Irinotecan and Fixed-Dose-Rate Gemcitabine in Advanced Pancreatic and Biliary Cancer: Phase I Study

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It is a continuing challenge for oncologists to effectively treat advanced/metastatic pancreatic and biliary cancer. Both irinotecan (CPT-11, Camptosar) and gemcitabine (Gemzar) have shown activity against these diseases with different mechanisms. Preclinical and clinical data also suggest additive or synergistic effects of the combination of these two agents with few or no overlapping toxicities. Phosphorylation of gemcitabine, a process of intracellular activation of the agent, is dose-rate dependent. It has been suggested that the fixed-dose-rate infusion of gemcitabine increases the concentration of intracellular triphosphate gemcitabine, which in turn may result in more objective responses and longer median survival compared to the standard infusion. This phase I study tests the toxicity of the combination of irinotecan with fixed-dose-rate infusion of gemcitabine, and determines the dose of the combination for phase II investigation.

Pancreatic cancer is one of the leading causes of cancer death in the United States, with a total of 30,700 new cases and 30,000 deaths projected for the year 2003.[1] Median survival is 6 to 10 months for patients with locally advanced disease and 3 to 6 months for metastatic disease, depending on performance status and extent of disease at diagnosis.[2] Most patients have their disease diagnosed at an advanced or metastatic stage, because of nonspecific early symptoms of the disease. Although there have been advances in treatment of the disease in recent years, the effectiveness of chemotherapy is still disappointing. New strategies both to improve outcome and to develop effective treatments for pancreatic cancer beyond gemcitabine (Gemzar) are desperately needed. Advanced biliary cancer is another aggressive gastrointestinal malignancy. The prognosis for unresectable biliary cancer is very poor. It is projected that there will be 6,800 new cases and 3,500 deaths in 2003.[1] There is no standard chemotherapy regimen available, although some chemotherapeutic agents have shown some activity for this disease. Therefore, the goal of this phase I study is to assess the maximum tolerated dose and dose-limiting toxicity of the combination of fixed-dose-rate gemcitabine and irinotecan in advanced pancreatic and biliary cancer.

Mechanisms of Action

Gemcitabine (2',2'-difluorodeoxycytidine [dFdC]) is a nucleoside analog that has a broad spectrum of antitumor activity in solid tumors and leukemia.[3,4] A prodrug with high membrane permeability and a high affinity for deoxycytidine kinase, gemcitabine is converted intracellularly to its active metabolite difluorodeoxycytidine triphosphate (dFdCTP). dFdCTP achieves higher intracellular concentrations and is retained significantly longer than the triphosphate of other pyrimidine analogs despite feedback inhibition of cytidine deaminase, the enzyme responsible for its degradation. It competes with dCTP for incorporation into DNA, where it acts as a chain terminator.[5,6] The drug also depletes intracellular deoxynucleoside triphosphate pools, presumably by inhibiting ribonucleotide reductase.[7] Responses to gemcitabine as a single agent have been reported in several common solid tumors in phase II studies. Doses ranged from 800 to 1,250 mg/m² weekly for 3 weeks every 28 days, and toxicity was considered tolerable.[8,9] Burris et al conducted a pivotal phase III trial in patients with advanced pancreatic cancer and demonstrated that gemcitabine at 1,000 mg/m² weekly was more effective than fluorouracil (5-FU) in producing clinical benefit, as measured by a specific scale.[4] Other outcomes, including response rate, time to progression, and overall survival, also favored gemcitabine in this study. Encouraging information for the activity of gemcitabine in biliary cancer has also been reported from some small studies (combined N = 98 evaluable patients), with response rates reaching 25% to 36%.[10-12] Gemcitabine undergoes dose-rate-dependent intracellular phosphorylation to form the active di- and triphosphates. A randomized phase II trial suggested that a fixed-dose-rate infusion of gemcitabine (10 mg/m²/min, 1,500 mg/m² total dose) resulted in more objective responses, longer medial survival, and higher 1-year survival than the standard infusion rate.[13] Pharmacokinetic studies showed much higher median gemcitabine triphosphate levels in mononuclear cells by fixed-rate infusion. Irinotecan (CPT-11, Camptosar), a camptothecin derivative, is a topoisomerase I inhibitor that traps the topoisomerase I-DNA cleavable complex following cleavage of single-strand DNA.
Collision of the replication fork converts this single-strand break into a double-strand break, thus inducing apoptosis. The antitumor activity of irinotecan has been well documented in colorectal cancer both as a first-line single agent, a second-line single agent, and most recently by Saltz and coworkers as first-line combination chemotherapy with 5-FU and leucovorin.[14] In upper gastrointestinal malignancies, irinotecan has shown activity as a single agent[15] and also in combination with 5-FU and cisplatin.[16] As a single agent, or combined with other cytotoxic agents, irinotecan possesses broad antitumor activity against other malignancies.[17-21] The toxicities of irinotecan are primarily nausea, vomiting, diarrhea, and myelosuppression. The activity of irinotecan in treatment of pancreatic cancer as a single agent has also been demonstrated in two phase II studies with response rates of approximately 10%.[17,22]

The distinct mechanisms of action, different intracellular targets, and activity of both gemcitabine and irinotecan against various tumors provide the rationale for their combination. Theoretically, the topoisomerase I-dependent single-strand breaks stabilized by irinotecan offer sites for the insertion of gemcitabine triphosphate during religation of DNA. The effects of gemcitabine on DNA integrity in both quiescent and cycling cells may potentially interact with those of irinotecan on DNA repair processes in which topoisomerase I plays a key role. Preclinical data evaluating the combination of irinotecan and gemcitabine suggested dose-dependent synergistic interaction in SCOG small cell lung cancer and MCF-7 breast cancer cell lines.[23] **Irinotecan and Gemcitabine Trials** A combination of standard infusion (30 minutes intravenous [IV] infusion) gemcitabine with irinotecan (90 minutes IV infusion) has been studied in a phase I study with administration of both agents on days 1 and 8 every 3 weeks. The maximum tolerated dose was irinotecan at 100 mg/ m² and gemcitabine at 1,000 mg/ m².[24] A multicenter phase II trial of irinotecan and gemcitabine in 45 chemotherapy-naive locally advanced or metastatic pancreatic cancer patients demonstrated an overall objective response of 20%.[25] One-third of the patients had a carbohydrate antigen (CA) 19-9 decrease of more than 50%. The median survival was 5.7 months and the 1-year survival was 27%. Toxicity was modest, with 2% grade 4 neutropenia, 2% grade 4 vomiting, and 7% grade 3 diarrhea. A randomized multicenter phase III study of irinotecan and gemcitabine compared to gemcitabine alone in patients with locally advanced or metastatic pancreatic adenocarcinoma is ongoing, with patients assigned to the two-drug arm receiving them in the same schedule as that used in the phase II trial. Those assigned to the gemcitabine-alone arm will receive the agents at the U.S. Food and Drug Administration-approved regimen (1,000 mg/m² weekly * 7) for consecutive weeks for the first cycle followed by a days 1, 8, and 15 every-28-day cycle for cycle 2 and beyond.
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Since the additive or synergistic effects of the combination of irinotecan and gemcitabine have been suggested in the treatment of pancreatic adenocarcinoma with modest toxicity, the fixed-dose-rate infusion of gemcitabine may be superior to standard infusion. Based on this rationale, a combination of irinotecan and gemcitabine with fixed-dose-rate infusion warrants investigation. **Phase I Study Design**

This study is designed as an open-label phase I dose-escalating trial to evaluate the safety of a combination of gemcitabine with fixed-dose-rate infusion and irinotecan for treating advanced/metastatic pancreatic and biliary cancer. The primary end points are to find the dose for a phase II study, the dose-limiting toxicity, and the maximum tolerated dose. The response to the combination will also be determined for those patients with measurable or evaluable disease. Gemcitabine is infused intravenously with a fixed dose rate of 10 mg/m²/min; the infusion time will be based on the dose level. Irinotecan is administered IV over 60 minutes after gemcitabine. Both gemcitabine and irinotecan are given on days 1 and 8 of a 21-day cycle (Figure 1). Patients with histologically confirmed and clinical advanced/metastatic pancreatic or biliary adenocarcinoma are eligible for the study. They should be older than 18 years with relatively good overall performance status and reasonable liver and kidney function. Since the study is designed to test the hypothesis that the fixed-dose-rate infusion may be more effective than standard infusion gemcitabine, and to assess the combination of irinotecan and gemcitabine, patients who previously had either drug are eligible to be enrolled on the study. Patients who were previously treated with both drugs would not qualify for the trial. The dose-escalating schedule of the study is listed in Table 1. Based on published data and clinical experience, the recommended doses for the following phase II study would be approximately 100 mg/m² for irinotecan, the commonly accepted "standard" weekly dose, and fixed-dose-rate infusion of gemcitabine at about 70% to 80% of the single-agent dose. The dose-limiting toxicities attributed to the study are defined as toxicities related to the treatment requiring discontinuation or significant dose reduction in study drugs. Toxicities are to be assessed according to the National Cancer Institute Common Toxicity Criteria scale. The maximum tolerated dose is defined as one dose level below the dose that induced dose-limiting toxicity in greater than onethird of patients in a given cohort. The dose modification is designed based on the type (hematologic vs nonhematologic) and grade of toxicities a patient may have.

**Preliminary Results**

The trial is still in its early stages. At present, five patients have been enrolled (three patients at level 1, two at level 2). Four of them have pancreatic cancer and one has metastatic biliary cancer. The preliminary results of the study are encouraging. There have been no dose-limiting toxicities recorded. Grade 2 hematologic toxicity (neutropenia) has been observed in one patient at dose level 1 who previously had a Whipple procedure and adjuvant chemoradiation with epirubicin (Ellence), cisplatin, and 5-FU. Grade 1 nonhematologic toxicities (alopecia and nausea/vomiting) have also been recorded in two patients. Although response is not the primary study end point, all three evaluable pancreatic cancer patients had stable disease and a more than 60% decrease of their CA 19-9 level. All patients have tolerated the treatment well so far. Enrollment of the study is continuing.

**Conclusion**

Irinotecan and gemcitabine possess significant activity against various tumors, including pancreatic and biliary carcinoma. Data also suggest that these two agents may be additive or synergistic with few or no overlapping toxicities. Compared to the standard infusion of gemcitabine, a fixed-dose-rate infusion increases the concentration of intracellular triphosphate.
gemcitabine, which may result in increased response rates and median survival. Thus, our ongoing phase I study is investigating the toxicity of irinotecan combined with a fixed-dose-rate infusion of gemcitabine, and determining the dose for phase II study. Preliminary results are encouraging, and accrual of patients continues.

**Disclosures:** The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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