Using a day 1 and 8, every-3-week schedule, our purpose was to determine the maximum tolerated dose of irinotecan (CPT-11, Camptosar) that can be administered immediately after gemcitabine (Gemzar) at a dose of 1,000 mg/m² IV. In this phase I trial, the maximum tolerated dose was defined as the dose level immediately below the level in which two of the first three patients in any cohort, or at least two of six patients in any expanded cohort, experienced dose-limiting toxicity. Dose-limiting toxicity pertained only to toxicity during the first cycle of treatment. Escalation of irinotecan was planned in groups of three patients, with three additional patients added at the first indication of dose-limiting toxicity. A total of 19 patients have been enrolled.

**Gemcitabine** (2′, 2′-difluorodeoxycytidine [dFdC, Gemzar]) is a pyrimidine analog antimetabolite with single-agent activity in a variety of solid tumors.[1-3] It is activated by intracellular phosphorylation and has multiple mechanisms of cytotoxicity. The predominant intracellular moiety, difluorodeoxycytidine triphosphate (dFdCTP), is incorporated as a substrate during DNA synthesis causing inhibition of DNA elongation and chain termination after the addition of another base or another molecule of dFdCTP.[2, 4, 5]


Preclinical data evaluating the combination of irinotecan and gemcitabine are limited. Kanazawa et al,[16] evaluating the combination effects of anti-cancer drugs, suggested dose-dependent interactions between gemcitabine and irinotecan. Moreover, our recent laboratory data suggest antagonism at low concentrations, but synergism at concentrations of gemcitabine above 0.1 µM and irinotecan above 3.2 µM in the SCOG small-cell lung cancer cell line.[17] Absolute, marked synergism was evident in the HL-60 acute myeloid leukemia cell line. Synergism at concentrations of 0.1-2 µM gemcitabine and 0.2-10 µM irinotecan, but antagonism at high concentrations (ie, concentrations > 2 µM gemcitabine and 20 µM irinotecan), was seen in MCF7 breast cancer cells (unpublished data). In addition, preclinical data also suggest synergy with concurrent administration of cytosine arabinoside (a gemcitabine analog) and irinotecan or SN-38.[18-20] In this phase I trial, initially reported by our group in 1999 [21] and updated here, the dose of gemcitabine was fixed at 1,000 mg/m² and irinotecan doses were escalated until a maximum tolerated dose for the combination was defined. Because other studies of gemcitabine combinations using a day 1, 8, and 15 schedule had shown substantial day 15 marrow toxicity, we chose to administer both drugs on days 1 and 8 of a 21-day treatment cycle.

**Patients and Methods**

**Patient Selection**

Adult patients with pathologically confirmed solid tumors refractory to standard therapy were eligible if they had adequate organ function (granulocyte count of at least 1,500/µL, platelet count of at least 100,000/µL, serum creatinine less than 2.1 mg/dL, and serum bilirubin less than 2.1 mg/dL), and performance status of 0 to 2. Patients were ineligible if they had bone marrow metastases, New York Heart Association class III or IV heart disease or myocardial infarction within 6 months, uncontrolled infection, whole pelvic radiation, prior gemcitabine and irinotecan, or a psychiatric condition.
Measurable or evaluable disease was not required. All patients gave written informed consent.  

**Treatment Plan**  
Gemcitabine at a fixed dose of 1,000 mg/m² was given intravenously over 30 minutes on days 1 and 8 of each 3-week cycle. Irinotecan was given intravenously by a 90-minute intravenous infusion after gemcitabine. The dose levels of irinotecan are shown in Table 1. Cohorts of at least three patients were treated at each dose level. Patients were taken off protocol if they had progressive disease, severe allergic reaction, or if the treating physician elected to stop therapy.  

**Drug Administration**  
All patients received prophylactic antiemetic therapy with an HT₃ blocker and dexamethasone. Irinotecan and gemcitabine were administered as described previously. No other chemotherapy, immunotherapy, or radiation therapy was permitted.  

**Dose-Escalation Rules and Maximum Tolerated Dose**  
The maximum tolerated dose was defined as the dose level immediately below the dose level at which two out of the first three patients in any cohort, or at least two out of six patients in any expanded cohort, experienced a dose-limiting toxicity. If one of three patients at any dose level experienced DLT, three additional patients were accrued. If none of these three additional patients experienced DLT, then the dose was escalated in the next cohort.  

**Dose-Limiting Toxicity**  
Toxicity was graded according to the NCI Common Toxicity Criteria. Dose-limiting toxicity was defined as follows: (1) grade 4 nonhematologic toxicity (excluding nausea, vomiting, fever, anorexia) or hemorrhage or thrombocytopenia; (2) Grade 3 nonhematologic toxicity other than nausea, vomiting, fever, anorexia, stomatitis, esophagitis/dysphagia; (3) grade 3 stomatitis or esophagitis/dysphagia lasting 7 days or more; (4) grade 4 neutropenia lasting 4 days or longer; (5) failure to recover neutrophils (1,500/µL or more) or platelets (100,000/µL or more) by day 28. During this phase I trial, cycle 1 day 8 treatment was given at full doses if the neutrophil count was 1,500/µL or more, platelets were 75,000/µL or more, and there were no nonhematologic toxicities worse than grade 1. Cycle 1 day 8 treatment was canceled in patients with either counts below this level or grade 2 or higher nonhematologic toxicity on that day. Dose adjustments for subsequent cycles are shown in Table 2.  

**Patient Evaluation**  
At enrollment, patients were evaluated with a complete history and physical examination and performance status assessment. Required blood counts, serum chemistries, and urinalysis were completed within 14 days of study entry. Any x-ray, scan, CT, MRI, or ultrasound that was utilized for tumor measurement in patients with measurable or evaluable disease had to have been performed within the 28 days prior to study entry. During the first cycle of chemotherapy a physician monitored patients at least weekly. For subsequent cycles patients were assessed at each chemotherapy visit. Complete blood count with differential and serum chemistries were repeated on day 1 and day 8 of each chemotherapy cycle. Subsequently the complete blood count with differential was repeated every 3 days until the end of the treatment cycle. Response criteria were standard.  

**Results**  

**Patient Characteristics**  
Between July 1997 and February 1998, 19 patients were registered onto study at the Hollings Cancer Center, Medical University of South Carolina. One patient at dose level 2 had a grade 2 allergic reaction during her second dose (cycle 1, day 8) of irinotecan. She declined further protocol therapy. All the remaining 18 patients received at least two cycles. The baseline characteristics and tumor types of the 19 patients are shown in Table 3 and Table 4, respectively.  

**Hematologic Toxicity**  
Hematologic toxicity during cycle 1 is shown in Table 5. No patient experienced hematologic dose limiting toxicity. Day 8 cycle 1 chemotherapy was held in one patient due to thrombocytopenia (46,000 platelets), 1 for neutropenia (1,000 neutrophils), and another for both neutropenia (900/µL) and thrombocytopenia (67,000/µL). Generally, no dose response relationship for hematologic toxicity was demonstrated. Six patients had non-neutropenic fever (> 100.5°F) at some time during therapy.  

**Nonhematologic Toxicity**  
All severe or life-threatening nonhematologic toxicities occurring during this trial were gastrointestinal. The grade III/IV nonhematologic toxic events during cycle 1 are shown in Table 6.  

**Response Evaluation**
Eighteen patients had measurable disease and were evaluated for response to treatment (Table 7). Three previously untreated patients, one in cohort 3 (100 mg/m²) and two in cohort 4 (115 mg/m²), had a documented partial response. Among the responders, two had pancreatic cancer and one had metastases from unknown primary.

Two additional patients, one at dose level 4 with previously untreated pancreatic cancer and one at dose level 3 with previously treated non-small-cell lung cancer, have had symptomatic benefit (increased appetite with weight gain and decrease in requirement of narcotic analgesic) and radiologic evidence of a decrease in tumor size that did not meet criteria for a partial response.

**Recommended Doses for Phase II Studies**
The maximum tolerated dose of irinotecan was 100 mg/m² in combination with gemcitabine (1,000 mg/m²). This dose and schedule is recommended for phase II studies. Escalation of irinotecan to 115 mg/m² may be considered for subsequent cycles in patients who do not experience grade 1 or higher hematologic or nonhematologic toxicity.

**Discussion**

Both gemcitabine and irinotecan are active single agents in a number of solid tumors. Their toxicity profiles and differences in mechanism of cytotoxicity make evaluation of a gemcitabine and irinotecan combination attractive.

Previous gemcitabine combination studies have frequently resulted in marked myelosuppression on day 15, limiting drug administration on that day.[22-26] The use of the day 1 and 8 schedule was designed to avoid this problem. Other investigators have used the same strategy when combining gemcitabine with other myelosuppressive agents.[27,28] No hematologic DLT was observed in any patient in this trial during the first cycle.

The dose-limiting toxicity in this trial was diarrhea, which was not unexpected based on other experiences with irinotecan.[29-35] Delayed onset diarrhea occurs between the second and fourteenth day of irinotecan administration, and lasts on average between 5 and 7 days. It is unpredictable, varying from one cycle to another, and is sometimes severe enough to require parenteral hydration.[33,35]

Gemcitabine is approved in the United States as a single agent for management of patients with advanced pancreatic cancer. This approval resulted from phase III data demonstrating an improved rate of clinical benefit and an overall survival advantage for gemcitabine therapy compared to treatment with fluorouracil. However, in this phase III trial the objective gemcitabine partial response rate was only 5.4%.[36]

Phase II data suggest that irinotecan has activity against pancreatic cancer. In previously untreated patients with advanced pancreatic cancer, Sakata et al[37] reported an 11% partial response rate (4 out of 35 patients) using irinotecan at 100 mg/m²/wk or 150 mg/m² every other week. Wagener et al[38] saw 3 partial responders out of 32 patients (9%) with pancreas cancer treated with an irinotecan dose of 350 mg/m² by 30 minute IV infusion every 3 weeks.

Three patients, two of which had pancreatic cancer, achieved a partial response. These observations have encouraged us to further evaluate the combination of gemcitabine and irinotecan in patients with pancreas cancer. A multicenter phase II trial of the combination of gemcitabine and irinotecan described in this article has recently been reported.[39] A phase III trial for similar patients testing gemcitabine alone vs gemcitabine plus irinotecan using this day 1 and 8 gemcitabine/irinotecan schedule has recently been closed to accrual after 350 patients with advanced, metastatic pancreatic cancer have been enrolled.

**References:**


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