NONLINEAR PHARMACOKINETICS OF CYCLOPHOSPHAMIDE AND 4-HYDROXYCyclophosphamide/aldophosphamide in Patients with Metastatic Breast Cancer Receiving High-Dose Chemotherapy Followed by Autologous Bone Marrow Transplantation

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ABSTRACT:

The pharmacokinetics of cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide has been evaluated in 12 patients with metastatic breast cancer undergoing high-dose chemotherapy followed by bone marrow transplantation. Each patient received an initial dose of 4 g/m² of cyclophosphamide over 90 min to prime peripheral blood progenitor cells (the first course), and 3 weeks later, 6 g/m² of cyclophosphamide with 800 mg/m² of thiotepa by 96-hr infusion before marrow stem cell infusion (the second course). Whole blood cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide concentrations were measured by a GC-EIMS method using deuterium labeled compounds as internal standards. In addition, plasma and urine cyclophosphamide concentrations were determined by a GC assay. Whole blood concentrations of cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide were vs. time data and urinary excretion of cyclophosphamide data from the first course were co-modeled using a one-compartment model with Michaelis-Menten saturable elimination in parallel with first-order renal elimination (N = 7) or first-order metabolic and renal elimination (N = 5) for cyclophosphamide and one-compartment model with first-order elimination for 4-hydroxycyclophosphamide/aldophosphamide. The parallelism between cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide disposition curves implies that the pharmacokinetics of 4-hydroxycyclophosphamide/aldophosphamide is formation limited; only the fractional 4-hydroxycyclophosphamide/aldophosphamide clearance rate (Clmet/Fmet) can be estimated. The mean Vmax and Km for cyclophosphamide were 0.78 µM/min and 247 µM, respectively. The mean nonrenal clearance (Cln) of cyclophosphamide for five patients with apparent first-order elimination of cyclophosphamide was 67 ml/min. The mean Clmet/Fmet of 4-hydroxycyclophosphamide/aldophosphamide was 2982 ml/min. The mean renal clearance (Clin) of cyclophosphamide was 29 ml/min and 24 ml/min for the first course and the second course, respectively. The correlations between cyclophosphamide AUCs and 4-hydroxycyclophosphamide/aldophosphamide AUCs were sought for both drug courses. Blood and plasma cyclophosphamide concentrations were remarkably similar, indicating that cyclophosphamide partitions equally in the red cell and plasma volume. Computer simulation of the effect of potential alterations in Michaelis-Menten saturable elimination and renal clearance on 4-hydroxycyclophosphamide/aldophosphamide has been used to illustrate the complex relationship between the exposure to parent compound and active metabolite.

Cyclophosphamide is one of the most frequently used antitumor agents in patients receiving high-dose chemotherapy prior to bone marrow transplantation. It is a prodrug that undergoes complex metabolic activation and detoxification. The current understanding of cyclophosphamide activation is presented in fig. 1. Cyclophosphamide is enzymatically metabolized to 4-hydroxycyclophosphamide/aldophosphamide, which exists in equilibrium with its open ring tautomer, aldoephosphamide (1–3). 4-Hydroxycyclophosphamide/aldophosphamide serve as the transport forms for the toxic species of phosphoramid mustard and acrolein (1–3). They also undergo enzymatic oxidative detoxification to form inactive urinary excretion products, 4-ketocyclophosphamide and carboxyphosphamide (1, 3). The extent of metabolism by these pathways depends, in part, on the activity of aldehyde dehydrogenase in the tissues; this may account for the tissue selectivity as well as drug resistance (2–6). Since the active metabolites are formed from the 4-hydroxycyclophosphamide/aldophosphamide equilibrium mixture, measurement of these intermediates is crucial to determine the relationship between the drug exposure and the therapeutic outcome in patients.

We have published nonlinear pharmacokinetics of high-dose cyclophosphamide in patients (7), but co-modeling with its circulating metabolite 4-hydroxycyclophosphamide/aldophosphamide has not been reported. The primary limitation of the assessment of 4-hydroxycyclophosphamide/aldophosphamide exposure has been the evanescent nature of this chemical, which has a t1/2 of 6 min in human blood at 37°C (8). Thus, although several investigators reported the dispo-
sition of cyclophosphamide and its metabolites in patients receiving moderate doses of cyclophosphamide, the relative degradation prior to assay was not quantified (3, 9, 10). Slattery et al. (11) recently described a new LC-MS method, which included a solid phase extraction procedure without using an internal standard, for quantitation of plasma 4-hydroxycyclophosphamide/aldophosphamide only. The development of a GC-EIMS method using deuterium labeled compounds as internal standards with a pre-assay stabilizing procedure to simultaneously quantitate cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide (12, 13) has facilitated a formal description of the metabolic process and disposition of cyclophosphamide and its circulating metabolite, 4-hydroxycyclophosphamide/aldophosphamide in patients.

We have carried out a comprehensive pharmacokinetic analysis of cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide in 12 patients with metastatic breast cancer undergoing high-dose chemotherapy with alkylating agents followed by autologous bone marrow transplantation. Eleven of 12 patients’ cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide AUCs have been reported previously (13), but no pharmacokinetic modeling was presented. The purpose of this study was (a) to co-model whole blood cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide concentration vs. time data after a 90-min infusion of cyclophosphamide alone using suitable kinetic models; (b) to analyze the correlation between cyclophosphamide AUC and 4-hydroxycyclophosphamide/aldophosphamide AUC in whole blood after a 90-min infusion of cyclophosphamide alone and after a 96-hr infusion of cyclophosphamide concurrently with thiotepa; and (c) to compare cyclophosphamide concentrations in whole blood with that in plasma; and (d) to discuss the variability of disposition of cyclophosphamide and its circulating metabolite, 4-hydroxycyclophosphamide/aldophosphamide, in patients and illustrate this variability through computer simulation. The clinical responses and toxicities of this treatment will be the subject of a separate report.

Patients and Methods

Patient Population and Study Design. Women with stage IIIB or IV breast cancer undergoing autologous bone marrow transplantation were eligible for this study. Patients were required to have a histologically documented breast cancer responsive to conventional therapy, an age between 18 and 60 years old, an Eastern Cooperative Oncology Group (ECOG) performance status of less than 2, normal hematopoietic function, and adequate cardiac (LVEF>45%), pulmonary (FVC and FEV1>65%) of predicted for patient’s height and weight), renal (serum creatinine concentration <2.0 mg/dl) and hepatic (serum AST concentration <60 IU/ml and serum bilirubin concentration <1.5 mg/dl) functions. Creatinine clearance (Cr Cl) was calculated for each patient using the method of Cockcroft and Gault (14). The study was approved by the Joint Committee for Clinical Investigation of the Johns Hopkins Hospital and written informed consent was obtained from each patient.

After the initial marrow harvest, patients received 4 g/m2 of cyclophosphamide administered iv over 90 min, for mobilization of peripheral blood progenitor cells (the first course). Three weeks later, the patients received a combination of cyclophosphamide (6 g/m2) and thiotepa (800 mg/m2) administered simultaneously as a 96-hr continuous iv infusion (the second course). Novobiocin (2 g every 12 hr orally for 14 doses starting 36 hr prior to the chemotherapy) was added to inhibit the development of alkylating agent resistance (15). Ondansetron (0.15 mg/kg loading dose followed by 1 mg/min continuous iv infusion) and lorazepam (1 mg every 4 hr iv) were administered simultaneously as a 96-hr continuous iv infusion started until 24 hr after treatment finished. Prochlorperazine (5 mg every 3 hr iv) was given as needed.

Blood and urine specimens were collected for the determination of whole blood cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide concentrations, and plasma and urine cyclophosphamide concentrations. For the first course, blood samples were obtained at 0, 45, and 80 min, and 2, 3, 4, 5, 8, 10, 16, 24, 27 hr from the beginning of the infusion. For the second course, blood samples were obtained at 0, 3, 6, 12, 18, 24, 30, 42, 54, 64, 78, 90, 96 hr during the infusion, and 1, 3, 5, 8, and 24 hr after the end of the infusion. Two aliquots of blood samples were drawn: a 1 ml of blood drawn in a 1 ml TB syringe was immediately (<1 min) placed in a pre-weighted tube containing the trapping agent for stabilizing 4-hydroxycyclophosphamide/aldophosphamide (12), and each tube was re-weighted to obtain the exact amount of whole blood added; a 5 ml of blood was drawn into a heparinized Vacutainer for plasma collection. Urine was collected up to 32 hr and 120 hr after the infusion began for the first course and second course, respectively. Plasma and urine aliquots were stored at −20°C until analysis.

Analytical Methods. Whole blood cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide concentrations were simultaneously quantitated by a GC-EIMS assay (12, 13). In this method, the trapping agent o-(2, 3, 4, 5, 6-pentafluorobenzyl)hydroxylamine reacted with aldophosphamide and, indirectly, with its tautomer, 4-hydroxycyclophosphamide, to provide a stable oxime. This oxime represented a combined concentration of aldophosphamide and any species (most notably, 4-hydroxycyclophosphamide) with which it spontaneously interconverts. The oxime and unchanged parent drug, cyclophosphamide, were extracted from the biological fluid and assayed by a GC-EIMS method. Deuterium labeled oxime and cyclophosphamide were used as internal standards (12, 13). Plasma (first course only) and urine cyclophosphamide levels were measured by a gas chromatography assay described previously (7).

Pharmacokinetic Analysis. Blood cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide disposition curves from the first course were first examined visually to assess suitable models. If both cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide elimination curves exhibited convex-downward curves on a semilog scale, a Michaelis-Menten satur-
able elimination process was anticipated (16). We evaluated the fit of a one-compartment model with Michaelis-Menten metabolic elimination coexisting with first-order renal elimination for cyclophosphamide (CP) and a one-compartment model with first-order elimination for 4-hydroxycyclophosphamide/aldophosphamide (4-OH) (16):

\[
\begin{align*}
\frac{dC_{\text{met}}}{dt} &= \frac{V_{\text{max}} C}{(K_m + C) V_{\text{met}}} - K C_{\text{met}} \\
\frac{dC}{dt} &= \frac{R}{V} - \frac{C}{V} - \frac{V_{\text{max}} C}{K_m + C} \\
\frac{dX_u}{dt} &= C IC
\end{align*}
\]

**Scheme 1.**

where \(dC_{\text{met}}/dt\) and \(dC/dt\) are the rate of change of drug concentration at time \(t\) for 4-hydroxycyclophosphamide/aldophosphamide and cyclophosphamide, respectively, \(R\) is the rate of infusion (\(>\)infusion time, \(R = 0\)), \(C_{\text{met}}\) and \(C\) are whole blood concentrations for 4-hydroxycyclophosphamide/aldophosphamide and cyclophosphamide, respectively, \(V_{\text{met}}\) and \(V\) are the apparent volume of distribution for 4-hydroxycyclophosphamide/aldophosphamide and cyclophosphamide, respectively, \(K\) is the elimination rate constant of 4-hydroxycyclophosphamide/aldophosphamide, \(C_l\) is the calculated renal clearance rate of cyclophosphamide, \(V_{\text{met}}\) and \(K_m\) are the theoretical maximum rate of the elimination process and Michaelis-Menten constant for cyclophosphamide, respectively, and \(X_u\) is the amount of urinary excretion of cyclophosphamide. A weight of \(1/C\) was used in the iterative fitting process.

For data sets that were not well fit by the above models, i.e., when visual inspection of these disposition curves of cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide were straight lines on a semilog scale, and when the asymptotic standard error for \(K_m\) was >50% associated with estimates of \(K_m > 2 C_{\text{max}}\), a one-compartment model with constant input and first-order elimination for both cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide was used to fit the data (16):

\[
\begin{align*}
\frac{dC_{\text{met}}}{dt} &= \frac{Cl_{\text{nr}} C}{V_{\text{met}}} - K C_{\text{met}} \\
\frac{dC}{dt} &= \frac{R}{V} - \frac{Cl_{\text{nr}} + Cl_r}{V} - \frac{V_{\text{max}} C}{K_m + C} \\
\frac{dX_u}{dt} &= Cl_r C
\end{align*}
\]

**Scheme 2.**

Computer simulation was performed by varying one of these parameter estimates at a time, \(Cl_r\), \(V_{\text{met}}\) \((Cl_{\text{nr}})\), and \(K_m\) while holding others constant using mean values from this report. Areas of under simulated time-concentration curves of cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide were calculated as described above and relationships between these two were sought. The mean, median, and SD of pharmacokinetic parameters were calculated using Quattro Pro for Windows (Borland International, Inc., Scotts Valley, CA). The statistical analyses were completed by using InStat (GraphPad Software, Inc., San Diego, CA).

**Results**

Twelve of 14 women with stage IIIIB (2 patients) or IV (10 patients) breast cancer undergoing autologous bone marrow transplantation between March 1994 and July 1995 had pharmacokinetic sampling performed and are included in this report. The median age of the patients was 46.5 years (range 30–61 years). Two patients had liver metastases but normal liver enzymes. In the first course, all 12 patients had complete blood cyclophosphamide and 4-hydroxyxycyclo-

AUC (AUC \(_{\text{met}}\)), the extrapolated area under the blood cyclophosphamide (4-hydroxycyclophosphamide/aldophosphamide) disposition curve was calculated using a combined linear and logarithmic trapezoidal rule (17) for data obtained from both courses. The percentage of urinary excretion of cyclophosphamide (\(X_u\)) and \(Cl_r\) for the second course were calculated from \(X_u/dose\) and \(X_u/AUC\), respectively (16). Correlation between \(Cl_r\) and cyclophosphamide \(Cl_r\) was sought for data obtained from the first course.

All pharmacokinetic modelings were performed by nonlinear regression analysis using PCNONLIN (Statistical Consultants, Apex, NC). The codes for Model 1 and Model 2 can be obtained from the authors of this report.
After a 90-min infusion, blood cyclophosphamide and 4-hydroxy-
cyclophosphamide/aldophosphamide disposition curves were parallel.
This phenomenon implies that the pharmacokinetics of 4-hydroxy-
cyclophosphamide/aldophosphamide was formation limited (16). Since
the bioavailability of 4-hydroxycyclophosphamide/aldophosphamide
(Fmet) was unknown, only the fractional 4-hydroxycyclophospha-
drome (Vmet) and elimination parameter estimates for

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<th>Km (µM)</th>
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regression, $y$

cyclophosphamide and its circulating metabolite, 4-hydroxycyclo-
mide (12, 13) has been a valuable tool for a complete description of
cyclophosphamide and 4-hydroxycyclophosphamide/aldophospha-

interpatient variability of the metabolic processing of cyclophospha-

high doses (concentration- and time-dependent kinetics) has been of

capacity of hepatic biotransformation of cyclophosphamide varies

clearance pattern was obviously nonlinear or

Any conventional sample handling without the stabilizing step will

because of this variability remains unclear.

In patients ($N = 5$) with apparent linear elimination, one-third of

70 $M$, while others

preclinical co-modeling of the
cyclophosphamide data by using a time-variant model as described previously (7).

The presence of the nonlinear elimination of cyclophosphamide at

moderate doses (3). For decades it has been widely accepted that

impaired renal function would not alter the pharmacokinetic behavior

to nonrenal mechanisms. It is unclear whether this is valid

when high doses of cyclophosphamide are used.
AUC and \( C_{\text{max}} \) data for cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide by computer simulation

<table>
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<th>( K_m ) (( \mu M ))</th>
<th>( CP ) AUC (( \mu M \cdot hr ))</th>
<th>( 4-OH ) AUC (( \mu M \cdot hr ))</th>
<th>( CP ) ( C_{\text{max}} ) (( \mu M ))</th>
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CP, cyclophosphamide; 4-OH, 4-hydroxycyclophosphamide/aldophosphamide. Other parameter estimates used in simulation are: dose = 6387 mg, infusion time = 90 min, \( V_{\text{max}} \) = 0.78 \( \mu M/\text{min} \), \( CL_r \) = 29 \( ml/\text{min} \), \( CL_{\text{met}}/F_{\text{met}} \) = 2982 \( ml/\text{min} \).

Ayash et al. have previously reported an inverse correlation between cardiac toxicity and tumor response and cyclophosphamide AUC in patients receiving high-dose chemotherapy (cyclophosphamide 6 \( g/m^2 \); thiotepa 500 \( mg/m^2 \); and carboplatin 800 \( mg/m^2 \) by 96-hr infusion) followed by autologous bone marrow transplantation (27). They found that patients who developed congestive heart failure and who also showed tumor response had a lower AUC of total cyclophosphamide. They have suggested that a lower cyclophosphamide AUC might be related to an increase in conversion of cyclophosphamide to its active alkylating metabolites and may enhance both end-organ and tumor cytotoxicity. Slattery et al. also reported an inverse relationship between cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide in patients receiving cyclophosphamide after busulfan or with total body irradiation (11). We compared cyclophosphamide AUC and 4-hydroxycyclophosphamide/aldophosphamide AUC in these 12 patients receiving cyclophosphamide as a single agent after a 90-min infusion and receiving cyclophosphamide concurrently with thiotepa after a 96-hr infusion. In contrast to the hypothesis by Ayash et al. and the laboratory finding by Slattery et al., we found that there was a positive correlation between cyclophosphamide AUC and 4-hydroxycyclophosphamide/aldophosphamide AUC in patients receiving cyclophosphamide as a single agent. However, in the clinical situation paralleling the treatment received by Ayash’s patients (96-hr infusion with thiotepa), no correlation was found between these two AUCs.

These clinical and laboratory findings have given rise to an important question: what is the relationship between total cyclophosphamide exposure and 4-hydroxycyclophosphamide/aldophosphamide exposure in patients with nonlinear elimination or apparent linear elimination. Based on Model 1 and Model 2 used in this report, we have performed computer simulation, which may provide possible explanations for the variability of cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide disposition in patients with various physical (interpatient variability) and medical conditions (by disease or by drug interactions).

When the other kinetic parameter estimates are held constant (mean values from table 1) and \( CL_r \) is varied, there is a positive correlation between cyclophosphamide AUCs and 4-hydroxycyclophosphamide/aldophosphamide AUCs, i.e. higher cyclophosphamide exposure is associated with higher 4-hydroxycyclophosphamide/aldophosphamide exposure (figs. 6a and b). Simulation revealed that a 90% reduction of the renal clearance of cyclophosphamide may be associated with 30% increase in 4-hydroxycyclophosphamide/aldophosphamide AUC. However, considering the much larger interpatient variability of AUC, our simulation suggests that no dose adjustment of...
cytochrome enzymes enhance the and therapeutic efficacy or toxicity has not been well established. A peak concentration of 4-hydroxycyclophosphamide/aldophosphamide.

20%. The $K_{nr}$ of 4-hydroxycyclophosphamide increases 75% whereas AUC only increases 55% CHEN ET AL.

 patients receiving ondansetron and cyclophosphamide. They observed drug interaction between novobiocin and cyclophosphamide.

Another possible drug interaction was the combination of antiemetic drugs with chemotherapy agents. It is a common practice that several antiemetic drugs (e.g., ondansetron, lorazepam, and prochlorperazine) are coadministered with the preparative chemotherapy regimen to patients before bone marrow transplantation.

As the use of combination chemotherapy has become more frequent, drug interactions have been a major concern in clinical management. We cannot elucidate the complex metabolic processing of cyclophosphamide in humans with the limited clinical data thus far available. Variations are expected and unpredictable.

Earlier trials have shown that bolus injection of cyclophosphamide at 120 mg/kg caused fatal heart failure, but at a much slower infusion rate of the same dose, heart failure was rare. This observation suggested that there might be a direct correlation between peak concentration of active metabolite and cardiac toxicity.

In patients with normal hepatic and renal function, a positive relationship between cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide should be expected when cyclophosphamide is given as a single agent. This is because the kinetics of 4-hydroxycyclophosphamide are formation limited and plasma AUC values for 4-hydroxycyclophosphamide/aldophosphamide increase with an increase in the amount (exposure) of cyclophosphamide. Patients who are enrolled in the solid tumor bone marrow transplantation program are generally in fair physical condition. Therefore, it is not surprising that such a relationship was observed in this cohort of patients.

As the use of combination chemotherapy has become more frequent, drug interactions have been a major concern in clinical management. We cannot elucidate the complex metabolic processing of cyclophosphamide in humans with the limited clinical data thus far available. Variations are expected and unpredictable. This may explain why different results have been reported by us and other investigators when cyclophosphamide was administered with various agents. More detailed pharmacokinetic-pharmacodynamic studies are warranted to define the relationship between cyclophosphamide and active metabolites in patients.

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1 O. M. Colvin, unpublished observation.

References


Simulated AUC and $C_{max}$ values of cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide by varying the $K_m$ value only are shown in table 2. This simulation suggests that $C_{max}$ is more affected by the $K_m$ value. When $K_m$ decreases 5-fold, $C_{max}$ of 4-hydroxycyclophosphamide increases 75% whereas AUC only increases 20%. The $V_{max}$ value but not the $K_m$ value influences the total exposure of 4-hydroxycyclophosphamide/aldophosphamide. Although many investigators have alleged that the cytotoxic effects of cyclophosphamide are directly proportional to AUC values of 4-hydroxycyclophosphamide/aldophosphamide (3), the relationship of peak concentration of 4-hydroxycyclophosphamide/aldophosphamide and therapeutic efficacy or toxicity has not been well established.


