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ORIGINAL ARTICLE

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Phase II trial of carboplatin and infusional cyclosporine in platinum-resistant recurrent ovarian cancer

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Abstract *Purpose*: To determine the response rate to 26-h continuous infusion cyclosporine A (CSA) combined with a fixed dose level of carboplatin (CBDCA) in patients with recurrent ovarian cancer, and to determine the effect of CSA on the pharmacokinetics of CBDCA. *Experimental design*: To examine the effect of duration of CSA exposure on reversal of CBDCA resistance, clonogenic assays were performed in vitro in platinum-resistant A2780 cells. CBDCA (AUC 4) with CSA repeated every 3 weeks was then administered to patients on this phase II study. Pharmacokinetics of CSA and CBDCA were determined in a subset of patients. *Results*: Preincubation of platinum-resistant A2780 cells with CSA reversed CBDCA resistance in a concentration-dependent and time-dependent manner. A group of 23 patients received 58 courses of CBDCA/CSA therapy. One partial response was observed. Eight patients achieved disease stabilization. Toxicity was similar to that observed in our previous phase I study and consisted of myelosuppression, nausea, vomiting, and headache. The mean ± SD end-of-infusion CSA level (HPLC assay) was 1253 ± 400 μg/ml. The pharmacokinetic studies suggest that CSA does not increase CBDCA AUC. *Conclusions*: Steady-state levels of > 1 μg/ml CSA (HPLC assay) are achievable in vivo. Modest partial reversal of platinum resistance (in one patient with an objective response and in eight patients with stable disease noted) is achievable in vivo in patients pretreated with CSA. This phenomenon is not explained by alterations in CBDCA pharmacokinetics.

Keywords Chemomodulation · Chemotherapy · Phase II

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Introduction

The development of platinum analogues has altered strategies for the treatment of advanced epithelial ovarian cancer over the past 20 years, changing the outlook for these patients from that of virtual incurability to the possibility of long-term disease control with aggressive surgery and chemotherapy. Patients with recurrent or persistent disease following initial therapy for whom, however, there is no proven curative approach, continue to pose a major therapeutic challenge.

Cyclosporine A (CSA) [1, 2, 23] has been shown to potentiate the cytotoxic activity of platinum, possibly

through alterations in the expression of the c-*fos*, c-*myc*, and c-H-*ras* oncogenes [13, 20] and other genes related to the repair of platinum-mediated DNA damage. The induction of these genes is suppressed by CSA, potentially contributing to the reversal of cellular resistance to CBDCA.

Preclinical studies and a phase I trial have been completed and suggest that CSA at this dose and on this schedule could be safely administered without safety concerns including renal toxicity or hypertension, and could partially reverse CBDCA chemoresistance [18]. We designed and performed this phase II study in patients with recurrent ovarian cancer to examine the clinical efficacy. The goals of this study were: to estimate the chemomodulatory effect of a 26-h continuous infusion of CSA; to further define whether levels of CSA capable of modulating CBDCA resistance in vitro are clinically achievable on this schedule with acceptable toxicity; and to determine whether CSA alters CBDCA pharmacokinetics.

Patients and methods

Clonogenic assays in vitro

To document the effect of exposure duration on the reversal of CBDCA resistance by CSA, cytotoxicity assays utilizing A2780 human ovarian carcinoma cells which were 2.5-fold resistant to CBDCA were performed [18]. The molecular characteristics of this cell line have been previously described by Scanlon et al. [20]. Briefly, the cells were exposed to 0 or 2 μg/ml CSA for either 18 or 24 h. Clonogenic survival following exposure to increasing concentrations of CBDCA was then determined. After CBDCA treatment, the cells were washed, counted, and plated in duplicate as single-cell suspensions. Colonies were allowed to form over 5–7 days and were then stained and counted. Results were calculated as percentages in relation to control colony formation.

Patient selection

Between February 1995 and April 1999, 23 patients were treated on this phase II protocol. Eligibility requirements included: histologically confirmed ovarian, Fallopian tube, or primary peritoneal cancer which was "platinum-resistant" as defined as progression on treatment with platinum-containing regimens, progression within 6 months of treatment with platinum-containing regimens, persistent clinically measurable disease with best response as stable at the completion of planned first-line platinum-based therapy; or persistent disease with best response as stable with rising CA-125 while receiving first-line therapy. The CA-125 increase in this group was documented by two independent measurements with the last level being >100 U/ml. Patients with a Karnofsky performance status of 60–70% could have received at most two prior courses of chemotherapy, while patients with Karnofsky performance scores of 80–90% could have received three prior courses of chemotherapy. All patients had an estimated survival of at least 2 months. Adequate renal and bone marrow function were defined as creatinine ≤ 1.5 mg/dl or measured creatinine clearance ≥60 ml/min, platelets ≥150,000 μl^{-1}, and total white blood count ≥3500 μl^{-1} or absolute granulocyte count of ≥1500 μl^{-1}. In addition, the bilirubin was required to be ≤ 1.5 mg/dl, and hepatic transaminases and alkaline phosphatase were required to be less than three times the institutional upper limit of normal. Patients had to have recovered from the toxicity of any previous chemotherapy; patients having had whole abdominal radiotherapy were ineligible. All patients gave their voluntary, informed consent and signed an informed consent document approved by the Clinical Protocol Review and Monitoring Committees and the Institutional Review Boards of the City of Hope National Medical Center, University of California, Davis, or the University of Southern California.

Pretreatment evaluation

Pretreatment evaluation included a complete history and physical examination, complete blood count with differential, chemistry panel including liver function tests and serum creatinine, urinalysis, 24-h urine creatinine clearance, electrocardiogram, chest radiograph, appropriate serum tumor markers, serum magnesium, and radiographic examinations for tumor measurements. Serum chemistries and blood counts were repeated weekly. Patients with bidimensionally measurable disease were required to have baseline evaluations within 2 weeks prior to the first course of treatment. CA-125 levels were determined prior to each cycle of chemotherapy. Repeat radiographic evaluations were performed after every two cycles of therapy.

Treatment plan

Standard Southwest Oncology Group response criteria [11] were used. A partial response in patients having nonmeasurable disease was defined as a CA-125 level (initially >100 U/ml) decreasing to a value $<50\%$ of the pretreatment level with complete resolution of at least one evaluable lesion. An increase of CA-125 alone did not define progression in any circumstance; in patients with a CA-125 increase to $>125\%$ of baseline for two successive measurements, a diligent search for clinical or radiologic progression was performed. However, patients without unequivocal evidence of progression were treated with a subsequent cycle of therapy on-study. Toxicity was measured using the Common Toxicity Criteria (version 1) of the National Cancer Institute. CBDCA dosage was fixed at an AUC of four.

Dosage escalations of one AUC unit were allowed in any patient experiencing toxicity of grade 2 or less on any treatment course. For any grade 3 or 4 white count or granulocyte toxicity following the first cycle of therapy, patients received Neupogen, 5 μg/kg per day subcutaneously, for 7 days. Grade 3 or 4 white count or granulocyte toxicity on subsequent cycles resulted in a CBDCA AUC dosage reduction of one. Any grade 3 or 4 platelet count toxicity resulted in a dosage reduction of 10% for all drugs.

CSA was begun as an i.v. loading dose of 6 mg/kg over 2 h. A continuous infusion of 9 mg/kg per day of CSA was then delivered over the next 24 h (total CSA time 26 h). CBDCA was administered over 60 min during hour 18 of the CSA infusion.

Pharmacokinetics

Whole blood for measurement of CSA levels were taken at 3 and 24 h after the beginning of CSA treatment from venipunctures on the arm opposite the site of the CSA infusion. Either or both of a high performance liquid chromatographic (HPLC) assay or a fluorescence polarization immunoassay (FPIA) were performed. The HPLC assay (Nichols Laboratories, San Juan Capistrano, Calif.), which measured parent CSA, was used to measure 21 samples from 15 patients at 3 h and 19 samples from 13 patients at 24 h (median 1 sample per patient, range 1–4). The FPIA (Abbott Laboratories, Abbott Park, Ill.), which included both parent CSA and metabolites, was used to measure 27 samples from 18 patients at 3 h and 26 samples from 16 patients at 24 h (median 1 sample per patient, range 1–4). Samples for CBDCA levels were obtained similarly from six patients at 0.5, 3, 6, and 24 h after the end of the carboplatin infusion by drawing 5 ml of whole blood into sodium heparin tubes. The tube were immediately placed on ice and ultrafiltered within 1 h utilizing Amicon Centrifree filters (Millipore Corporation, Bedford, Mass.). The ultrafiltrate was stored at −70°C until analysis by flameless atomic absorption spectrometry. For the pharmacokinetic analysis of total carboplatin levels, the data were fitted to a one-compartment first-order elimination model using the ADAPT II pharmacokinetic modeling software [9]. Carboplatin volumes of distribution, total systemic clearances, and expected AUCs based on the Calvert formula [3] were estimated for each patient and compared to measured AUCs using paired *t*-tests.

Statistical considerations

The primary goal of this trial was to obtain preliminary estimates of the antitumor efficacy of CBDCA given with CSA in patients with platinum-resistant recurrent ovarian cancer. A slight modification of the two-stage minimax design suggested by Simon [21] was used. It was assumed that a true response rate of less than 5% would not warrant further study of this combination. It was also assumed that a response rate of 20% would be considered promising for further studies in these patients. In the first stage, 14 evaluable patients were entered. If no responses were observed, the accrual would stop with the conclusion that the regimen was not promising for further study. Since one response was observed in the first 14 patients, an additional accrual of 13 patients was planned. It was assumed that four or more responses out of 27 patients would be considered sufficient evidence to warrant further study of the regimen providing other factors, such as toxicity and survival, also appeared favorable. If fewer than four responses out of 27 patients were observed, further study of the regimen would not be warranted. The study was closed with 23 patients enrolled because there were no further responses and it was considered unlikely that three or more of the next four patients would respond.

The probability of falsely declaring an agent with a 5% response probability as warranting further study is 0.04 (alpha) and the probability of correctly declaring an agent with a 20% response probability as warranting further study is 0.82 (power). With 27 patients (the planned accrual) the true probability of response could be estimated with a maximum standard error equal to 0.10. With 23 patients and a response rate near 0.05, the standard error is approximately 0.05. Durations of survival were estimated using the product-limit method of Kaplan and Meier [12].

Results

Clonogenic assays

Results of the preclinical experiments are shown in Fig. 1. In vitro resistance to carboplatin appeared to be

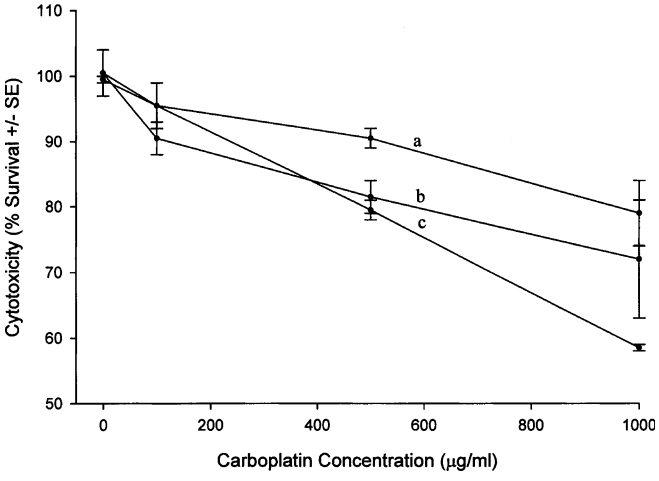

Fig. 1 Effect of 18 or 24 h preincubation with cyclosporine A (2 μg/ml) on the cloning efficiency in carboplatin-resistant A2780 cells (*a* without CSA, *b* CSA 2 μg/ml for 18 h, *c* CSA 2 μg/ml for 24 h)

partially reversed by CSA in a time- and concentration-dependent fashion. Exposure to CSA alone for 24 h did not result in cytotoxicity (data not shown).

Patient characteristics

A total of 23 patients received 58 courses of CBDCA chemotherapy (median 2, range 1–7; Table 1). All patients were female (Table 2). Their median age was 58 years (range 32–77 years). Median Karnofsky performance status was 80% (range 70–100%), and the tumor types included: adenocarcinoma not otherwise subtyped (nine), clear-cell carcinoma (one), endometrioid carcinoma (two), papillary serous carcinoma (ten), and undifferentiated carcinoma (one). Of the 23 patients, 17 were Caucasian, 4 were Asian, and 1 each was Hispanic and African-American. All patients had received prior treatment which included various combinations of surgery, hormonal therapy, radiation, and chemotherapy. All patients were platinum-resistant as previously defined. One patient had received prior radiotherapy.

Table 1 Number of courses completed

Course	No. of patients
1	6
2	8
3	4
4	3
5	1
6	0
7	1

Table 2 Patient characteristics (number of patients, except age in years)

Sex	
Female	23
Race	
Caucasian	17
Hispanic	1
Asian	4
African-American	1
Karnofsky performance status	
90–100%	5
70–80%	18
Histologic types	
Adenocarcinoma (not otherwise specified)	9
Clear cell	1
Endometrioid	2
Papillary serous	10
Undifferentiated	1
Age (years)	
Median	58
Range	32–77
Prior therapy	
Surgery	23
Radiation therapy	1
Chemotherapy	23
Platinum-resistant	23

Toxicities of therapy

Hematologic and nonhematologic toxicities of therapy are summarized in Table 3. Grade 3 or 4 granulocytopenia was noted in 17 of 58 courses of therapy (29%). Thrombocytopenia was mild and noted in 4 of 58 courses (7%). Grade 3 anemia (hemoglobin 6.5–7.9 g/dl) was observed in 4 of 58 courses. Gastrointestinal toxicity included three instances of grade 4 nausea and/or vomiting. Self-limiting diarrhea, constipation, and elevation of liver function studies were also noted. Hypertension was observed in 2 of 58 courses. Headache was not observed.

Therapeutic responses

One partial response was observed in a patient who received seven cycles of therapy before progressing at 6.4 months following initiation of therapy. An additional 8/23 patients had stable disease for a median of 4.9 months (range 2.8–9.2 months). Out of 23 patients, 14 were observed to have progressed at the time of the first response evaluation.

Two patients received only one cycle of therapy. They were considered to have progressed on therapy. One of these patients experienced myelosuppression with the development of bacteremia from a urinary tract stent requiring a treatment delay of more than 3 weeks; her tumor exhibited signs of clinical progression at the time of count recovery. The other patient developed increased fatigue thought to be due to worsening of a paraneoplastic dermatomyositis/polymyositis syndrome, and discontinued therapy. She had a decrease in CA-125 level from 1800 to 1000 U/ml following that cycle.

Cyclosporine concentrations

CSA concentrations in whole blood are shown in Fig. 2 which illustrates the direct correlation between the two

Table 3 Grade 3 and 4 toxicities (number of episodes)

Total no. of courses	58
Renal	
Serum creatinine >3.0 mg/dl (grade 3)	1
Hematologic	
Granulocyte nadir 500–999 μl^{-1} (grade 3)	14
Granulocyte nadir <500 μl^{-1} (grade 4)	3
Platelet nadir $25–50\times10^3$ μl^{-1} (grade 3)	3
Platelet nadir $<25\times10^3$ μl^{-1} (grade 4)	1
Hemoglobin 6.5–7.9 g/dl (grade3)	4
Nausea/vomiting	
Required hospitalization (grade 4)	3
Hypertension	
Requiring therapy (grade 3)	2
Miscellaneous (all grade 3)	
Diarrhea	1
Constipation	2
SGOT elevation	1
Bilirubin elevation	2

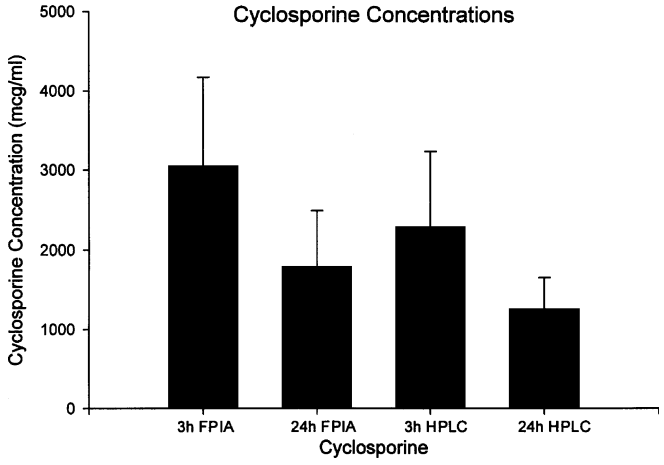

Fig. 2 CSA concentrations after the loading dose (3 h) and at steady state (24 h) as measured by FPIA and HPLC

assay methods over the 26-h interval of CSA treatment. The mean concentrations at 3 h and 24 h as determined by the FPIA, which measured CSA and its metabolites, were 3046 ± 1128 and 1784 ± 705 μg/ml (mean ± SD), and as determined by the HPLC assay, which measures only parent drug, were 2282 ± 954 and 1253 ± 400 μg/ml, respectively. These concentrations correspond to those shown to be effective in partially reversing CBDCA resistance as shown in Fig. 1.

CBDCA pharmacokinetics

A summary of the CBDCA pharmacokinetics determined in six patients is shown in Table 4. Carboplatin clearance was 60.68 ± 22.63 ml/min/m^2 (mean ± SD). The volume of distribution (Vd) was 12.97 ± 5.99 l/m^2 (mean ± SD). Target and measured CBDCA AUCs were 4 and 3.30 ± 0.73 mg min/ml, respectively ($P = 0.015$, paired *t*-test).

Discussion

Resistance to platinum analogues remains the primary limitation to curative chemotherapy in advanced ovarian cancer. Preclinical investigations have demonstrated the ability of CSA to reverse drug resistance mediated both by the multidrug transporter and by effects on oncogene expression in vitro [13, 19, 20, 24]. These observations led to phase I clinical trials [17, 18] in which we and others have demonstrated the feasibility of combining CSA with platinum analogues. We have previously reported that CSA is capable of partially reversing carboplatin resistance in vitro [18]. Our current study demonstrated the effectiveness of CSA in partially reversing CBDCA resistance in A2780 cells in a concentration- and time-dependent manner, and we also report a phase II trial in which one platinum-resistant patient achieved an excellent partial response to the combination of CSA and CBDCA, thus demonstrating modest partial reversal (in this patient) of CBDCA resistance in vivo. Our pharmacokinetic data demonstrated that the target CBDCA AUC was greater than or equal to the measured CBDCA AUC, suggesting that resistance reversal occurs independently of CSA-mediated alteration in CBDCA pharmacokinetics.

Table 4 CBDCA pharmacokinetics (Carboplatin equivalents) ($N = 6$)

CL (ml/min/m^2)	Vd (l/m^2)	AUC (mg min/ml) target/measured	*P* value[a]
60.68 ± 22.63	12.97 ± 5.99	$4/3.30 \pm 0.73$	0.066

[a]Paired *t*-test comparing target vs measured.

The ability of CSA to affect drug resistance appears to be dependent on both concentration and the duration of exposure. CSA has been measured by both radioimmunoassay (FPIA) [25, 27], which measures parent CSA and several of its metabolites, and HPLC which measures only the concentration of the parent drug or a single metabolite [14]. In our previous phase I study, we observed a direct correlation between the two methods over the 36-h infusion period, with the immunoassay consistently demonstrating higher values, as would be expected. We confirmed this direct correlation in this phase II study.

For chemomodulation to be a clinically useful therapeutic strategy, it must be possible to deliver effective concentrations of a drug resistance-modifying agent at an acceptable level of toxicity. CSA has been shown to reverse cellular resistance to platinum in vitro. Scanlon et al. [13, 20] have reported that preincubation with CSA concentrations of 5 μg/ml effectively reverses resistance in platinum-resistant human ovarian carcinoma cell lines. The data presented in this report suggest that preincubation with lower levels for varying time periods is also effective in partially reversing carboplatin resistance; however, higher concentrations for prolonged periods of exposure are superior to shorter durations at lower concentrations. Clinically, Yahanda et al. [26] have demonstrated sustained CSA concentrations of up to 4840 ng/ml (FPIA) at their highest administered dose level (21 mg/kg per day). Using a radioimmunoassay specific for parent CSA, Sonneveld et al. [22] found steady-state levels of 706–1010 ng/ml when infusions of 10 mg/kg per day were administered.

Chambers et al. [5–7] have reported phase I and II trials of carboplatin in combination with cyclosporine at higher doses. The dose-limiting toxicity in their phase I study was thrombocytopenia, and, in addition, a response rate of 14% in platinum-resistant patients was noted. In our previous phase I trial utilizing CBDCA with CSA, the dose-limiting toxicity was hypertension observed at CSA 10 mg/kg per hour; we based our Phase II doses on this observation. In our current study, we also observed significant grade 3 myelosuppression and hypertension. Although preclinical data suggest that

higher doses of CSA should be more effective in drug resistance reversal, the observed toxicity profile in this group of patients precludes higher doses. We observed one partial response in this platinum-refractory population, as well as eight patients with stable disease. These observations suggest that this combination is modestly effective in reversing CBDCA resistance in vivo.

Data regarding the mechanisms of the drug resistance induced by chemotherapeutic agents, and the reasons for the relative lack of efficacy of CSA in reversing platinum resistance in our patient population, are not definitive. The phenomenon of resistance is multifactorial, involving proteins that impair delivery (either increased efflux or decreased influx) of anticancer drugs to the tumor cells, the activation or induction of DNA repair enzymes, induction of alterations in the apoptotic pathways, and/or those that arise in the cancer cell itself due to genetic alterations that affect drug sensitivity [10]. Li et al. have demonstrated that exposure of A2780 cells in culture to cisplatin results in a four- to sixfold induction of ERCC-1 (excision repair cross-complementation group 1) mRNA [15]. This DNA repair protein is essential for life. Pre-exposure of these cells to CSA blocked the ERCC-1 induction. Other mechanisms of cellular resistance may, however, be implicated in the inability of CSA to improve the clinical activity of CBDCA in our patient population. CSA has been shown, in vitro, to inhibit the classical multidrug resistance pathway (MDR) that primarily affects drug transport of chemotherapeutic agents derived from natural products. Other members of this family of ATP-binding cassette (ABC) transporters, the multidrug-resistance-associated proteins (MRP2 and 3) have, however, been implicated in acquired platinum resistance [10]. However, data have been published suggesting that CSA may also be inhibitory to other proteins in the ABC family [4, 8].

Another possible mechanism of chemomodulation is alteration of platinum pharmacokinetics by CSA. Lum et al. [16] have reported that CSA alters the clearance of etoposide and increases systemic exposure and suggest that this pharmacokinetic alteration plays a role in the observed therapeutic effect of the combination. The carboplatin pharmacokinetics found in this study suggests that alterations in the pharmacokinetics of CBDCA do not play a significant role in chemomodulation, and other mechanisms must be responsible for increased sensitivity of ovarian cancer to CBDCA. The observed AUC of CBDCA in CSA-treated patients was lower than the target AUC. It is clear that CSA does not prolong tissue exposure to CBDCA.

In summary, steady-state levels of CSA of >1 μg/ml (HPLC assay) are achievable in vivo. These levels correspond to concentrations required for modulation of platinum resistance in vitro. FPIA and HPLC assays directly correlated over the measured 26-h infusion. Modest partial reversal of platinum resistance was achievable in some patients treated with cyclosporine, but the effect noted at these doses was not great, and other strategies to achieve the goal of chemosensitization are required. This phenomenon, however, is not explained by alterations in carboplatin pharmacokinetics. Longer CSA exposure times might prove more effective for resistance reversal in platinum-resistant patients; however, higher doses are contraindicated due to the side effect profile observed in these patients.

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