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Clinical report

Multicenter phase II study of gemcitabine in previously untreated patients with advanced epithelial ovarian cancer

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Gemcitabine has activity in advanced ovarian cancer, with responses in platinum-resistant disease. This study assessed the activity of gemcitabine in previously untreated patients with advanced epithelial ovarian cancer. All patients had histologically verified invasive epithelial ovarian cancer, International Federation of Gynecology and Obstetrics (FIGO) stage III/IV disease and no prior chemotherapy. Patients received gemcitabine 1250 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. Radiological response was assessed after two cycles. Between December 1992 and October 1995, 35 patients were enrolled. Of 33 evaluable patients, there was one complete response and five partial responses, for an overall response rate of 18% (95% confidence interval 7–36%). Forty-two percent of patients had a greater than 50% decrease in their CA-125 levels. Of the 25 patients who received platinum-based chemotherapy following treatment with gemcitabine, 12 achieved an overall response rate of 48%. Toxicity was mild, with two episodes of WHO grade 4 neutropenia (not associated with fever) and two episodes of grade 4 thrombocytopenia (not associated with bleeding). Gemcitabine has single-agent activity for poor-prognosis patients with advanced ovarian cancer. Similar results with subsequent platinum-based therapy indicate a lack of cross-resistance. This, combined with gemcitabine's favorable toxicity profile, warrants testing in comparative trials. [© 2001 Lippincott Williams & Wilkins.]

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Introduction

Although epithelial ovarian cancer is a chemosensitive tumor that has high response rates to platinum-based combination chemotherapy, long-term survival rates in patients with advanced disease remain low. Five-year survival rates of 15–35% for patients with stage III disease and 5% for patients with stage IV disease have been reported.[1] Patients with extensive residual disease after initial diagnosis and surgery do particularly poorly. In a large, randomized study conducted by the Gynecological Oncology Group (GOG), 388 patients with suboptimally debulked stage III and stage IV disease treated with paclitaxel/cisplatin versus cisplatin/cyclophosphamide demonstrated a response rate of 77% for the paclitaxel combination and a median progression-free survival of 18 months.[2] Despite these encouraging results, the majority of chemotherapy-treated patients still die from disease progression. Therefore, efforts to identify new, more active agents continue. Gemcitabine (2′,2′-difluorodeoxycitidine) is a nucleoside antimetabolite that structurally resembles cytosine arabinoside (cytarabine). In a multicenter phase II study by Lund *et al.*, 50 patients, all of whom had received previous platinum-based chemotherapy (40 were platinum-resistant and the majority also had bulky disease), received gemcitabine 800 mg/m^2 i.v. weekly for 3 weeks followed by a week of rest. Treatment was well tolerated and eight (19%) of 42 evaluable patients achieved a partial response [95% confidence interval (CI) 9–34%].[3] This compared favorably with response rates reported for paclitaxel of 11.9–29% in platinum-refractory patients.[4–6]

Because of gemcitabine's demonstrated activity in advanced ovarian cancer with significant responses even in platinum-resistant disease, we conducted a phase II multicenter study to evaluate the activity and toxicity of single-agent gemcitabine in previously untreated patients with advanced epithelial ovarian cancer.

Patients and methods

Eligibility criteria

All patients were required to have histologically verified, invasive, epithelial ovarian cancer, stage IV or non-maximally debulked stage III disease according to the International Federation of Gynecology and Obstetrics (FIGO) classification system, and no prior chemotherapy. In addition, patients needed to have bidimensionally measurable disease or unidimensionally measurable disease documented by more than one evaluation method (unidimensional measurable disease had to be present at more than one site) and had to be 18–75 years old, with a World Health Organization (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score $\leqslant 2$ and a life expectancy >3 months, and available for follow-up evaluation. Other study entry criteria included adequate renal function (serum creatinine <180 μmol/l), hepatic function [serum bilirubin <3 times the upper limit of normal (ULN), aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels <3 times the ULN, and prothrombin time (PT) and activated partial thromboplastin time (APTT) <1.5 times the ULN] and bone marrow reserve (leukocytes $>3\times10^9$/l, hemoglobin >10 g/dL and platelets $>100\times10^9$/l). Patients with hypercalcemia, a prior history or malignancy (except adequately treated basal cell carcinoma of the skin or *in situ* carcinoma of the uterine cervix) and central nervous system (CNS) disease, as well as those who were receiving concomitant cytotoxic or hormonal therapy, were excluded.

This study was conducted according to the principles stated in the latest version of the Declaration of Helsinki and the applicable guidelines for good clinical practice (GPC), and approved by the local ethics committees of the participating centers. Each patient gave written informed consent prior to study entry.

Study design

This multicenter, phase II study utilized a two-stage design for patient accrual to minimize the number of patients treated in the event that the regimen was not beneficial. If no responses occurred in the first 15 evaluable patients, accrual was to be stopped and the regimen was to be deemed unworthy of further study. If one or more, but less than four, response(s) occurred, accrual was to continue until an additional 15 evaluable patients were enrolled. In the event of four or more responses in the first 15 evaluable patients, the regimen was to be deemed promising and accrual was to be stopped. This procedure tested the null hypothesis that the true response probability is 20%, with a significance level (i.e. the probability of deciding whether the regimen is active) of 0.865.

Treatment

Patients recevied gemcitabine 1250 mg/m^2 weekly (on days 1, 8 and 15) for 3 weeks followed by 1 week of rest. Gemcitabine was administered as a 30-min infusion in an out-patient setting.

Dose modifications were made based on the blood counts prior to each course. If the white blood cell count (WBC) was $\geqslant 2.0\times10^9$ and $<3.0\times10^9$/l, or the platelet count was between 50×10^9 and 99×10^9/l, patients received 50% of the calculated dose. If the WBC was $<2.0\times10^9$/l or the platelet count was $<50\times10^9$/l, gemcitabine was omitted. Patients who developed grade 2 or greater skin toxicity or other grade 3 non-hematologic toxicity could have had a dose reduction of 50% at the discretion of the investigator. Hematopoietic growth factors and 5-HT$_3$ antagonists were not used prophylactically.

Assessments

Vital signs were monitored before and after each infusion. Full blood count, reticulocyte count, blood chemistry and dip-stick urinalysis were performed weekly. PT and APPT were assessed every 4 weeks. As an additional measure of response, CA-125 response was assessed every 8 weeks, which was defined as a 50% or more decrease in CA-125 level from baseline, confirmed with a repeated measurement performed 1 month later.

Radiologic assessment of response was made after two cycles of treatment and verified by a repeated assessment at 1 month. Radiologic tumor responses and toxicities were assessed according to standard WHO criteria. Patients who received two or more cycles were considered assessable for response. All patients who received gemcitabine were included in the safety analysis.

Results

Patient demographics

Between December 1992 and October 1995, 35 patients were enrolled in this study at eight centers. Patient characteristics are summarized in Table 1. Only five patients had previously undergone total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy or radical debulking. The majority of patients (66%) had FIGO stage IV disease. One patient with bulky stage II disease was inadvertently entered into the study. The most common (49%) histologic subtype was poorly differentiated disease.

Activity

Two patients were not evaluable for response: one developed a small bowel obstruction before receiving two cycles of chemotherapy and another had unidimensionally measurable disease at only one site. Of the 33 evaluable patients, one had a complete response and five had partial responses to gemcitabine therapy, for an overall response rate of 18% (95% CI 7–36%). Two patients with partial responses did not have computerized tomography (CT) scans repeated at 1 month to verify the response: one because of the development of left ventricular failure and poor renal function (not attributable to study drug) who received no further treatment or verification scan, and the other because of deteriorated renal function (causality uncertain) who was given carboplatin-based chemotherapy before a verification scan could be done. Thus, these responses were counted as stable disease. Responses were seen at all disease sites and occurred early during treatment, i.e. after a median of 2 courses (range 2–4). Median response duration was 6 months (range 3–11+). Fifteen (45%) patients had stable disease and 12 (36%) patients progressed.

In terms of CA-125 levels, 14 (42%) patients demonstrated a response (a 50% or more decrease in CA-125 levels confirmed 1 month later). Nine (27%) patients had a decrease in CA-125 levels of less than 50%, three (9%) had an increase in CA-125 levels and seven (21%) patients' measurements were not done. A total of 25 patients received platinum-based chemotherapy following treatment with gemcitabine (Table 2). Of these patients, 12 (48%) had radiological responses [three (12%) complete and nine (36%) partial responses]. At the time of this analysis, with a median follow-up of 10 months, the median survival has not been reached.

Dose adjustments

Patients received a median of 3 cycles of treatment (range 1–7). A total of 303 (93%) of a potential 327 gemcitabine injections were administered; there were 24 dose omissions and 59 dose reductions, primarily because of leukopenia. Four injections were delayed. The reasons for these dose modifications are delineated in Table 3.

Toxicity

All 35 patients were evaluated for toxicity. Hematologic toxicity was mild (Table 4). Twelve (34%) patients had grade 3 or 4 neutropenia; however, there were no episodes of neutropenic fever. Two (6%) patients had grade 4 thrombocytopenia, although neither of these cases was associated with bleeding.

Non-hematologic, laboratory toxicity also was mild, with few grade 3 or 4 non-laboratory toxicities reported (Table 4). Eleven (31%) patients had grade 2 or 3 changes in liver function tests, which were

Table 1. Summary of patient characteristics

No. patients enrolled	35
No. patients evaluable for response	33
Age (years)	
median (range)	61 (42–77)
Performance status (WHO–ECOG)	
0	6 (17%)
1	21 (60%)
2	8 (23%)
Grade of histological differentiation	
poor	17 (49%)
moderate	10 (29%)
well	1 (3%)
undifferentiated	1 (3%)
unknown	6 (17%)
FIGO stage	
IIIB	1 (3%)
IIIC	10 (29%)
IV	23 (66%)
II[a]	1 (3%)

[a]Protocol violation.

Table 2. Response to subsequent platinum-based chemotherapy (*N*=25)

Chemotherapy regimens	No. of patients (%)
Carboplatin alone	16
Carboplatin/cyclophosphamide	3
Carboplatin/paclitaxel	6
Responses	
complete response	3 (12)
partial response	9 (36)

mostly transaminase elevations. All of these episodes were self-limiting and asymptomatic. In terms of symptomatic toxicity (Table 5), 13 (37%) patients experienced a mild (grade 1 or 2) erythematous maculopapular rash, which usually occurred with the first or second injection of treatment and resolved with subsequent injections without the need for supportive treatment. One patient was discontinued from the study due to persistent rash. One (3%) patient experienced grade 3 lethargy, which, although present before the patient received gemcitabine, worsened upon two cycles of treatment; the investigator considered this event drug related. One patient had complete alopecia and one had grade 3 fever not accompanied by infection. Six (17%) patients had grade 3 nausea and vomiting, three of whom received ondansetron or granisetron. Four of these patients were subsequently given prophylactic i.v. ondansetron on a routine basis. Prophylactic antiemetics were not required in the first treatment cycle. Two patients each experienced grade 3 dyspnea, but neither episode was considered drug related. One event was a possible pulmonary embolism, and the other a left ventricular failure secondary to ischemic heart disease. One patient with pre-existing hypertension developed deteriorating renal function and left ventricular failure at the end of cycle 4. This patient received 1 week of treatment at cycle 5 with a 50% dose reduction, but came off study and died 1 week later because of further deterioration in her condition. Post mortem examination confirmed left ventricular failure and hypertensive changes. Ovarian cancer was present in the patient's abdominal lymph nodes.

Table 3. Dose modifications

Reason for dose modification	No. of injections
Dose reductions	59
leukopenia	45
asthenia	4
rash	4
thrombocytopenia	2
left ventricular failure	2
protocol violation	2
Dose omissions	24
leukopenia	7
fever	4
bowel obstruction	3
rash	3
thrombocytopenia	2
personal reasons	1
hematuria	1
surgical procedure	1
progressive disease	1
edema	1
Dose delays	4
concurrent viral illness	2
personal reasons	2

Discussion

Despite the activity of the new combinations using taxanes and platinum agents against ovarian cancer, the search for new active agents continues because patients continue to die from their disease. Gemcitabine has demonstrated single-agent activity in previously treated patients with relapsed ovarian cancer, with a response rate of 19% in 42 evaluable patients, 40 of whom were platinum-resistant.[3] Previously published response rates for single-agent, first-line chemotherapy include 50% for chlorambucil and cyclophosphamide, 25–40% for cisplatin, 50% for carboplatin, 30% for doxorubicin, and 32–61% for

Table 4. Summary of worst laboratory toxicities (N=35)

Laboratory parameter	WHO grade [*n* (%)]				
	0	1	2	3	4
Leukopenia	10 (29)	8 (23)	13 (37)	4 (11)	0 (0)
Neutropenia	13 (37)	2 (6)	8 (23)	10 (29)	2 (6)
Anemia	5 (14)	21 (60)	5 (14)	3 (9)	1 (3)
Thrombocytopenia	32 (91)	1 (3)	0 (0)	0 (0)	2 (6)
Bilirubinemia	35 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Elevated AST	10 (29)	14 (40)	8 (23)	3 (9)	0 (0)
Elevated ALT	13 (37)	12 (34)	7 (20)	3 (9)	0 (0)
Elevated ALP	15 (43)	12 (34)	7 (20)	1 (3)	0 (0)
Elevated BUN	32 (91)	3 (9)	0 (0)	0 (0)	0 (0)
Decreased creatinine clearance	30 (86)	4 (11)	1 (3)	0 (0)	0 (0)
Uric acid	35 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Proteinuria	18 (51)	17 (49)	0 (0)	0 (0)	0 (0)
Hematuria	12 (34)	12 (34)	1 (3)	0 (0)	0 (0)

Table 5. Summary of worst symptomatic toxicity (*N*=35)

Symptom	WHO grade [*n* (%)]				
	0	1	2	3	4
State of consciousness	27 (77)	7 (20)	0 (0)	1 (3)	0 (0)
Peripheral neuropathy	33 (94)	1 (3)	1 (3)	0 (0)	0 (0)
Constipation	29 (83)	5 (14)	1 (3)	0 (0)	0 (0)
Alopecia	25 (71)	7 (20)	2 (6)	1 (3)	0 (0)
Allergic	32 (91)	2 (6)	1 (3)	0 (0)	0 (0)
Infection	28 (80)	3 (9)	4 (11)	0 (0)	0 (0)
Fever	23 (66)	7 (20)	4 (11)	1 (3)	0 (0)
Pain	26 (74)	8 (23)	1 (3)	0 (0)	0 (0)
Nausea and vomiting	11 (31)	8 (23)	10 (29)	6 (17)	0 (0)
Diarrhea	30 (86)	4 (11)	1 (3)	0 (0)	0 (0)
Cutaneous	22 (63)	9 (26)	4 (11)	0 (0)	0 (0)
Cardiac function	32 (91)	2 (6)	1 (3)	0 (0)	0 (0)
Vardiac rhythm	34 (97)	1 (3)	0 (0)	0 (0)	0 (0)
Pericarditis	34 (97)	1 (3)	0 (0)	0 (0)	0 (0)
Pulmonary	30 (86)	3 (9)	0 (0)	2 (6)	0 (0)
Stomatitis	30 (86)	5 (14)	0 (0)	0 (0)	0 (0)

paclitaxel.[7–9] It is difficult, however, to compare these results due to possible variations among studies in selection criteria.

In this multicenter, phase II study of 33 evaluable, poor-prognosis patients, treatment with gemcitabine resulted in a response rate of 18% (95% CI 7–36%). Two additional patients had partial responses, but were not counted as such because they did not receive verification scans at 1 month. The 18% response rate was especially noteworthy because patients in this study had a particularly poor prognosis, with stage IV or bulky stage III disease in 94% of the patients. In addition, many patients had no debulking procedure performed and the most common histological subtype was poor differentiation (49%). A large proportion of patients (48%) responded to subsequent treatment with platinum-based chemotherapy. This suggests that prior treatment with gemcitabine does not influence response to second-line treatment and that cross-resistance to platinum is not occurring.

In addition to reporting responses, we documented a decrease in CA-125 levels in 23 patients. Fourteen (42%) patients had a decrease of more than 50% in their CA-125 levels, which lasted for at least 4 weeks. The large number of patients with a decrease in CA-125 of more than 50% after two cycles of treatment underscores gemcitabine's activity in epithelial ovarian cancer.

Gemcitabine was well tolerated on an out-patient basis, requiring few or no supportive measures (such as 5-HT_3 antagonists or hematopoietic growth factors) and a low proportion of dose adjustments (27% of planned injections). Only five (14%) of 35 patients experienced grade 4 hematologic toxicity. There were no incidents of neutropenic sepsis/fever or grade 3/4 infections and no patients required hematologic growth factor support. The incidence of non-hematologic toxicity was also low, with no patients with grade 4 and 11 (31%) patients with grade 3 non-hematologic toxicities. Prophylactic antiemetics were not given during the first treatment cycle and only three patients required 5-HT_3 antagonists for nausea/vomiting during treatment. Four patients received i.v. ondansetron prophylactically on a routine basis. Seven patients had self-limiting increases in hepatic transaminases, which were not associated with any clinical symptoms and did not require any dose adjustments. Thirteen (37%) patients experienced a mild erythematous maculopapular rash that usually occurred with the first or second injection and resolved with subsequent injections without supportive therapy. One patient was discontinued from the study because of persistent rash.

The lack of neurotoxicity or nephrotoxicity, the low incidence of hematologic and non-hematologic toxicities, and the apparent lack of cross-resistance to platinum agents suggest that gemcitabine could be combined with other active agents in epithelial ovarian cancer, in particular paclitaxel and platinum. Non-randomized studies have shown that the combination of gemcitabine and cisplatin is highly active and well tolerated in patients with non-small cell lung cancer.[10–12] Three European phase II trials are ongoing to investigate the efficacy of gemcitabine plus cisplatin in patients with advanced, previously untreated ovarian cancer.[13–15] Preliminary results from these studies look promising, with response rates ranging from 53 to 71%.

The results of the GOG-111 trial were published[2] during the time that our trial was open for accrual. Improved duration of progression-free survival and overall survival were shown in women with incompletely resected stage III and stage IV disease who received a combination of paclitaxel and cisplatin compared to standard cisplatin and cyclophosphamide. Following the announcement of these results, we re-examined the ethics of continuing our single-agent study. The various problems associated with testing new agents as initial treatment have been well discussed by Johnson.[16] The chemonaive patient is the ideal patient in which to test new agents, and the search for new active agents must continue. In this study, because we assessed response early (8 weeks), and because several patients responded to salvage platinum-based treatment following failure to respond to gemcitabine, we decided to continue to assess gemcitabine's actual activity in poor-prognosis patients.

Conclusions

Gemcitabine has demonstrated modest activity as a single agent in previously untreated patients with poor-prognosis, advanced, epithelial ovarian cancer. Toxicity is acceptable, with minimal nephrotoxicity, neurotoxicity and alopecia. In addition, gemcitabine does not appear to influence response to subsequent platinum-based chemotherapy. Gemcitabine's apparent lack of cross-resistance, combined with its activity and mild toxicity profile, suggest that further studies are justified in patients with better prognosis and in combination with other agents.

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