Phase I Trial of Intravenous Carboplatin and Cyclosporin A in Refractory Gynecologic Cancer Patients

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ABSTRACT

Our objective was to determine the maximum tolerated dose of cyclosporin A (CsA) delivered as a loading dose (LD) and continuous i.v. infusion (CI) in combination with carboplatin in patients with refractory gynecologic cancers. Twenty-nine heavily pretreated patients (25 ovarian epithelial, 2 cervical, and 2 endometrial carcinomas) received 113 cycles of CsA and carboplatin from September 1989 to September 1991. Twenty-four of these 29 carcinomas were strictly defined to be platinum resistant. CsA was administered as a LD escalated from 6 to 10 mg/kg followed by a 24-h CI from 2.5 to 14.5 mg/kg/day. Carboplatin was targeted to an area under the time versus concentration curve (AUC) of 6 mg/ml × min and was not dose escalated. Whole-blood CsA concentrations (fluorescence polarization immunoassay) at the maximum tolerated dose (10 mg/kg LD, 14.5 mg/kg/day CI) ranged from 2.4 to 3.0 μg/ml over 12 h. Estimated median carboplatin AUC, based on calculated carboplatin clearance, was 7.9 mg/ml × min. The dose-limiting toxicity of the combination of CsA and carboplatin was grade 4 thrombocytopenia. Grade 3 or 4 thrombocytopenia occurred in 35% of the patients, which could be explained by the effects of carboplatin (AUC of 6 mg/ml × min) alone. Overall, neutropenia occurred in 24% of the patients and anemia in 17% of the patients. Grade 3 or 4 nausea or vomiting was noted in 10 and 14% of the patients, respectively. Grade 3 hypertension during CsA administration occurred in 14% of the patients. No grade 3 or 4 nephrotoxicity was seen in this trial. Three objective responses were noted: one complete response (11 months) and one partial response (5 months), both in potentially platinum-sensitive patients with platinum-free intervals of only 9 months each. One platinum-resistant patient had a partial response for 21 months. Five additional patients experienced >75% reduction of CA-125 or a return to a normal CA-125 titer. We concluded that whole-blood CsA concentrations of >3.0 μg/ml (as seen when CsA is used as a modulator of multidrug resistance) were not achievable in this combination with carboplatin in this population of heavily pretreated gynecologic cancer patients. However, because CsA is used in this trial as a chemosensitizer in platinum-sensitive tumors and as a chemomodulator of platinum resistance, we targeted a CsA concentration of >1.0 μg/ml, which was achieved. The CsA dose recommended for a Phase II trial of this combination is 10 mg/kg LD and 11.6 mg/kg/day CI, which results in blood CsA concentrations ranging from 1.2 to 1.3 μg/ml over 12 h. Responses in this population of refractory gynecologic cancer patients are unusual, and these encouraging results form the basis for a Phase II trial of this combination.

INTRODUCTION

Epithelial ovarian cancer remains the leading cause of death among gynecologic malignancies, with no significant change in long-term prognosis over the last 30 years, despite an initial excellent 80% response rate to platinum combination chemotherapy. Primary platinum resistance is not common in these tumors. Unfortunately, advanced ovarian cancer patients ultimately relapse and die of disease, leading to 20% 5-year and 15% 10-year survival rates (1). In epithelial ovarian cancer patients, an important factor which underlies such poor results is the development of platinum resistance. Classic mdr (2) appears to play a secondary role in the development of drug resistance in ovarian cancers (2). MDR-1 protein was expressed by only 7% of the ovarian cancers, with no increase in expression after treatment (3). In one report, at the most, 15% of the primary ovarian cancers show diffuse cytoplasmic staining for MDR-1, whereas 47% do so after relevant chemotherapy treatment (4). Since intracellular paclitaxel concentrations can be modulated by the MDR-1 protein (5), with its increasing use, it is anticipated that the development of classic mdr may play a greater role in the resistance mechanisms of epithelial ovarian cancers.

There have been several Phase I studies detailing the activity of the immunosuppressive agent CsA as a modulator of classic mdr (6–11). The agents usually studied in combination with CsA include etoposide, vinblastine, or doxorubicin, since their intracellular concentration is markedly reduced when elevated levels of P-glycoprotein are expressed.

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However, *in vitro* and *in vivo* studies have demonstrated that CsA may have a dual mode of action. CsA is a chemosensitizer of several chemotherapeutic agents in drug-sensitive tumors and a chemomodulator of drug resistance, both with agents that are affected by MDR-1 expression as well as with agents belonging to the platinum family. We have documented enhancement of anthracycline growth inhibition by CsA in both mdr-negative parental and mdr variants of Chinese hamster ovary cell lines (12). In a resistant murine Ehrlich ascites tumor model, CsA can reduce anthracycline resistance; CsA can also enhance anthracycline efficacy in drug-sensitive Ehrlich ascites tumors (13, 14). *In vitro* studies have demonstrated the ability of CsA in combination with cisplatin to overcome resistance in two different human platinum-resistant ovarian cancer cell lines (15-18). *In vivo*, the activity of CsA in both platinum-resistant and platinum-sensitive ovarian cancer xenografts was studied in a subrenal capsular assay (19). The growth of tumors removed from patients with clinically platinum-resistant tumors was inhibited by the combination of cisplatin and CsA when compared to cisplatin alone. Similarly, tumors removed from patients who were platinum sensitive were inhibited more by the combination of CsA and cisplatin than with cisplatin alone. A subsequent Phase I Gynecological Oncology Group trial of CsA and cisplatin was performed in 20 patients with refractory ovarian cancer (20). CsA was administered at a dose of 1-5 mg/kg i.v. by short infusion on days 1 and 2, and cisplatin was delivered at 75 mg/m². The DLT was grade 4 nephrotoxicity, with an encouraging 25% response rate; however, activity in strictly defined platinum-resistant patients was not delineated (20).

Because of the potential activity of CsA as a chemosensitizer as well as a modulator of platinum resistance, it appeared to be rational to study the combination of these compounds in refractory ovarian cancer patients. Carboplatin was chosen to avoid potential overlapping toxicities (including nephrotoxicity) with CsA. No plasma protein binding is evidenced by carboplatin as contrasted to significant binding by cisplatin (21). Since CsA is 90% protein bound (22), it may interfere with cisplatin protein binding and elevate free plasma platinum levels. This potential interaction would be less likely to occur between CsA and carboplatin. A recent report has confirmed the feasibility of administering carboplatin (250 mg/m²) in combination with CsA (8.8 mg/kg/day for 36 h) to refractory cancer patients (18). Seven ovarian cancer patients were included in that trial; three of these patients, all with potentially platinum-sensitive disease, responded to the combination.

CsA is an attractive drug to study as a chemomodulator because its effects do not appear to be confined to tumors that express MDR-1. Other advantages include significant experience with this drug in humans, its lipophilicity, and excellent tissue penetration (23, 24). In addition, the *in vitro* effective dose of CsA as a chemosensitizer is as low as 0.5 μg/ml, whereas the minimal effective dose for reversal of mdr is 1.0 μg/ml (7, 12, 25). Both of these are achievable and reasonably well-tolerated blood concentrations compared to target blood concentrations of verapamil, which were not clinically achievable (26).

**PATIENTS AND METHODS**

**Patient Selection.** Patients with refractory gynecologic cancer were eligible for participation if they had recurrent or persistent disease after primary therapy and if no effective salvage regimen existed. Patients were required to have an Eastern Cooperative Oncology Group (27) performance status of ≤2 and a life expectancy of >2 months. They were required at initiation of each cycle to have adequate bone marrow function (WBC ≥ 3000/mm³, platelet count ≥ 100,000/mm³), adequate renal function (serum creatinine < 2.0 mg/dl), and hepatic function (total bilirubin < 2.0 mg/dl). Patients with known HIV serum positivity or with concurrent life-threatening illness were ineligible for the study. Drugs which were substantiated to interact adversely with CsA were discontinued prior to enrollment (24, 28). All patients gave informed consent to participate in the study; this protocol (#5317) was approved by the Yale University Human Investigations Committee in September 1989.

**Study Design.** All patients were admitted to the Yale-New Haven Medical Center for treatment. The LD of CsA was administered i.v., and the 24-h CI of CsA was begun 1 h later. During this hour, carboplatin was infused over 30 min, and the antiemetics were administered. Ondansetron was not available at the time of this Phase I trial. The Calvert formula (29) was utilized to calculate the carboplatin dose which was targeted to an AUC of 6 mg/ml X min. Creatinine clearance (substituted for glomerular filtration rate) was calculated from a 24-h urinary collection or estimated from the formula based on age, weight, and serum creatinine (30). If the initial measurement of creatinine clearance was <45 ml/min, timed urinary collections were obtained thereafter (30). This is a dose-seeking study of CsA, with the carboplatin dose remaining constant at a targeted AUC of 6 mg/ml X min. Cycles were administered every 28 days.

Because the half-life of both total and ultrafiltered plasma platinum concentrations after i.v. injection of 300 mg carboplatin/m² revealed biphasic decay with an α half-life of 16 min and a β half-life of 17.6 h (21), we designed the CsA LD and 24-h CI to cover the time period of bioavailability of platinum. Thus, an initial LD of 6 mg/kg over 2 h was chosen, and the CI dose was 2.5 mg/kg over 24 h. Furthermore, CsA persists in body tissues for a considerable period after the infusion is discontinued because of its lipid solubility (24). The starting dose for the CsA LD and CI was based on previous pharmacokinetic data derived from organ transplant patients. Organ transplant patients tolerate an i.v. LD of 5-6 mg CsA/kg (23, 31) with CI doses of 2-4 mg/kg/day (22) at the time of transplant surgery, a route of delivery which improves bioavailability without increasing toxicity (23). The initial design was to keep the LD the same but increase the CI dose at incremental levels of 20% until the MTD was reached. However, the protocol was amended during the trial, as described in detail below.

Three new patients were assessed at each dose level and each was dose escalated unless a DLT was observed. The common toxicity criteria of the National Cancer Institute was used to grade toxicities. DLT was defined as a nadir WBC < 750/mm³, a nadir platelet count < 30,000/mm³, or recovery to < 3,000/mm³ WBCs or < 100,000/mm³ platelets by 6 weeks after infusion of drugs, a nonhematological toxicity of >grade
3, or a toxicity of grade 2 persisting longer than 6 weeks of the following types: infection, hypertension, pulmonary, cardiac, neurocerebellar, fever, allergy, or creatinine. Granulocyte colony-stimulating factor was not available for this trial. If a hematological DLT was observed, the subsequent dose of CsA was delivered at the immediate lower dose level. The MTD was defined as that dose that produced DLT in >50% of the new patients at that dose level. If one of three new patients on a given dose level experienced a DLT, three additional patients were treated at that same dose.

The protocol was amended according to clinical experience and analysis of blood CsA levels at the earlier doses. The first three patients experienced serious hypertension, tremors, flushing, vomiting, and/or hypotension during the administration of the LD (6 mg/kg given as a 2-h infusion), which most likely represented previously reported acute toxicities from the CsA vehicle cremaphor (23). We thought this resulted from the LD rate of 3 mg/kg/h rather than the total LD. Therefore, the LD rate was decreased by 50%, so that 6 mg/kg was delivered over 4 h, and acute toxicity was greatly reduced. Whole-blood CsA concentrations (see below) at the first three dose levels (Cs of 2.5, 3.0, and 3.6 mg/kg/day) did not achieve the target blood concentration of 1.0 μg/ml, nor were CsA concentrations maintained during the subsequent infusion. Interim pharmacokinetic analysis led to a LD change to 8 mg/kg over 5½ h (1.5 mg/kg/h) for the next three dose levels (Cs of 4.5, 5.4, and 6.5 mg/kg/day); the CI dose continued to be escalated by 20%/dose level. Again, whole-blood CsA concentrations indicated that although the peak CsA concentration was improved, the CsA concentrations were not maintained during the subsequent infusion. Therefore, the LD was modified again to 10 mg/kg over 5 h, which represents a dose rate increase to 2 mg/kg/h, and the CI was subsequently increased by increments of 50% starting at the next dose level (9.7 mg/kg/day). The initial period of infusion was over 5 h to achieve and sustain target CsA concentrations as rapidly as possible without serious acute toxicity. Although not strictly a LD, this initial period will be referred to as such in this report.

Patient status was evaluated before each course of chemotherapy. A complete response was defined as complete disappearance of all known lesions; a partial response was defined as at least a 50% decrease in the product of the two largest perpendicular diameters of measurable lesions; stable disease required <25% increase or a 50% decrease in the products of the two largest perpendicular diameters of measurable lesions; and progressive disease was a >25% increase in the product of the two largest perpendicular diameters of any measurable lesion or the appearance of a new lesion.

CsA Pharmacokinetics. Whole-blood concentrations of CsA were measured before the CsA CI and at 4 and 12 h into the infusion. CsA concentrations were measured using a fluorescence-polarization immunoassay utilizing a monoclonal antibody which detects parent CsA compound only (TDX; Abbott Laboratories, North Chicago, IL). Blood samples were drawn into an EDTA-containing tube via a separate venipuncture or heparin lock i.v., making sure that it was not the line through which CsA was being or had been administered.

### Table 1: Toxicities of Phase 1 CsA/carboplatin trial (n = 29 patients)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1 or 2</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11</td>
<td>38</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>45</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>19</td>
<td>66</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Flushing</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Tremors</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Estimation of Carboplatin Clearance and Carboplatin AUC. Because carboplatin clearance was not measured, carboplatin clearance for each patient was calculated from the age, weight, and serum creatinine (32), and the carboplatin AUC was estimated by dividing the total dose of carboplatin delivered in that cycle by the calculated carboplatin clearance (32).

### RESULTS

#### Patient Characteristics. Twenty-nine patients (25 with ovarian epithelial carcinomas, 2 with cervical carcinomas, and 2 with endometrial carcinomas) received 113 cycles of CsA and carboplatin therapy from September 1989 to September 1991. This regimen comprised between second and sixth line therapy for these patients who had received between 1 and 3 prior platinum-based therapies. These 29 patients received between one and nine cycles per patient (median, 3) and between one and four dose levels per patient (median, 1). A platinum-resistant tumor in this trial was defined as one which progressed on or within 6 months of platinum-based therapy (33). By this strict definition, 24 of 29 patients in this Phase I trial had platinum-resistant tumors. Tumors that had initially responded to platinum-based therapy, but progressed after a platinum-free interval of 6 months, were deemed potentially platinum sensitive. Four of five of these tumors had short platinum-free intervals of ≤9 months.

#### Toxicities. All 29 patients were evaluable for toxicity (Table 1). Hematological toxicities were common. In fact, grade 3 or 4 thrombocytopenia occurred in 35% of the patients, neutropenia in 24%, and anemia in 17%. Grade 3 or 4 nausea or vomiting was noted in 10 and 14% of the patients, respectively. Hypertension during CsA infusion requiring medications (grade 3) involved 14% of the patients; 75% of these patients had a history of hypertension. This toxicity should be separated from the acute toxicities felt to be secondary to cremaphor (23), in which an acute rise or fall in blood pressure was part of a syndrome of tremors, flushing, and/or vomiting. Hyperbilirubinemia was not noted in any of the patients in this trial.

The MTD was reached at a LD of 10 mg CsA/kg over 5 h and a 24-h CI of 14.5 mg CsA/kg. The DLT was grade 4
thrombocytopenia, which was seen in three new patients at this dose level. Other grade 3 toxicities at the MTD included neutropenia in three patients and anemia, hypertension, and nausea in one patient each.

Although the incidence of severe thrombocytopenia at this dose level fulfilled the criteria for the definition of MTD, when analyzed specifically, the incidence of grade 3 or 4 thrombocytopenia does not appear to be closely related to dose level. Among 16 patients who received a LD of 6 or 8 mg CsA/kg and CI doses ≤6.5 mg CsA/kg, three incurred grade 3 and two incurred grade 4 thrombocytopenia. Among the 13 patients who received a LD of 8 or 10 mg CsA/kg and CI doses >6.5 mg CsA/kg, one patient experienced grade 3 and four patients experienced grade 4 thrombocytopenia. There was no significant difference using the two-tailed Fisher’s exact test in the incidence of grade 3 or 4 thrombocytopenia between the two groups. This lack of difference could not be explained by a predominance of more heavily pretreated patients among those who received lower LDs or CI doses ≤6.5 mg CsA/kg.

Estimation of the carboplatin AUC according to the method of Chatelut et al. (32) yielded a median AUC of 7.9 mg/ml × min (range, 5.5–11.0) for the whole group, which was higher than the AUC of 6 mg/ml × min targeted by the Calvert formula (29). For those 10 patients who experienced grade 3 or 4 thrombocytopenia, the carboplatin AUC was estimated for the median carboplatin AUC in those patients who did not incur grade 3 or 4 thrombocytopenia. The median carboplatin AUC of 9.2 (range, 5.7–11.0) in those patients who incurred this toxicity appeared to be higher than the median estimated carboplatin AUC of 7.4 mg/ml × min (range, 5.5–10.2) in those patients who did not incur this toxicity.

**Whole-Blood CsA Concentrations.** Whole-blood CsA concentrations (mean values given when available) are detailed in Table 2. CsA concentrations were available for the majority of dose levels. It should be noted that within each dose level, variability in CsA concentrations existed among individual patients, presumably due to their differing rates of metabolism of CsA. At early dose levels, the target CsA concentration of 1.0 μg/ml was not reached, nor were these concentrations maintained during the CsA infusion. When CsA was delivered as an 8 mg/kg LD followed by a 4.5 mg/kg CI, the peak whole-blood CsA concentration was 1.0 μg/ml; however, during the CsA infusion, the CsA concentrations fell to approximately 0.7 μg/ml. When a 10-mg CsA/kg LD and 9.7 mg/kg CI was delivered, CsA concentrations appeared to be maintained at 1.0 μg/ml, and the MTD was not achieved. At the MTD, the CsA concentrations remained stable during the infusion at the time points measured, measuring between 2.4 and 3.0 μg/ml.

<table>
<thead>
<tr>
<th>CsA LD (mg/kg)</th>
<th>6</th>
<th>6</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA CI (mg/kg)</td>
<td>2.5</td>
<td>3.0</td>
<td>3.6</td>
<td>4.5</td>
<td>9.7</td>
<td>11.6</td>
</tr>
<tr>
<td>Time, h</td>
<td>1 h</td>
<td>0.8</td>
<td>0.8</td>
<td>0.9</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Time, 4 h</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Time, 12 h</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>1.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

* LD infused over 2 h for the first three patients, subsequently over 4 h.
* LD infused over 5/4 h.
* LD infused over 5 h.
* Time after start of CI.

**DISCUSSION**

We chose to study carboplatin (a drug whose concentration is not modulated by MDR-1) in combination with CsA. Thus, the known mechanism of alteration of pharmacokinetics of mdr-related agents by CsA [attributed to the presence of P-glycoprotein in normal tissues such as biliary tract and proximal renal tubules (25)] would appear not to play a role in our trial. Of particular concern was the possibility that nephrotoxicity of CsA may reduce the clearance of carboplatin, leading to excessive toxicity. We carefully measured creatinine clearance monthly and detected no grade 3 or 4 nephrotoxicity in this trial. This is in contrast to the findings of Morgan et al. (18) where grade 3 nephrotoxicity determined the MTD in a Phase II trial of carboplatin (250 mg/m²) and CsA (9.5 mg/kg/day for 36 h). The dose of carboplatin in our trial was targeted to an AUC of 6 mg/ml × min, taking into account changes in creatinine clearance. Although we cannot rule out an increase in the delivered AUC of carboplatin in the presence of CsA, a recent preliminary report on the pharmacokinetic study of CsA, paclitaxel, and

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*Table 2: Whole-blood CsA levels determined using fluorescence-polarization immunoassay (μg/ml)*

<table>
<thead>
<tr>
<th>Time after start of CI.</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.8</th>
<th>1.0</th>
<th>1.3</th>
<th>2.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA LD (mg/kg)</td>
<td>2.5</td>
<td>3.0</td>
<td>3.6</td>
<td>4.5</td>
<td>9.7</td>
<td>11.6</td>
<td>14.5</td>
</tr>
</tbody>
</table>
carboplatin suggested that the carboplatin AUC was not increased in the presence of CsA (34).

The DLT was thrombocytopenia, which is a marker of carboplatin activity rather than that of CsA. Indeed, we find that the incidence of grade 3 or 4 thrombocytopenia appears not to be closely related to the dose of CsA, although this observation may be limited by small numbers. Five of 16 patients (31%) who received a CsA LD of 6 or 8 mg/kg and a CI of 4.6-18 mg/kg/day (8, 11) measured both the parent CsA compound and metabolites, whereas our assay only determines parent compound. This could account for an approximate 2-fold difference in CsA concentrations observed. Since we sought to use the dual action of CsA in both platinum-sensitive and platinum-resistant tumors, we targeted a whole-blood CsA concentration of at least 1.0 µg/ml, which we achieved at both the Phase II dose and the MTD.

Responses in a Phase I trial of heavily pretreated gynecologic cancer patients are rare. It is gratifying to see both a response in a patient with strictly defined platinum resistance and in two patients who had potentially platinum-sensitive tumors but who had short platinum-free intervals. The duration of responses was also unusual in this setting. Thus, we were encouraged by these results and have performed a Phase II trial of this combination of carboplatin and CsA in refractory ovarian cancer patients.

ACKNOWLEDGMENTS

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Phase I trial of intravenous carboplatin and cyclosporin A in refractory gynecologic cancer patients.

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