Evaluation of Carboplatin Pharmacokinetics in the Absence and Presence of Paclitaxel

Coleman K. Obasaju, Steven W. Johnson, Andre Rogatko, Debbie Kilpatrick, James M. Brennan, Thomas C. Hamilton, Robert F. Ozols, Peter J. O’Dwyer, and James M. Gallo
Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111

ABSTRACT
In a clinical trial of paclitaxel (Taxol) and carboplatin in combination, the severity of thrombocytopenia was less than would be expected with an equivalent dose of carboplatin alone. To determine whether a pharmacokinetic interaction was responsible for this observation, the effect of pretreatment with Taxol on the pharmacokinetics of carboplatin was examined in 11 patients. Each patient was randomized to one of two treatment groups that determined the order of drug treatments. The treatments were carboplatin as a 30-min infusion alone or immediately following 175 mg/m² Taxol administered as a 3-h i.v. infusion. The treatments were separated by 1 week. The carboplatin dose was chosen to produce a target area under the concentration-time curve (AUC) of 3.75 mg-min/ml according to a previously published formula (A. H. Calvert et al., J. Clin Oncol., 7: 1748–1756, 1989). The mean administered dose of carboplatin was 338 mg. Serial blood samples were collected over 24 h and analyzed for total and free platinum, and, in some patients, Taxol. The pharmacokinetics of carboplatin (i.e., total clearance and volume of distribution at steady state), was not significantly affected by pretreatment with Taxol. Total clearances of carboplatin were 67.2 ± 28.8 ml/min and 64.6 ± 27.9 ml/min in the absence and presence of Taxol, respectively (P = 0.56). The AUC of free carboplatin (3.45 mg-min/ml) obtained in the absence of Taxol was not significantly different from that measured in the presence of Taxol (3.27 mg-min/ml). The AUC of carboplatin in both the absence and presence of Taxol agreed with the projected target AUC of 3.75 mg-min/ml. In conclusion, the application of an individualized dosing strategy is valid for the calculation of the carboplatin dose in this combination. The pharmacokinetics of carboplatin is not altered by pretreatment with Taxol at a standard dose, and a pharmacokinetic interaction is not responsible for the altered toxicity of the combination.

INTRODUCTION
Paclitaxel (Taxol) has demonstrated substantial activity as a single agent in the treatment of various solid tumors, including ovarian, breast, and lung cancers (1–6). Preclinical studies indicated that the combination of Taxol and platinum compounds was superadditive in several models (1, 7, 8). The cellular basis for this favorable interaction has not yet been elucidated, but aspects of appropriate dosing strategies have been described in preclinical and early clinical studies. In MCF-7 breast cancer and A549 lung cancer xenografts, the activity of simultaneous drug administration and that of the sequence Taxol preceding carboplatin administration was superior to that of the reverse order (9). In a Phase I clinical trial of cisplatin and Taxol, more severe neutropenia was associated with the sequence in which cisplatin was given first, and this sequence was associated with a lower clearance of Taxol (10). The substantial clinical activity of the Taxol/cisplatin combination has been demonstrated in a randomized trial in ovarian cancer (11), and studies in other diseases are in progress.

Early clinical combination studies of Taxol with carboplatin lagged behind those with cisplatin because of concern regarding additive myelosuppression. In a Phase I trial in ovarian cancer, in which the carboplatin dose was individualized according to the formula of Calvert et al. (12), we found that full doses of each agent could be administered safely. Indeed, the severity of thrombocytopenia appeared to be even less than expected. The kinetics of both agents was characterized in that study; although an initial impression suggested that carboplatin AUC values were less than predicted, the analysis of the completed study demonstrated that the mean measured carboplatin AUC was 7.2 mg-min/ml at a targeted AUC of 7.5 mg-min/ml. To determine more precisely whether the apparent alteration in platelet toxicity could be explained by a pharmacokinetic interaction between Taxol and carboplatin, we designed a study in which patients were treated both with carboplatin alone and with carboplatin following a 3-h infusion of Taxol.

MATERIALS AND METHODS
Study Design
This trial was designed to test the effect of Taxol on carboplatin pharmacokinetics. Each patient received both car-

2 To whom requests for reprints should be addressed, at Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111. Phone: (215) 728-2461; Fax: (215) 728-2741.
3 The abbreviations used are: AUC, area under the concentration-time curve; GFR, glomerular filtration rate; AUC₉₃, partial area under the curve to 24 h; Vdss, volume of distribution of steady state.
Carboplatin alone and Taxol in combination with carboplatin. To minimize patient loss from the trial, the carboplatin dose was split, and half administered in successive weeks. Patients received the Taxol before the first or second carboplatin dose by random assignment. The end point of the study was the comparison of the carboplatin AUC and other pharmacokinetic parameters with or without Taxol.

**Eligibility Criteria**

The eligibility criteria included patients with histologically confirmed malignant tumor for which treatment with Taxol and carboplatin was appropriate therapy. Patients were required to have an Eastern Cooperative Oncology Group performance status 0–2, adequate bone marrow function (neutrophils ≥2000/mm³, platelet count ≥100,000/mm³), renal function (creatinine ≤2 mg/dl), and hepatic function (bilirubin ≤2 mg/dl). Pregnant or lactating women were excluded from the trial. Patients with child-bearing potential had to implement adequate contraceptive measures during participation in this study. They had to be free of clinically significant infection and must have signed an approved informed consent.

**Treatment Plan**

Patients were randomized to one of two treatment groups.

**Group A.** Patients received carboplatin as a 30-min i.v. infusion at a dose calculated to produce a target AUC of 3.75 mg-min/ml on day 1. The dose was determined based on the formula of Calvert et al. (12): Dose (mg) = AUC (GFR + 25). This was followed on day 8 by the administration of 175 mg/m² Taxol as a 3-h i.v. infusion, followed immediately by carboplatin at the same dose as on day 1. GFR was estimated as (13):

\[
GFR (\text{ml/min}) = \frac{(140 - \text{age}) \times \text{weight in kgs}}{72 \times \text{serum creatinine}}
\]

for males, and for females GFR is 0.85 times this formula. In this formula, age is in years, weight in kgs, and serum creatinine in mg/dl.

**Group B.** Patients received the two treatments in reverse order.

All patients were premedicated with dexamethasone (20 mg i.v or p.o.) 12 h, 6 h, and 1 h prior to Taxol. Diphenhydramine (50 mg i.v.) and cimetidine (300 mg i.v.) were also given 1 h prior to Taxol.

**Carboplatin Sampling**

Blood samples (8 ml) were obtained at the following times in relation to carboplatin administration: at 0, 15, 30 (end of infusion), 45, 60, and 75 min and 1.5, 2, 2.5, 4.5, 6.5, 12.5, 18.5, and 24.5 h. Serum was harvested from blood samples with one half of the serum centrifuged through an ultrafree filter (Mr cutoff 30,000; Millipore Corporation, Bedford, MA) to obtain a serum ultrafiltrate. The remaining serum and serum ultrafiltrate were stored at −80°C until analyzed for total platinum and free platinum, respectively, by atomic absorption spectrophotometry.

**Taxol Sampling**

Two 8-ml blood samples were collected at the end of the Taxol infusion and at 10 h from the start of infusion. Serum was obtained from the blood samples and stored at −80°C until analyzed for Taxol by a high-pressure liquid chromatography assay.

**Measurements of Carboplatin and Taxol**

Total platinum in serum and ultrafiltrate platinum in serum were measured with a flameless atomic absorption spectrophotometry. Samples were diluted in duplicate with 0.2% nitric acid containing 0.1% (v/v) Triton X-100 and injected (20 μl) onto a Perkin Elmer/Cetus model 3100 atomic absorption spectrometer equipped with an HGA 600 graphite furnace. Platinum concentrations were determined relative to a freshly prepared standard curve for elemental platinum (0.2–4.0 ng). The limit of detection was 0.01 μg/ml (14).

A previously published high-pressure liquid chromatography method was used to quantitate Taxol in serum (15). In brief, a solid-phase extraction procedure was used to extract Taxol from serum. Cephalomannine (final concentration 10 μM) was used as an internal standard. Taxol was eluted from a C₁₈ Bond-Elut extraction column with acetonitrile. The acetonitrile was evaporated, and the dried residue was reconstituted in 150 μl mobile phase. The mobile phase consisted of 45% (v/v) acetonitrile: water, pumped at 1 ml/min through a C₁₈ Hypersil column at 40°C. The fluorescence was detected at 230 nm, with a limit of quantitation of 15 ng/ml.

**Pharmacokinetic Analysis**

Pharmacokinetic analysis of carboplatin was conducted by noncompartmental analysis using the LAGRAN computer program (16), Cl, Vdᵣ, and the terminal elimination half-life (t1/2) (22) in the absence and presence of Taxol were obtained using standard formulas and examined for significant differences with paired t tests. A AUC₁₂₄ was also obtained from the noncompartmental analysis and used for comparisons to the target AUC of 3.75 mg-min/ml.

**RESULTS**

Patient characteristics are shown in Table 1. A total of 13 patients were accrued to the study; however, only 11 patients completed the pharmacokinetic studies.

Fig. 1 illustrates a typical free carboplatin serum concentration-time profile in the absence and presence of Taxol. Minor differences are noted throughout the time course. Pharmacokinetic parameters of carboplatin for all 11 patients are summarized in Table 2. There were no significant differences in any of the measured parameters. These values agreed with those previously reported (17). Variability in the pharmacokinetic parameters was appreciable both in the absence and presence of Taxol, and further indicated by the large 95% confidence intervals (Table 3). The measured AUC₁₂₄ values (3.22 ± 0.762 and 3.40 ± 0.89) were slightly less than the target AUC of 3.75 mg.min/ml used to determine the carboplatin dosage, and were not statistically different from the target AUC (P = 0.064 and P = 0.27, respectively).
Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>Patients entered/evaluable</th>
<th>13/11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>5/8</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>65 (32–79)</td>
</tr>
<tr>
<td>Performance status</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Primary site</td>
<td>Lung</td>
</tr>
<tr>
<td></td>
<td>Head and neck</td>
</tr>
<tr>
<td></td>
<td>Esophagus</td>
</tr>
<tr>
<td></td>
<td>Gastric</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
</tr>
<tr>
<td>Previous treatment data</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Neither</td>
</tr>
<tr>
<td>Body surface area</td>
<td>Median, m² (range)</td>
</tr>
<tr>
<td></td>
<td>1.67 (1.32–1.96)</td>
</tr>
<tr>
<td>Calculated creatinine clearance</td>
<td>Median, ml/min (range)</td>
</tr>
<tr>
<td></td>
<td>71 (33–88)</td>
</tr>
</tbody>
</table>

Similar to pharmacokinetic parameters based on free carboplatin, parameters based on total carboplatin serum concentrations were comparable in the absence and presence of Taxol (Table 3). The mean Taxol plasma concentration at the end of the 3-h infusion was 6.26 ± 0.51 µM, and at 10 h declined to 0.35 ± 0.97 µM, and agreed with previously published peak values (5.9 ± 0.9 µM; Ref. 18).

**DISCUSSION**

Since combinations of carboplatin and Taxol are achieving promising clinical results in several solid tumors, we investigated the potential of a pharmacokinetic drug interaction to explain an apparent alteration in clinical toxicity. Pharmacokinetic interactions between anticancer agents have not been widely investigated. Gianni (19) has reported an inhibitory effect of Taxol on doxorubicin clearance. Taxol is itself cleared 25% less efficiently when administered after, rather than before, cisplatin (10). Our previous clinical trial suggested that the platelet toxicity of carboplatin was reduced with the concomitant administration of Taxol.3

The current study was designed to minimize confounding variables while maintaining acceptable treatment intensity in these patients with advanced cancer. By administering one half of the carboplatin dose in successive weeks (a sufficient washout interval), each patient served as his/her own control. Sequence effects were eliminated by randomizing the order of treatments. Based on the repeated measure study design in the current investigation, and an acceptable 80% power of the t test, a patient sample size of 11 would detect a 25% difference in AUC24 assuming a SD of 0.8, as observed (20). Detection of differences <25%, given an analogous parameter variability would require a larger number of subjects, yet such differences may not be clinically relevant.

The 3-h i.v. infusion schedule is now the most widely used method of Taxol administration. This schedule was used in the original pilot study of Taxol/carboplatin in which we found an unexpectedly low incidence of platelet toxicity.3 The end infusion Taxol concentrations in the current study were consistent with previously published data (19). Therefore, the patients and the treatment schedule seem optimal to detect a pharmacokinetic interaction.

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**Table 2** Pharmacokinetic parameters of free carboplatin obtained in the absence and presence of 175 mg/m² Taxol administered as a 3-h infusion

<table>
<thead>
<tr>
<th></th>
<th>Carboxpletin alone</th>
<th>Carboxpletin and Taxol</th>
<th>Paired t test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>AUC24 (mg-min/ml)</td>
<td>3.40</td>
<td>0.89</td>
<td>3.22</td>
</tr>
<tr>
<td>Cl_r (ml/min)</td>
<td>107.5</td>
<td>34.5</td>
<td>112.8</td>
</tr>
<tr>
<td>Vd (liter)</td>
<td>22.0</td>
<td>5.9</td>
<td>22.1</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>3.50</td>
<td>0.44</td>
<td>3.11</td>
</tr>
</tbody>
</table>

a Harmonic mean half-lives and pseudo-SD are reported and used in the t test (22).

**Table 3** Pharmacokinetic parameters for total carboplatin obtained in the absence and presence of 175 mg/m² Taxol administered as a 3-h infusion

<table>
<thead>
<tr>
<th></th>
<th>Carboxpletin alone</th>
<th>Carboxpletin and Taxol</th>
<th>Paired t test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Cl_r (ml/min)</td>
<td>67.2</td>
<td>28.8</td>
<td>64.6</td>
</tr>
<tr>
<td>Vd (liter)</td>
<td>66.1</td>
<td>45.5</td>
<td>69.0</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>9.5</td>
<td>7.3</td>
<td>8.1</td>
</tr>
</tbody>
</table>

a 95% confidence interval of the difference in carboplatin pharmacokinetic parameter.
b Harmonic mean half-lives and pseudo-SD are reported and used in the t test (22).
The target carboplatin AUC of 3.75 mg-min/ml, calculated using the Calvert formula (12), was achieved when carboplatin was given alone (measured AUC 3.40 ± 0.89 mg-min/ml). The Calvert formula was originally derived from measurements of $^{51}$Cr EDTA clearances to estimate the GFR, whereas in our investigation GFR was based on the Cockcroft-Gault formula (13). Although $^{51}$Cr EDTA clearances provide an accurate measure of GFR, the serum creatinine-based approximation served here as an adequate estimate of GFR for dose selection. It is reported however that following carboplatin treatment, serum creatinine may not predict GFR (12). Therefore, this conclusion may not be valid for subsequent drug cycles. The implication of this observation is for carboplatin dose modification. A dose reduction of carboplatin in response to excessive toxicity in the first cycle should probably be based on a fixed reduction of the first cycle dose, rather than a reaplication of the Calvert formula using serum creatinine estimates of GFR.

In the 11 patients studied here, the AUC of carboplatin was similar whether or not the dose had been preceded by 175 mg/m$^2$ Taxol (3.22 ± 0.76 versus 3.40 ± 0.89 mg-min/ml). Additional pharmacokinetic parameters, including $C_l$, $V_d$, and terminal half-life, were similarly unaffected by Taxol pretreatment. We may reasonably conclude therefore that Taxol has no influence on the disposition of carboplatin at this dose level. Indeed, a clearance interaction would be unlikely since Taxol is primarily eliminated by metabolism, whereas carboplatin’s major route of elimination is renal excretion (17, 21). Unlike cisplatin, plasma protein binding of carboplatin is low, and its displacement from protein binding sites by another drug would not significantly alter unbound drug concentrations (17). The reported interaction of cisplatin and Taxol (10) may perhaps result from such differences. However, for carboplatin/Taxol, it is clear that an apparent clinical interaction does not have a pharmacokinetic basis.

REFERENCES

Evaluation of carboplatin pharmacokinetics in the absence and presence of paclitaxel.
