A Phase II Study of Gemcitabine Plus Cisplatin in Previously Untreated Advanced Ovarian Cancer

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Abstract. *Background: The primary objective was the evaluation of the effects of gemcitabine plus cisplatin on the overall response rate (ORR) of patients with advanced ovarian cancer; the secondary assessments included toxicity, time to progressive disease (TtPD) and the duration of response. Materials and Methods: Chemonaive patients with stage III/IV ovarian cancer received gemcitabine 1250 mg/m^2 (d 1,8) and cisplatin 75 mg/m^2 (d 1), every 21 days for a maximum of six cycles. Results: Between March 1999 and June 2003, 28 patients (median age 52 years, range 23-72) had received chemotherapy. Of 26 assessable patients, the ORR was 57.7% (95% CI, 42.7%-83.6%) based on four complete responses and eleven partial responses, six patients experienced stable disease, while five had progressive disease. The median survival was 28.1 months (95% CI, 11.4-33.4 months), the median TtPD was 10.5 months (95% CI, 1.4-44.2 months) and the median duration of response was 24.3 months (95% CI, 12.3-33.4 months). The most common grade 3/4 toxicities were nausea/vomiting (15.2%) and neutropenia (10.7%). There was no grade 3 or 4 thrombocytopenia. Conclusion: Gemcitabine plus cisplatin exhibited activity in advanced ovarian cancer with an acceptable toxicity profile.*

Ovarian cancer is the fourth most frequent cause of cancer death in women and currently the leading cause of gynecological malignancy worldwide (1). In 75% of the cases, cancer is diagnosed at an advanced stage (2). In Mexico, 1,937 new cases of ovarian cancer made it the sixth leading cause of cancer-related deaths in 2001 (3).

Exploratory laparotomy is used for diagnosis and the subsequent disease staging. Debulking surgery is often performed to reduce malignant tumors (2). A platinum combined with paclitaxel is considered to be the standard postoperative chemotherapy (4) In chemonaive patients, the combination has demonstrated an overall response rate (ORR) of 59% to 73%, with a median time to progressive disease (TtPD) of 16 to 19 months and a median survival time of 31 to 49 months (5-8). However, the long-term survival remains generally poor, with patients frequently relapsing or developing resistance to the standard regimens after an initial response. Thus, there is a substantial need for more effective and less toxic chemotherapeutic agents and combinations.

Gemcitabine, a pyrimidine antimetabolite, has shown activity in a variety of solid tumors, including ovarian cancer. Single-agent gemcitabine produced response rates of 13% to 22% in poor-prognosis patients with recurrent ovarian cancer (9, 10). The combination of gemcitabine and cisplatin demonstrated *in vitro* and *in vivo* synergism (11-14) and promising phase II activity in ovarian cancer for first-line (ORR 62%-77%) (15-18) and second-line treatment (ORR 44%-55%) (19-21). The combination was also shown to be active in other tumor types (22-25).

On the basis of these observations, a multicenter, single-arm, open-label, phase II trial of gemcitabine plus cisplatin, as first-line chemotherapy in patients with advanced ovarian cancer, was conducted. The primary objective was to determine the response rate, while secondary objectives were to evaluate the toxicity of the combination and time-to-event rates, including TtPD and duration of response.

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Materials and Methods

Eligibility criteria. Chemonaive patients, with histologically-proven stage III or IV epithelial ovarian cancer and with measurable lesions not amenable to cytoreductive surgery, were eligible for enrollment. Other eligibility criteria included the patients to be at least 18 years old, have a minimum life expectancy of 12 weeks, a Karnofsky performance status (KPS) of 70 or higher, adequate bone marrow reserve (absolute granulocyte count [AGC] $\geq 1.5x10^9$/L, platelets $\geq 100x10^9$/L and hemoglobin >9.0 g/100 mL), to use an approved contraceptive method during and 3 months after the treatment, patient compliance and their geographical proximity to allow adequate follow-up. Measurable disease was defined as a tumor lesion with clearly defined margins, as observed during exploratory laparotomy or by computed tomography (CT) scan or ultrasound imaging before the initial treatment. Patients were excluded when pleural effusion or ascites were the only evidence of disease, active infection was present, or there was a history of cancer within the previous 5 years. Additional exclusion criteria included the presence of metastasis to the brain or bone, secondary intestinal obstructions, inadequate liver and renal function (total bilirubin >1.5 times upper limit of normal [ULN], alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 times ULN [in case of liver metastasis, >5 times ULN], or serum creatinine 1.25 times ULN), the use of any investigational agent, pregnancy, or breast-feeding. This study was conducted according to the tenets of the Declaration of Helsinki and the applicable guidelines for good clinical practice and was approved by the local ethical review board. Prior to study enrollment, the patients gave their written informed consent.

Study design. This was a multicenter, single-arm, open-label, phase II study of gemcitabine plus cisplatin in chemonaive patients with stage III or IV ovarian cancer. A maximum of 46 qualified patients were to be enrolled in a two-stage sequential design with 16 patients enrolled into the first stage. If more than eight of the 16 patients responded, then another 30 patients were to be enrolled into the second stage. This study was designed to ensure a 72% chance of terminating enrollment early if the true response was as low as 40%, and a 14% chance of stopping early if the true response rate was as high as 60%.

Chemotherapy. The patients were administered gemcitabine 1250 mg/m^2 intravenously (*i.v.*) over 30 to 60 minutes on days 1 and 8, followed by cisplatin 75 mg/m^2 *i.v.* over 30 to 120 minutes on day 1, every 21 days, for a maximum of six cycles. Prior to chemotherapy and according to institutional standards, ranitidine 50 mg and ondansetron 8 mg were administered *i.v.* to prevent nausea and vomiting. The cisplatin dose was preceded by *i.v.* hydration, according to institutional guidelines. The patients received full supportive care, including transfusions of blood and blood products, antibiotics and antiemetics (steroids, antidiarrheals and analgesics).

The patients were allowed growth factor support for prolonged myelosuppression. No other chemotherapy, immunotherapy, hormonal therapy, radiation therapy, or experimental medications were permitted during the study. The treatment was discontinued for patients with progressive disease (PD), unacceptable toxicity, or on request of the physician or patient.

If a patient with PD had developed brain metastases during the study, but had attained a complete response (CR), partial response (PR), or stable disease (SD), the therapy was interrupted, and radiotherapy was administered to the brain. Palliative radiation for any other purpose was excluded.

Dose modifications were based on toxicities assessed 24 hours prior to therapy. The gemcitabine dose was decreased by 25% for an AGC of 0.5 to $0.99x10^9$/L or a platelet count of 50 to $74x10^9$/L. Gemcitabine was withheld if the AGC was less than $0.5x10^9$/L or the platelet count was less than $50x10^9$/L. Patients with febrile neutropenia, grade 4 thrombocytopenia, or bleeding associated with thrombocytopenia, received 75% of the starting doses of gemcitabine and cisplatin in the previous cycle. Cisplatin administration was withheld if the creatinine clearance was less than 45 mL/min/1.73 m^2, while for a creatinine clearance of 45 to 59 mL/min/1.73 m^2, cisplatin prehydration was increased, according to the manufacturer's directions. For grade 3/4 neurotoxicity, the treatment cycle was delayed. In the case of grade 3 non-hematological toxicities (except nausea/vomiting and alopecia), in subsequent cycles the cisplatin dose was reduced by 25% and the gemcitabine dose was reduced by 50%. On presentation of grade 4 non-hematological toxicities, the doses were either reduced by 50% or withheld from subsequent cycles, at the doctor's discretion. If a dose was withheld or missed on day 1 of a cycle, the next cycle officially started when the patient received the first dose. If the day-8 dose was withheld or missed, the cycle was continued as per the protocol.

Baseline and treatment assessments. The treatment evaluation at baseline and before every therapy cycle included a complete medical history, physical examination, Karnofsky performance status evaluation, vital signs, blood chemistry, urine analysis and electrocardiogram tracings. Complete blood counts and serum creatinine were determined prior to the day-1 and day-8 chemotherapy treatments. Toxicity was assessed at the end of each cycle according to World Health Organization (WHO) criteria. Tumor measurements were assessed at baseline to determine the disease status, the same assessment method being used for efficacy evaluation throughout the study. The tumors were measured at every medical visit by physical examination and every third cycle by radiological imaging (CT scan or pelvic ultrasound). The response was assessed after every three cycles, again by physical examination and radiological imaging studies. Laparotomy, at baseline and/or after three cycles, could be employed to confirm the response.

Radiologically-determined tumor responses were assessed according to the modified WHO criteria. A CR was defined as the complete disappearance of all known disease as determined by two observations not less than 3 weeks apart. A PR was indicated when at least a 50% decrease in total tumor size of the measured lesions had been determined by two observations not less than 3 weeks apart, as well as the absence of progression of any lesion or appearance of new lesions. SD was indicated when a >50% decrease or a <25% increase in the size of at least one measurable lesion could not be established. PD was defined as at least a 25% increase in the size of at least one measurable lesion or the appearance of new lesions. Patients with CR or PR received two additional cycles for confirmation of response, up to a maximum of six cycles.

The duration of PR was measured from the time of initial combination drug administration to the date of documented PD. The duration of CR was measured from the date of documented CR until the date of documented PD. The TtPD was from the date of the first drug dose until PD or death; patients, who were alive and without PD at the time of the analysis, were censored. The

Table I. *Patient characteristics (n=28).*

Characteristic	no. (%)
Age, years	
Median	52
Range	(23-72)
Karnofsky performance status	
70	2 (7.1)
80	4 (14.3)
90	13 (46.4)
100	9 (32.1)
Tumor stage	
Stage IIIC	17 (60.7)
Stage IV	11 (39.3)
Tumor histology	
Papillary	9 (32.1)
Mucinous	2 (7.1)
Endometroid	4 (14.3)
Adenocarcinoma	13 (46.4)
Exploratory laparotomy	
No (cytological study only)	12 (42.9)
Yes	16 (57.1)
No cytoreduction	26 (92.8)
Optimal cytoreduction (<2 cm residual tumor)	2 (7.2)

overall survival (OS) was measured from the time of first dose administration until death; patients who were alive at the time of this analysis were censored. Post-study follow-up visits were performed approximately every 3 months until PD. The data collected during these visits included a limited medical history, Karnofsky performance status, tumor measurement, post-study treatment (surgery and/or chemotherapy), duration of response to post-study chemotherapy and date of death. Confirmation of the response was collected at 3-month intervals during the first and second year and every 6 months thereafter.

Statistical methods. Patients who had been treated with at least one dose of the study drug combination were considered evaluable for toxicity. All confidence intervals (CIs) for the estimated response and time-to-event parameters were constructed with a significance level of p=0.05 (95% CI). Kaplan-Meier estimates (using SPSS for Windows statistical application software: SPSS Inc., Chicago, IL, USA) were calculated for the distribution of TtPD.

Results

Patient characteristics. Between March 1999 and June 2003, a total of 30 chemonaive patients were recruited and signed informed consent forms. In the first stage of the study, 16 patients were enrolled. While waiting for the response confirmation of at least 50% from the first stage, an additional 14 patients were included. When it had been confirmed that seven of the first 16 patients (<50%) were responders (three CR and four PR), the study was stopped due to lack of efficacy in the 30-patient population. Of these patients, two had withdrawn from the study prior to chemotherapy, meaning that the remaining 28 patients received the combination therapy (Table I). The median age was 52 years (range, 23-72). The majority of patients had a Karnofsky performance status of at least 90 (78.6%) and stage III disease (60.7%). Fourteen patients underwent exploratory laparotomy without cytoreductive surgery. An additional two were optimally debulked, representing a protocol violation, therefore, these two were not included in the response analysis. The surgical procedure was contraindicated for the remaining 12 patients, so only cytological study established the diagnosis.

Dose administration. The 28 enrolled patients completed a median of five cycles (range, 2-6) and a total of 127 cycles. Of the 254 planned doses of gemcitabine, there were 27 dose reductions (10.6%) and 24 dose omissions (9.4%). Of the 127 planned doses of cisplatin, there were two dose omissions (1.6%). These dose reductions and omissions were due mainly to neutropenia. A total of 29 cycles (22.8%) had to be delayed, mainly because of scheduling conflicts. The planned mean dose intensity for gemcitabine had been 833.3 mg/m^2/week, though the actual mean dose was 643.6 mg/m^2/week, for a relative dose intensity of 77.2%. The planned mean dose-intensity for cisplatin had been 25 mg/m^2/week, but that achieved was 21.3 mg/m^2/week, for a relative dose intensity of 85.2%.

Efficacy. Of the 28 enrolled patients, two had optimal cytoreduction at baseline and were excluded from the efficacy analysis; three failed to return for follow-up response evaluation and were classified as having PD in the response analysis. According to the modified WHO criteria, four CRs (15.4%) and eleven PRs (42.3%) were reported, for an ORR of 57.7% (95% CI, 42.7-83.6). Six patients (23%) had SD and five (19.2%) had PD. The median survival was 28.1 months (95% CI, 11.4-33.4 months), while the median TtPD was 10.5 months (95% CI, 1.4-44.2 months) and the median duration of response 24.3 months (95% CI, 12.3-33.4 months). At the time of analysis, three patients were alive with no appearance of tumor activity, 20 patients had died due to PD, and five had been lost to follow-up. Nine of the 26 assessable patients underwent interval surgery after cycle 3 or 7 and were confirmed to have <2 cm residual disease upon laparotomy.

Toxicity. The most common hematological toxicities were neutropenia (13.3% of cycles) and leukopenia (6.2%) (Table II). No grade 3/4 thrombocytopenia was reported and no patient developed febrile neutropenia or required red blood cell or platelet transfusions. The predominant grade 3/4 non-hematological toxicity was nausea/vomiting (15.7%). One patient with diabetes developed a grade 4 respiratory tract infection that was not related to chemotherapy, and also experienced temporary renal failure due to dehydration. No

Table II. *World Health Organization (WHO) grade toxicity (n=127 cycles).*

Toxicity	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	37 (29.1)	17 (13.4)	–	–
Leukopenia	39 (30.7)	16 (12.6)	5 (3.9)	3 (2.3)
Neutropenia	33 (26.0)	20 (15.7)	13 (10.2)	4 (3.1)
Thrombocytopenia	2 (1.6)	–	–	–
Nausea/vomiting	27 (21.2)	47 (37.0)	20 (15.7)	–
Diarrhea	20 (15.7)	5 (3.9)	2 (1.6)	–
Constipation	10 (7.9)	4 (3.1)	1 (0.8)	–
Mucositis	12 (9.4)	3 (2.3)	1 (0.8)	–
Alopecia	71 (55.9)	4 (3.1)	1 (0.8)	–
Infection	2 (1.6)	–	–	1 (0.8)
Peripheral neurotoxicity	20 (15.7)	2 (1.6)	–	–
Blood urea nitrogen	6 (4.7)	–	–	1 (0-8)
Serum creatinine	2 (1.6)	1 (0.8)	–	–

grade 3 or 4 neurotoxicity was observed, while grade 1/2 was seen in 17.2% of cycles. There were no withdrawals due to toxicity, neither death during the study period.

Discussion

The addition of paclitaxel to platinum in the first-line setting showed a survival improvement in some ovarian cancer studies (5, 6), but not in others (26, 27). These mixed results underscored the need to identify and develop more effective platinum-based combination therapies. In the present study, gemcitabine 1250 mg/m^2 plus cisplatin 75 mg/m^2 was evaluated in chemonaive patients with stage III or IV ovarian carcinoma. Of the 26 assessable patients, the ORR was 57.7%; the median duration of response was 24.3 months; the median TtPD 10.5 months; and the survival was 28.1 months. The regimen was well tolerated, with no clinically significant sequelae from the infrequently observed grade 3/4 hematological toxicities. The dose intensities of gemcitabine (77.2%) and cisplatin (85.2%) were acceptable.

Gemcitabine plus cisplatin has been demonstrated to be an active chemotherapy scheme against platinum-resistant ovarian cancer (21); a study with 22 patients, who were treated with gemcitabine 450 to 600 mg/m^2 and cisplatin 30 mg/m^2, both on days 1 and 8, showed ORR 64% with seven CR and seven PR; the progression-free interval was 3.9 months and the OS 15.8 months. However, toxic side-effects grade 3 and 4 were seen in 59% of the cycles.

The combination of gemcitabine plus cisplatin as first-line therapy, evaluating the same 21-day schedule as that of the current study in patients with suboptimally debulked stage III or IV ovarian cancer, has been studied in various phase II trials (15-18). Nogue and colleagues (15) administered the same regimen to 42 patients, but employed a higher cisplatin dose (100 mg/m^2). The clinical and pathological response rate was 70.7%, with a median progression-free survival of 10.4 months and a median survival of 23.4 months. Despite the favorable efficacy results, the dose intensities of both drugs were modest (gemcitabine 71.9%, cisplatin 73.0%), and presumably reflected the incidence of grade 3/4 neutropenia (52.4% of patients) and nausea/ vomiting (67% of patients), that necessitated dose modifications. Given the comparatively lower frequency of grade 3/4 neutropenia (13.3%) and nausea/vomiting (15.7%) observed in our study, the higher frequency of these events in the Nogue study was probably related to the higher cisplatin dose.

In a study by Bauknecht and colleagues, the combination was evaluated in 44 older patients (median age 70 years), of whom the vast majority (95%) had suboptimally-debulked ovarian cancer and approximately one-third of whom had a Karnofsky performance status <80. In this study, an ORR of 62% was reported, with a median progression-free survival of 13.8 months and a median survival of 27.7 months (16). In spite of the high incidence of grade 3/4 neutropenia (60%) and nausea/vomiting (67%), the toxicity had generally been manageable with minimal clinical sequelae.

Another study by Belpomme and colleagues yielded an ORR of 64.9% in 37 assessable patients (17). The median TtPD was 13.4 months and median survival was 24 months. The most common toxicities were neutropenia (grade 3/4 neutropenia in 69% of patients) and emesis (grade 3/4 in 36% of patients), but these had also been considered manageable. Finally, in a small study by Shaharyar and colleagues, the ORR was 77% in 30 evaluable patients (18), with a mild toxicity profile and no grade 3/4 toxicities reported.

Conclusion

In conclusion, the results of this study further underscore the activity and tolerability of this 3-week regimen of gemcitabine (1250 mg/m^2) plus cisplatin (75 mg/m^2) as first-line treatment for patients with advanced ovarian carcinoma, yielding results consistent with similar trials in first-line ovarian cancer patients. Given the activity and modest toxicity profile of gemcitabine plus cisplatin, especially the notable absence of significant neurotoxicity, further evaluation of this combination in the phase III setting may be warranted.

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