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Phase II Trial of Gemcitabine plus Cisplatin Repeating Doublet Therapy in Previously Treated, Relapsed Ovarian Cancer Patients[1]

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Objectives. **The aim was to determine the safety and efficacy of gemcitabine plus cisplatin for patients with relapsed ovarian carcinoma and to compare** *ex vivo* **drug sensitivity profiles with clinical outcomes.**

Patients and methods. **Previously treated patients with ovarian carcinoma received cisplatin (30 mg/m^2) plus gemcitabine (600–750 mg/m^2) on Days 1 and 8 of each 21-day cycle. Seventeen of the 27 patients underwent** *ex vivo* **analyses for correlation with clinical response.**

Results. **Of 27 patients, there were 7 (26%) complete and 12 (44%) partial responses, for an overall response rate of 70% (95% CI: 53–87%). Toxicities included neutropenia Grade III in 51.9%, Grade IV in 29.6%; anemia Grade III in 18.5 %; thrombocytopenia Grade III in 66.7 %, Grade IV in 29.6%; nausea and vomiting Grade III in 14.8 %; peripheral neuropathy Grade III in 3.7%; and alopecia Grade IV in 11.1% of patients. The median time to progression for objective responders was 7.9 months with a range of 2.1 to 13.2 months. There were no treatment-related deaths.** *Ex vivo* **results correlated with response, time to progression, and survival, remaining significant when adjusted for platin-resistance and number of prior therapies. Adjustment for platin-free interval decreased the significance but did not, in and of itself, predict significantly for progression-free survival.**

Conclusions. **Cisplatin plus gemcitabine is active for patients with relapsed ovarian cancer. Toxicities, primarily hematologic, are manageable with dose modifications. Responses observed in heavily pretreated and platin-resistant patients indicate activity in drug-refractory patients. The results of the** *ex vivo* **analyses correlate with clinical outcomes.**

INTRODUCTION

Ovarian cancer strikes 23,000 women and causes 14,000 deaths in the United States each year. The 5-year survival rate for all stages of ovarian carcinoma is 50%, which falls to 28% for patients who present with advanced disease [1]. Despite the introduction of new chemotherapeutic agents and the development of novel combinations, a review of clinical outcomes in relapsed disease concluded that there had been little change in duration of response or survival over the years 1980–1997 [2]. Strategies designed to improve these results continue to be investigated.

Gemcitabine (2′, 2′-difluorodeoxycytidine; dFdC) is a novel nucleoside analog, with fluorine substitutions on the ribose ring in a geminyl configuration. Following sequential phosphorylation by deoxycytidine kinase to the triphosphate, dFdCTP, gemcitabine is incorporated into DNA, causing masked chain termination [3]. The diphosphate, dFdCDP, also functions as an inhibitor of ribonucleotide reductase [4]. Gemcitabine has *in vitro* activity against a broad array of human tumor cell lines and has provided objective responses in a number of human solid tumors, including both treated [5] and previously untreated [6] ovarian cancers.

Cisplatin, [*cis*-diaminedichloroplatinum (II)] is among the most widely used antineoplastic drugs with broad clinical activity. Since its introduction in the 1970s, it has become a mainstay in the management of advanced ovarian cancer [7]. The crucial role of the platinums in ovarian cancer has been established in a number of clinical trials [8,9]. Clinical "platinum resistance" is widely recognized as a major prognostic factor in ovarian cancer management.

Our laboratory has extensively examined the interaction between cisplatin and gemcitabine and has identified activity and synergy for the combination in a wide variety of human tumors [10]. This combination was approved by the Food and Drug Administration for the treatment of non-small-cell lung cancer. We have previously reported activity in advanced breast cancers [11], and we [12] and others [13] have shown activity in relapsed ovarian cancers. The achievement of a durable complete remission using cisplatin plus gemcitabine as fifth-line therapy in a patient with recurrent ovarian cancer in

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1995 provided the rationale for a pilot study that culminated in the current phase II trial.

Based upon the established impact of HER-2 overexpression in the management of breast cancer, we included HER-2 determination to assess possible relevance to patient outcomes.

PATIENTS AND METHODS

Eligible patients had measurable or evaluable, histologically confirmed ovarian carcinoma. Patients had ECOG performance status ≤ 3, with adequate bone marrow, hepatic, and renal function. An absolute neutrophil count of 1000, platelet count of 100,000, creatinine less than 2.0, and bilirubin less than two times normal were required. Also, absence of active infection, clinical congestive heart failure, hypoxemia, or second malignancy within 5 years were all necessary for participation. Concurrent radiation or hormonal therapy was not allowed. Patients who had completed radiation therapy and had clinically stable brain or other sites of metastases were permitted on study. Patients were eligible regardless of the nature of prior therapy, including high-dose therapy with stem cell rescue, or prior exposure to cisplatin or gemcitabine, provided the two drugs were not given together. Patients with accessible sites of recurrence had tissue submitted for blinded *ex vivo* laboratory analysis of sensitivity to gemcitabine plus cisplatin (samples included pleural effusions, ascites, cutaneous metastases, or palpable lymphadenopathy). Trial design stipulated that no patient be subjected to major surgery for the purpose of *ex vivo* analysis. The results of *ex vivo* analyses were embargoed until completion of therapy and were not used in the selection of patients for the trial. The primary endpoints of the trial were the safety of the therapy and its efficacy measured as objective response rate and time to progression, with a secondary endpoint comparing *ex vivo* drug sensitivity with clinical outcome. All patients were provided a thorough explanation of the study and all patients signed written informed consents. The study was approved by the sponsoring organization, Eli Lilly Co., and by the Western Institutional Review Board and the Memorial Health Services Institutional Review Board.

The *ex vivo* analyses of sensitivity to gemcitabine plus cisplatin were conducted upon fresh specimens of tumor submitted to the laboratory as previously described [14]. Following completion of accrual, the 17 patients for whom assay results were available were divided into the "assay-sensitive" or the "assay-resistant" group by median concentration of drugs required to kill 50% of the cells in culture (IC_{50} value.) The fixed ratio combination of gemcitabine at 263 μg/ml and cisplatin at 6.6 μg/ml provided a median IC_{50} of 16.9 μg/ml. Clinical response, time-to-progression, and survival correlations were then determined. The detection of HER-2 overexpression was conducted using anti-c-erbB-2 mouse monoclonal IgG1 as previously described with results scored from 1-plus to 4-plus [15].

Patients with bidimensional disease were included in the "measurable" disease category and were evaluated every two cycles. Patients lacking measurable disease were included in the evaluable group and were assessed for response according to Rustin's criteria [16] for CA 125 response. Progression at cycle 2 was deemed progressive disease resulting in withdrawal from protocol therapy. Patients with stable disease at cycle 2 were allowed to remain on study per physician and patient wishes. Time to progression was calculated from date of first cycle to documentation of progression. Patients with CA 125 only who revealed elevations had a second CA 125 repeated for confirmation of elevation. If confirmed, then progression was documented.

Data processing procedures incorporated a number of quality-control measures, including verification of patient variables by different individuals both before and after entry into computer files. Statistical calculations were performed using the Statistical Package for Social Sciences (SPSS) Version 11.0 software. Clinical response was compared to laboratory assay results using the chi-square test. Survival analyses (time to progression in months) were conducted using the Kaplan–Meier survival analysis and Cox regression, with controls introduced to adjust for effects of the number of prior therapies, platinum resistance, and elapsed time in months between patient's most recent platinum-based therapy and the present study regimen. Results were considered significant at the $P \leq .05$ level.

TREATMENT PLAN

The original trial design included therapy on Days 1, 8, and 15 on a 28-day cycle. After the accrual of the first four ovarian cancer patients and following our experience in a companion breast cancer trial using the same drug schedule, we eliminated the Day 15 treatment and reduced the starting dose of gemcitabine due to toxicity, primarily thrombocytopenia. The repeating doublet schedule of cisplatin plus gemcitabine was thereafter administered on Days 1 and 8 of each 21-day cycle as follows. Consistent with our experience in breast cancer, the starting dose of gemcitabine was reduced by 25% in the less heavily treated and by 40% in the heavily pretreated patients (>2 prior therapies). A dose modification schedule was incorporated into trial design based upon the known toxicity profiles of the drugs. Hematologic toxicities resulted in gemcitabine dose reductions while nausea and vomiting, neuropathy, or renal toxicity resulted in cisplatin dose reductions.

All patients received hydration with D5 1/2 NS at 200 cc over 1 h. Patients were premedicated with granisetron (Kytril) 1 mg IV and dexamethasone 10 mg iv. Cisplatin at 30 mg/m^2 was administered in 250 ml of NS with 12.5 g of mannitol and 1 g of MgSO4, over 1 h. Posthydration with 250 cc D5 1/2 NS over 1 h was followed by gemcitabine at 750 mg/m^2 in 250 cc NS over 1 h. Patients with two or more prior chemotherapy regimens were started at a gemcitabine dose of 600 mg/m^2. Treatments were administered on an outpatient basis.

TABLE 1
Patient Characteristics

Patient No.	Age	Platinum-resistant	No. of prior	Prior regimen(s)	Measurable/ evaluable
1	71	Yes	2	TAX/PP; TOPO	Eval
2	62	Yes	2	TAX/PP; HEX	Eval
3	66	No	5	CTX/PP; TAX; TAX; 5-FU; TOPO	Eval
4	63	No	3	TAX/PP; TOPO; PP	Meas
5	56	No	6	CDDP/CTX; TAX; TOPO; HEX; IFX; VP-16	Eval
6	63	No	3	PP; TAX; VP-16/CDDP	Meas
7	35	Yes	1	TAX/PP	Meas
8	63	No	2	CDDP/PP/CTX; TAX	Meas
9	47	Yes	2	CDDP/TAX; BMT	Eval
10	68	No	2	TAX/CDDP; PP	Meas
11	48	Yes	4	CDDP/TAX; DOX-L; TOPO; FUDR	Meas
12	64	Yes	2	TAX/PP; HEX	Meas
13	67	No	4	TAX/CDDP; PP; DOX-L; TAX	Meas
14	64	No	4	TAX/PP; TAX; GEM; BMT	Meas
15	49	No	5	CDDP/VP-16; TAX/PP; CTX; 5-FU; TAX	Meas
16	70	No	1	TAX/PP	Eval
17	66	Yes	2	TAX/PP; TOPO	Meas
18	65	Yes	1	TAX/PP	Eval
19	52	Yes	1	TAX/PP	Meas
20	82	Yes	1	TAX/PP	Eval
21	61	Yes	2	Tax/PP; TOPO	Eval
22	81	Yes	4	TAX/PP; CDDP/VP-16; CTX; VP-16	Meas
23	52	No	3	TAX/CDDP; PP/CTAX; TOPO	Meas
24	62	Yes	1	TAX/PP	Meas
25	66	No	3	TAX/PP; TAX; TOPO	Meas
26	53	Yes	3	TAX/PP; DOX-L; TOPO	Meas
27	77	No	3	TAX/PP; 5-FU; TAX/PP	Meas

Note. BMT, bone marrow transplant—high-dose therapy with stem cell support; CDDP, cisplatin/platinol; CTX, cytoxan/cyclophosphamide; DOX-L, doxil; 5-FU, 5-fluorouracil; FUDR, floxuridine; GEM, gemcitabine; HEX, altretamine; IFX, ifosfamide; PP, carboplatin/paraplatin; TAX, Taxol/Paclitaxel; TXT, taxotere/docetaxel; TOPO, topotecan; VP-16, etoposide.

RESULTS

Twenty-seven patients entered the study between February 1997 and December 2000. Six of 27 (22%) patients had recurred after initial postoperative therapy, while 21 (78%) had progressed after one or more chemotherapy regimens for systemic recurrence. Baseline characteristics for the participants are shown in Table 1. The 27 patients who received at least one cycle of therapy are included in the analysis. Eighteen of 27 patients had measurable disease, primarily CT scans, and 9 of 27 patients had evaluable disease by elevated CA 125. Response for patients with measurable disease was based upon the GOG criteria. Patients were assessed after cycle 2 and then after every second cycle. Response for evaluable patients using CA 125 was determined in accordance with Rustin criteria. Eleven of 18 measurable (61%) and 8 of 9 evaluable (89%) patients responded. Among the 14 patients who met GOG criteria for platinum-resistant disease [17], there were 3 complete responses (CRs) and 5 partial responses (PRs), for an overall response rate of 57%. Among the 13 platinum-sensitive patients, there were 4 CRs and 7 PRs, for an overall response rate of 84%. The median platinum-free interval for platinum-sensitive patients was 12 months (range 4–86), while for the platinum-resistant patients it was 8 months (range 3–16). The clinical response rates for all 27 patients are provided in Table 2. Responses were observed in soft tissue, lung, and liver.

One patient presented with metastases to the lung and abdomen, a CA 125 of 363, and a septated abdominal mass. The rapid resolution of CT-measurable lesions in the lung and several abdominal masses and a >75% decrease in the CA 125 after several cycles of therapy revealed no change in the septated mass. When referral for surgery to assess the nature of

TABLE 2
Patient Response ($N = 27$)

Type of response	No. of patients	%
CR	7	26
PR	12	44
SD	7	26
DP	1	4

the mass was declined due to comorbid conditions, the patient remained on therapy for 13 cycles as an evaluable response.

For the 17 patients for whom tissue was provided, the assay-sensitive group showed a 9/10 (90%) response (CR or PR), whereas the assay-resistant group showed a 2/7 (29%) response ($P = 0.035$). Time to progression was analyzed using the Kaplan–Meier survival method (Fig. 1). Results showed that the assay-sensitive group exhibited greater progression-free survival ($P = 0.012$), which remained significant when controlled for platinum resistance ($P = 0.022$). Additional multivariate analyses utilizing Cox regression were used to adjust for possible effects of the number of prior therapies, and time in months since the last platinum-based therapy. Findings from these covariate analyses revealed that assay results remained a significant predictor of time to progression when controlled for the number of prior therapies ($P = 0.027$) but failed to achieve significance when adjusted for time since prior platinum therapy ($P = 0.145$). Notably, none of these additional factors or covariates proved to be significant predictors of patient outcome. When these 17 patients were divided at the median IC_{50} value of 16.9 μg/ml, survival also significantly favored the assay-sensitive group ($P = 0.05$). Among responding patients (CR and PR), the times to progression revealed a median of 7.9 months. For all 27 patients the mean time to progression of 5.97 months and mean survival of 20.2 months compare favorably with the 5.75 months and 14.9 months, respectively, reported in the prior metaanalysis [2]. Sixty-three percent of patients survived more than 1 year and 7/27 (26%) of patients remain alive at 13–51 + months of follow-up. Of 20 patients for whom tissue blocks were evaluable, 2 (10%) were found positive and 18 (90%) negative for HER-2 overexpression.

Toxicity was primarily hematologic and is provided in Table 3. Seven of 27 (26%) patients tolerated full doses without dose reduction, while 8/27 (30%) required one, 8/27 (30%) required two, and 4/27 (15%) required four dose reductions. Additional toxicities included Grade III and IV nausea and vomiting in 14.8%, peripheral neuropathy in 3.7%, and alopecia in 11.1% of patients. Mild to moderate fatigue was common but only 3.7% of patients experienced Grade III and IV.

TABLE 3
Toxicities ($N = 27$ Patients)

	Grade III		Grade IV	
Toxicity	*N*	%	*N*	%
Leukopenia	10	37.0	2	7.4
Anemia	5	18.5	0	
Neutropenia	14	51.9	8	29.6
Thrombocytopenia	18	66.7	8	29.6
Nausea/vomiting	4	14.8	0	
Peripheral neuropathy	1	3.7	0	
Alopecia	0		3	11.1
Fatigue	1	3.7	0	

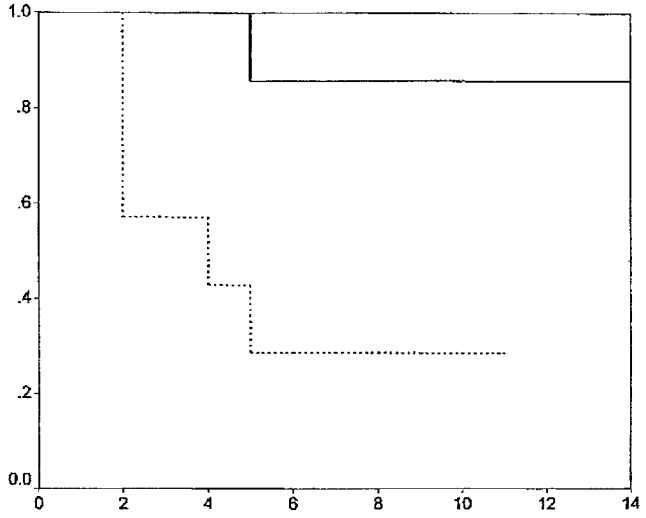

FIG. 1. Time to progression versus assay sensitivity (assay sensitivity, combined $IC_{50} \leq 16.9$; assay resistance, combined $IC_{50} > 16.9$). *Y axis,* cumulative survival; *X axis,* time to progression (months).

DISCUSSION

Ovarian cancer remains the leading cause of death from gynecologic malignancies in the United States. The majority of patients present with advanced stage disease at initial diagnosis. Most patients receive chemotherapy, often in the form of carboplatin or cisplatin plus paclitaxel for initial management, yet the majority of patients relapse within 5 years. As a result, there is a crucial need to develop new strategies for the management of relapsed disease.

Our laboratory has applied a cell death endpoint, *ex vivo,* to examine drug actions and interactions. Contrary to older, cell proliferation-based endpoints ([^{3}H]thymidine incorporation, Clonogenic, etc.), cell death measures as surrogates for drug-induced apoptosis may provide more clinically relevant information [18]. The laboratory observation that cisplatin plus gemcitabine revealed high degrees of cytotoxic activity and synergy in ovarian cancer specimens, including many obtained from clinically drug-resistant patients, provided the scientific basis for the current clinical trial. The rationale for this treatment is examined below.

The platins remain the most important drugs for advanced ovarian cancer. While various definitions of platinum-resistance have been suggested, the most common is that used by the Gynecologic Oncology Group (GOG) [17]. Fourteen of the 27 (52%) patients in this study met GOG criteria for platinum resistance; however, all patients had recurred following platinum-based therapy. Despite the utility of platins in ovarian cancer, its activity is limited by the development of drug resistance. An important mechanism of cisplatin resistance is nucleotide excision repair (NER) associated with up-regulation of the excision–repair–cross-complementing proteins (ERCC1 and ERCC2), xeroderma pigmentosa group A (XPA), and other DNA excision repair complexes. In a study of human

ovarian cancer tissue, Reed identified high levels of ERCC1 mRNA in the drug-resistant specimens and lower levels in the drug-sensitive specimens [19]. Altered DNA mismatch repair may also contribute to the resistant phenotype [20].

The repair of cisplatin–DNA adducts mediated by nucleotide and mismatch repair mechanisms is dependent upon adequate intracellular pools of deoxynucleosides. Gemcitabine can influence these repair mechanisms on two levels. The first is through direct incorporation of gemcitabine as the triphosphate dFdCTP. The second mechanism occurs through gemcitabine's capacity as a diphosphate, dFdCDP, to inhibit ribonucleotide reductase. This results in a depletion of intracellular nucleoside pools. The majority of cisplatin–DNA adduct repair occurs within the first 24 h following exposure to a single dose of cisplatin [21]. To capture cells during this "sensitive" time period we have developed a "repeating doublet" sequence wherein cisplatin and gemcitabine are both administered on Days 1 and 8 on a 21-day schedule.

In keeping with prior observation in ovarian cancer cell lines [22], concurrent or closely temporally sequenced administration of both drugs has the capacity to overcome cisplatin resistance. Repair-efficient cells may manifest collateral sensitivity to the doublet sequence. It has been shown that the down-regulation of ERCC1 by antisense mRNA abrogates the synergy between cisplatin and gemcitabine [23], while recent observations have further clarified the role of gemcitabine incorporation in the induction of cellular apoptosis [24]. This supports the contribution of the cell's own repair capacity to the sensitivity to the combination. Responses observed in relapsed ovarian [12] and breast [11] cancers lend clinical support to this concept in repair-efficient tumors.

Our results in the platinum-resistant subgroup and in the two patients following high-dose stem cell therapies suggest that this may offer an option for patients with other drug-refractory tumors. The favorable results in the current trial led to the initiation of GOG study 126-L, designed specifically to test this combination in platinum-resistant ovarian carcinomas. That, and the related trial in recurrent cancer of the uterine cervix, GOG 127-Q, will evaluate the repeating doublet concept in these diseases. *Ex vivo* results correlated with response, time to progression, and survival, remaining significant when adjusted for platin-resistance and number of prior therapies. Adjustment for platin-free interval decreased the significance but did not, in and of itself, predict significantly for progression-free survival. Future trials directly comparing *ex vivo* results with other predictive factors may provide additional insights.

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