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Clinical report

Phase II study of gemcitabine and cisplatin in chemonaive patients with advanced epithelial ovarian cancer

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This phase II study evaluated the activity of gemcitabine (Gemzar) plus cisplatin (Platinol) as first-line treatment of advanced epithelial ovarian cancer. Forty-two chemonaive patients with advanced (stage III and IV) epithelial ovarian cancer received gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 100 mg/m^2 on day 1, every 3 weeks, up to eight cycles. The median number of cycles completed was 5 (range 2–8). Of the 41 patients evaluable for tumor response, 20 had a partial response and nine had a complete response, for an overall clinical and pathologic response rate of 70.7% (95% CI 56.8–84.6%). Median overall survival for all 42 patients was 23.4 months (95% CI 15.9–29.9 months) and the median progression-free survival time was 10.4 months (95% CI 9.4–13.5 months). The combination was generally manageable. Hematologic toxicity (grade 3/4 neutropenia: 31.0/21.4%; grade 3/4 thrombocytopenia: 9.5/4.8%; grade 3/4 anemia: 11.9/0%) and nausea and vomiting (grade 3/4: 35.7/31.0%) were the most common toxicities. There was one toxic death (septic shock due to hematologic toxicity-induced infection). We conclude that gemcitabine plus cisplatin is active and feasible as first-line treatment of advanced epithelial ovarian cancer. Further clinical trials with the addition of gemcitabine to first-line treatment appear warranted. [© 2002 Lippincott Williams & Wilkins.]

Key words: Gemcitabine, chemonaive, cisplatin, ovarian cancer.

Introduction

Ovarian cancer is the fifth most frequent cause of cancer death in women and is currently the leading gynecologic malignancy. Worldwide, there are 166 000 cases and 101 000 deaths from ovarian cancer annually.[1] The majority of ovarian cancers have already progressed to an advanced stage by the time of diagnosis. Although survival rates for patients with advanced ovarian cancer have increased during the past 2 decades, most patients continue to relapse and die from their cancer, despite high initial response rates. The addition of paclitaxel (Taxol) to cisplatin (Platinol) has improved survival in some studies.[2,3] However, other studies failed to demonstrate an advantage with the addition of paclitaxel to first-line therapy,[4,5] probably indicating that it lacks benefit over its sequential administration after progression. Despite this, most clinicians have adopted paclitaxel and carboplatin (Paraplatin) as the standard first-line regimen. There remains a need, however, to identify new regimens that might further improve these results. Several cytotoxic agents with antitumor activity in recurrent disease, such as topotecan (Hycamtin), liposomal doxorubicin (Doxil) and gemcitabine (Gemzar), are logical candidates for incorporation into front-line regimens. In developing such combinations, two strategic approaches are employed: the addition of the new drug to paclitaxel/platinum as a triplet and the development of platinum-based doublets that can be given in sequence with paclitaxel/carboplatin.[6]

Gemcitabine, a nucleoside antimetabolite, is an active agent in ovarian cancer. Second-line gemcitabine monotherapy has demonstrated response rates of 18–22%.[7,8] In subsets of patients previously treated with both cisplatin and paclitaxel, it achieved response rates of 13–13.9%,[9,10] comparable to the activity of other commonly used agents in this

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setting.[11] Experimental studies have also shown *in vitro* synergy (and at least *in vivo* additivity) between gemcitabine and cisplatin in various models.[12] In clinical studies, the combination of gemcitabine and cisplatin has been used successfully in phase III trials in non-small cell lung (response rate 30.4%) and bladder cancers (49%).[13,14]

Therefore, we performed this multicenter phase II study to evaluate the activity of gemcitabine and cisplatin in chemonaive patients with advanced ovarian cancer. The primary objective of this study was to determine the objective tumor response rate; the secondary objectives were to characterize the nature of the toxicity, time to progression and duration of survival of gemcitabine and cisplatin in this patient group.

Materials and methods

Eligibility criteria

Female patients at least 18 years of age, with a histologic or cytologic diagnosis of epithelial ovarian cancer, were enrolled in the study. Other selection criteria included: International Federation of Gynecology and Obstetrics (FIGO) stage IIB, IIC, III or IV disease, not amenable to curative surgery or radiotherapy; no prior chemotherapy; Zubrod performance status (PS) of 0–2; residual disease consisting of postoperatively bidimensionally measurable lesions (at least 1×1 cm) with clearly defined margins on radiologic scan or physical examination (lesions remaining post-surgery and documented intraoperatively were included); and adequate bone marrow reserve [white blood cell (WBC) count $\geqslant 3.5 \times 10^9$/l, platelets $\geqslant 100 \times 10^9$/l and hemoglobin $\geqslant 10$ g/dl].

Study exclusion criteria were: presence of serious concomitant systemic disorders, second primary malignancy (except *in situ* carcinoma of the cervix, adequately treated basal cell carcinoma of the skin or prior malignancy treated >5 years before study start without recurrence), complete bowel obstruction, brain metastases or borderline ovarian tumor histology. Other exclusion criteria included inadequate liver function [bilirubin >1.5 times the upper limit of normal (ULN)]; abnormal prothrombin time (PT) or activated partial thromboplastin time (aPTT) >1.5 times control; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the ULN (or >5 times the ULN in patients with known metastatic liver disease); inadequate renal function (creatinine >1.5 mg/dl); calcium above the ULN; or concomitant cytotoxic immunotherapy, hormonal therapy or other therapy using an experimental agent. A local ethics committee approved the study protocol and all patients gave informed, written consent.

Study design

The phase II trial design was an open-label, non-randomized, single-arm study using a two-stage sequential design. Enrollment was to be interrupted after the first 20 patients. If more than four patients from the first cohort showed response to therapy, another 20 qualified patients were to be enrolled in the second stage of the study, for a maximum enrollment of 40 qualified patients.

The study design ensured a 63% chance of terminating enrollment early at the end of the first stage if the true response was as low as 20% and a 12% chance of stopping early if the true response rate was as high as 35%. If enrollment continued through the end of the second stage, the procedure allowed a sufficiently accurate estimate of the true tumor response rate. The width of the interval varied according to the actual observed response rate, but a response in 14 of 40 (35%) patients would produce a 95% confidence interval (CI) of 21–52%.

Treatment plan

Gemcitabine 1250 mg/m^2 was administered i.v. over 30 min, once weekly for 2 weeks (days 1 and 8), followed by a 1-week rest period. Cisplatin 100 mg/m^2 was administered i.v., per institutional procedure, before gemcitabine on day 1. This 3-week (21-day) schedule defined one cycle of treatment. Standard prophylactic antiemetic treatment with a 5-HT_3 antagonist, plus dexamethasone, was administered. Each patient received two cycles of study treatment unless disease progression or unacceptable toxicity occurred.

Following the first two cycles, the type of response determined continuation of treatment. Patients with progressive disease (PD) were removed from the study. For stable disease (SD), patients received two additional cycles, for a total of four; upon tumor reassessment, if SD was still evident, further treatment continued at the discretion of the investigator. For a partial response (PR), patients received another two cycles of chemotherapy, for a total of four; upon

reassessment, if a PR was still evident and the disease was operable, patients underwent surgery and were discontinued from the study. If a PR was still evident after the two additional cycles of therapy but the disease was inoperable, patients received another two cycles of therapy, for a total of six. Patients with a complete response (CR) were permitted to complete six additional cycles of therapy, for a maximum of eight, at the discretion of the investigator.

Cycles were not started unless the WBC count was $\geqslant 3.5 \times 10^9$/l and platelets were $\geqslant 100 \times 10^9$/l. The day 8 gemcitabine dose was omitted for absolute granulocyte counts $\leqslant 0.5 \times 10^9$/l and platelets $< 50 \times 10^9$/l. Missed doses or doses held due to toxicity were not given at a later time. If the day 8 gemcitabine dose was missed, it was not given; the treatment cycle remained at 3-week intervals. Both drug doses were adjusted or omitted for WHO grade 3/4 non-hematologic toxicity, excluding nausea/vomiting and alopecia. Subsequent doses were also adjusted for hematologic toxicity. Patients with sustained febrile neutropenia, grade 4 thrombocytopenia or bleeding associated with thrombocytopenia were treated at 75% of the starting dose. The dose reduction applied to all infusions within a cycle. Subsequent dose escalations back to the original dose were allowed, provided the patient tolerated the doses given at 75%. The cisplatin dose was adjusted for renal toxicity based on serum creatinine levels of 1.5–2.0 mg/dl and omitted for serum creatinine > 2.0 mg/dl. Cisplatin therapy was reduced or stopped for ototoxicity.

Baseline and treatment assessments

Before enrolling on study, the disease status of each patient was assessed by medical history and physical examination, full and differential complete blood counts, blood chemistry, urinalysis, electrocardiogram, vital signs, evaluation of Zubrod PS, chest X-ray, serum CA-125 levels and measurement of palpable or visible tumor lesions by gynecologic examination. The disease status of the patient was also assessed using computed tomography scanning, magnetic resonance imaging, ultrasound or laparotomy, as indicated. Before each administration of each gemcitabine dose the patients' weight was measured and PS evaluated. The CA-125 levels, a limited medical history and physical examination (including tumor measurements) were obtained before every therapy cycle. Gynecologic examination, chest X-ray and radiologic imaging studies were undertaken before every other therapy cycle or earlier when indicated by CA-125 elevation or physical examination.

Clinical response assessments (clinical CR or PR) were based on the imaging modality used at baseline or physical examination (clinically confirmed response: clinical CR or PR). Pathologic responses were assessed by laparotomy (pathologically confirmed response: pathologic CR or PR). The same assessment methodology that was used to determine baseline disease status was used consistently throughout the study for efficacy evaluation.

All eligible patients who received at least one cycle of gemcitabine and cisplatin were evaluable for response. Clinical radiologic response was evaluated according to standard WHO criteria. Complete response was defined as the disappearance of all known disease, determined by two observations $\geqslant 4$ weeks apart and a normal CA-125 level. Partial response was indicated if there was a $> 50\%$ decrease in total tumor size of the lesions by two observations $\geqslant 4$ weeks apart. In addition, there could be neither appearance of new lesions nor progression of any lesion. Stable disease was indicated if a 50% decrease in total tumor size could not be established. Alternately, stable disease was noted if a 25% increase in the size of one or more measurable lesions could not be demonstrated. Progressive disease was defined as a $> 25\%$ increase in the size of at least one measurable lesion or the appearance of new lesions.

For patients with baseline lesions detected solely through laparotomy, response was based on assessment of serum CA-125 levels at baseline and throughout the study.[15] Response could then be confirmed by a second-look laparotomy. Complete response in these patients was defined as a normal CA-125 level and PR as a $\geqslant 50\%$ decrease of CA-125 from baseline. Stable disease was indicated when either a 50% decrease or 25% increase of CA-125 could not be established. Progressive disease was defined by a $\geqslant 25\%$ increase of CA-125 and/or appearance of new lesions.

Each patient's best response was determined as follows: for patients undergoing second-look laparotomy for pathologic confirmation of response, the pathologically determined response was considered the best response and took precedence over CA-125 response or clinically confirmed response. For patients who did not have pathologic confirmation of response, the best response was based on clinical or CA-125 response criteria, as noted above.

Survival was measured from the administration of the first dose until the date of death. Disease

progression was measured from the first dose until the date of PD or death due to tumor.

All patients who received at least one dose of gemcitabine or cisplatin were evaluated for safety, which included summaries of the number of blood transfusions required, side effects, laboratory changes and toxicity (the patient's maximum toxicity grade for each parameter). Toxicity for hematologic and non-hematologic parameters was evaluated at the end of each cycle using standard WHO criteria. Ototoxicity was evaluated using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale (version 1).

Statistical assessments

In addition to the calculation of tumor response rate, based on the patient's best response, Kaplan–Meier estimates, including 95% CIs, were calculated for the distributions of overall survival and time to progressive disease. The 95% CI for median progression-free survival time was calculated according to the method of Brookmeyer and Crowley.[16]

Results

Patient characteristics

Forty-two chemonaive female patients with advanced epithelial ovarian cancer from seven institutions in Spain entered the study from October 1995 through May 1996. The median age of these patients was 63 years (range 41–77 years). Patient characteristics are presented in Table 1.

Response

The best responses for 41 evaluable patients are summarized in Table 2. One patient was not considered evaluable because of a lack of residual bidimensionally measurable disease after baseline laparotomy, although she had elevated levels of CA-125. Nine patients had a CR and 20 had a PR, for an overall response rate of 70.7% (95% CI 56.8–84.6%). In addition, nine (21.9%) patients had SD and three (7.3%) progressed. Twenty-one patients had determination of best response by second-look laparotomy: five showed a pathologic CR, 15 a pathologic PR and one developed PD. The non-evaluable patient described above achieved a CR based on CA-125 and if her data is included, the overall response rate would be 71.4% (30 of 42).

Table 1. Baseline patient characteristics

No. patients enrolled	42
Age (years) [median (range)]	62.5 (41–77)
Race (Caucasian)	42 (100%)
Debulking surgery	
optimally debulked	7 (16.7%)
suboptimally debulked	22 (52.4%)
not done	13 (31%)
Zubrod performance status[a]	
0	3 (7.1)
1	26 (61.9)
2	12 (28.6)
Tumor stage	
III	27 (64.3%)
IV	15 (35.7%)
Grade of differentiation	
well	1 (2.4%)
moderate	9 (21.4%)
poor	24 (57.1%)
unknown	8 (19.0%)
Histologic type	
serous	29 (69.0%)
endometrioid	3 (7.1%)
mucinous	3 (7.1%)
clear cell	2 (4.8%)
undifferentiated	5 (11.9%)

Table 2. Best response ($n=41$ evaluable patients)

	Total (%)
Overall response rate[a] (complete + partial)	29 (70.7)
95% CI	56.8–84.6
CR	9 (21.9)
PR	20 (48.8)
SD	9 (21.9)
PD	3 (7.3)
Clinical response assessment	20
CR	4
PR	5
SD	9
PD	2
Pathologic response assessment	21
CR	5
PR	15
PD	1

Survival and time to progressive disease

All 42 patients were included in the analyses of survival. A total of 29 patients had died as of the date of the last post-study follow-up. Thirteen patients

were either known to be alive or were lost to follow-up. The median overall survival time was 23.4 months (95% CI 15.9–29.9 months), with a 1–year survival rate of 78.2% (95% CI 65.6–90.8%). The 2–year survival rate was 47.5% (95% CI 31.3–63.7%) and the 3-year survival rate was 18.2% (95% CI 3.0–33.4%). The median progression-free survival time was 10.4 months (95% CI 9.4–13.5 months), with a 1–year progression-free survival rate of 46.4% (95% CI 31.0–61.8%). Figures 1 illustrates the respective data for overall survival and time to progressive disease.

Toxicity

All 42 patients entered on study were evaluable for toxicity. Grades 3/4 hematologic and non-hematologic toxicities are provided in Table 3. None of the 22 (52%) patients with grade 3/4 neutropenia experienced neutropenic fever, although there was one toxic death during the study (cycle 6) due to septic shock from *Escherichia coli* infection associated with hematologic toxicity (grade 3 anemia, and grade 4 neutropenia and thrombocytopenia). One patient with grade 3 thrombocytopenia received a platelet transfusion in cycle 3. No patients experienced grade 3/4 elevations of creatinine. Three (7.1%) patients experienced NCI-CTC grade 3 ototoxicity. Five (12%) patients discontinued treatment because of drug-related toxicity: severe nausea/vomiting ($n=2$), infection, vomiting and pre-renal impairment ($n=1$), kidney tubular disorder ($n=1$), and moderate paresthesia ($n=1$).

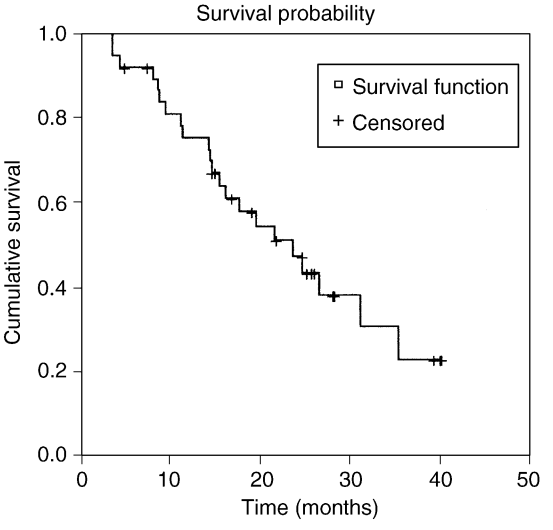

Figure 1. Overall survival and time to progressive disease ($n=42$).

Table 3. WHO toxicity grades[a] ($n=42$ patients)

	Grade 3 [*n* (%)]	Grade 4 [*n* (%)]
Hematologic toxicity		
anemia	5 (11.9)	0 (0)
leukopenia	8 (19.0)	2 (4.8)
neutropenia	13 (31.0)	9 (21.4)
thrombocytopenia	4 (9.5)	2 (4.8)
Non-hematologic toxicity		
alopecia	13 (31.0)	2 (4.8)
infection	1 (2.4)	1 (2.4)
nausea/vomiting	15 (35.7)	13 (31.0)
oral	1 (2.4)	0 (0)

[a]Worst toxicity in any cycle.

Study treatment administration

All 42 patients completed at least one cycle of cisplatin and gemcitabine (median 5 cycles; range 2–8). A total of 20 (47.6%) patients received at least six cycles of therapy. The mean dose intensity of gemcitabine was 71.9% of the planned dose intensity and that of cisplatin was 73.0%. There were 26 gemcitabine dose omissions (6.2% of the 416 protocol-planned doses). The most common reason for dose omission was leukopenia (46.2% of omissions), followed by diarrhea and malaise (each accounting for 11.5% of omissions). There were seven cisplatin dose omissions (3.4% of the 208 protocol-planned doses), all due to leukopenia.

A total of 68 gemcitabine doses were reduced. The most common reason for these dose reductions was leukopenia (82.4% of reductions). A total of 26 doses of cisplatin were reduced, of which leukopenia was the primary cause (73.1% of reductions).

Discussion

This study demonstrates that the combination of gemcitabine and cisplatin is an active treatment in patients with advanced ovarian cancer, achieving a 70.7% overall response rate, a 23.4-month median survival and a 10.4-month median time to progressive disease. The enrolled patients had a poor prognosis—35 (83.3%) patients had suboptimal residual disease and more than half had poorly differentiated disease.

The gemcitabine and cisplatin regimen was well tolerated, with patients receiving a median of five

cycles of therapy. The most frequent toxicities were hematologic, nausea/vomiting and alopecia. The high rate of neutropenia and nausea/vomiting is almost certainly related to the high dose of cisplatin delivered,[17,18] as were four of the five drug toxicity-related discontinuations. There was one death from neutropenic complications. Our study design employed a high dose of cisplatin (100 mg/m^2) based on phase III data from Muggia *et al.*[5] who used cisplatin 100 mg/m^2 as the standard arm of the Gynecologic Oncology Group (GOG) 132 study. Because most investigators now agree that cisplatin at 75 mg/m^2 is adequate for the optimal combination treatment of ovarian cancer,[2,3] it is probable that this dose would produce a more tolerable regimen (without loss of efficacy) when used with the same gemcitabine dose/schedule.

The combination of gemcitabine and cisplatin has been studied in two other phase II trials of patients with advanced ovarian cancer. Using a cisplatin dose of 75 mg/m^2, Krakowski *et al.*[19] reported a 71% response rate, although they noted that 63% of patients developed grade 3/4 neutropenia and 28% grade 3/4 thrombocytopenia. Emesis was lower, probably due to the lower dose of cisplatin. Survival data were not available at the time of the preliminary report. Another study, using similar schedules and doses of drugs in patients aged 60 years or older, obtained a 53% response rate with similar toxicity: 50% of patients developed grade 3/4 neutropenia, 22% had grade 3 thrombocytopenia, 17% had grade 3 anemia and 28% had grade 3 emesis.[20] Survival data were not reported.

Hansen *et al.* examined a triplet combination of gemcitabine, carboplatin and paclitaxel in the first-line treatment of ovarian cancer, and reported a preliminary overall response rate of 100% in 24 evaluable patients.[21] Responses included 14 CRs (58%) and 10 PRs (42%). In a study by Geertsen *et al.*, a similar combination of gemcitabine and paclitaxel, with either carboplatin or cisplatin, also achieved a 100% response rate (in 19 evaluable patients), including 7 (37%) patients with a CR and 12 (63%) with a PR who were treated previously with platinum.[22]

Conclusion

The combination of gemcitabine with full doses of cisplatin is feasible and active when administered as first-line treatment of ovarian cancer. Hematologic toxicity and emesis are the most common adverse effects. These results, and those reported with first-line triplet combinations, justify further evaluation of the addition of gemcitabine to standard first-line therapy with platinum and paclitaxel, either as sequential or triplet combinations.

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