The Effects of Cyclosporine on the Pharmacokinetics of Doxorubicin in Patients with Small Cell Lung Cancer

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Background. **The authors compared the pharmacokinetics of doxorubicin when administered with and without concomitant high dose cyclosporine for multidrug resistant (MDR) tumor modulation in small cell lung cancer.**

Methods. **Eight patients with small cell lung cancer served as their own controls and were studied first during an initial course of doxorubicin without cyclosporine, and then subsequently during a cyclosporine-modulated doxorubicin course. All patients received cyclophosphamide and vincristine in each course. Doxorubicin was administered as a 1-hour infusion after a 2-hour cyclosporine loading infusion, and cyclosporine was infused continuously for the next 48 hours. Serum concentrations of doxorubicin, doxorubicinol, and cyclosporine all were assayed by high-pressure liquid chromatography. Pharmacokinetic analysis of doxorubicin included area under the curve (AUC), clearance, apparent volume of distribution at steady state (V_{ss}), and elimination half-life ($T^1/_2$). The percent of change and surviving fraction of leukocyte count and platelets were determined as pharmacodynamic indices.**

Results. **Cyclosporine modulation increased the AUC_{0-36} of doxorubicin by 48% ($P = 0.042$) and the AUC_{0-36} of doxorubicinol by 443% ($P = 0.0001$), whereas the doxorubicin clearance declined by 37% ($P = 0.0495$). No difference was found in the V_{ss} or $T^1/_2$ for doxorubicin when cyclosporine was added to the regimen. The ratio of the doxorubicinol AUC_{0-36} to the doxorubicin AUC_{0-36} increased significantly with cyclosporine modulation (8.88 vs. 2.19; $P = 0.001$). Drug-related toxicity was also greater with the cyclosporine-modulated course of doxorubicin. A 91% reduction in the leukocyte count followed the modified course, compared with an 84% reduction following the initial course ($P = 0.0074$). A more prolonged and greater degree of myelosuppression was observed and a significant relationship was found between the systemic exposure to doxorubucin (defined by AUC) and the surviving fraction of the leukocyte count ($r = -0.69$; $P = 0.006$). Similarly, the reduction in the platelet count was significantly greater after the cyclosporine-modulated course (72.8%) than after the initial course (36.4%) ($P = 0.0016$). A significant correlation was found between the AUC of doxorubicinol and the surviving fraction of platelets ($r = -0.71$; $P = 0.004$). In addition, patients showed decreased performance status associated with significant weight loss and severe myalgias.**

Conclusions. **The addition of high dose cyclosporine for MDR modulation resulted in the significant alteration of doxorubicin disposition and remarkable toxicity in all patients. The mechanisms responsible for the decreased doxorubicin clearance may include cyclosporine's ability both to interfere with P-glycoprotein in normal tissues and to selectively inhibit the cytochrome P-450 enzyme system. Further study of this potentially significant drug-drug interaction is warranted.** *Cancer* **1994; 74:834–41.**

Key words: doxorubicin, doxorubicinol, cyclosporine, pharmacokinetics, small cell lung cancer, resistance modulation, lung cancer.

Doxorubicin is a major component of combination chemotherapy regimens for small cell lung carcinoma.[1] The primary limitations to doxorubicin therapy include a dose-dependent myelosuppression and cardiotoxicity related to cumulative dose. In addition, tumors are capable of developing resistance to doxorubicin; when this happens, resistance is crossed over to other structurally unrelated antineoplastic agents, such as etoposide and vincristine, producing multidrug resistance

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(MDR).[2] This type of resistance is a result of overexpression of the *mdr*1 gene, which encodes for P-glycoprotein, an energy-dependent efflux pump responsible for transporting the drugs affected by MDR out of the cell.[2,3] This action prevents intracellular drug accumulation and, subsequently, cytotoxic activity in the tumor cells.[2,3]

In an attempt to overcome MDR, cyclosporine has been added to doxorubicin-based regimens to modify the action of P-glycoprotein.[4–6] Cyclosporine which is transported by P-glycoprotein, competitively inhibits the efflux of doxorubicin at clinically achievable concentrations and allows accumulation of doxorubicin within the MDR tumor cell.[4,7] However, P-glycoprotein also is found in normal tissues involved with drug metabolism and elimination. Thus, cyclosporine could be expected to increase tumor response and potentially increase toxicity caused by the interference of doxorubicin clearance.

Successful cyclosporine modulation of MDR recently was accomplished with acceptable toxicity in patients receiving etoposide-based regimens.[7] However, etoposide clearance was markedly reduced in the presence of high dose cyclosporine therapy, leading to increases in the area under the curve (AUC) and the elimination half-life of etoposide.[8]

We have begun to prospectively study the possibility that cyclosporine could be used to modulate MDR in patients with small cell lung cancer who are receiving doxorubicin, cyclophosphamide, and vincristine (CAV) chemotherapy. In the context of this study, we determined the pharmacokinetics of doxorubicin and its metabolite, doxorubicinol, when administered with and without concomitant cyclosporine. We chose the pharmacokinetics of doxorubicin on the basis of our previous data showing that a significant relationship exists between myelotoxicity and systemic doxorubicin exposure (AUC) in CAV chemotherapy regimens.[9]

Patients and Methods

Patients

After completion of a medical history, physical examination, electrocardiogram, and chest roentgenography, adult patients with histologically confirmed diagnosis of small cell carcinoma of the lung were included in the study. The protocol was approved by the Institutional Review Board of Marshfield Clinic, and all patients signed informed consent forms. Patients were evaluated using Karnofsky Performance Status before and after completion of each course. Laboratory studies obtained before and repeated after treatment included a complete blood cell count, serum creatinine and electrolytes, albumin, and liver function tests (aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, and bilirubin). Hemoglobin, platelets, and leukocyte counts were monitored three times weekly during the anticipated period of myelosuppression.

Treatment

Patients were studied during two separate courses of CAV chemotherapy. Patients continued to receive CAV without cyclosporine until tumor progression or disease stabilized. Cyclosporine was added to the next course of CAV. Each patient served as his or her own control by being studied during an initial course without cyclosporine and subsequently during a course involving MDR modulation with cyclosporine.

The CAV regimen was administered every 21 days as long as myelosuppression did not persist. For each course of therapy, patients received doxorubicin (mean dose, 51 mg/m^2) given as a 1-hour infusion in addition to cyclophosphamide 1000 mg/m^2 and vincristine 2 mg. Doses were based on body surface area calculated by the method of Dubois and Dubois[10] using actual body weight. In an attempt to reverse MDR in the subsequent course, patients received concomitant cyclosporine of 6 mg/kg bolus infused during a period of 2 hours, followed by a continuous infusion of 16 mg/kg/24 hours for 48 hours. The 2-hour bolus of cyclosporine was infused immediately before the infusion of doxorubicin. The doses of cyclosporine were selected on the previous experiences of Yahanda et al.[7]

Sampling

Blood samples for determination of doxorubicin and doxorubicinol concentrations were collected at 0.5 hours (midpoint of infusion); 1.0 hour (end of infusion); and at 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 hours after infusion. Serum was separated from the blood samples by centrifugation and immediately frozen at −20°C in polypropylene tubes until the time of analysis. Cyclosporine concentrations were collected from central or peripheral blood samples obtained at 6 hours after the start of the continuous infusion and at 12-hour intervals until discontinuation.

Analytic Procedure

Serum concentrations of doxorubicin and doxorubicinol were assayed at the Marshfield Medical Research Foundation by high pressure liquid chromatography according to a method modified from that of Robert.[11] A description of this analytic procedure has been pub-

lished elsewhere.[12] The intraassay coefficients of variation for doxorubicin were 8.6%, 2.4%, and 2% at 1.0, 10, and 120 ng/ml, respectively. The intraassay coefficients of variation for doxorubicinol were 12%, 2.5%, and 7.2% at 1, 5, and 20 ng/ml, respectively. The interassay coefficient of variation for doxorubicin at 52 ng/ml was 8.6%.

Whole blood samples were assayed for cyclosporine by an high pressure liquid chromatography methodology at the Mayo Clinic (Rochester, MN) using their previously published procedure.[13,14]

Pharmacokinetic Analysis

Doxorubicin concentration versus time data was modeled using nonlinear weighted least squares regression by Adapt II modeling software.[15] Weighting was by the inverse of the observation variance. Selection of the appropriate pharmacokinetic model was based on Akaike's Information Criterion and visual inspection of the observed versus fitted concentration-time points.[16] The terminal rate constant (λ_z) of the doxorubicin concentration versus time plot was divided into the natural log of 2 for calculation of the elimination half-life. The area under the curve (AUC_{0-36}) and area under the first moment curve ($AUMC_{0-36}$) from the beginning of the infusion to 36 hours were calculated for doxorubicin and doxorubicinol using the trapezoidal method.[17] Because the doxorubicin doses were not identical in all of the paired pharmacokinetic studies, AUC_{0-36} was normalized for the dose administered by dividing AUC_{0-36} by dose (mg/m^2). The AUC for doxorubicin also was extrapolated to infinity ($AUC_{0-\infty}$) by dividing the final measured serum concentration by λ_z.[17] Standard noncompartmental equations were used to calculate clearance and apparent volume of distribution at steady state, as we have previously described.[12,17] The ratio of doxorubicinol AUC to doxorubicin AUC was used to describe the exposure of the active metabolite to the parent drug.

Pharmacodynamic Analysis

The percent change of leukocytes and platelets was determined after each course of therapy using the following equation:

$$\%\ \text{change} = \frac{\text{baseline value} - \text{nadir value}}{\text{baseline value}} \times 100\%$$

The relationships between systemic exposure (defined by AUC) for doxorubicin and doxorubicinol with surviving fraction of leukocytes or platelets was examined by the following equation:

$$SF = \frac{\text{nadir value}}{\text{baseline value}}$$

Statistical Analysis

A paired Student *t* test was used to compare the pharmacokinetic parameters, laboratory values, and pharmacodynamic indices between the initial CAV course and the modified CAV course in which the patients received cyclosporine. Linear least-squares regression was used to determine significance between AUC and surviving fraction of leukocytes or platelets. Calculation of the sample size required to achieve a power of 80% with a two-tailed alpha value of 0.05 was performed. A *P* value of less than 0.05 was considered significant.

Results

Patients

Eight patients completed the study protocol. Demographics are summarized in Table 1. Four of the patients treated had disease in partial remission with their first series of chemotherapy. One patient was treated at the time of first relapse, and three patients were treated during the time of known refractory disease. Two of the patients with refractory disease had relapse from previous complete remission and had disease refractory to other known drugs; the third patient had primary refractory disease.

Analysis was done on the first and second consecutive courses for three patients. The other five patients received cyclosporine with their third (n = 2), fourth (n = 1), or fifth (n = 2) course of CAV. Patients received the same dose of doxorubicin with each course, with the exception of one patient, who had a dose increase between the time of the initial pharmacokinetic study (course 1) and the addition of cyclosporine (course 5).

Table 1. Patient Demographics

Age (yr)	63.6 ± 8.4
Sex	4 male/4 female
Actual body weight (kg)	79.2 ± 21.0
BSA (m^2)	1.92 ± 0.30
Doxorubicin dose (mg/m^2)	
Initial course	48 ± 13
CsA-modulated course	54 ± 13
Cyclosporin dose	
Bolus (mg/kg)	6.1 ± 0.1
Infusion (mg/kg/day)	16.4 ± 0.3

Values are mean ± SD.
BSA: body surface area.

Table 2. Laboratory Values Before Each Doxorubicin Course

	Standard regimen (n = 8)	CsA-modified course (n = 8)
Hemoglobin (mg/dl)	13.3 ± 1.1	12.3 ± 1.9
Leukocytes (10^3/mm^3)	8.95 ± 2.68	5.94 ± 2.61*
Platelets (10^3/mm^3)	322 ± 122	290 ± 110
Albumin (g/dl)	3.9 ± 0.4	4.2 ± 0.2*
AST (IU/ml)	37.0 ± 36.8	24.8 ± 19.9
GGT (IU/ml)	76.1 ± 79.1	89.5 ± 155.7
Bilirubin (mg/dl)	0.46 ± 0.18	0.40 ± 0.15
Alk Phos (IU/ml)	106 ± 27	125 ± 60
SCr (mg/dl)	1.0 ± 0.2	1.1 ± 0.2

Values are mean ± SD.

AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; Alk Phos: alkaline phosphatase; SCr: serum creatinine.

* Statistically significant at $P < 0.05$.

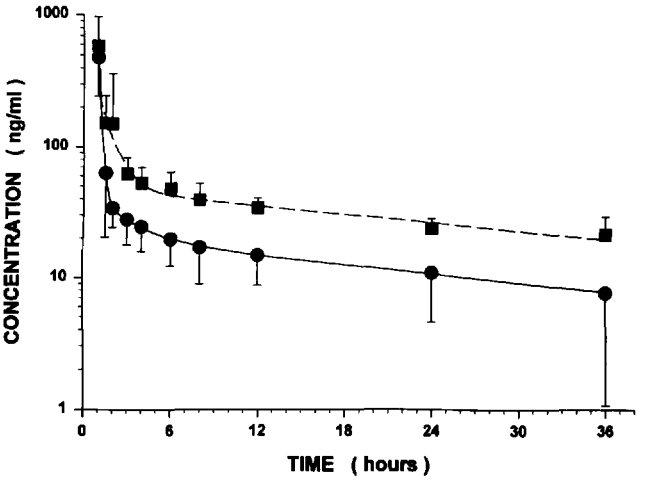

Figure 1. Mean serum concentration versus time curves for patients receiving doxorubicin with (■) and without (●) cyclosporine. Error bars represent the standard deviation. The solid and dotted lines represent the computer-fitted nonlinear least-squares regression analysis of serum concentration-time data.

Baseline laboratory values for both courses are given in Table 2. Leukocyte count was significantly lower ($P = 0.048$) before the cyclosporine-modified course, whereas albumin was found to be increased significantly ($P = 0.028$) before the cyclosporine-modified treatment course. No other differences in baseline laboratory indices were observed. Seven patients experienced a transient hyperbilirubinemia after cyclosporine treatment, with total bilirubin concentrations ranging from 1.0 to 4.2 mg/dl.

Pharmacokinetics

One patient was excluded from pharmacokinetic analysis because of the unavailability of serum concentrations for the cyclosporine-modified course of doxorubicin. Concentration-time profiles of doxorubicin with and without cyclosporine treatment are shown in Figure 1. Doxorubicin disposition exhibited a biexponential or triexponential decay, as we have described previously.[9]

Mean pharmacokinetic parameters for both study courses are summarized in Table 3. The dose-adjusted AUC_{0-36} of doxorubicin was significantly higher for the cyclosporine-modified course 31.92 ± 9.78 ng × hour/ml/mg/m^2 compared with 21.51 ± 4.13 ng × hour/ml/mg/m^2 for the initial course ($P = 0.042$). Similarly, the dose-adjusted AUC_{0-36} of the active metabolite doxorubicinol was significantly increased from 49.21 ± 31.14 ng × hour/ml/mg/m^2 without cyclosporine to 267.4 ± 58.57 ng × hour/ml/mg/m^2 with the cyclosporine-containing regimen ($P = 0.0001$). This corresponds to a 48% and 443% increase in doxorubicin and doxorubicinol exposure, respectively. The ratio of doxorubicinol AUC to doxorubicin AUC increased significantly from 2.19 to 8.88 ($P = 0.001$).

Doxorubicin clearance significantly decreased from 617.6 ± 193.3 ml/minute/m^2 with the initial course to 391.3 ± 143.3 ml/minute/m^2 with the cyclosporine-modified course ($P = 0.0495$). No difference was observed in volume of distribution at steady state or elimination half-life when cyclosporine was added to the regimen. The elimination half-life of doxorubicinol could not be determined for the cyclosporine-modified course because serum concentrations continued to

Table 3. Pharmacokinetic Parameters of Doxorubicin in Patients Without and With Cyclosporin (CsA) Modification

	Standard regimen (n = 7)	CsA-modified course (n = 7)
Doxorubicin		
AUC_{0-36}/mg/m^2 *	21.5 ± 4.1	31.9 ± 9.8†
$AUC_{0-\infty}$ (ng·hr/ml)	1422 ± 959	2580 ± 638†
CL (ml/min/m^2)	617.6 ± 193.3	391.3 ± 143.3†
V_{ss} (L/m^2)	776.6 ± 397.6	745.3 ± 461.8
$T_{1/2}$ (hr)	31.0 ± 18.5	29.5 ± 19.7
Doxorubicinol		
AUC_{0-36}/mg/m^2 †	49.2 ± 31.1	267.4 ± 58.6†
DOL:DOX ratio	2.19 ± 1.11	8.88 ± 2.49†

AUC: area under the curve; CL: clearance; V_{ss}: apparent volume of distribution at steady state; $T_{1/2}$: elimination half-life; DOL: doxorubicinol; DOX: doxorubicin.

* AUC_{0-36} in units of ng·hr/ml divided by dose in mg/m^2.

† Statistically significant at $P < 0.05$.

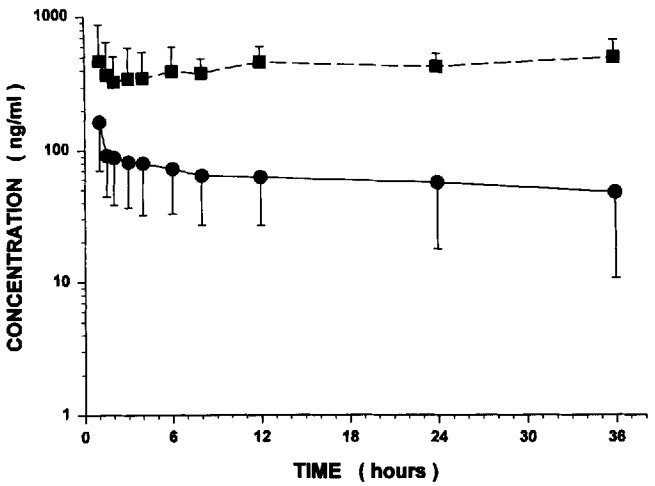

Figure 2. Mean serum concentration versus time curves of doxorubicinol with (■) and without (●) cyclosporine. Error bars represent the standard deviation. The solid and dotted lines represent the connecting of each of the mean serum concentration-time points during each course.

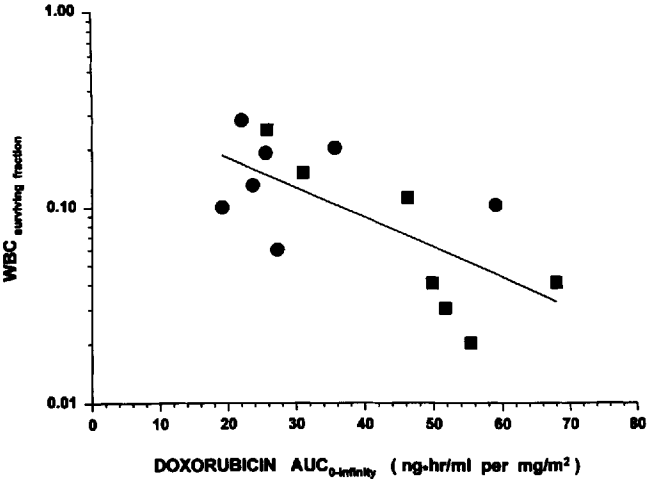

Figure 3. Doxorubicin systemic exposure (AUC) versus leukocyte count surviving fraction for individual patients with (■) and without (●) cyclosporine. A significant relationship was noted between doxorubicin AUC and ln leukocyte surviving fraction ($r = -0.69$; $P = 0.006$).

increase at 36 hours after doxorubicin administration (Fig. 2).

In the study course involving P-glycoprotein modulation, five patients had cyclosporine concentrations evaluated at 24 hours. The concentrations were highly variable, ranging from 1262 to 2163 ng/ml. No relationship was observed between cyclosporine concentrations and any pharmacokinetic or pharmacodynamic parameters.

Pharmacodynamics

An increase in drug related toxicity was observed after the cyclosporine-modified course (Table 4). A decrease in leukocytes of 84% resulted from the initial CAV course, whereas administration of concomitant cyclosporine was followed by a 91% reduction in leukocytes ($P = 0.0073$). A significant relationship was found between doxorubicin AUC and ln leukocyte surviving fraction ($r = -0.69$; $P = 0.006$; Fig. 3) but not with the AUC of doxorubicinol. The percent reduction in platelets also was greater after the cyclosporine-modified course (36.4% versus 72.8%; $P = 0.0016$), indicating a more significant degree of myelosuppression with the modified course. A significant relationship was noted between doxorubicinol AUC and ln platelet surviving fraction ($r = -0.71$; $P = 0.004$; Fig. 4) but not the AUC of doxorubicin.

The duration of neutropenia was significantly longer after the cyclosporine-modified course. In seven patients with available data, the mean (±SD) number of days with a leukocyte count of less than 1000 cells/m^3 was significantly higher after cyclosporine-modified therapy than after CAV alone (0.29 ± 0.49 days versus 3.71 ± 1.89 days; $P = 0.0024$).

In addition, nadir albumin, body weight, and performance status values were available and evaluated for seven patients. Although pretreatment albumin val-

Table 4. Pharmacodynamic Parameters in Patients Without and With Cyclosporin (CsA) Modification

	Standard regimen	CsA-modified course
Nadir leukocytes (cells/mm^3)	1.50 ± 1.01	0.64 ± 0.93*
% reduction in leukocytes	84.0 ± 7.3	91.1 ± 8.0*
Nadir platelets (10^3/mm^3)	191.0 ± 37.2	82.6 ± 65.5*
% reduction in platelets	36.4 ± 18.7	72.8 ± 12.1*
Nadir albumin (mg/dl)	3.9 ± 0.2	3.0 ± 0.5*

Values are mean ± SD.

* Statistically significant at $P < 0.05$.

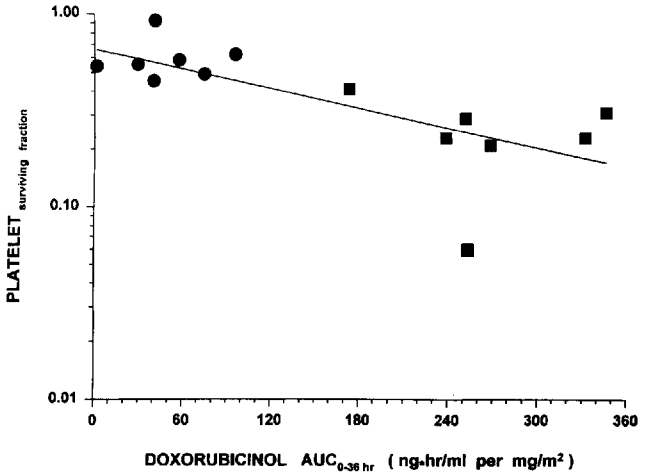

Figure 4. Doxorubicinol systemic exposure (AUC) versus platelet count surviving fraction for individual patients with (■) and without (●) cyclosporine. A significant relationship was noted between doxorubicinol AUC and ln platelet count surviving fraction ($r = -0.71$; $P = 0.004$).

ues were significantly higher before the cyclosporine-modified course, the nadir values were significantly lower ($P = 0.0036$) after the modified course than after the initial course, also suggesting increased toxicity with cyclosporine modulation. Similarly, the patients experienced essentially no change in body weight after the initial course, whereas an average weight loss of 4.5 kg was observed after the modified course ($P = 0.0318$). Performance status decreased significantly from 90.0 ± 5.77 before the cyclosporine-modified course to 52.1 ± 37.62 after treatment ($P = 0.047$). No difference was found between the pretreatment and after treatment performance status with the initial doxorubicin course.

Toxic death occurred in one patient with primary refractory disease. The patient was 69 years of age and had a performance status of 80 before treatment of his disease with CAV plus cyclosporine. The patient was thought to have died of overwhelming sepsis. His leukocyte count dropped from 2600 cells/m^3 to 100 cells/m^3 in 24 hours, and he died within 6 hours from the onset of septic shock.

Discussion

Doxorubicin-based combination chemotherapy regimens continue to play a primary role in the therapy of small cell carcinoma of the lung. However, the development of tumor cells exhibiting MDR to doxorubicin and other structurally unrelated antineoplastic agents may lead to therapeutic failure. Overexpression of the *mdr*1 gene, and consequently the membrane efflux pump P-glycoprotein, has been implicated as the basis for this MDR.[2,3] In an attempt to overcome MDR, cyclosporine has been added to antineoplastic regimens to modulate the function of P-glycoprotein. Because P-glycoprotein is found not only in tumor tissue, but also in normal tissue of organs involved in drug elimination, modulation of this efflux pump has the potential to alter the distribution and elimination of antineoplastic agents.[2]

The results of this clinical study indicate that a significant drug-drug interaction occurs between cyclosporine and doxorubicin, and that the increase in relative systemic exposure (quantitated by AUC) of doxorubicin and doxorubicinol has an influence on the probability of clinical toxicity. Our observations are consistent with preliminary Phase I studies that demonstrate that the AUC of doxorubicin and doxorubicinol are significantly affected by cyclosporine.[5,6] Scheulen et al.,[5] who administered doxorubicin as a 30-minute infusion, observed a 40% increase in doxorubicin AUC and a greater than 250% increase in the AUC of doxorubicinol when cyclosporine was given concomitantly. Bartlett et al.[6] also reported a 70% increase in the dose-adjusted AUC of doxorubicin, with a corresponding increase in doxorubicinol AUC of 285% when doxorubicin and cyclosporine were administered as continuous intravenous infusions.

In our patients, cyclosporine modulation increased the AUC of doxorubicin by approximately 48%, whereas the AUC of doxorubicinol, the active metabolite, was increased by 443%. The pharmacokinetic parameters obtained during the first course of doxorubicin treatment are consistent with those previously reported.[9,12,18] We have previously shown the disposition of doxorubicin to be similar with repeated dosing.[18] In using two separate study periods in the same patient, we have attempted to minimize the effects of interpatient variability. In addition, all patients had a serum creatinine level of 1.5 mg/dl and a bilirubin level of less than 1.0 mg/dl before dosing in both courses. Although a transient hyperbilirubinemia was observed after cyclosporine treatment, this was an expected occurrence.[7] Finally, one patient received a higher doxorubicin dose with the cyclosporine-modulated course. Nevertheless, the data are comparable between study periods because the AUC were normalized for the dose administered.

One patient was concomitantly receiving verapamil, a drug with the potential to interact with doxorubicin.[19] However, the patient received the same dose of verapamil during both regimens. The same significant differences are observed for the pharmacokinetic and pharmacodynamic parameters, even if this patient is removed from the data analysis.

Clinically we observed that the addition of

cyclosporine additionally increases the toxicity of the CAV regimen. The clinical toxicities seen with the cyclosporine-modified course in this study were severe and persistent. Patients experienced severe myalgias that required administration of narcotic agents for control. A significant reduction in leukocyte and platelet counts was noted after the cyclosporine-modified course compared with the standard CAV regimen. More importantly, the duration of neutropenia was significantly prolonged. After the standard CAV regimen, two of seven patients experienced leukocyte counts of less than 1000 cells/m^3. With each of those patients, the duration of neutropenia was 1 day. However, after the cyclosporine-modified course, six of seven patients were neutropenic, with leukocyte counts of less than 1000 cells/m^3, and the duration of this neutropenia was 3–6 days. In addition, one patient experienced a toxic death after the cyclosporine-modified course, with a leukocyte count of less than 100 cells/m^3.

The toxicities seen in this study also may be attributable to increased concentrations of cyclophosphamide, vincristine, or their metabolites. Serum concentrations for these compounds were not determined in this study. A few patients experienced greater obstipation and confusion, in addition to the other toxicities, which may be a combined effect from increased systemic exposure to vincristine and doxorubicin.[20] One patient also had hematuria, possibly related to prolonged excretion of cyclophosphamide. Another argument could be made based on previous exposure to chemotherapy. Five patients in the study were receiving cyclosporine with their third to fifth chemotherapy regimen. Thus, it is possible that previous episodes of myelosuppression contributed to increased toxicity.

Despite these possibilities, we believe that doxorubicin is responsible for the severe myelotoxicity seen in this study and in our previous report.[9] This premise is supported by the significant relationships observed between decreases in leukocyte (Fig. 3) and platelet (Fig. 4) counts and the AUC for doxorubicin and doxorubicinol, respectively. The addition of cyclosporine resulted in marked alterations in the magnitude and duration of doxorubicinol concentrations in this study (Fig. 2). This explains in part why we have observed a significant correlation in platelet counts and the AUC of doxorubicinol in this study but not during CAV therapy without cyclosporine in our previous report.[9]

The mechanisms responsible for the decreased doxorubicin clearance when given with cyclosporine remain unknown but are likely to involve both P-glycoprotein and enzyme inhibition. First, the membrane efflux pump, P-glycoprotein, is expressed in normal tissues, such as the brush border of the kidney and the luminal surface of the biliary tract.[2] Modulation of this pump may interfere not only with the movement of doxorubicin out of tumor cells, but also with the normal elimination of doxorubicin and its metabolites in the bile. Riggs et al.[21] found 41% of the total doxorubicin dose to be eliminated in the bile. Of this, 42% was the parent drug, and 22% was the major metabolite, doxorubicinol. This inhibition of biliary excretion may account for the decreased total clearance of doxorubicin.

A potential drug-drug interaction also exists between cyclosporine and doxorubicin. Cyclosporine selectively inhibits the cytochrome P-450 enzyme system, the primary pathway responsible for doxorubicinol metabolism.[22] By inhibiting the conversion of doxorubicinol to 7-deoxy-doxorubicinol aglycone,[23] an accumulation of doxorubicinol may occur. This mechanism would account for the markedly increased doxorubicinol concentrations observed during the cyclosporine-modified course. Thus, two potential mechanisms may contribute to the findings of this study.

The results of this study generate several additional questions. Doxorubicinol concentrations continued to increase, even after 36 hours (Fig. 2). Thus, it is unknown at what time concentrations begin to decline. Future studies should use extended sampling guidelines to adequately characterize doxorubicinol elimination. Second, the appropriate dosage of doxorubicin in the cyclosporine-modified regimen is unknown. In preliminary work by Bartlett et al.[6] using continuous infusion doxorubicin, the authors recommended a 40–50% reduction in doxorubicin dose when the agent was given with cyclosporine. Although this seems to be a reasonable approach, efficacy data may yield a different perspective. If patient outcomes are shown to significantly improve, consideration should be given to the use of hematopoietic growth factors to counteract toxicity while attaining maximum cytotoxic activity. This alternative view could be the topic of an extended risk-versus-benefit discussion. Finally, potential relationships between cyclosporine blood levels and toxicity or efficacy should be examined. Although we did not find a relationship between cyclosporine levels and toxicity, the concentrations we achieved were lower than those previously reported. In a study of continuous infusion etoposide, Lum et al.[8] reported that a lower leukocyte nadir was observed when cyclosporine levels were greater than 2000 ng/ml.

The addition of high dose cyclosporine for MDR modulation resulted in significant alteration of doxorubicin disposition and remarkable toxicity in all patients. Additional elucidation of the mechanisms involved and additional studies of this significant drug-drug interaction are warranted. The use of cyclosporine for modulation of MDR remains experimental and should be used only for MDR modulation in clinical trials.

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