Phase I Trial of Intraperitoneal Gemcitabine in the Treatment of Advanced Malignancies Primarily Confined to the Peritoneal Cavity

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Abstract

Purpose: To determine the maximally tolerated dose, toxicity, and pharmacokinetics of i.p. gemcitabine.

Experimental Design: Patients had peritoneal carcinomatosis. Gemcitabine (40, 80, 120, or 160 mg/m^2) was administered into the peritoneal cavity in 2 L of warmed saline on days 1, 4, 8, and 12 of a 28-day cycle.

Results: Thirty patients received 63 (median, 2; range, 0-6) courses. Tumors included ovary (14), uterus (2), colon (6), pancreas (3), and others (5). Dose-limiting toxicity included nausea, vomiting, diarrhea, dyspnea, fatal respiratory failure, and grade 3 elevation of alanine aminotransferase in three patients. Hematologic toxicity and pain were ≤grade 2. Three patients had decreased or resolved ascites. Of 19 patients evaluable for response, 10 had stable disease (median, 3.5 courses) and 9 had progressive disease. The median peak peritoneal concentration was 1,116-fold (range, 456-1,886) higher than the peak plasma level. Plasma and peritoneal levels were undetectable within 8 to 12 h. At 120 mg/m^2, the median peritoneal area under the concentration versus time curve (AUC) was 82,612 ng/mL × h (range, 53,296-199,830) and the plasma AUC was 231 ng/mL × h (range, 47.6-259.5). The mean peritoneal advantage ($AUC_{peritoneal}$/AUC_{plasma}) was 847 (range, 356-1,385).

Conclusions: I.p. administration of gemcitabine is tolerated within the tested dosage range. Technical problems with the Porta-Cath device and i.p. therapy per se may have been exacerbated by the enrollment of many patients with a variety of advanced i.p. diseases. Given the significant increase in local dose intensity and the documented activity of this drug, this agent may be an excellent candidate for i.p. therapy in optimally debulked ovarian cancer, either alone or in combination.

Steep dose-response relationships have been observed for chemotherapy agents in epithelial neoplasms (1–3). Efforts to increase dose intensity include the i.p. delivery of chemotherapy, which enhances drug exposure in patients with peritoneal carcinomatosis, a common complication of advanced ovarian and gastrointestinal malignancies (4–6). I.p. chemotherapy confers a pharmacologic advantage [defined as the ratio of the area under the concentration versus time curve (AUC) of i.p. drug to simultaneously determined plasma AUC] and may represent an advance in our ability to treat these neoplasms. Three recent studies document an increased median survival in ovarian cancer patients treated with i.p. chemotherapy compared with control groups of patients treated with i.v. chemotherapy alone (7–9), and one recent randomized trial documents a survival benefit in patients with peritoneal carcinomatosis due to colon cancer using i.p. chemotherapy in combination with aggressive debulking surgery (10).

Gemcitabine, a chemotherapeutic agent that is incorporated into DNA and acts as a chain terminator during DNA synthesis, is active in a large number of epithelial neoplasms either as a single agent and in combinations that include taxanes and platinum drugs. It has also been shown to be a potent radiosensitizer (11).

The pharmacokinetics of i.v. gemcitabine have been carefully described (12). We undertook a phase I study designed to

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Received 7/17/06; revised 10/26/06; accepted 11/8/06.

Grant support: Grant CA62505 and National Cancer Institute Cancer Center Support grant CA33572.

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Note: Reported in part in *Proceedings of American Society Clinical Oncology* 20:93b, 2001 and in *Proceedings of the American Association for Cancer Research*. 43:2741, 2002.

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doi:10.1158/1078-0432.CCR-06-1735

determine the maximally tolerated dose, dose-limiting toxicities (DLT), pharmacokinetics, and possible pharmacokinetic advantage of gemcitabine administered as an i.p. infusion on a twice-weekly schedule in patients with peritoneal carcinomatosis. We report here the results of that study.

Patients and Methods

Patient selection. Thirty patients with advanced, histologically proven malignancies primarily confined to the peritoneal cavity were entered on this phase I trial. Patients were required to have chemotherapeutically unresponsive malignancies, to have relapsed following previous chemotherapeutic regimens, or to have malignancies for which no defined "standard" chemotherapeutic regimen exists. Patients were required to have a Karnofsky performance status ≥50%, age ≥18 years, and an expected survival of at least 3 months. Adequate renal function was defined as a serum creatinine ≤1.5 mg/dL or a 24-h creatinine clearance ≥50 mL/min. Adequate bone marrow function for enrollment was defined as a total white count ≥3,500/μL or absolute neutrophil count ≥2,000/dL and platelet count ≥150,000/μL. Adequate hepatic function was defined as a serum bilirubin ≤1.5 mg/dL and aspartate aminotransferase and alanine aminotransferase within twice the institutional upper limit of normal. Prior radiation or chemotherapy must have been completed at least 4 weeks before beginning treatment on this protocol. There was no limit on the number of prior courses or types of chemotherapy. Female patients could not be pregnant. Patients must have been willing to undergo the necessary surgical procedure for insertion and removal of an i.p. catheter. All patients gave their voluntary informed consent and signed a consent document that had been reviewed and approved by the City of Hope National Medical Center Clinical Protocol Review and Monitoring Committee and Institutional Review Board.

Pretreatment evaluation. All patients underwent a complete history and physical examination, including documentation of weight, Karnofsky performance status, presence of measurable or evaluable disease, as well as a complete blood count with platelet count and differential, 18 channel blood chemistry analysis, CA-125 level, chest X-ray (if indicated), and computed tomographic scans of the chest, abdomen, and pelvis as needed to document measurable or evaluable disease. In addition, all patients underwent peritoneal fluid analysis for cell count, cytology, and culture for bacteria. Patients with measurable disease were required to have radiographic procedures for analysis of that measurable disease repeated no less often than every 8 weeks.

Treatment plan. This trial was designed as a phase I study with patients treated in cohorts of three. The starting dose of i.p. gemcitabine was determined by using preclinical animal data recognizing that toxicity of this class of agents is schedule dependent (13). Doses were subsequently escalated according to a modified Fibonacci scheme. The drug was administered by i.p. infusion, initially at 40 mg/m^2/dose delivered on days 1, 4, 8, and 12 and then repeated every 3 weeks from day 1 of therapy. The levels were then 80, 120, and 160 mg/m^2/dose (see Table 1 for dosage escalations), with no intrapatient dose escalation. Antiemetic premedications were administered at the discretion of the treating physician.

Gemcitabine was prepared by reconstituting the supplied vials consisting of a white lyophilized powder in 2 L of 0.9% normal saline instilled via a Porta-Cath catheter through a Huber needle. Immediately before the gemcitabine instillation, 500 mL of warmed saline were instilled into the peritoneal cavity and allowed to stand for 15 min. Peritoneal fluid samples were then obtained through the peritoneal catheter, and then the chemotherapy was instilled as quickly as possible and allowed to remain in the peritoneal cavity. Patients were turned hourly to bathe all areas of the peritoneal cavity. No attempt was made to drain the instilled chemotherapy. After 4 h, the Huber needle was removed and the Porta-Cath was cleaned and covered with a dressing.

Patients experiencing any reversible grade 3 toxicity with stable disease or responding tumor were allowed to receive subsequent cycles of therapy at a dose reduction of one level. If a second grade 3 or any grade 4 toxicity was observed on a subsequent cycle, the patient was taken off study. A minimum of three patients evaluable for treatment toxicity were entered at each dose level before any dose escalation. Dosage escalations were determined by the toxicity encountered after the first cycle of i.p. chemotherapy. Patients must have received all four planned doses of i.p. chemotherapy or have experienced a grade 3 or 4 toxicity to be considered evaluable for toxicity evaluation. If after one complete course of therapy there were no grade 3 or 4 toxicities observed in any member of the cohort, the dosage of gemcitabine was escalated by one level for the next three patients. A single instance of grade 3 toxicity resulted in the accrual of three additional patients at that dose level. If no further grade 3 toxicities were observed in the additional patients (i.e., only one of six patients with grade 3 toxicity), drug doses were escalated in the next cohort. In the event of a single instance of grade 4 toxicity at any dose level or a second grade 3 toxicity in the additional three patients, no further dose escalation was permitted and a total of six patients were to be treated at the next lower dose. The maximal tolerated dose was defined as the highest dose at which no grade 4 toxicities and at most one grade 3 toxicity were encountered in a six-patient cohort. Standard Southwest Oncology Group response criteria were used in patients having measurable or evaluable disease (14). Tumor markers were not used for response evaluation. Toxicity was measured using the Common Toxicity Criteria of the National Cancer Institute, version 2.0, January, 30, 1998.

Plasma sampling. Immediately before the initiation of the gemcitabine administration, in a subset of patients at each dose level, samples were collected for pharmacokinetic analysis. Two 4-mL tubes of blood in heparinized (green-top) tubes were collected and immediately placed on ice. The samples were separated, and the plasma was frozen within 1 h. One additional 4 mL of heparinized tube of blood were collected immediately on completion of the gemcitabine infusion (0 h) and at 1, 2, 4, 6, 8, 12, and 24 h following completion of the infusion of the gemcitabine and were similarly processed. Ten milliliters of peritoneal fluid were simultaneously withdrawn from the peritoneal catheter at the time of each plasma sample collection for i.p. gemcitabine levels and were processed similarly.

Peritoneal fluid analyses. Immediately before the instillation of gemcitabine during each cycle and at 24 h following each cycle, 500 mL of warmed saline were instilled into the peritoneal cavity via the Porta-Cath, and a sample was immediately withdrawn and evaluated for cytology, cell count, and differential.

Analysis of gemcitabine concentration. The concentration of gemcitabine in plasma and peritoneal fluid was measured according to a modification of a previously published high-performance liquid chromatography method (15). Briefly, following the addition of 2′,3′-dideoxycytidine as an internal standard, a solid-phase extraction step was used to eliminate interfering substances from plasma and peritoneal fluid. The high-performance liquid chromatography system consisted of a Shimadzu model SCL-10AVP controller, two model LC-10AS solvent delivery pumps, a model SIL-10A autoinjector, and a model SPD-10A UV-VIS detector (Shimadzu, Columbia, MD) at a wavelength of 275 nm. Separation was achieved using a Beckman C18 analytic column (5 μm, 250 × 4.6 mm i.d.; Fullerton, CA) followed by a Waters (Milford, MA) C18 guard column. Mobile phase A was 0.05 mol/L phosphate buffer (pH 3.0), and mobile phase B was 100% methanol. The gradient program was as follows: linear increase from 2% to 5% of B by 8 min, hold at 5% of B until 16 min; linear increase from 5% to 10% of B by 18 min, hold at 10% of B until 25 min; linear decrease from 10% to 2% of B by 28 min; and equilibrate at 2% of B until 30 min. Elution was done at 1.0 mL/min and ambient temperature. Data acquisition and integration was done using the Class-VP Chromatography Data System (Shimadzu). The lower limit of quantitation was 5 ng/mL, and the within-day and between-day assay precision and accuracy were within ±10% of target concentrations.

Table 1. Courses completed, summary of DLT, and responses

Dose level	Dose (mg/m^2)	No. pts treated	Courses, median (range)	No. pts excluded from course one toxicity evaluation	No. cycles	No. DLTs	DLT description	Best responses during therapy
1	40	5	4 (1-4)	2	15	0	NA	SD 3, PD 1, Ineval 1
2	80	8	1.5 (0-6)	5	18	0	NA	SD 2, PD 2, Ineval 4
3	120	12	1.5 (0-3)	6	20	1	Grade 3 LFTs	SD 2 (DLT 1), PD 6, Ineval 4
4	160	5	1 (1-3)	3	10	2	Grade 3 nausea/emesis; grade 4 dyspnea/grade 5 respiratory failure	SD 3, Ineval 2 (DLT 2)

Abbreviations: pts, patients; NA, not applicable; LFT, liver function test; SD, stable disease; PD, progressive disease; Ineval, inevaluable.

Pharmacokinetic calculations. Estimates of total gemcitabine exposure (ng/mL × h) were defined as the AUC. Gemcitabine AUCs in plasma and peritoneal fluid were calculated by noncompartmental methods using the rule of linear trapezoids over the interval beginning with the fluid instillation and extrapolated to infinity using an elimination rate constant derived from a weighted least squares fit of the last three measured concentrations. The pharmacologic advantage was defined as the gemcitabine $AUC_{peritoneal}/AUC_{plasma}$. Peak plasma and peritoneal fluid gemcitabine concentrations (ng/mL) were defined as the highest measured drug concentrations in those respective fluids.

Statistical methods. This study was a phase I trial designed to establish the maximal tolerated dose and the DLTs of gemcitabine administered as an i.p. infusion. The dose levels are provided in the treatment plan section above. The DLT in a given patient was defined as any therapy-related grade 3 or 4 nonhematologic toxicity (with grade 3 mucositis being an inability to eat or drink), grade 4 thrombocytopenia, or grade 4 neutropenia lasting more than 5 days or associated with fever. To be evaluable for toxicity, a patient must have completed at least one treatment cycle consisting of four doses of i.p. gemcitabine and have been observed at for at least 2 weeks after the first course or have experienced DLT. All patients who were not evaluable for toxicity due to disease progression or catheter-related complications (described in Results) were replaced.

Results

Patient characteristics. Thirty patients enrolled on this phase I trial received 63 (median, 2; range, 0-6) courses of treatment (Table 1). Seven patients were male; 23 were female (Table 2).

Table 2. Patient characteristics (N = 30)

Gender	
Male	7
Female	23
Race	
Caucasian (5 Hispanics)	27
Asian	3
Histologic types	
Pancreatic cancer	3
Endometrial cancer	2
Colon cancer	6
Ovarian cancer	14
Other cancers	5
Karnofsky performance status	
80-90%	22
60-70%	7
50%	1
Age, y, median (range)	59 (39-76)

The median age was 59 years (range, 39-76 years), and the median Karnofsky performance status was 80% (range, 50-90%). Twenty-seven patients were Caucasian (five Hispanics) and three were Asian. The tumor types included ovary (14), uterus (2), colon (6), pancreas (3), and one patient each with carcinoma of unknown primary, carcinoid, mesothelioma, endometrial sarcoma, and small bowel. All patients had prior abdominal surgery; 22 patients had received prior chemotherapy (median number of regimens, 3; range, 1-7), and four patients had received prior radiation, three with external beam radiation to the abdomen and one using i.p. radioimmunotherapy. No other patient had received i.p. therapy of any type.

DLT of therapy. The dosage escalation and toxicity by dose level are summarized in Table 3. Toxicity was mild at dose levels 1 and 2 (40 and 80 mg/m^2/dose). No DLTs were noted in the six evaluable patients enrolled. The first patient enrolled on dose level 3 (120 mg/m^2/dose) developed elevation of transaminases that were asymptomatic and self-limited. Neither of the subsequent two patients on this dose level experienced grade 3 or 4 toxicity. At the next dose level, 160 mg/m^2, two episodes of DLT were encountered. One patient experienced self-limited grade 3 nausea, vomiting, and diarrhea and grade 4 dyspnea. A second patient with a Karnofsky performance status of 50% on protocol entry experienced grade 4 dyspnea of uncertain etiology and subsequently died of respiratory failure. It was uncertain if this was related to the i.p. chemotherapy but, due to the severe toxicity, was considered dose limiting. The dose level lower was then expanded by three further evaluable patients without further episodes of DLT, thus establishing 120 mg/m^2 as the recommended phase 2 dose level.

Other grade 3 or 4 toxicities that were not considered dose limiting included the following: nausea/vomiting, constipation, anemia requiring transfusion, thrombocytopenia, leucopenia, hypertension, fatigue, anorexia, abdominal cramping, and dehydration.

Cycles completed, responses, and reasons for discontinuation of protocol therapy. The number of cycles administered and range per dose level are summarized in Table 1. The median numbers of cycles per dose level were 4, 1.5, 1.5, and 1 for dose levels 1 to 4, respectively, ranging from 0 to 6 completed courses across all dose levels. Nineteen of the 30 patients treated on this study were evaluable for response. Ten patients had stable disease for a median of 3.5 cycles (range, 2-6). One patient with ovarian cancer, who had required weekly paracenteses, completely resolved her ascites for 2 months following the first dose of i.p. chemotherapy. She progressed 2 months later

Table 3. Gemcitabine pharmacokinetics (N = 9)

Dose	PL Peak (ng/mL)	Perit PK (ng/mL)	Ratio	AUC PL ng/mL × h	AUC Perit ng/mL × h	Ratio
40	11.2	15,988	1,427	29.7	32,129	1,082
40	10	N/D	N/D	14.2	N/D	N/D
40	8.7	6,433	739	35.8	15,230	425
80	23.6	26,339	1,116	62.9	44,436	706
80	22.7	31,960	1,408	88.1	75,512	857
80	26.5	49,980	1,886	55.7	77,137	1,385
120	19.4	20,856	1,075	47.6	53,296	1,120
120	42.2	N/D	N/D	259.5	N/D	N/D
120	86.9	39,598	456	231.9	82,612	356
		Median	1,116		Median	857
		Mean	1,158		Mean	847
		SD	473		SD	378

Abbreviation: PL Peak, peak plasma; Perit PK, peak peritoneal; PL, plasma; Perit, peritoneal; N/D, not determined.

with recurrent ascites and a pleural effusion. One patient with pancreatic cancer and ascites had a minor response in the pancreas and decreased accumulation of persistent ascites. One patient with signet ring carcinoma of unknown primary had a marked decrease in ascites accumulation, which recurred on progression of disease. All three of these patients had decreases in blood CA-125 levels (500 to 102, 291 to 63, and 714 to 438, respectively). Nine patients had progressive disease following a median of two cycles (range, 1-3) of i.p. gemcitabine. Eleven patients were inevaluable for response due to completing only zero (2 patients) or one course of therapy (9 patients).

Reasons for inevaluable patients. There were several reasons why patients were inevaluable for toxicity and/or response; these reasons varied by dose level. On dose level 1, two patients experienced incomplete cycles due to Porta-Cath malfunctions. Two patients on dose level 2 developed small bowel obstructions due to disease progression; one patient had a Porta-Cath malfunction, and two patients missed one or two of the planned doses due to abdominal discomfort. At dose level 3, one patient experienced a Porta-Cath malfunction; three patients developed clinical disease progression; two patients missed one dose of chemotherapy, one due to the development of infectious pneumonitis from the primary disease process and the other for a family emergency. Three patients were inevaluable for toxicity on dose level 4, one due to Porta-Cath failure and two because they did not have laboratory studies done that were necessary for protocol toxicity evaluation.

Pharmacokinetics. Plasma and peritoneal pharmacokinetic analyses were done on nine patients and are summarized in Table 3. The mean values of the peak plasma concentration and AUC concentration at the maximally tolerated level of 120 mg/m^2/dose were 49.5 and 236 ng/mL × h, respectively. The mean peak peritoneal concentration and AUC were 64,657 and 111,913 ng/mL × h. The mean pharmacokinetic advantage ($AUC_{peritoneal}/AUC_{plasma}$) across all dose levels was 847 (range, 356-1,385). The median peritoneal AUC was 82,612 ng/mL × h (range, 53,296-199,830), whereas the median plasma AUC was 231 ng/mL × h (range, 47.6-259.5). The peritoneal AUC at 120 mg/m^2 is ~10-fold higher than the plasma AUC measured following i.v. administration of standard doses of gemcitabine. Peak plasma and peritoneal concentrations increased linearly with dose as did the plasma and peritoneal AUCs and the peritoneal/plasma AUC ratios. The median gemcitabine peak peritoneal concentration was 1,116-fold (range, 456-1,886) higher than the peak plasma level. Both plasma and peritoneal levels were undetectable within 8 to 12 hours of instillation.

Discussion

Increased dose intensity of chemotherapeutic agents results in improved response rates and potential survival benefit for those agents that have steep dose-response relationships against sensitive tumors (1–3). Tumors that are predominantly confined to the peritoneal cavity allow a unique opportunity to deliver increased doses of active agents directly to the area of the greatest tumor involvement. Peritoneal advantages of 50 to 1,000 times the concentrations possible by the i.v. route are possible by i.p. drug delivery (16–19). Results of second-line chemotherapy for ovarian cancer with i.p. floxuridine have been encouraging with a reported median survival of 38 months in patients with minimal residual disease following second-look laparotomy (20). Although i.p. chemotherapy has been used since the initial description of the rationale by Dedrick et al. (21), it is only recently that randomized trials have shown survival advantages through its use. This was initially shown in 1996 when Alberts et al. (22) reported a survival advantage in patients treated with i.p. chemotherapy compared with standard i.v. chemotherapy. Subsequent randomized trials in ovarian cancer have confirmed these findings (8, 23). Most recently, Armstrong et al. (9) have reported a survival advantage of 16 months in newly diagnosed, optimally debulked ovarian cancer patients treated with i.p. chemotherapy compared with a similar group receiving i.v. chemotherapy. Based on these data, the National Cancer Institute has issued an alert stating that i.p. chemotherapy should be considered in appropriate patients as initial treatment (24).

The role of i.p. chemotherapy in addition to aggressive surgical resection is being investigated in non-ovarian malignancies. Verwaal et al. (10) have shown recently a survival advantage for patients with advanced colon cancer treated with surgery followed by i.p. chemotherapy compared with those treated with standard i.v. chemotherapy. Although the definitive role of the i.p. chemotherapy versus aggressive surgical resection alone is not clear, this trial suggests that further clinical trials must be done to further elucidate the relative

contribution of each treatment modality to explain the observed survival improvement.

Because of these encouraging data, it is important to characterize recently approved agents to determine their suitability for i.p. administration, for potential use as a single agent, in combination chemotherapy regimens, or possibly as a radiation sensitizer for i.p. treatment with radiotherapy. Gemcitabine is a potent radiation sensitizer at doses lower than those used traditionally for i.v. therapy (25).

Several schedules of administration of gemcitabine have been examined in preclinical and clinical trials. Braakhuis et al. (13) and Boven et al. (26) have given gemcitabine to athymic nude mice bearing xenografts of several tumors. They found that 3-day interval injections were more effective than daily or weekly schedules. Tempero et al. (27) administered gemcitabine by fixed dose rate infusions in pancreatic cancer in a randomized phase II study and found increased response rates, median survivals, and 1-year response rates, suggesting that this approach should be used in further investigations of possible schedule-dependent improved activity of this agent. Based on these data, we chose a twice-weekly schedule in this trial and found that it is feasible. No objective responses were noted; however, this is a phase I trial in patients who were multiply pretreated. Despite this, patients were noted to derive palliative benefit from the treatment approach with control of ascites noted in three patients. It is unlikely, although possible, that local effects of gemcitabine on the peritoneal surfaces could account for the fluid control; however, the clinical correlation with CA-125 levels suggests a true cytostatic effect. Clinically, fixed dose rate infusions have also been shown to have potentially improved responses. We have used gemcitabine in this study and have shown that administration on the twice-weekly schedule at low doses is feasible.

Sabbatini et al. (28) administered i.p. gemcitabine at a dose of 500 mg/m^2/wk in combination with i.p. cisplatin on a 3-week schedule in patients with ovarian cancer. Reported toxicities included evidence of peritoneal irritation by this agent in patients who underwent subsequent laparotomies as well as substantial myelosuppression, renal insufficiency, fatigue, and hypokalemia. We also noted similar toxicities; however, these were not considered dose limiting and were primarily noted during subsequent administration of the i.p. gemcitabine. The DLTs included dyspnea, severe nausea and vomiting, and elevated liver function tests. Our group of heavily pretreated patients otherwise tolerated the treatment well with minimal clinical peritoneal irritation. Apparently, observed toxicity, including the pulmonary symptoms, may be less if a less heavily pretreated group of patients is studied. Because the maximal dose instilled in our study was 160 mg/m^2, it is possible that peritoneal irritation is a concentration-related phenomenon. Several of our patients were inevaluable due to the development of bowel obstructions from disease progression. One patient with colon cancer had multiple adhesions and required multiple bypasses to palliate the obstruction. Although the causes of inevaluability were many, the major reason for incomplete cycles was Porta-Cath failure, a common problem in the treatment of peritoneal carcinomatosis with i.p. therapy. Walker et al. (29) have assessed reasons for difficulties completing prescribed courses of i.p. chemotherapy and suggest that there may be an association between colorectal surgery and the ability to initiate i.p. chemotherapy. They suggest that further research is necessary to allow successful completion of therapy delivered directly into the peritoneal space. These findings indicate that i.p. chemotherapy should be considered earlier in the disease process when free flow of the chemotherapeutic agent is more likely and when there is less underlying pathology leading to the development of tumor-related symptoms that prevent adequate therapy.

The current study was designed to define the maximal tolerated dose of gemcitabine delivered directly into the peritoneal cavity. We determined that the median pharmacologic advantage of gemcitabine across all dose levels tested in this study is 857 (range, 356-1,385), which is comparable or superior with other chemotherapeutic agents administered via the i.p. route. This >800-fold pharmacokinetic advantage suggests that gemcitabine may be useful when delivered via the i.p. route to less heavily pretreated patients. Our results confirm those reported by Sabbatini et al. (28).

I.p. chemotherapy provides the ability to deliver high concentrations of a cytotoxic agent directly to the peritoneal space. Systemic concentrations of drugs are, however, achievable due to absorption of the agent through the peritoneal surface. The pharmacokinetic properties of gemcitabine administered as a standard i.v. infusion are well described. Our data indicate that the systemic AUCs of i.p. gemcitabine are comparable with the IC_{50} concentrations used in preclinical *in vitro* experiments in sensitive ovarian and resistant colon cancer cell lines (30). This phenomenon seems to be schedule dependent, suggesting that more frequent administration of drug may result in greater sustained accumulation of the agent by the malignant cell population. The clinical tolerance of i.p. gemcitabine in our trial at the maximal tolerated dose of 120 mg/m^2 given twice weekly was acceptable. Although no objective responses were noted in our study, nine patients received three to six courses of treatment resulting in symptom palliation, with three patients experiencing control of ascites.

Based on this trial, the recommended phase II dose of gemcitabine administered by the i.p. route is 120 mg/m^2/dose administered on days 1, 4, and 8 and repeated every 3 weeks. A follow-up phase I study using i.p. gemcitabine on this schedule in combination with i.p. radioimmunotherapy to determine the DLT of regional chemoradioimmunotherapy is ongoing.

Acknowledgments

We thank the excellent secretarial assistance of Yolanda Tamayo in the preparation of this manuscript.

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