Modulation of Platinum Sensitivity and Resistance by Cyclosporin A in Refractory Ovarian and Fallopian Tube Cancer Patients: A Phase II Study

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ABSTRACT

Our objective was to assess the activity of cyclosporin A (CsA) used as a chemomodulator of carboplatin in refractory ovarian and fallopian tube cancer patients. Fifty-one patients (47 epithelial ovarian, 1 ovarian mixed mesodermal tumor, and 3 fallopian tube carcinomas) were enrolled in a prospective Phase II trial of CsA and carboplatin. CsA was infused as a loading dose of 10 mg/kg over 5 h, followed by carboplatin infused over 30 min at an AUC of 6 mg/ml × min, then a 24-h continuous infusion of 11.6 mg/kg CsA. The patients received this protocol as second- to sixth-line therapy and had received between 1 and 3 prior platinum-based regimens. Eight patients received more than six cycles every 28 days, 34 patients received three to six cycles; and 9 patients received only one or two cycles. Thirty-eight patients were evaluable for objective response, and in an additional nine patients, CA-125 was the only marker of response. Four patients had no marker of disease. Of evaluable patients, 74% were platinum resistant. There were nine objective responses (one complete and eight partial responses) for an overall response rate in evaluable patients of 24%, with a median duration of response of 7 months (range, 3–38+ months). No responses were seen in patients who had received only one or two cycles of therapy. Among the strictly defined platinum-resistant patients, there was an overall 14% response rate, including one partial response seen after five prior regimens of chemotherapy including paclitaxel, and one ongoing complete response for 38+ months. Among the rest of the patients (those who were potentially platinum sensitive), there was an overall 50% response rate; four of five responses were seen in patients with a platinum-free interval of <24 months, with only one response seen in a patient with a platinum-free interval of >24 months. Of evaluable patients, 34% had stable disease for a duration of 3–19 months. The most common grade 3 or 4 toxicity, thrombocytopenia, was seen in 22% of the patients. Hypertension, which responded to medications, was seen in 18% of the patients during the CsA infusion. We concluded that this CsA/carboplatin regimen is active in potentially platinum-sensitive patients and compares well with the expected response rate of 30% in patients with a platinum-free interval <24 months who are retreated with platinum. Moreover, this regimen had modest but real activity in platinum-resistant patients.

INTRODUCTION

Although epithelial ovarian cancer remains one of the few solid tumors that is chemosensitive, with an initial 80% response rate to platinum combination chemotherapy, long-term survival still remains a major problem. Favorable prognostic factors for long-term survival in patients with epithelial ovarian cancer have been identified and include the use of platinum-based chemotherapy in stage III patients (1). The 20% 5-year survival in advanced ovarian cancer patients however has remained without change for 30 years, and 10-year survivals after initial platinum combination chemotherapy remain a disappointing 15% (2).

An important factor which underlies such poor results is the development of platinum resistance. Classic mdr² appears to play a secondary role in the development of drug resistance in ovarian cancers, but this may change with inclusion of paclitaxel in the first-line therapy of advanced ovarian cancer patients. A prospective randomized trial of the comparison of cisplatin and paclitaxel to the standard regimen of cisplatin and cyclophosphamide as primary therapy for advanced ovarian cancer patients demonstrated a significant overall survival advantage for the cisplatin/paclitaxel arm (3). Use of the single agent paclitaxel in a Phase II trial of 47 patients with refractory ovarian cancer led to a 30% response rate (1 complete and 11 partial responses), with a median duration of 6 months (4). Most notable in that Phase II trial was a 24% response rate in strictly defined platinum-resistant patients. This level of activity had not been previously reported in such patients. The patients in that trial were heavily pretreated, having received between one and three prior platinum-based regimens (4).

Other active drugs available for the treatment of refractory ovarian cancer patients include hexamethylmelamine, which yields a 20% response rate but is probably not active in strictly defined platinum-resistant disease (5); ifosfamide with a 20% response rate and modest activity in platinum-resistant disease (5, 6); and iproplatin with a 26% response rate in platinum-sensi-

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2 The abbreviations used are: mdr, multidrug resistance; CsA, cyclosporin A; AUC, area under the time versus concentration curve.
tive patients and a 12% response rate in patients who are defined to be platinum resistant based on the failure of their tumors to achieve a complete response during platinum treatment (7).

Attempts have been made to address this problem using chemosensitizers to either sensitize tumors to standard chemotherapeutic agents or reverse drug resistance or both. CsA is well accepted as an effective modulator of classic mdr (8–10), and may play an important role in the future in ovarian cancer patients whose disease is refractory on the basis of development of mdr secondary to exposure to paclitaxel. Furthermore, CsA is an agent capable of acting as a chemosensitizer of platinum in platinum-sensitive tumors and as a chemomodulator of platinum resistance (11–14). This was the rationale for our Phase I study of the combination of carboplatin and CsA in refractory gynecological cancer patients (15). On the basis of our encouraging results (15), we have performed a Phase II trial of carboplatin and CsA.

In this study, a platinum-resistant tumor was defined as a tumor that had progressed on platinum-based therapy or within 6 months of previous platinum-based therapy (16). Those who had an initial response to platinum-based therapy and a recurrence after a platinum-free interval of 6 months were designated potentially platinum sensitive. Patients who had potentially platinum-sensitive tumors were subdivided by duration of platinum-free interval, since previous studies have documented that increased response rates were correlated with prolonged platinum-free intervals (17). Ondansetron was utilized in this Phase II trial; it was anticipated that this medication would ameliorate the toxicity of nausea and vomiting seen during the Phase I trial, at which time ondansetron was not available.

PATIENTS AND METHODS

Patient Selection. Fifty-one eligible patients were entered into this Phase II trial from July 1991 to May 1994; all were treated at Yale-New Haven Medical Center. The eligibility criteria were the same as those for the Phase I trial (15). No patient who had been enrolled in the Phase I trial was included in the present trial. Informed consent was given by all patients (Yale University Human Investigations Committee protocol 5317). Forty-seven patients had epithelial ovarian cancer and three patients had fallopian tube adenocarcinomas. One patient undergoing a pathology review was found to have an ovarian mixed mesodermal tumor, but because the biology of this tumor was similar to those of the remaining patients, this patient was not excluded from this trial. No exclusions were made based on the number of previous chemotherapy regimens received by the patients. This population of patients was heavily pretreated, having received a mean of 1.8 prior therapies: 31 patients received the regimen as second-line, 8 as third-line, 7 as fourth-line, 1 as fifth-line, and 4 as sixth-line therapy. They received between one and three prior platinum-based therapies. Six patients died within 2–4.5 months after entry into the study. In addition, 10 patients were believed to have disease so advanced on presentation that they received neoadjuvant chemotherapy rather than an attempt at standard primary surgical debulking (18, 19).

Thirty-eight patients were evaluable for objective response, and there were an additional nine patients for whom CA-125 was the only marker of response. Five of the nine patients had undergone debulking surgery for their persistence/recurrence and had no residual marker of disease, except for their elevated CA-125 levels. Four of the nine patients had elevated, rising CA-125 levels but had normal diagnostic imaging studies and physical examinations. The remaining four patients who had no marker of disease by physical examination, diagnostic imaging studies, or serological markers had biopsy-documented disease that was debulked just before entry into this protocol.

Clinical Protocol. The Phase II i.v. loading dose for CsA was 10 mg/kg over 5 h at a dose rate of 2 mg/kg/h. This was followed by a 1-h interval before the initiation of the 24-h continuous infusion of 11.6 mg/kg CsA. During this interval, carboplatin was delivered over 30 min to a target AUC of 6 mg/ml × min based on the Calvert formula (20). The initial creatinine clearance (substituted for glomerular filtration rate) was measured by a 24-h urinary collection, and, if >45 ml/min, subsequently estimated by a creatinine clearance formula based on age, weight, and serum creatinine (21). Patients were hospitalized overnight for each treatment course, which was delivered every 28 days.

Toxicity was graded using the National Cancer Institute Common Toxicity Criteria. Dose reductions in the continuous infusion dose of CsA by 20% was necessary in three patients because of grade 4 thrombocytopenia or a grade 3 decrease in creatinine clearance. Granulocyte colony-stimulating factor was not included in this regimen. Performance status was evaluated using the Eastern Cooperative Oncology Group criteria (22).

Patients were evaluated for response every 28 days prior to each course of chemotherapy. Complete response was defined as a total disappearance of all disease. Partial response was defined as ≥50% reduction in the sum of the products of the perpendicular diameters of the measurable disease without the appearance of any new lesions. Stable disease was defined as growth by <25% or shrinkage of <50% without the appearance of new lesions. Progressive disease was defined as ≥25% increase in disease or the appearance of new lesions.

Although not commonly accepted as an indicator of response to therapy, it has been suggested by some that the CA-125 response by strict definition gives similar conclusions as objective criteria (23). In this study, only objective responses were counted; analysis of the CA-125 curves are included as supporting data and to give some indication as to the outcome of those nine patients evaluable using CA-125 alone.

RESULTS

Patients. Two hundred thirty-four cycles were delivered to 51 patients. Eight of 51 patients received more than six cycles of CsA and carboplatin, and 34 patients received between three and six cycles of the combination. Nine patients received only one or two cycles, which included three patients who were treated with neoadjuvant chemotherapy for their advanced disease (18–19). This regimen was given for their platinum-resistant disease after one, two, and five prior therapies and was discontinued secondary to progressive disease. Among the remaining six patients, five were platinum resistant and had received between one and five prior therapies. This regimen was discontinued secondary to progressive disease in two patients, delayed (2 weeks) secondary to thrombocytopenia in two patients, and prolonged (4–6 weeks) delays unrelated to the ther-
apy in two patients. Four of the nine patients died within 2–4.5 months after entry into the study. Of the 38 evaluable patients in this trial, 74% were platinum resistant. The demographic and clinical characteristics of the patients and responders are presented in Table 1.

**Responses.** When the 38 evaluable patients were analyzed, there was a 24% response rate. There was one complete response and eight partial responses for a median duration of 7 months, with a range of 3–38+ months. A decrease in CA-125 was observed either before or concomitant with all objective responses. Six CA-125 values fell to the normal range and one each by 98%, 73%, and 47%. Of these evaluable patients, 34% had stable disease for a duration of 3–19 months. Among the 10 potentially platinum-sensitive patients, there was an overall 50% response rate. Although the numbers are small, when responses were analyzed with respect to duration of platinum-free intervals, the responses appear to be more common in patients with a short platinum-free interval. Two of three patients with a platinum-free interval of 0–12 months responded as did two of three patients with a platinum-free interval of 13–24 months. Thus, four of the five responses were seen in those with a platinum-free interval of <24 months, with only one response seen in four patients with a platinum-free interval of >24 months.

Among the 28 platinum-resistant patients, there was an overall 14% response rate. Notable among these responses is: (a) an ongoing complete response for at least 38 months and (b) a partial response seen after five prior therapies, including paclitaxel.

Among the nine patients who were evaluable using CA-125 only, four patients remained free of disease with a CA-125 drop of >50% or to normal levels for 6, 11, 19, and 28+ months. Four patients remained free of disease with no significant change in the CA-125 level and one patient had progressive disease on treatment. The four patients who had no marker of disease remained free of disease for 8, 9, 18+, and 23 months. The duration that these unevable ovarian cancer patients have remained disease free, especially those for 18+, 19, 23, and 28+ months, is notable, but may reflect the natural history of the disease.

The median time to response was after two cycles of CsA and carboplatin therapy, with the mean time (in cycles) to response being after 2.7 cycles of this regimen. No responses were noted in patients who received two or less than two cycles of therapy. If the analysis is limited to those evaluable patients who received more than two cycles of therapy, there was a 31% overall response rate to the combination of CsA and carboplatin. In these patients there was a 56% response rate among the platinum-sensitive patients and a 20% response rate among the platinum-resistant patients.

**Toxicities.** All 51 patients were evaluable for toxicity analysis (Table 2). The grade 3 or 4 toxicities were less in this Phase II trial than those seen in the Phase I trial (15), with the exception of hypertension which was not related to the CsA dose in the Phase I trial and may reflect hypersensitivity to the vehicle (cremaphor). In line with our earlier experience, grade 3 or 4 thrombocytopenia was the most common toxicity seen in 22% of the patients. The majority (8/11) of these significant thrombocytopenic events were transient and did not result in treatment delays. When treatment delays were experienced, they were of 3-, 14-, and 21-day duration. These 11 patients were not more heavily pretreated than the study population, having received a mean of 1.4 prior therapies. Hypertension requiring medications (grade 3) during CsA infusion was seen in 18% of the patients. This toxicity was more commonly seen in patients with an underlying history of hypertension and was easily controlled during CsA infusion by medications. Nausea and vomiting were significantly ameliorated with the use of ondansetron, with only one grade 3 nausea seen in this trial. Hyperbilirubinemia was not noted in any of the patients in this trial. Grade 3 or 4 neutropenia occurred in 10% of the patients, grade 3 anemia in 8%, and grade 3 leukopenia in 6%. The only grade 4 toxicities seen in this trial were three patients with thrombo-

**Table 1** Demographic and clinical characteristics of all patients and responders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 51)</th>
<th>Potentially platinum-sensitive (n = 5)</th>
<th>Platinum-resistant (n = 4)</th>
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<tr>
<td>Median ages, yr (range)</td>
<td>62 (34–83)</td>
<td>51 (43–68)</td>
<td>68 (45–83)</td>
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<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>28</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>21</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
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<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
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<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Previous chemotherapy</td>
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<td></td>
</tr>
<tr>
<td>regimens</td>
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<td></td>
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<tr>
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<td>5</td>
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</tr>
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<td>8</td>
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<td>1</td>
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<tr>
<td>Mean</td>
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<td>1.0</td>
<td>2.5</td>
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<tr>
<td>Range</td>
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<td>(1–5)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Toxicities of CsA/carboplatin (n = 51 patients)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1 or 2</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
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<tr>
<td>Thrombocytopenia</td>
<td>29</td>
<td>57</td>
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<tr>
<td>Leukopenia</td>
<td>35</td>
<td>69</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>27</td>
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<tr>
<td>Anemia</td>
<td>22</td>
<td>43</td>
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<tr>
<td>Nausea</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>20</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>2</td>
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<td>Creatinine clearance</td>
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<td>Weight loss</td>
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<td>12</td>
</tr>
<tr>
<td>Headache</td>
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<td>8</td>
</tr>
<tr>
<td>Tremors</td>
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<td>1</td>
</tr>
<tr>
<td>Flushing</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*a Two additional patients with a history of hypertension had congestive heart failure (one patient) or tachycardia (one patient), each responded to medical therapy.*
cytopenia and two patients with neutropenia. There were treatment delays of 1–2 weeks in 14 (28%) patients, with 8 (57%) due solely to a WBC count < 3.0 × 10^9/mm³. The other causes of treatment delays were secondary to thrombocytopenia < 100,000/mm³ (three patients) or a combination of thrombocytopenia and leukopenia (three patients).

The responders did not suffer excessive toxicity when compared to the rest of the group. There were no grade 4 toxicities. Grade 3 thrombocytopenia and neutropenia were seen in two patients each. One patient had grade 3 hypertension. The incidence of grade 1 or 2 thrombocytopenia, leukopenia, neutropenia, and anemia in the responders were also not different from the nonresponders.

**DISCUSSION**

The results reported in this Phase II trial of heavily pretreated ovarian cancer patients are similar to those of the Phase II trial of the single agent paclitaxel in a comparable group of patients (4). The 24% response rate in this trial is slightly less than the 30% response rate seen in the paclitaxel trial, and the responders in the paclitaxel trial had been more heavily pretreated. In each study, one complete response was noted and the remaining were partial responses. The median duration of 7 months was similar to that of the 6 months seen in the paclitaxel trial. The time in cycles to response was also similar (a mean of 2.7 cycles in this trial compared to a mean of 3.0 cycles in the paclitaxel trial).

An important advantage of paclitaxel is its superior activity (24% response rate) in strictly defined platinum-resistant patients (4). We have defined platinum resistance in the same manner and show a 14% response rate in strictly defined platinum-resistant patients from our combination.

Among potentially platinum-sensitive patients, the expected response rate for retreatment with a platinum-based agent in patients who have a platinum-free interval of ≥24 months is approximately 30% (17). Our reported response rate of 50% is thus almost twice that expected from the literature. These findings would lend support to the activity of CsA as a chemosensitizer of platinum as well as having modest but real activity with carboplatin in strictly defined platinum-resistant ovarian cancer patients.

For this trial, we chose a target AUC of 6 mg/ml × min for carboplatin in combination with CsA, which slightly exceeds the mean target AUC value of 5 mg/ml × min for single-agent carboplatin recommended for previously treated ovarian cancer patients (20). An AUC of 6 mg/ml × min was the maximum carboplatin dose found to lead to manageable hematological toxicity, when used as a single agent, in previously treated patients (20).

Although an increase in free plasma platinum levels may have contributed to our results, several lines of evidence make this unlikely. (a) The activity seen in platinum-sensitive patients is significantly higher than that expected of retreatment of a similar group of platinum-sensitive patients even with the inclusion of high-dose platinum (17). The role of dose intensity of platinum is controversial; any positive effect of dose intensity of platinum may be restricted to patients who have small volume platinum-sensitive disease only (24), which is not the case in this Phase II trial. Moreover, the probability of response from carboplatin in ovarian cancer patients does not increase at AUC values >5 mg/ml × min (25). (b) Our activity in platinum-sensitive patients is seen preferentially in patients who have a short platinum-free interval, although our observation may be limited by small numbers. If our activity is secondary to dose intensity of platinum, we would expect to see an effect predominantly among patients with a long platinum-free interval. (c) We are not aware of any data that would suggest that dose intensity would overcome strictly defined platinum resistance; in fact, salvage i.p. cisplatin which delivers extremely high doses of platinum had essentially no activity in patients who appear to be platinum resistant (5, 24). (d) Preliminary results of a trial looking at the combination of CsA, paclitaxel, and carboplatin indicate that carboplatin kinetics in plasma were not affected by CsA (26).

We are encouraged by the results of this Phase II trial. The results may reflect the apparent dual activity of CsA, acting both as a chemosensitizer of carboplatin and as a means to overcome strictly defined platinum resistance in this heavily pretreated group of epithelial ovarian cancer patients. Inclusion of colony-stimulating factors which support granulocyte or platelet (when available) function should considerably ameliorate the thrombocytopenia and neutropenia noted with this combination and allow us to deliver the regimen on schedule.

An obvious extension of our findings, one we plan to explore, would be a study of the combination of CsA and paclitaxel. This would target the group of ovarian cancer patients who have either intrinsic or acquired mdr by taking advantage of the well-accepted ability of CsA to reverse mdr. It is not known whether CsA can sensitize the activity of paclitaxel in drug-sensitive tumors. It is anticipated that paclitaxel AUCs may be significantly increased by that combination (27, 28), despite the preliminary finding that CsA does not alter the pharmacokinetics of paclitaxel (26); therefore, careful consideration of the dose of paclitaxel in combination with CsA would be prudent. The significantly more potent reverser of mdr, the nonimmunosuppressive, nonnephrotoxic CsA analogue PSC-833 (29), could be explored for its activity in combination with paclitaxel or carboplatin. However, in preliminary studies, replacing CsA with PSC-833 did not result in chemosensitization by PSC-833 of etoposide activity in murine drug-sensitive tumors (30) as was shown for CsA (31). We believe the activity of CsA in this trial may result from two modes of action and would be concerned that by eliminating one, the chemosensitizing effect of CsA on drug-sensitive tumors, the therapeutic results in ovarian cancer patients could be compromised.

**ACKNOWLEDGMENTS**

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