Gemcitabine (Gemzar) and irinotecan (CPT-11, Camptosar) are active cytotoxic drugs against pancreatic cancer. Preclinical data evaluating the combination of gemcitabine and irinotecan suggest dose-dependent synergistic effects.

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in males and females in the United States.[1] Worldwide, 170,000 new cases and 168,000 deaths were projected for the year 2000.[1] The anatomy of the pancreas, with its close proximity to other vital tissues, as well as the propensity of pancreatic cancer for early spread, make the treatment of this disease difficult. 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] Overall, only 1% to 4% of all patients with pancreatic cancer will be alive 5 years after diagnosis.

Despite recent progress, the treatment of patients with locally advanced and metastatic disease continues to be palliative. Use of chemotherapy and/or radiation should not jeopardize quality of life in patients with advanced and metastatic pancreatic cancer who are candidates for treatment. Many single agents and chemotherapy combinations have been evaluated in this disease and, with few exceptions,[3] there had been little evidence of a meaningful impact on survival or quality of life until the advent of gemcitabine (Gemzar).

The antimetabolite gemcitabine has been approved by the US Food and Drug Administration (FDA) as a single agent for the treatment of advanced pancreas cancer. To better evaluate the impact of gemcitabine in this disease, an alternative methodology to measure clinical benefit—one that focuses on patient symptoms—was developed.[4,5] Applying the clinical benefit criteria, a phase III trial in previously untreated pancreatic cancer patients was performed comparing gemcitabine with fluorouracil (5-FU). This trial demonstrated an improved rate of clinical benefit and an overall survival advantage for gemcitabine.[6] At 12 months of follow-up, 18% of the gemcitabine-treated patients remained alive compared with only 2% of the 5-FU-treated patients. In that pivotal phase III trial, the statistically significant advantages for gemcitabine were seen despite an objective partial response rate of only 5.4%. [6] This level of activity of gemcitabine was also observed in phase II trials (Table 1).[7-9]

Gemcitabine Combinations

Improvements in the management of locally advanced and metastatic pancreatic cancer are clearly needed. Developing gemcitabine combinations is one strategy to achieve this goal. The experience with gemcitabine combinations in non-small-cell lung cancer suggests that the gemcitabine doublets are feasible and active. Translating the lung cancer experience to pancreatic cancer patients might not be a simple task. Choosing the right gemcitabine partner is very important for the success of the combination. The agents active against non-small-cell lung cancer are not necessarily active against pancreatic cancer.

The topoisomerase I inhibitor irinotecan (CPT-11, Camptosar) is approved by the FDA for the management of relapsed and metastatic colon cancer and is active in other gastrointestinal malignancies. In pancreas cancer, irinotecan was tested in two phase II trials.[10,11] The level of activity of irinotecan is apparently similar to that of gemcitabine, with equivalent median survival, as
suggested by results of the European Organization for Research and Treatment of Cancer (EORTC) trial (Table 1).[10]

**Gemcitabine/Irinotecan: Preclinical Data and Phase I Trials**

Preclinical data for the combination of gemcitabine and irinotecan 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. Synergism at concentrations of 0.1 to 2 µM for gemcitabine and 0.2 to 10 µM for irinotecan, but antagonism at high concentrations (ie, concentrations > 2 µM for gemcitabine and 20 µM for irinotecan), was seen in MCF-7 breast cancer cells.[12]

**IrinoGem Study**

These preclinical observations were translated into a phase I trial in which both agents were administered on a day 1, day 8 every-3-week schedule (IrinoGem).[13] The gemcitabine dose was fixed at 1,000 mg/m$^2$ and the irinotecan dose was escalated from an initial dose of 50 mg/m$^2$. The maximum tolerated dose of irinotecan was 100 mg/m$^2$ given intravenously over 90 minutes on days 1 and 8 every 3 weeks immediately following gemcitabine at 1,000 mg/m$^2$ on days 1 and 8 given intravenously over 30 minutes (Figure 1). The dose-limiting toxicity was grade 3 diarrhea in two of seven patients at an irinotecan dose of 115 mg/m$^2$.

A total of 18 patients were accrued to the trial. Two of three previously untreated pancreas cancer patients and one patient with metastatic carcinoma of unknown primary (possible pancreatic cancer primary) had documented partial responses. The third previously untreated pancreas cancer patient had tumor reduction short of a partial response based on radiologic assessment, and clinical benefit for eight cycles of treatment (Table 2).[13]

**MSKCC Trial**

O'Reilly et al from Memorial Sloan-Kettering Cancer Center (MSKCC) reported their phase I experience with a different schedule of gemcitabine and irinotecan.[14] Both drugs were given on days 1, 8, and 15 on an every-4-week cycle. As in the IrinoGem study, the gemcitabine dose was fixed at 1,000 mg/m$^2$ over 30 minutes and the irinotecan dose was escalated. Thirty-five patients were accrued and both sequences of drug administration were tested.

Preliminary results of pharmacokinetic studies assessing levels of gemcitabine, the uridine metabolite of gemcitabine, irinotecan, SN-38, and SN-38G did not show pharmacokinetic differences between the two administration sequences.[14] When gemcitabine was given first immediately followed by irinotecan, diarrhea, nausea/vomiting, neutropenia, and fatigue were dose-limiting. When irinotecan was given first, immediately followed by gemcitabine, the dose-limiting toxicities were neutropenic fever and diarrhea. The maximum tolerated doses in both sequences were 1,000 mg/m$^2$ of gemcitabine and 60 mg/m$^2$ of irinotecan (Figure 2).

A durable partial response was observed in one patient with gastric cancer, and five other patients had stable disease for ≥ 6 months (Table 2). There was no clear evidence of a superior drug sequence, although patients who achieved long-term stable disease and response had received gemcitabine first followed by irinotecan.

**Multicenter Phase II Trials of Irinotecan/Gemcitabine**

Maintaining single-agent doses of chemotherapy drugs when used in combination regimens may be more challenging in pancreatic cancer patients, as they are generally more frail and less tolerant of toxic side effects. A strategy one might consider to improve the dose intensity of gemcitabine and irinotecan combinations is related to the schedule of administration.

Gemcitabine regimens using the day 1 and 8 every-21-day cycle instead of the day 1, 8, and 15 every-28-day cycle have been associated with increased dose intensity. By avoiding the day-15
dose, when marrow suppression frequently prevented delivery of the gemcitabine combinations, the every-3-week schedule has been better tolerated, requiring fewer doses to be withheld. With single-agent irinotecan, a schedule of four weekly doses for an every-6-week cycle is generally associated with more diarrhea during weeks 3 and 4.

By developing the day 1 and 8 every-3-week cycle in IrinoGem, the irinotecan-induced diarrhea and the myelosuppression of gemcitabine and irinotecan have been minimized, allowing almost single-agent doses of these two drugs in combination. In addition, the activity in previously untreated pancreas cancer patients observed in the phase I trial with IrinoGem led us to perform a phase II study of this combination in previously untreated patients with locally advanced or metastatic pancreatic cancer (Figure 3).

The phase II trial accrued 45 chemotherapy-naive (7% had been treated previously with radiation therapy), locally advanced (unresectable), or metastatic pancreatic cancer patients at eight US centers from July 1998 through June 30, 1999. Measurable disease, adequate organ function, and performance status of 0 to 2 were required. No previous chemotherapy except for 5-FU given as a radiation sensitizer was allowed. The primary efficacy parameter was tumor response; secondary efficacy parameters were CA 19-9 response, response duration, and overall survival. Median age was 60 years (range: 31 to 89 years), and the male/female ratio was 60%/40%. A performance status of 0/1/2 was recorded in 24%, 60%, and 16%, respectively. Seventy-three percent of patients had metastatic and 27% had locally advanced disease.

Preliminary results were reported at the American Society of Clinical Oncology (ASCO) 2000 meeting, and suggest that the combination is active and well tolerated in patients with locally advanced and metastatic pancreatic cancer. Of 351 total doses delivered (day 1 or 8), full doses of irinotecan and gemcitabine were given for 91% and 88%, respectively. Toxicity has been modest, with no reports of toxic deaths or neutropenic fever thus far (Table 3). Preliminary radiologic response rate is 20% (9 out of 45), and the rate of CA 19-9 decrease of more than 50% from baseline value is 32.5% (13 out of 40). Median survival is 6 months (range: 0.9 to 12.2+ months) and median time to treatment failure is 2.9 months (range: 0.1 to 11.3+ months) (Table 4).

Follow-Up Studies With IrinoGem

Multicenter Phase III Trial

Based on the phase I and II experience with IrinoGem in locally advanced and metastatic pancreas cancer, an international phase III trial comparing gemcitabine alone to gemcitabine plus irinotecan has been initiated. A total of 75 participating centers from the United States, Canada, South America, Japan, and Australia will have the study activated.

The patients accrued for this trial will be randomly assigned to receive day 1 and 8 IrinoGem as used in the phase II study or gemcitabine at 1,000 mg/m²/wk for 7 consecutive weeks for the first cycle followed by a day 1, 8, and 15 every-28-day cycle for cycle 2 and beyond (Figure 4). This gemcitabine administration schedule is the same as that used in the pivotal phase III trial that supported FDA approval of gemcitabine therapy for pancreas cancer. Patient eligibility criteria are consistent with those used in the phase I and II evaluations of IrinoGem.

The primary end point of the trial is overall survival; secondary end points will be antitumor activity including objective response and a CA 19-9 decline of ≥ 50% when elevated at baseline, time to treatment failure, safety, clinical benefit (measured by time to performance status decline, time to weight loss, and time to albumin level decrease), and quality-of-life analyses (as assessed by FACT-Hep, the Functional Assessment of Cancer Therapy-Hepatobiliary).

The trial is powered to detect a 40% improvement in median survival (from 4.8 to 6.8 months) and 1-year survival (from 18% to 29%) for patients receiving IrinoGem. A total of 306 deaths are required at a significance level of 0.05 and a power of 0.85. The target accrual is 175 patients per treatment arm with the expectation that approximately 5% of patients will be lost to follow-up. If the planned monthly accrual of 20 patients per month is reached, the accrual period will be approximately 18
Randomized Phase II Trial

Drs. Matthew Kulke and Margaret Tempero of Cancer and Leukemia Group B (CALGB) will chair a four-arm randomized phase II trial that will include the IrinoGem regimen (personal communication, M. Kulke, July 2000). Two other gemcitabine doublets with promising activity and median survivals in phase II trials involving pancreas cancer patients—gemcitabine/cisplatin (Platinol)[17-19] and gemcitabine/docetaxel (Taxotere)[20,21]—and fixed-rate infusion 1,500 mg/m² of gemcitabine at 10 mg/m²/min[22] will also be studied (Figure 5). Patients with measurable metastatic disease, performance status of 0 to 2, and chemotherapy-naive status (except for previous treatment with 5-FU) will be eligible.

Conclusions

The combination of gemcitabine and irinotecan as administered in the IrinoGem study has proved to be safe, active, and well tolerated in pancreas cancer patients. The ongoing international phase III trial comparing gemcitabine alone to IrinoGem has been initiated. By assessing survival, quality of life, and clinical benefit as end points in the randomized phase III trial, the role of this new combination in advanced and metastatic pancreas cancer patients will be more comprehensively defined. If the results establish the superiority of IrinoGem over single-agent gemcitabine, other opportunities for testing this doublet in earlier stages of the disease as neoadjuvant and adjuvant therapy will be considered. Both gemcitabine and irinotecan are potent radiation sensitizers, and the combination should be studied with radiation therapy in patients with pancreas cancer and other malignancies.

The easy tolerability, modest toxicity, and the percentage of drug delivered (approximately 90% of full doses of irinotecan and gemcitabine) in the phase II trial of IrinoGem in advanced and metastatic pancreas cancer make this combination attractive for the addition of a third drug. Phase I trials with DIG (IrinoGem plus docetaxel) and PIG (IrinoGem plus cisplatin [Platinol]) are currently accruing patients.

In addition, the single-agent activities of gemcitabine and irinotecan in a variety of solid tumors led us and other investigators to study IrinoGem in other cancer types. Several ongoing phase II trials will help define the activity of this two-drug combination in first-line therapy for non-small-cell lung cancer and colon and biliary cancers, as first- and second-line therapy in small-cell lung cancer, and in taxane- and antracycline-resistant breast cancer patients (Table 5).

References:


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