

# Intraperitoneal Cisplatin with Intraperitoneal Gemcitabine in Patients with Epithelial Ovarian Cancer: Results of a Phase I/II Trial

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## ABSTRACT

**Purpose:** The aims of this study were to determine the dose and schedule of i.p. cisplatin with i.p. gemcitabine in patients with persistent disease at second-look assessment, the toxicity of this regimen, and the time to treatment failure and overall survival.

**Experimental Design:** We performed a Phase I/II evaluation of i.p. cisplatin at 75 mg/m<sup>2</sup> on day 1 with planned gemcitabine at 500, 750, 1000, or 1250 mg/m<sup>2</sup> i.p. on days 1, 8, and 15 on a 28-day schedule for four courses. Eligible patients completed surgical cytoreduction followed by adjuvant platinum-based chemotherapy. They had second-look assessment showing microscopic or macroscopic ( $\leq 1$  cm) disease, followed by i.p. port placement.

**Results:** The Phase I dose-limiting toxicity was grade 3 thrombocytopenia at day 15 on dose level 1 ( $n = 5$ ). The protocol was amended, and the Phase II portion accrued to 30 patients, who were given i.p. cisplatin (75 mg/m<sup>2</sup>) on day 1 and gemcitabine at 500 mg/m<sup>2</sup> on days 1 and 8 on a 21-day schedule for four courses. Nine patients were removed from the study: one each for hypersensitivity, cellulitis, and i.p. port malfunction; two for progression of disease; and four for renal toxicity. Other toxicities included grade 3 nausea (7%) and transient grade 3 neuropathy (3%). Grade 1 or 2 neuropathy was frequently seen (80%). Five patients (17%) returned to the operating room at a median of 6 months (range, 1–20 months) after i.p. therapy for evaluation of

abdominal pain; two patients had recurrence, and all had areas of fibrous tissue with encasement of the bowel. In two patients, the fibrous tissue was causing partial bowel obstruction. No other patients had symptoms prompting surgical exploration. Pharmacokinetic (PK) studies showed a median area under the curve (AUC) i.p. of 3041 h· $\mu$ M (range, 676–5702 h· $\mu$ M) and AUC in plasma of 4.0 h· $\mu$ M (range, 0.92–8.2 h· $\mu$ M) reached between 120 and 240 min; the pharmacological advantage was 759-fold (range, 217–1415-fold) for i.p. versus plasma drug levels. The mean residence time of gemcitabine with i.p. administration was 4.7 h. The median time to progression of the intent to treat population was 15.93 months (95% confidence interval, 9.13–25.9 months), with a median overall survival of 43.5 months [95% confidence interval, (34.66– $\infty$ )]. No statistical differences were seen with respect to overall survival if patients were grouped in terms of optimal debulking or not (median not reached versus 34.8 months, respectively;  $P = 0.16$ ) or whether visible disease was present or not at the start of i.p. therapy (34.8 versus 47.7 months;  $P = 0.47$ ). With regard to time to treatment failure, a statistical difference favored patients with optimal versus nonoptimal primary debulking (25.2 versus 10.2 months, respectively;  $P = 0.03$ ).

**Conclusions:** The median time to treatment failure and overall survival of 15.9 months and 43.5 months, respectively, are consistent with our historical data in patients receiving i.p. platinum-based regimens for consolidation. The fibrotic changes seen in explored patients suggest local toxicity of this combination. The absolute benefit of i.p. consolidation requires randomized trials to assess efficacy.

## INTRODUCTION

The majority of patients with ovarian cancer are in clinical remission after primary surgical debulking and adjuvant platinum- and taxane-based chemotherapy (1). Despite the initial response, 70–90% of patients relapse at a median of 18–24 months, indicating that most patients have persistent microscopic or macroscopic small-volume disease (2). Attempts at improving outcome after primary therapy have included additional systemic chemotherapy with the same or different agents (3, 4) or with regional therapy via the i.p. approach. A variety of novel biological and immune-directed therapies are also now being studied in this patient group.

The propensity of relapsed ovarian cancer to remain confined to the peritoneal cavity makes it suitable for the investigation of i.p. consolidation therapy. The strategy of using i.p. delivery to improve the pharmacokinetic advantage by increasing concentration and exposure time of drug to tumor has been studied extensively. The ability to bypass poorly developed vasculature supporting small-volume disease makes this partic-

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ularly attractive to evaluate in the consolidation setting (5, 6). The only prospective randomized study evaluating i.p. therapy used it as a part of the primary treatment regimen, and the results are not directly applicable to the consolidation setting. Nonrandomized Phase II data have suggested a benefit of i.p. therapy in patients with a negative second look compared with historical controls (7). Other published data for i.p. consolidation therapy consist of a series of Phase II trials in which patients with small-volume ( $\leq 1$  cm) residual disease treated with i.p. platinum combinations generally showed surgically defined complete response rates of 25–35%. These Phase II data have suggested a clinically meaningful impact on survival compared with historical controls in those patients achieving a complete response after i.p. treatment, with a median survival in small-volume responders of 40 months *versus* 10 months for nonresponders ( $P = 0.009$ ; Ref. 8). A large retrospective review from our institution recently described the relapse characteristics of a heterogeneous group of patients treated with a variety of platinum-containing i.p. regimens largely used in the consolidation setting that can serve as a benchmark for patients in this study (9).

The synergy (10–12) and clinical activity of systemic cisplatin and gemcitabine in patients with ovarian cancer are well described both in the chemotherapy-naïve and relapse populations (13, 14). Several characteristics of gemcitabine have suggested that it is a reasonable candidate for exploration in the i.p. setting. These characteristics include (a) the structural similarity to 1- $\beta$ -D-arabinofuranosylcytosine, which has been successfully administered i.p.; (b) a dose-limiting toxicity that has largely been related to plasma levels; (c) i.p. administration in animal models without toxicity; and (d) data suggesting that prolonged exposure achieved with i.p. administration would maintain gemcitabine levels above the threshold for nucleotide incorporation into cells, which has been correlated with cytotoxic activity (15, 16).

In this Phase I/II study, we sought to define the maximum tolerated dose of i.p. gemcitabine with i.p. cisplatin given in consolidation in patients with microscopic or macroscopic ( $\leq 1$  cm) disease after primary treatment of ovarian cancer. The purposes of the Phase II portion were to determine the time to treatment failure and overall survival of the treated population and, by comparison with historical data, to determine whether additional prospective studies of this combined i.p. approach were warranted.

## PATIENTS AND METHODS

Eligible patients had histologically documented epithelial ovarian, fallopian tube, or peritoneal carcinoma after initial cytoreductive surgery and chemotherapy with a platinum-containing regimen followed by normalization of CA-125. All patients underwent second-look surgical reassessment (laparotomy or laparoscopy) and had confirmation of residual disease (microscopic or gross  $\leq 1.0$  cm) at the end of the procedure. Patients had adequate hematological (WBC count  $\geq 3,000$  cells/mm<sup>3</sup>; platelets  $\geq 100,000$  cells/mm<sup>3</sup>), renal (serum creatinine  $< 1.6$  mg/dl), and hepatic (bilirubin, aspartate aminotransferase, and alkaline phosphatase less than three times the upper limit of normal) function. Karnofsky performance status was  $> 60\%$ .

Eligible patients had a functioning s.c.-implanted i.p. catheter. Patients were excluded if residual disease was  $> 1$  cm, neuropathy was grade 2 or higher, or if they had any contraindication to i.p. therapy, such as intra-abdominal infection or widespread adhesions. The Memorial Sloan-Kettering Cancer Center Institutional Review Board approved the protocol, and informed consent was obtained.

**Treatment Plan and Pharmacokinetic Sampling.** Cisplatin (i.p.) was given at a fixed dose of 75 mg/m<sup>2</sup> via the i.p. catheter on day 1. Gemcitabine (i.p.) was initiated in dose level 1 at 500 mg/m<sup>2</sup> on days 1 and 8 and was originally planned to be administered on day 15 of a 28-day cycle. The i.p. chemotherapy was administered in 1 liter of normal saline. An additional 1 liter of normal saline was given as tolerated by gravity feed. The i.v. hydration for cisplatin followed standard institutional protocols. Three patients were to be enrolled at each dose level in the Phase I portion, with planned escalation of gemcitabine from 500 mg/m<sup>2</sup> to 750, 1000, and 1250 mg/m<sup>2</sup>, respectively, with subsequent cohorts if dose-limiting toxicity was not present. Each patient was to receive four cycles of therapy (one cycle = 28 days). For retreatment, on day 1 of each cycle patients were required to have an absolute neutrophil count  $\geq 1,000$  cells/mm<sup>3</sup> and platelets  $\geq 100,000$  cells/mm<sup>3</sup> for cisplatin and gemcitabine administration. On days 8 and 15 of each cycle, patients were required to have an absolute neutrophil count  $\geq 500$  cells/mm<sup>3</sup> and platelets  $\geq 50,000$  cells/mm<sup>3</sup> for gemcitabine administration. Patients with progression to grade 3 neuropathy or grade 2 abdominal pain were removed from the study. If one patient had toxicity higher than grade 2, an additional three patients were accrued to the respective dose level. If two or more patients were seen with toxicity higher than grade 2 for a given dose level, this was considered a dose-limiting toxicity and further accrual to that cohort did not proceed. The protocol would accrue a total of 30 patients at the determined Phase II dose level. History and physical examination, complete blood cell counts, and a comprehensive panel, including creatinine and magnesium, were performed at each visit before treatment. CA-125 levels were measured with each course.

Blood samples for pharmacokinetic analysis were collected at 0.5, 1, 2, 4, 6, and 24 h after completion of drug instillation. Peritoneal fluid for pharmacokinetic analysis was obtained by discarding the initial 10 ml of fluid withdrawn from the i.p. catheter. An additional 7 ml were obtained at 0.5, 1, 2, 4, 6, and 24 h after completion of drug instillation with the addition of additives according to the method of Freeman *et al.* (17). If the i.p. catheter was not functioning for fluid withdrawal, no samples were obtained. Patients were evaluated by physical examination, CA-125 measurements, and a computed tomography scan every 3 months after completion of treatment.

**Statistical Considerations.** Standard dose escalation criteria were used. If at any dose level two or more patients developed toxicity higher than grade 2, the dose was not escalated. The maximum tolerated dose is the dose level at which at most one of three or two of six toxicities are observed. A minimum of 3 patients and maximum of 24 patients could be enrolled in the Phase I portion. In the Phase II portion, a total of 30 patients were to be studied at the determined Phase II dose. The endpoints of the study were to assess the tolerated dose and safety of i.p. gemcitabine when given with i.p. cisplatin (Phase

Table 1 Patient characteristics (n = 30)

Median age (range), years	55 (22–76)
Median KPS <sup>a</sup> (%)	90 (80–90)
Disease site, n (%)	
Ovarian	25 (83)
Fallopian tube	3 (10)
Peritoneal	2 (7)
Stage, n (%)	
II	2 (7)
III	27 (90)
IV	1 (3)
Histological type, n (%)	
Serous	20 (67)
Endometrioid	2 (7)
Adenocarcinoma, NOS	7 (23)
Mucinous	1 (3)
Size of residual at primary debulking, n (%)	
Optimal (≤1 cm)	15 (50)
Suboptimal (>1 cm)	15 (50)
Size of residual at initiation of IP, n (%)	
Microscopic	8 (27)
Macroscopic (≤1 cm)	22 (73)

<sup>a</sup> KPS, Karnofsky performance status; NOS, not otherwise specified; IP, intraperitoneal therapy.

I) and to determine time to radiographic progression and overall survival (Phase II). Overall survival and time to progression distributions were estimated using Kaplan–Meier curves, and the prognostic effect of categorical covariates was assessed using the log-rank test.

## RESULTS

**Patient Characteristics.** Between June 1998 and July 2000, 30 patients were entered in the study. The patient characteristics are outlined in Table 1. The median age was 55 years (range, 22–76 years), with a median Karnofsky performance status of 90%. Patients predominantly had ovarian cancer (83%), with 10% and 7% having fallopian tube and peritoneal cancer, respectively. The majority of patients were stage III, with papillary serous histology. Patients were equally split between those with optimal (50%) and suboptimal (50%) debulking. Most patients had macroscopic disease ≤1 cm (73%) at the start of i.p. therapy, with 7% having only microscopic disease. All patients received platinum- and taxane-based therapy as primary treatment with responding disease.

**Phase I Results.** The first three patients experienced grade 3 asymptomatic thrombocytopenia at day 21, which required treatment delay. The cohort was expanded according to the protocol with similar findings in the fourth and fifth patients. Day 21 thrombocytopenia was considered to represent dose-limiting toxicity. The protocol was amended, and the schedule was changed to 75 mg/m<sup>2</sup> i.p. cisplatin on day 1, with i.p. gemcitabine at 500 mg/m<sup>2</sup> on days 1 and 8 of a 21-day schedule. Hence, additional dose escalation was not performed. The modified schedule allowed for the accrual of 30 patients without difficulty.

**Treatment Toxicities.** The median number of cycles received was four, as planned. All 30 patients (each treated with the 21-day schedule and initial dose cohort) received at least one treatment. Nine patients were removed from the study: one each

for platinum hypersensitivity, gemcitabine-related cellulitis, and i.p. port malfunction; two for disease progression; and four for renal toxicity (Table 2). Abdominal discomfort was common but not dose limiting (grade 1, eight patients; grade 3, one patient). The remaining spectrum of toxicities is outlined in Table 3 and includes the toxicities typically reported with cisplatin. Grade 3 nausea occurred in 7% of patients, with most patients reasonably controlled with standard antiemetics. Grade 1 or 2 neuropathy was reported in 80% of the patients, with most patients having residual disease from primary therapy. Only one patient reported transient grade 3 neuropathy. Four patients had grade 2 or 3 renal toxicity, prompting their removal from the study by the investigator. No other unexpected toxicities occurred.

Five patients (17%) had returned to the operating room at the time of this report (median follow-up, 24 months) after completion of i.p. therapy for the evaluation of abdominal pain, as outlined in Table 4. The median number of months after i.p. therapy for surgery was 6 (range, 1–20 months). Of the five patients, two had radiographic evidence of partial obstruction, and one had free air after a routine colonoscopy. Two patients were explored for abdominal pain with tenderness but had no radiographic abnormalities. Two patients had pathological evidence of recurrence, whereas the remaining three had no recurrent cancer. Each of the five patients was noted as having multiple adhesions, with areas of fibrous tissue forming a capsular encasement. Adhesiolysis was performed when appropriate.

**Progression-Free Interval and Overall Survival.** The median time to progression of the intent-to-treat population was 15.93 months (95% confidence interval, 9.13–25.9 months), with a median overall survival of 43.5 months [95% confidence interval, ≥34.66 months (some patients were still alive at the

Table 2 Patients removed from study (n = 9)

POD <sup>a</sup> (n)	2
Platinum hypersensitivity (n)	1
Renal toxicity (n)	4
Gemcitabine cellulitis (n)	1
Port malfunction (n)	1

<sup>a</sup> POD, progression of disease.

Table 3 Adverse events (n = 30)

	Grade			
	1	2	3	4
Neutropenia, n (%)		3 (10)	7 (23)	3 (10)
Anemia, n (%)		8 (27)	1 (3)	1 (3)
Thrombocytopenia, n (%)		6 (20)	7 (23)	
Hypokalemia, n (%)	1 (3)		2 (7)	
Hypomagnesemia, n (%)	3 (10)	9 (30)	1 (3)	
Creatinine, n (%)	1 (3)	2 (7)	2 (7)	
Abdominal pain, n (%)	8 (27)		1 (3)	
Diarrhea, n (%)	5 (17)	1 (3)	1 (3)	
Fever, n (%)	3 (10)	1 (3)		
Nausea, n (%)	12 (40)	15 (50)	2 (7)	1 (3)
Vomiting, n (%)	13 (43)	5 (17)	1 (3)	1 (3)
Neuropathy, n (%)	16 (53)	8 (27)	1 (3)	
Fatigue, n (%)	7 (23)	17 (57)	3 (10)	
Rash (cellulitis), n (%)	4 (13)	1 (3)		

Table 4 Patients having exploratory laparotomy during follow-up

Patient	PostIP <sup>a</sup> (mo)	Pain	Radiographic findings	Intervening chemotherapy	Pathological recurrence	Fibrosis
1	20	Y	Obstruction		Y	Y
2	6	Y	Unremarkable	Y	N	Y
3	6	Y	Obstruction	Y	N	Y
4	3	Y	Unremarkable	N	N	Y
5	1	Y	Free air after colonoscopy	N	Y	Y

<sup>a</sup> IP, intraperitoneal therapy.

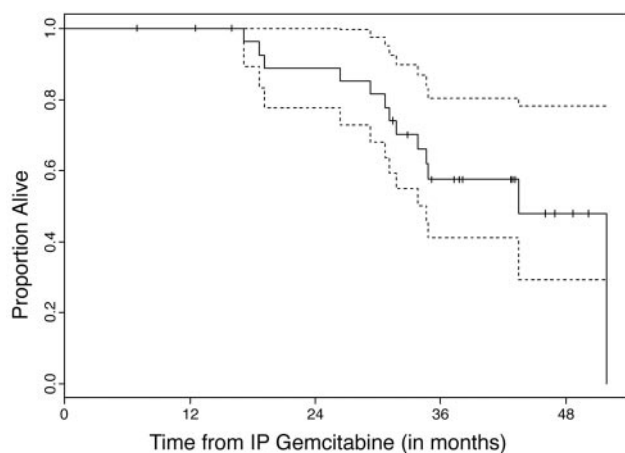


Fig. 1 Overall survival ( $n = 30$ ).

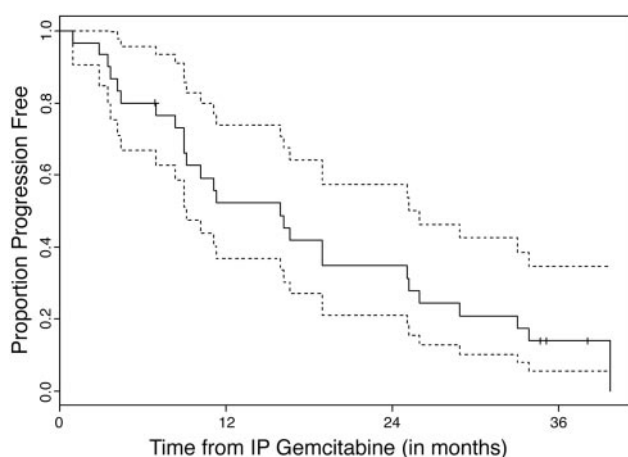


Fig. 2 Time to treatment failure ( $n = 30$ ).

time of publication; therefore, the interval is open-ended at present); see Figs. 1 and 2]. No statistical differences were seen with respect to overall survival if patients were grouped in terms of optimal debulking or not (median not reached *versus* 34.8 months;  $P = 0.16$ ) or whether visible disease was present or not at the start of i.p. therapy (34.8 *versus* 47.7 months;  $P = 0.47$ ). With regard to time to progression, a statistical difference favored patients with optimal *versus* nonoptimal primary debulking (25.2 *versus* 10.2 months;  $P = 0.03$ ). No statistical difference was seen with regard to time to progression based on

whether visible disease was present or not at the start of i.p. therapy (11.1 *versus* 22.0 months;  $P = 0.21$ ), as seen in Table 5.

**Pharmacokinetics.** Previous studies have summarized the performance of i.p. catheters with regard to pharmacokinetic sampling and have reported that pericatheter sheaths can develop with a one-way valve effect, preventing aspiration of fluid in ~50% of patients (18). We were able to aspirate peritoneal fluid, yielding pharmacokinetic data, from 13 patients (43%), a percentage that is consistent with published reports. In these 13 patients, the median area under the curve for i.p. administration of gemcitabine was 3041 h· $\mu$ M (range, 676-5702 h· $\mu$ M), and the median plasma area under the curve was 4 h· $\mu$ M (range, 0.95-7.5 h· $\mu$ M), reached between 120 and 240 min (Table 6). A mean pharmacological advantage of 791-fold (range, 217-1415-fold) was seen when we compared i.p. to plasma drug areas under the curves. The mean residence time for i.p. gemcitabine was 4.7 h. All patients ( $n = 13$ ) had i.p. gemcitabine levels  $>20 \mu$ M at 2 h after instillation (above threshold for maximum triphosphate accumulation), and 10 patients (77%) still had levels  $>20 \mu$ M at 6 h.

## DISCUSSION

The need to identify effective consolidation regimens for patients with ovarian cancer is illustrated by the consistent relapse rates of 70-90%, occurring at a median of 18-24 months (1, 19). The findings of the Gynecologic Oncology Group protocol 132 reported by Muggia *et al.* (2), which evaluated paclitaxel or cisplatin or paclitaxel with cisplatin as primary treatment, was particularly informative in demonstrating persistent disease at second-look assessments in 69, 88, and 63% of patients, respectively. This would imply that to improve the outcome of patients with ovarian cancer, either primary

Table 5 Results for all patients

Patients receiving $> 1$ cycle ( $n$ )	24 (4; 3-4) <sup>a</sup>
Patients removed from study ( $n$ )	9
Time to treatment failure (mo)	
Intent to treat ( $n = 30$ )	15.9 (9.13-25.95) <sup>b</sup>
Microscopic at start of IP <sup>c</sup>	22.0 (16.1- $\infty$ ) <sup>b</sup>
Macroscopic at start of IP ( $\leq 1$ cm)	11.1 (8.97-25.9) <sup>d</sup>
Overall survival (mo)	
Intent to treat ( $n = 30$ )	43.5 months (34.6- $\infty$ ) <sup>b</sup>
Microscopic at start of IP	47.7 months (43.5- $\infty$ ) <sup>b</sup>
Macroscopic at start of IP ( $\leq 1$ cm)	34.8 months (31.7- $\infty$ ) <sup>b,e</sup>

<sup>a</sup> Values in parentheses are median (and range) number of cycles.

<sup>b</sup> 95% confidence interval,  $\infty$ , infinity.

<sup>c</sup> IP, intraperitoneal therapy.

<sup>d</sup> Range.

<sup>e</sup>  $P = 0.47$ .

Table 6 Peritoneal and plasma concentrations

Patient	AUC <sup>a</sup> (h·μM)	
	IP	Plasma
1	3279.2	2.66
2	1588.83	6.84
3	4706.7	3.32
4	3521.5	3.88
5	2089.86	4.0
6	5702.50	8.28
7	3285.0	7.50
8	949.18	4.36
9	3041.83	7.20
10	924.08	2.79
11	3102.66	0.92
12	676.43	2.96
13	1719.16	5.73

<sup>a</sup> AUC, area under the curve; IP, peritoneal fluid.

therapy must be made more effective or treatment needs to be directed at this small-volume disease persisting after primary treatment, which has been termed “consolidation.”

The randomized data for the i.p. delivery of cytotoxic agents address its use as part of the primary treatment regimen. Recognizing the limitations and controversies surrounding three primary treatment studies, each has suggested an advantage for i.p. administration (20–22). Nonrandomized Phase II data have suggested a benefit of i.p. therapy used as consolidation in patients with a negative second look compared with historical controls (7). In the study by Barakat *et al.* (7), patients with negative second looks received i.p. cisplatin with i.p. etoposide for a 12-week total course. Historically, patients with negative second looks have a 50% failure rate at a median of 24 months. In contrast, the median time to failure was not reached at 36 months of follow-up in the i.p.-treated patients. The four cycles of i.p. consolidation in this study were empirically based on providing a 12-week course of consolidation while minimizing cumulative toxicity. Furthermore, from a systemic standpoint, which is not directly comparable, older studies have shown no benefit for prolonged platinum administration when comparing 5 *versus* 10 cycles of administration (23). Recently, a Southwest Oncology Group and Gynecologic Oncology Group study evaluating 3 *versus* 12 additional cycles of paclitaxel was stopped early and has been reported in abstract form as demonstrating a progression-free survival advantage of 28 *versus* 21 months ( $P = 0.0035$ ) in favor of prolonged paclitaxel administration. These patients did not have second-look assessment, but one can estimate from the original demographics (stratified for optimal stage III, suboptimal stage III, and stage IV) that at least 30% of these patients (and likely more) would have a negative second look and, thus, would represent a better prognostic group than our patients, who all have disease and 73% of whom have macroscopic disease, preventing any direct comparison of time to treatment failure between the two groups (3).

As an overall benchmark, our recently summarized experience of the long-term outcomes in a large series of patients with a variety of second-look findings treated with i.p. platinum-containing regimens can be used (9). Patients with microscopically positive second looks had an overall survival of 57.6

months, and those with macroscopic disease but with disease of <1 cm (as in 73% of patients in our study) had an overall survival of 39.6 months. This range is consistent with the results in our study, with an overall survival of 43.6 months.

The efficacy of gemcitabine has been correlated with concentrations of gemcitabine triphosphate accumulation, which is related to plasma concentration (24). No further increments in triphosphate accumulation have been seen with doses resulting in plasma concentrations >20 μM, suggesting enzymatic saturation at higher doses, and cytotoxicity has been seen in cell lines with concentrations as low as 1 μM. Plasma concentrations in our study were considerably below the threshold for maximum incorporation, ranging from 0.92 to 8.2 μM. Despite the low plasma concentrations, these levels were high enough to provide hematological toxicity, preventing dose escalation. Intraperitoneal concentrations remained above the threshold for maximum triphosphate accumulation a minimum of 2 h and a maximum of 6 h, which suggests that any benefit of i.p. administration might be duplicated with a 2-h fixed dose rate infusion (10 mg/m<sup>2</sup>/min) as suggested in multiple ongoing studies (25). The benefit of fixed dose rate infusion, however, depends on an adequate blood supply that brings the agent to tumors, and we cannot exclude a therapeutic benefit by direct delivery of a drug to poorly vascularized tumor in certain settings. Patel *et al.* (26) allowed patients to serve as their own controls, comparing gemcitabine at 1000 mg/m<sup>2</sup> given over the traditional 30 min *versus* a pharmacologically based fixed dose rate infusion. Patients with the prolonged infusion had a 1.4-fold increase in maximum intracellular 2',2'-difluorodeoxycytidinetriphosphate concentration compared with those with short infusions (1.0–2.6-fold;  $P = 0.016$ ). The potential clinical benefits of prolonged fixed dose rate infusions are under investigation. Moreover, the high levels of gemcitabine (>20 μM) represent no pharmacological advantage for i.p. administration.

The reported toxicities in our study are generally consistent with toxicities associated with cisplatin- and gemcitabine-based therapies. The thrombocytopenia seen on day 15 has prompted adoption of a day 1 and 8 administration during every 21-day schedule in other i.v. administration trials with cisplatin and gemcitabine (27). Fixed dose rate i.v. schedules have been associated with more hematological toxicity, and although our systemic drug levels are low, they are clearly sufficient to cause dose-limiting myelosuppression in combination with cisplatin. We noted that the toxicity associated with cisplatin at 75 mg/m<sup>2</sup> i.p. appears less than reported at 100 mg/m<sup>2</sup> in the abstract of Armstrong *et al.* (22), suggesting that if the i.p. approach is to be carried forward in any setting, the lower dose may be better tolerated. The five patients (17%) that came to exploratory surgery for evaluation of abdominal pain are noteworthy in that each had areas of fibrous encasement of the bowel requiring adhesiolysis. Two patients had recurrent disease, but three had adhesion formation and intermittent partial bowel obstruction, the likely source of their discomfort. No other patients have required intervention. No peritoneal inflammation was seen in the animal studies evaluating the preclinical pharmacokinetics of gemcitabine by i.p. administration (16, 28). Other agents evaluated for i.p. delivery, such as doxorubicin and mitoxantrone, have also caused this phenomenon (29, 30). Because no apparent advantage was seen with i.p. delivery of gemcitabine

and because of the noted peritoneal fibrosis in some patients, we would recommend that any additional consolidation studies proceed with i.v. administration.

In summary, the median time to treatment failure and overall survival of 15.9 and 43.5 months, respectively, are consistent with historical data in second-look-positive patients receiving a variety of i.p. platinum-based regimens for consolidation. In addition, the fibrotic changes seen in explored patients and the pharmacokinetic profile, which may be duplicated with prolonged fixed dose rate infusion, suggest that future studies of gemcitabine should be performed with i.v. administration. Finally, the absolute benefit of i.p. consolidation requires randomized trials to assess efficacy. The prolonged survival in this patient population, with largely macroscopically positive second-look surgical assessments, is noteworthy.

## REFERENCES

- McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1-6.
- Muggia FM, Braly PS, Brady MF, et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. *J Clin Oncol* 2000;18:106-15.
- Markman M, Liu PY, Wilczynski S, et al; Southwest Oncology Group; Gynecologic Oncology Group. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy. *J Clin Oncol* 2003;21:2460-5.
- Bolis G, Scarfone G, Tateo S, Mangili G, Villa A, Parazzini F. Response and toxicity to topotecan in sensitive ovarian cancer cases with small residual disease after first-line treatment with carboplatinum and paclitaxel. *Gynecol Oncol* 2001;80:13-5.
- Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. *J Natl Cancer Inst (Bethesda)* 1997;89:480-7.
- Schneider JG. Intraperitoneal chemotherapy. *Obstet Gynecol Clin North Am* 1994;21:195-212.
- Barakat RR, Almadrone L, Venkatraman E, et al. A phase II trial of IP cisplatin and etoposide as consolidation therapy in patients with stage II-IV epithelial ovarian cancer following negative surgical assessment. *Gynecol Oncol* 1998;69:17-22.
- Markman M, Reichman B, Hakes T, et al. Impact on survival of surgically defined favorable responses to salvage intraperitoneal chemotherapy in small volume residual ovarian cancer. *J Clin Oncol* 1992;10:1479-84.
- Barakat RR, Sabbatini P, Bhaskaran D, et al. Intraperitoneal chemotherapy for ovarian carcinoma: results of long-term follow-up. *J Clin Oncol* 2002;20:694-8.
- Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Peter GJ. Synergistic interaction between gemcitabine and cisplatin in vitro. *Clin Cancer Res* 1996;2:521-30.
- Peters GJ, Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Braakhuis BJ. Interaction between cisplatin and gemcitabine in vitro and in vivo. *Semin Oncol* 1995;22:72-9.
- Moufarij MA, Phillips DR, Cullinane C. Gemcitabine potentiates cisplatin cytotoxicity and inhibits repair of cisplatin-DNA damage in ovarian cancer cell lines. *Mol Pharmacol* 2003;63:862-9.
- Nogue M, Cirera L, Arcusa A, et al. Phase II study of gemcitabine and cisplatin in chemo-naïve patients with advanced epithelial ovarian cancer. *Anticancer Drugs* 2002;13:839-45.
- Bauknecht T, Hefti A, Morack G, et al. Gemcitabine combined with cisplatin as first-line treatment in patients 60 years or older with epithelial ovarian cancer: a phase II study. *Int J Gynecol Cancer* 2003;13:130-7.
- Plunkett W, Huang P, Searcy CE, Gandhi V. Gemcitabine: preclinical pharmacology and mechanisms of action. *Semin Oncol* 1996;23:3-15.
- Hertel LW, Boder GB, Kroin S, et al. Evaluation of the antitumor activity of gemcitabine. *Cancer Res* 1990;50:4417-22.
- Freeman KB, Anliker S, Hamilton M, et al. Validated assays for the determination of gemcitabine in human plasma and urine using high-performance liquid chromatography with ultraviolet detection. *J Chromatogr* 1995;665:171-81.
- Makhija S, Leitao M, Sabbatini P, et al. Complications associated with intraperitoneal chemotherapy catheters. *Gynecol Oncol* 2001;81:77-81.
- Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst (Bethesda)* 2000;92:699-708.
- Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996;335:1950-5.
- Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* 2001;19:1001-7.
- Armstrong D, Bundy BN, Baergen R, et al. Randomized phase III study of intravenous paclitaxel and cisplatin versus IV paclitaxel, intraperitoneal cisplatin and IP paclitaxel in optimal stage III epithelial ovarian cancer: a Gynecology Oncology Group trial (GOG 172) [abstract]. *Proc Am Society Clin Oncol* 2002:803.
- Hakes TB, Chalas E, Hoskins WJ, et al. Randomized prospective trial of 5 versus 10 cycles of cyclophosphamide, doxorubicin, and cisplatin in advanced ovarian cancer. *Gynecol Oncol* 1992;45:284-9.
- Plunkett W, Huang P, Xu YZ, Heinemann V, Grunewald R, Gandhi V. Gemcitabine: metabolism, mechanisms of action, and self-potential. *Semin Oncol* 1995;22:3-10.
- Brand R, Capadano M, Tempero M. A phase I trial of weekly gemcitabine administered as a prolonged infusion in patients with pancreatic cancer and other solid tumors. *Investig New Drugs* 1997;15:331-41.
- Patel SR, Gandhi V, Jenkins J, et al. Phase II clinical investigation of gemcitabine in advanced soft tissue sarcomas and window evaluation of dose rate on gemcitabine triphosphate accumulation. *J Clin Oncol* 2001;19:3483-9.
- Huisman C, Giaccone G, van Groeningen CJ, Sutedja G, Postmus PE, Smit EF. Combination of gemcitabine and cisplatin for advanced non-small cell lung cancer: a phase II study with emphasis on scheduling. *Lung Cancer* 2001;33:267-75.
- Braakhuis BJ, van Dongen GA, Vermorken JB, Snow GB. Preclinical in vivo activity of 2',2'-difluorodeoxycytidine against human head and neck cancer. *Cancer Res* 1991;51:211-4.
- Markman M, George M, Hakes T, et al. Phase 2 trial of intraperitoneal mitoxantrone in the management of refractory ovarian carcinoma. *J Clin Oncol* 1990;8:146-50.
- Husain A, Sabbatini P, Spriggs D, et al. Phase II trial of intraperitoneal cisplatin and mitoxantrone in patients with persistent ovarian cancer. *Gynecol Oncol* 1999;73:96-101.