Cyclosporin A Reverses Chemoresistance in Patients With Gynecologic Malignancies [1]

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Abstract

Multidrug resistance is a major obstacle in successful systemic therapy of gynecologic malignancies. The objectives of this study are to evaluate the activity of cyclosporin A used to overcome drug resistance in a variety of gynecologic malignancies. Forty women (29 with ovarian cancer, 7 with uterine cancer, 3 with cervical cancer, and 1 with choriocarcinoma) were treated with cyclosporin A, 4 mg/kg intravenously, 6 hours before and 18 hours after the specific chemotherapeutic agent, to which the tumor had developed drug resistance. All patients had shown resistance to the chemotherapy agent used in combination with cyclosporin A. All patients had been heavily pretreated (mean, 2.8 previous chemotherapy regimens). Overall, among 38 available patients with gynecologic malignancies, a 29% objective response rate was observed. Twenty-six (65%) of all patients received three or more cycles of cyclosporin A. There was a 25% response rate for patients with ovarian cancer patients and 50% for those with uterine cancer. There were no responses among the three patients with cervical cancer, and the patient with choriocarcinoma had a complete response. All patients were evaluable for toxicity. Leukopenia and nausea were the most common toxic reactions, but in most cases they were transient, and only three patients required a treatment delay. The most common grade 3 or 4 toxicity was thrombocytopenia, which was observed in 22% of the patients. Cyclosporin A is well tolerated and has significant potential for reversal of chemoresistance in heavily pretreated patients with ovarian and uterine malignancies.

Keywords: multidrug resistance, cyclosporine, resistance modulation.

Introduction

Despite advances in combination chemotherapy, the successful management of advanced or recurrent gynecologic malignancies is often difficult due to both intrinsic and acquired resistance of cancer cells to chemotherapeutic agents. Even in ovarian cancer, which routinely shows apparent complete response to chemotherapy, regrowth of resistant cancer cells is a major hindrance to improvement in progression-free interval and long-term survival. Several mechanisms of drug resistance have been proposed, including multidrug resistance (MDR), detoxification of potentially cytotoxic metabolites, and enhanced DNA repair. Although several mechanisms may be involved simultaneously, a significant proportion of drug resistance is attributed to amplification of the *MDR* gene [1]. The *MDR* gene is known to code for a membrane-associated protein that acts as an adenosine triphosphate (ATP)–dependent efflux pump to transport the chemotherapeutic agents out of the cell.

Recent *in vitro* studies have revealed several agents that can down-regulate MDR function and enhance response to cytotoxic agents. These modifiers of MDR function include calcium channel blockers, calmodulin inhibitors, quinidine, tamoxifen, and cyclosporin A [2]. Cyclosporin A is an immunosuppressive cyclic polypeptide with unique pharmacodynamic properties. It interferes with T-cell growth and differentiation by inhibiting production of interleukin-2 at the transcriptional level [3]. Previous studies with cyclosporin A have shown *in vitro* and *in vivo* reversal of chemoresistance to compounds associated with MDR elevation in the resistance mechanism. Such compounds include etoposide, vincristine, doxorubicin, and daunorubicin [1,4–8]. Cyclosporin A has also been shown to reverse resistance to cisplatin unrelated to MDR gene amplification. The maximum tolerated dose, as well as the pharmacokinetics of cyclosporin A, have been reported [9–11]. In an attempt to overcome drug resistance we evaluated response rates, duration of response, and toxicity with a variety of agents in heavily pretreated patients with gynecologic malignancies.

Materials and Methods

All patients with advanced gynecologic malignancies who were treated with cyclosporin A at the University of Iowa Hospitals and Clinics between July 1, 1993, and December 31, 1996, were identified through the Department of Pharmaceutical Care comprehensive database and the University of Iowa Tumor Registry. Forty women were identified, and all charts were available for review. Records were retrospectively reviewed with particular attention to the initial history and physical examination, histopathologic findings, operative and postoperative treatment including chemo-

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therapy, and follow-up. Diagnosis was verified by pathology review at the institutional Gynecologic Oncology Tumor Board. All patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. Complete follow-up was available for all patients.

All patients treated with cyclosporin A were heavily pretreated with multiple chemotherapy regimens, and all had demonstrated chemoresistance to the specific agent used in combination with cyclosporin A. Resistance to a chemotherapeutic agent was defined as disease progression during treatment with the agent or recurrence within 6 months of previous therapy [12]. Cyclosporin A, 4 mg/kg, was administered intravenously 6 hours before and 18 hours after the specific chemotherapeutic agent. This dose was derived from the phase I trial conducted by the Gynecologic Oncology Group (GOG) [9]. Treatment was repeated every 21 days until disease progressed or unacceptable toxicity developed.

Before each cycle of chemotherapy, a complete blood count with differential, platelet count, serum electrolytes, liver function tests, and serum creatinine was obtained on each patient. Serum CA 125 levels were also obtained before each cycle of chemotherapy in patients with ovarian cancer. Antiemetic regimens usually consisted of ondansetron and dexamethasone surrounding the infusion of platinum, and dexamethasone and metoclopramide for 3 days after platinum infusion. All toxicity was graded according to the GOG criteria [13]. Granulocyte colony stimulating factor (G-CSF) was administered in accordance with the American Society of Clinical Oncology (ASCO) guidelines [14].

Patients were evaluated for response before each course of chemotherapy. Only patients with measurable disease and/or CA 125 levels were considered evaluable for assessing response to chemotherapy. In patients with measurable disease, complete response (CR) represented disappearance of clinical evidence of all disease, and partial response (PR) denoted a decrease of at least 50% in the tumor volume. Progression denoted a 25% or more increase in tumor volume or the appearance of new lesions. CA 125 was used to follow disease when two separate values were >100 U/mL at least 24 hours apart. The status of each patient was recorded as alive without disease, alive with disease, dead of disease, or dead of other causes.

Results

Forty patients with refractory gynecologic malignancies were treated with a total of 182 cycles of cyclosporin A in combination with platinum, Taxol, or etoposide chemotherapy. Demographic characteristics are listed in Table 1. Most patients in this study had recurrent ovarian cancer (72%). Other cancers included were uterine cancer (18%), cervical cancer (8%), and choriocarcinoma (2%). All patients had been heavily pretreated; 82% of patients had received two or more chemotherapy regimens previously with a mean of 2.8 regimens.

Table 1. Clinicopathologic Characteristics of Patients Treated with Cyclosporin A.

Mean age (years)	55.8
Parity	
Nulliparous	8
Primiparous	5
Multiparous	27
Cancer type	
Ovary	29
Uterus	7
Cervix	3
Choriocarcinoma	1
Previous chemotherapy (No. regimens)	
1	7
2	7
3	15
4	7
5	4
Mean	2.8
Resistance	
Platinum	39
Taxol	21
Adriamycin	4
Ifosfamide	1
Etoposide	2

All patients showed chemoresistance to the chemotherapeutic agent that was given in conjunction with cyclosporin A. Ninety-seven percent of the patients showed resistance to platinum agents, and 52% also showed resistance to Taxol. All patients had measurable disease. (Two patients were followed with CA125 only.) Twenty-seven (70%) of the patients received three or more courses of cyclosporin A–based chemotherapy. Ten patients received only two courses because of progression despite cyclosporin A–based chemotherapy. Patients were considered evaluable if they survived 28 days after treatment with cyclosporin A–based chemotherapy. Thirty-eight of the 40 patients were evaluable. Eighty-eight percent received platinum alone in conjunction with cyclosporin A, and 8% received Taxol (Table 2). Twenty-six (65% of all patients) received three or more cycles of cyclosporin A–based treatment. Two patients were treated with two chemotherapy agents with cyclosporin A (Table 2).

Because response rates may vary with tumor type, results were analyzed separately for this characteristic (Table 3). The distribution of response to chemotherapy with cyclosporin A is presented in Table 4. Table 4 is structured based on the time interval between the chemotherapy agent plus cyclosporin A and the previous use of the same agent. Among the 29 patients with ovarian cancer, 28 were evaluable. There was a 25% response rate, with three complete and four partial responses. The duration of response ranged from 5.2 to 27 months, with a median duration of 6.8 months. Two patients with ovarian cancer were followed solely on the basis of their CA 125 levels. One of these patients had progression during treatment with platinum for recurrent ovarian cancer. She underwent secondary optimal cytoreduction, followed by six cycles of cyclosporin A and carboplatin chemotherapy. The CA 125 level declined from 178 to 32 U/mL and the patient remains disease free after

Table 2. Treatment Characteristics of Patients Receiving Cyclosporin A.

	No. of Patients
Number of treatment courses with CSA	
1	2
2	10
≥ 3	28
Associated chemotherapy Agents	
Platinum	35
Taxol	3
Taxol/platinum	1
Etoposide/platinum	1

(CSA, cyclosporin A).

2.3 years. The second patient had a partial response, and her CA 125 levels declined from 1969 to 753 U/mL after four cycles. She completed six total cycles and died 6 months later with progressive disease.

To further define drug resistance, the data were analyzed based on the time period between relapse or progression and start of the same chemotherapy agent with cyclosporin A. Table 4 presents patients with ovarian cancer. Among the responders (CR or PR), 71% progressed while on chemotherapy, and cyclosporin A was added to their chemotherapy regimen. Among patients who had disease progression during treatment with the agent, 5 of 11 (45%) had a response with the addition of cyclosporin A. In contrast, 17 patients had recurrence within 6 months of previous chemotherapy, and only 2 patients (12%) had a response with the addition of cyclosporin A. The difference between these groups was not statistically significant ($P = .08$).

There were six available patients with uterine cancer, and three of these showed a complete response, for a 50% response rate. The median duration of response was 11 months, with a range of 5 to 23 months. Among the responders, two patients had recurrent papillary serous endometrial carcinoma and the third patient had endometroid adenocarcinoma.

There were no responders among the three patients with cervical cancer. All patients with cervical cancer had squamous lesions. One progressed on initial cisplatin-based chemotherapy, and cyclosporin A was added to the chemotherapy regimen. The other two developed a recurrence in a previously radiated field. Both of these patients had progressive disease despite cisplatin chemotherapy, and cyclosporin A was added in an attempt to modulate chemoresistance. One patient with choriocarcinoma had failed multiple chemotherapy regimens but had a complete response to

Table 3. Patient Response to Cyclosporin A–Based Chemotherapy.

Cancer type	Complete response	Partial response	Stable	Progression	Not evaluable
Ovary					
Serous	3	2	9	9	1
Other	-	2	1	2	-
Uterus					
Papillary serous	2	-	-	-	-
Sarcoma	-	-	1	-	1
Endometroid	1	-	-	2	-
Cervix					
Squamous	-	-	-	3	-
Choriocarcinoma	1	-	-	-	-
Total	7	4	11	16	2

Table 4. Distribution of Response to Chemotherapy with Cyclosporin A Based on Time from Development of Resistance for Patients with Ovarian Cancer.

Patient no.	Time (mo)[a]	Chemotherapy	Response
3	0	Carboplatin	CR
35	0	Carboplatin	CR
7	0	Taxol	PR
24	0	Cisplatin	PR
38	0	Carboplatin	PR
26	0	Taxol/Carboplatin	Stable
30	0	Cisplatin	Stable
10	0	Cisplatin	Progression
19	0	Carboplatin	Progression
32	0	Cisplatin	Progression
6	0	Cisplatin	Progression
14	2	Carboplatin	Stable
11	2	Carboplatin	Progression
29	2	Cisplatin	Not evaluable
16	3	Carboplatin	Stable
31	3	Carboplatin	Stable
27	3	Cisplatin	Progression
17	4	Taxol	Stable
4	4	Carboplatin	Stable
34	4	Cisplatin	Stable
22	5	Cisplatin	CR
40	5	Carboplatin	Stable
2	5	Carboplatin	Progression
5	5	Carboplatin	Progression
33	5	Carboplatin	Progression
8	6	Carboplatin	PR
37	6	Cisplatin	Stable
36	6	Cisplatin	Progression
39	6	Carboplatin	Progression

[a]Interval between chemotherapy agent + cyclosporin A and the previous use of the same agent. Time 0 represents addition of cyclosporin A after progression while on the same chemotherapy drug. (CR, complete response; PR, partial response).

Table 5. Distribution of Response to Chemotherapy with Cyclosporin A Based on Time from Development of Resistance for Patients with Gynecologic Malignancies.

Patient no.	Time (months)[a]	Chemotherapy	Response	Cancer type
15	0	Cisplatin	Progression	Cervix
20	0	Cisplatin	Progression	Cervix
21	0	Cisplatin	Progression	Cervix
25	0	Etoposide/ Cisplatin	CR	Choriocarcinoma
1	0	Cisplatin	CR	Uterus
13	0	Taxol	CR	Uterus
28	0	Cisplatin	CR	Uterus
9	0	Cisplatin	Stable	Uterus
23	0	Carboplatin	Progression	Uterus
12	5	Carboplatin	Progression	Uterus
18	0	Cisplatin	Not evaluable	Uterus

[a]Interval between chemotherapy agent + cyclosporin A and the previous use of the same agent. Time 0 represents addition of cyclosporin A after progression while on the same chemotherapy drug. (CR, complete response; PR, partial response).

Table 6. Adverse Effects with Cyclosporin A–Based Chemotherapy.

Adverse effect	Patients with grade 1 or 2 response (%)	Patients with grade 3 or 4 response (%)
Leukopenia	10 (25)	6 (15)
Thrombocytopenia	8 (20)	9 (22)
Anemia	8 (20)	3 (8)
Nausea	15 (38)	1 (2)
Vomiting	7 (18)	1 (2)
Diarrhea	1 (2)	0 (0)
Renal	0 (0)	1 (2)
Neurological	1 (2)	1 (2)
Flushing	10 (25)	0 (0)

etoposide and cisplatin given with cyclosporin A. The response lasted for 3 months. Overall, among the 38 available patients with gynecologic malignancies, a 29% objective response rate (18% complete, 11% partial) was observed.

Table 5 presents patients with other gynecologic malignancies and the time period between relapse or progression and start of the same chemotherapy agent with cyclosporin A. All three patients with uterine cancer who had a complete response had progressive disease while on the same chemotherapy agent used with cyclosporin A.

All patients were available for toxicity, and the rates for each toxic reaction are reported in Table 6. Hematologic toxicity was common. Grade 3 or 4 leukopenia was present in 15% and grade 3 or 4 thrombocytopenia in 22%. In most cases the toxicity was transient, and only three patients required a treatment delay (1 week for two patients and 2 weeks for one patient). G-CSF was used in 18 patients (45%) per ASCO guidelines. Mild (grade 1 or 2) gastrointestinal toxicity was commonly observed; however, severe (grade 3 or 4) nausea or vomiting was rare. Ondansetron was effectively used as a part of the standard premedication regimen, resulting in minimal severe gastrointestinal toxicity. Renal toxicity was uncommon, and only one patient had grade 3 renal toxicity. In this patient the serum creatinine increased to 3.8, and the chemotherapy (carboplatin) was stopped. Neurological toxicity was also uncommon, but vasomotor flushing occurred in 10 (25%) patients.

Discussion

Chemotherapeutic resistance continues to be a significant obstacle to treatment of gynecologic malignancies. This is especially true for epithelial ovarian carcinoma, for which initial response rates are often greater than 80%. Unfortunately, the long-term survival for advanced stage disease does not reach 50% at 5 years. The MDR gene and its product, P-glycoprotein, have been shown to play a role in resistance to chemotherapeutic agents [15]. This appears to be the dominant mechanism for resistance in many chemotherapy agents including etoposide, vincristine, doxorubicin, daunorubicin, and paclitaxel. Cyclosporin A has been shown to reverse MDR and to reduce chemotherapeutic resistance and cross resistance *in vitro* to all of these agents [16-17].

The mechanisms for platinum resistance appear to be different than MDR and may include enhanced DNA repair, increased intracellular levels of glutathione or metallothionein, or increased expression of enzymes responsible for the regulation of DNA repair [18]. Cyclosporin A has also been shown to have the ability to reverse platinum resistance [19]. Recently, several studies have evaluated potential molecular mechanisms underlying resistance reversal. Kashani-Sabet and colleagues have shown that administration of cyclosporin A to cisplatin-resistant epithelial ovarian cancer cells reduces levels of the *c-fos* gene product, which was found to be elevated in the resistant cell line and induced in the cisplatin-sensitive line by administration of cisplatin [20]. The reduction of *c-fos* gene product was followed by a reduction in thymidylate synthase and DNA polymerase beta, which plays a role in DNA synthesis and repair [20]. The reduction in levels of these enzymes corresponds with restoration of platinum sensitivity. As a corollary, *in vitro* induction of platinum resistance is often accompanied by elevation of these enzymes. Further support for the important role of *c-fos* in platinum-resistant cancer comes from the observation that ribozyme-mediated cleavage of *c-fos* mRNA effects reversal of platinum resistance and concomitant reduced expression of DNA polymerase II and metallothionein mRNA [18]. Ribozyme-mediated reversal of chemoresistance in a multiple drug resistant cell line by directing the ribozyme against the p-glycoprotein mRNA has also been used as a strategy to reverse drug resistance [21]. These studies provide a logical model of resistance reversal by cyclosporin A on which to base clinical studies.

The effectiveness of cyclosporin A in reversal of chemoresistance may be dependent on tumor type (Table 7). Trials of cyclosporin A in renal carcinoma have shown dismal results [22,23]. However, cyclosporin A appears to be highly effective in treatment of acute leukemia [24]. Clinical studies of cyclosporin A in gynecologic malignancies are limited. The phase I study of cyclosporin A with platinum in advanced gynecologic malignancies performed by the GOG established a tolerable dose regimen and reported a total response rate of 25% [9]. Similarly, Chambers, and colleagues reported an overall 24% response rate in ovarian and fallopian tube malignancies [11]. However, in the recently reported phase II trial by the GOG, only a 12% response was found [25]. In the present study, evaluable

Table 7. Response Rates to Cyclosporin A–Based Treatment Regimens.

Author	Tumor type	Evaluable patients *(n)*	Chemotherapy	Complete response *(n)*	Partial response *(n)*
Rodenberg et al. [22]	Renal	15	Vinblastine	-	-
Verweij et al. [23]	Renal	10	Vinblastine	-	-
	Colorectal	23	Epirubicin	-	1
List et al. [24]	Acute leukemia	33	Cytarabine + daunomycin	20	2
Chambers et al. [11]	Ovarian	38	Carboplatin	1	8

patients with chemorefractory ovarian cancer had a 25% response rate. Patients with uterine cancer responded even better, with a 50% response rate. Unfortunately, no responses were seen in women with cervical malignancies.

Cyclosporin A was well tolerated. The major nonhematologic toxic reaction was nausea; however, severe nausea or vomiting was avoided by the use of effective antiemetics such as ondansetron in most cases. Even though many patients had grade 3 or 4 hematologic toxicity, this was transient, and treatment delays were needed only in a small fraction of patients. It has been shown that most hematologic toxicity is more likely due to the chemotherapy rather than cyclosporin [11]. The GOG study reported grade 4 nephrotoxicity in 4 of 20 patients (20%) in the phase I trial [9]. However, no renal toxicity was observed in subsequent studies [10,25]. In the present study renal toxicity was minimal. Even among heavily pretreated patients, hematologic toxicity was not significantly different from other studies.

A recent article by Hojo et al. has raised concerns that prolonged treatment with cyclosporin A may promote cancer progression mediated by induction of transforming growth factor-β [26]. Although this finding would be a concern in patients who have prolonged exposure to cyclosporin A alone, it does not seem to apply to the patients treated in combination with chemotherapy. In addition, the patients treated in this study received cyclosporin A only for a short duration to modify chemoresistance.

Due to potential concerns of hepatic and renal toxicity as well as for the potent immunosuppressive properties of cyclosporin A, cyclosporin analogues have been developed with fewer immunosuppressive properties and improved or similar resistance-reverting potential. PSC833 appears to be more potent than cyclosporin A with minimal immunosuppressive properties [27-29]. This agent is currently under investigation in several clinical trials. Our data suggest that cyclosporin A or possibly its analogues should be studied in less heavily treated patients. In addition, these agents appear promising for treatment of recurrent uterine cancer and should be investigated further.

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