-up trial to their study described in the first paragraph of this “Discussion.” Their randomized trial demonstrated that the group of patients whose chemotherapy doses were individualized to achieve a target systemic exposure had a significantly better outcome compared with a group dosed based on body surface area alone (41). The data presented in our study also suggest that individualization of a patient’s systemic ablative regimen exposure should optimize therapy. However, formal prospective approaches will be needed to confirm the benefit of such a strategy and assess its impact on both the short- and long-term chemotherapy-related toxicities (42, 43).

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We thank all of the patients who participated in this trial, as well as the clinicians and nurses who cared for them.

REFERENCES


