



Cisplatin plus gemcitabine in platinum-refractory ovarian or primary peritoneal cancer: A Phase II Study of the Gynecologic Oncology Group

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Abstract

Objectives. To evaluate the safety and efficacy of cisplatin plus gemcitabine in persistent or recurrent platinum-resistant ovarian and primary peritoneal cancer.

Study Design. Eligible, consenting subjects with measurable disease and one prior platinum-based regimen, but no prior gemcitabine, were to receive intravenous cisplatin followed by gemcitabine on days 1 and 8 every 28 days.

Results. Between December 2000 and March 2003, 59 patients were enrolled from 24 institutions; two were ineligible. During the first stage of accrual, 27 subjects received cisplatin 30 mg/m² and gemcitabine 750 mg/m². In the second stage, gemcitabine was reduced to 600 mg/m² because of hematologic toxicity at the higher dose. There were 4 complete and 5 partial responses for an overall response rate of 16% (9/57). Thirty-one women (54%) had stable disease. Median time to progression was 5.4 months. Overall survival was 14.9+ months. Grade 4 toxicities were hematologic, except one cutaneous reaction.

Conclusions. Cisplatin plus gemcitabine, in the doses and schedule employed, has modest activity in this patient population.

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Introduction

In recent years, the outcome with platinum-based regimens in stages III and IV ovarian cancer has improved, but the majority of women with advanced disease relapse and die within 5 years of diagnosis. Thus, one of the challenges confronting oncologists is the management of recurrent disease that has become drug-refractory.

Platinum-resistant ovarian cancer, defined by the Gynecologic Oncology Group as persistent disease or progression

within 6 months following platinum-based therapy, is associated with a low response rate to further treatment, poor prognosis and median survival of 1 year or less. Though responses to taxanes were observed in the second-line setting [1,2], currently the vast majority of ovarian cancer patients have received taxanes as part of their initial therapy. Some other drugs have single agent activity in refractory cases, but the response rates are low (10–20%) and without a clear survival benefit.

Gemcitabine is a nucleoside analog of deoxycytidine. Myelosuppression is the most common dose-limiting toxicity. Elevated liver enzymes, pulmonary toxicities and rare hemolytic-uremic syndrome are also reported [3,4]. Skin rashes may

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rarely occur, usually as radiation recall phenomena [5,6]. The drug is generally well tolerated without significant cumulative toxicity or overlapping toxicity with cisplatin and has activity in ovarian cancer [7,8].

Laboratory experiments revealed significant synergy [9,10] between cisplatin and gemcitabine in the A2780 ovarian cancer cell line and its platinum-resistant subclones, with a suggestion of schedule dependence [10]. Subsequent tests in human tumor primary cultures indicated activity for this combination in drug-refractory breast and ovarian cancers, which was then studied in clinical trials [11,12]. This combination produced a high response rate in platinum-resistant ovarian cancer, in single institution reports [12,13]. The present trial was conducted to further elucidate the efficacy and toxicity of this regimen in platinum-resistant ovarian cancer. Since prophylactic hematopoietic growth factor support was not to be employed, and since at least one of the earlier trials [12] had had frequent hematologic toxicity with retreatment every 21 days, it was decided to repeat the course of therapy every 28 days.

Materials and methods

Women with persistent or recurrent platinum-resistant epithelial ovarian or primary peritoneal cancer, at least 18 years of age, with bidimensional disease measurable by physical exam or medical imaging including CT, MRI, or ultrasound, without prior gemcitabine, and with GOG performance status 0, 1, or 2 were eligible. Eligible subjects were to have received one, but not more than one, prior platinum-based regimen and were to be platinum-resistant, that is, progression on or relapse within 6 months of platinum-based therapy. Histological confirmation of the original primary tumor by the GOG Pathology Committee was required. Pre-existing sensory and motor neuropathy was to be less than or equal to CTC grade 1.

Those with concomitant or prior malignancy other than a non-melanoma skin cancer within the preceding 5 years were not eligible. Tumor-directed hormonal therapy was to be discontinued for at least 1 week and chemotherapeutic, biologic, or immunologic agents at least 3 weeks prior to registration. Prior radiation to the sites of measurable disease or to more than 25% of marrow-bearing areas was not allowed. Subjects who met protocol criteria, with adequate hematologic, renal, hepatic, pulmonary, and cardiac function and no active infections, were accrued after signing informed consent consistent with Federal, state, and local requirements.

The treatment consisted of cisplatin 30 mg/m² administered intravenously over 1 h followed by gemcitabine 750 mg/m² over 1 h, given day 1 and day 8 every 28 days. Day 8 could be adjusted \pm 1 day to accommodate scheduling problems. The gemcitabine dose was reduced to 600 mg/m² at the time that the second stage of accrual was initiated, due to hematological toxicity in the earlier patients.

A course of therapy was not administered unless the absolute neutrophil count was \geq 1500/ μ l and platelets were \geq 100,000/ μ l. For the first occurrence of neutropenic fever and/or documented grade 4 neutropenia persisting \geq 7 days, the gemcitabine was reduced one dose level [to 600 mg in the first cohort, and 450 mg/m² in the second] in subsequent courses. Only subjects who experienced recurrent neutropenic fever, or recurrent documented grade 4 neutropenia, persisting \geq 7 days after dose reduction were to receive growth factor support. Patients with further episodes of neutropenic fever or recurrent documented grade 4 neutropenia persisting \geq 7 days (after dose reduction and the addition of growth factors) underwent an additional dose reduction of gemcitabine. Treatment modifications applied equally for day 1 and day 8, with the day 8 treatment held if the ANC was <1000 cells/ μ l or platelets were <75,000/ μ l.

Prophylactic growth factor support was not allowed. Subjects who failed to recover adequate counts within a 2-week delay were removed from study. Erythropoietin was allowed for management of anemia after documentation of a hemoglobin count of less than ten grams. Prophylactic thrombopoietic agents could be given for recurrent thrombocytopenia only after treatment modifications. Grade 3 elevations in liver enzymes, alkaline phosphatase or bilirubin

required a dose reduction of one level in gemcitabine and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1. Recurrent grade 3 nausea and vomiting despite adequate antiemetic therapy required a dose reduction of cisplatin to 20 mg/m². Similarly, a grade 2 or greater peripheral neuropathy, or grade 2 or greater renal toxicity, required a dose reduction in cisplatin and a delay in subsequent therapy for a maximum of 2 weeks. Amifostine or other protective agents were not allowed.

A complete response (CR) was defined as the disappearance of all measurable disease for at least 4 weeks. A partial response (PR) was defined as a 50% or greater reduction in the products of each measurable lesion for at least 4 weeks duration. Increasing disease was defined as a 50% or more increase in the product of any indicated lesion or the appearance of any new lesions within 8 weeks of study entry. Stable disease was defined as any condition not meeting any of the above criteria. Survival is the observed length of life from initiation of treatment to death or the date of last contact. Progression-free survival is the period from study entry until disease progression or the last date of contact. Subjects who received one or more courses of drug and lived at least 4 weeks were evaluable for response. Subjects who received one or more doses of drug were considered evaluable for adverse effects regardless of subsequent survival. However, based on intent to treat, patients deemed invaluable for response were still utilized in calculation of the response rates. CA 125 values, when elevated, were requested prior to each course of therapy. A patient could remain on the study until progression or unacceptable toxicity. All subjects were to be followed until death.

The study employed a two-stage accrual design with an early stopping rule in the event that the treatment demonstrated insufficient activity. During the first stage, 19–26 patients were to be entered and evaluated. If there were more than 2 out of 19–25, or 3 out of 26 eligible patients responding (complete or partial response) and medical judgment indicated, accrual to the second stage of the trial was to be initiated. The regimen would be considered active and worthy for additional investigation if at least seven responses were observed among 44–45 patients, or at least eight responses were observed among 46–51 patients. If the true probability of responding was only 10%, the study provided a 90% chance of correctly classifying the treatment as inactive. Conversely, if the true response rate was 25%, then the average probability of correctly classifying the treatment as active was 90%.

Results

The initial period of enrollment from 12/18/2000 through 5/07/2001 included 27 subjects. The study was then suspended

Table 1
Patient characteristics (N=57)

Characteristic	Number of cases
Performance status	
0	41
1	14
2	2
Cell type	
Serous	41
Mucinous	5
Clear cell	3
Mixed epithelial	5
Adenocarcinoma, unspecified	2
Endometrioid	1
Grade	
1	8
2	15
3	33
Age	
Median	56.0
Range	22–84
Prior chemotherapy	57
Prior radiotherapy	1

Table 2
Response rates

Response rate	Number of cases	%
Complete response	4	(7.0)
Partial response	5	(8.8)
Stable disease	31	(54.3)
Increasing disease	12	(21.1)
Inevaluable	5	(8.8)
Total	57	(100.0)

for a preliminary assessment of response and toxicity. It reopened 4/29/2002 through 03/31/2003 based on activity in the first stage, with a dose modification for gemcitabine from 750 to 600 mg/m² based on toxicity observed in the earlier group; 32 additional subjects were enrolled, for a total of 59 entries. One woman was excluded for a second malignant diagnosis and one for inadequate pathology documentation. Eight patients had primary peritoneal cancer; all others had ovarian cancer. The median age of eligible subjects was 56 years (Table 1). All subjects received 1 or 2 prior regimens of chemotherapy, and one also had been irradiated. All had received carboplatin with a mean number of 7 courses; twenty-three (40%) had received eight or more courses of carboplatin. All but one had received a taxane. Of the 57 evaluable subjects, 29 (51%) had persistent and 28 (49%) had recurrent disease. The mean time from completion of primary therapy to initiation of protocol therapy was 3 months with a mean time to recurrence from initial diagnosis of 8.5 months (median 8 and range 0–16 months). These times were similar for responders and non-responders. Nine of twelve patients with increasing disease were from the second phase of accrual, and overall, approximately 30% less of each drug per patient was administered in the second phase.

Nine subjects were age 70 years or older and 2 subjects were greater than 80 years of age. The median number of chemotherapy cycles administered was four (range 1–15).

Fifty-two patients were evaluable for response (Table 2). The response rate as calculated for all 57 was 16% with 5 partial (9%) and 4 complete responses (7%). Thirty-one (54%) had stable disease, while 12 (21%) had increasing disease. The median time to progression was 5.4 months. Eight patients with stable disease had CA 125 declines greater than 50% (406 to 119, 2700 to 235, 674 to 145, 74 to 15, 243 to 87, 268 to 84, 897 to 261, and 300 to 115).

The median overall survival is 14.9+ months with eighteen patients still alive, seven of which had not progressed at the time of the analysis. For the 9 responders, the median survival was

Table 3
Hematologic adverse events *N*=57 (first phase accrual/second phase)

	Grade			
	1	2	3	4
Leukopenia	6 (3/3)	23 (11/12)	21 (12/9)	2 (1/1)
Thrombocytopenia	8 (5/3)	11 (7/4)	25 (13/12)	9 (1/8)
Neutropenia	4 (2/2)	9 (5/4)	16 (9/7)	22 (10/12)
Anemia	16 (10/6)	27 (14/13)	9 (3/6)	2 (0/2)
RBC transfusion	0	0	9 (1/8)	0
Platelet transfusion	0	0	2 (1/1)	0

Table 4
Non-hematologic adverse events *N*=57

	Grade			
	1	2	3	4
Hemorrhage	2	0	3	0
Gastrointestinal	12	14	6	1
Nausea/vomiting	13	21	7	0
Dermatologic	2	3	1	1
Neurologic	13	13	1	0
Pain	8	8	1	0
Fatigue	18	17	3	0
Allergy	0	2	1	0
Metabolic	7	3	2	0
Infection	0	3	2	0
Constitutional	0	2	1	0
Hematochezia	0	0	1	0
Alopecia	9	10	0	0
Pulmonary	3	3	0	0
Genitourinary	2	7	0	0

18.3+ months. The median survival for the 31 with stable disease was 17.2+ months. For those with increasing disease, the median time to progression was 1.7 months, with a median survival of 5.8 months.

The most common adverse events were hematologic (Table 3), although one grade 4 cutaneous reaction was noted. Three grade 3 bleeding episodes and two grade 3 infections were related to low counts. Grade 2 neuropathy occurred in 13 patients and grade 3 in one (Table 4). Because of the short treatment-free interval, it was not possible to clearly distinguish how much of the neuropathy was residual from the previous therapy and how much was from protocol treatment. One grade 4, GI event was felt to be unlikely secondary to therapy. Seven subjects with stable disease discontinued treatment because of fatigue or at the discretion of the investigator. One was removed for a new diagnosis of breast cancer. There were no treatment-related deaths.

Discussion

The management of platinum-resistant ovarian cancer remains unsatisfactory. Although responses to single agent liposomal doxorubicin [14], topotecan [15,16] and gemcitabine [7,8] have been reported in phase II trials, the median time to progression and median survival have characteristically been short. Experimental approaches to the reversal of platinum resistance have included the pharmacologic inhibition of DNA repair enzymes and their downregulation via antisense oligonucleotides. Despite successes in cell line models, the clinical utility of these approaches remains to be established.

Based on experimental models, combining cisplatin with gemcitabine also has the potential to address platinum resistance. The recognition that cisplatin-resistant cells upregulate nucleotide excision repair enzyme complexes ERCC1, ERCC2, and XPA [17–20] provides a potential target for gemcitabine. Gemcitabine, when directly incorporated into DNA as a triphosphate dFdCTP, results in “masked” chain termination. Concurrently, the diphosphate dFdCDP depletes cells of needed deoxynucleoside pools by inhibiting ribonucleotide reductase.

Using single agent gemcitabine in resistant cases, D'Agostino et al. treated 50 patients, of whom 7 (14%) had objective partial responses [7]. In the trial reported by Markman et al., the response rate in patients with measurable disease was 9%; the median time to progression was 4 months [8].

The current clinical trial, with cisplatin followed by gemcitabine, had an objective response rate of 16% in this platinum- and taxane-resistant cohort. This result was disappointing in view of published single institution reports. Rose et al., using gemcitabine followed by cisplatin days 1 and 8 every 3 weeks, reported 13/30 (43%) responses in resistant cases with measurable disease. The frequency of grades 3 and 4 neutrophil toxicity was 53% and platelet toxicity 36% [13]. Nagourney et al. reported on a mixed population, but in resistant cases, the majority of which had measurable disease, they observed 8/14 (57%) objective responses to cisplatin followed by gemcitabine, sequenced as in the present trial, but repeating the course every 21 days; in addition, they recorded grades 3 and 4 neutrophil toxicity in 82% and platelet toxicity in 97% of patients [12]. Both reports noted that toxicity was manageable with dose reductions. Neither study used prophylactic growth factor support.

Both trials included evaluable disease by Rustin [21] criteria and noted CA 125 responses. Some patients in the present trial had CA 125 data, and CA 125 responses were observed, but this was not a primary assessment.

The disparity between our results and those previously reported might be explained, in part, by the cooperative group multicenter trial setting, short platinum-free interval (mean duration of 3 months) and the inclusion of patients with intensive prior exposure, such as triplet or alternating doublet regimens. The increased thrombocytopenia seen in the second phase, even after dose reduction, likely reflects heavier pretreatment. Many of these women had completed a first-line protocol, GOG 182, which included eight cycles of carboplatin.

The clearest difference in this trial, however, is the drug schedule employed. It appears that more frequent dosing increases the response rate, as well as toxicity. Questions regarding timing and sequence will require further study. Van Moorsel reported a prolonged retention of gemcitabine in plasma when it was given 4 h after cisplatin [22]. However, a schedule-finding study by Kroep et al. actually suggested less leukopenia if the cisplatin was given first using a 4-h interval. Conversely, with a 24-h interval, there was significantly less leukopenia if the gemcitabine preceded cisplatin in the schedule [23].

We conclude that cisplatin plus gemcitabine has activity in platinum-resistant ovarian cancer. More frequent dosing of the combination, that is, every 21 days, with prophylactic growth factor support, should be studied. At the same time, it would be of interest to examine the cisplatin gemcitabine versus gemcitabine–cisplatin sequences and timing in more detail, for the possibility that the therapeutic index could be improved.

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