Second-Line Therapy for Gemcitabine-Refractory Pancreatic Cancer: Is There a Standard?

September 01, 2008
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Pancreatic cancer is the fourth leading cause of cancer mortality in the United States. According the American Cancer Society, about 37,680 new cases are anticipated in the year 2008, and 34,290 patients will die from the disease.[1] This malignancy is a very aggressive tumor, and patients often present with advanced-stage disease. Surgical resection, when possible, provides the only opportunity for cure. Even with R0 resection, pancreatic cancer still carries an overall dismal prognosis, and therefore adjuvant treatment is offered.

Pancreatic cancer is the fourth leading cause of cancer mortality in the United States. According the American Cancer Society, about 37,680 new cases are anticipated in the year 2008, and 34,290 patients will die from the disease.[1] This malignancy is a very aggressive tumor, and patients often present with advanced-stage disease. Surgical resection, when possible, provides the only opportunity for cure. Even with R0 resection, pancreatic cancer still carries an overall dismal prognosis, and therefore adjuvant treatment is offered.

Treatment with the pyrimidine antagonist gemcitabine (Gemzar) has been the standard of care for metastatic pancreatic cancer for more than a decade, based on a phase III randomized trial in which 126 patients with advanced symptomatic pancreatic cancer were randomized to gemcitabine vs fluorouracil (5-FU). The primary endpoint of this study was clinical benefit, which was a composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. The investigators found a clinical benefit in 23.8% of gemcitabine-treated patients compared to 4.8% of 5-FU–treated patients (P = .0022). The median survival durations were 5.65 and 4.41 months for gemcitabine-treated and 5-FU–treated patients, respectively (P = .0025).[2] Since then, multiple agents have been tested in combination with gemcitabine in order to improve overall outcome in patients with metastatic pancreatic cancer, with limited success. In a randomized phase III trial, the combination of gemcitabine and erlotinib (Tarceva) led to a median survival of 6.24 months compared to 5.91 months in the gemcitabine-only arm, which was statistically significant.[3] That said, the meaning of a 2-week survival difference at the expense of increased toxicity and cost might not be significant. Capecitabine (Xeloda), a prodrug of 5-FU, has also been combined with gemcitabine in phase III trials in patients with metastatic pancreatic cancer. Preliminary results of one such study were presented at the 13th annual European Cancer Conference (ECCO) in 2005 and reportedly demonstrated a survival benefit for combined therapy over gemcitabine alone.[4] However, the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group did a similar study with the same combination and failed to show any survival benefits; median overall survival was 8.4 months in the combination arm vs 7.2 months in the single-agent arm. (P = .234).[5] Other gemcitabine combinations failed to show any benefits compared to gemcitabine alone.
Gemcitabine is also widely used in the adjuvant setting, based on data from the Charit Onkologie (CONKO) study. In this open, multicenter, randomized controlled phase III trial, patients who received gemcitabine after resection had a significantly longer median disease-free survival and a trend toward improved overall survival compared to observation. To date, the role of second-line treatment after gemcitabine failure is unclear, and no standard treatment approach has been defined. In this review, we summarize the published results of second-line treatment in patients with pancreatic cancer, and discuss future strategies. We identified 9 single-agent studies (5 in abstract form only) and 24 multidrug studies (13 in abstract form only). The regimens used, response rates, and progression-free and overall survival data are summarized in Tables 1, 2, and 3.

**Second-Line Therapy for Metastatic Pancreatic Cancer**

Progression-free survival is generally short in pancreatic cancer. A large percentage of patients with metastatic and resected pancreatic cancer who were treated with gemcitabine will be in relatively good clinical condition when their disease relapses, and they will require second- and even third-line therapy. Benefit from second-line treatment vs best supportive care alone was suggested in a preliminary report of a randomized phase II trial in which 46 (out of a planned 165) patients with gemcitabine-refractory pancreatic cancer were randomized to best supportive care with or without chemotherapy (5-FU, leucovorin, and oxaliplatin [Eloxatin] combination). The chemotherapy group had a significantly longer median overall survival (40 vs 34 weeks, P = .0312).

Although many regimens have shown modest activity in the second-line treatment of pancreatic cancer, it is not clear whether that modest response translates into survival or clinical benefit.

### Cytotoxic Agents

#### Platinum Drugs

Platinum compounds have been used in the first-line treatment of pancreatic cancer with modest activity, which has encouraged their use in the salvage setting. As presented at the 2007 American Society of Clinical Oncology (ASCO) annual meeting, pooled data and meta-analysis showed an overall survival benefit of a platinum-based regimen in the first-line treatment of metastatic pancreatic cancer. Oxaliplatin, because of its better toxicity profile, was used in combination with thymidylate synthetase inhibitors such as 5-FU or capecitabine in gemcitabine-refractory pancreatic cancer. Doses of oxaliplatin ranged from 85 to 130 mg/m². Response rates ranged from 3% to 23%, with median overall survival ranging from 20 to more than 48 weeks. These combinations produced grade 3/4 gastrointestinal (GI) toxicities, neutropenic fever, and neuropathy. Oxaliplatin has also been used in combination with raltitrexed (Tomudex) and gemcitabine. Response rates were modest (24% at best), with a median survival of approximately 20 weeks. This combination produced significant GI and hematologic toxicities.

Gemcitabine was used with platinum compounds as a salvage regimen in gemcitabine-pretreated patients. Combining gemcitabine and cisplatin with regional hyperthermia in 12 patients showed an encouraging time to disease progression and median 1-year event-free survival. Gemcitabine was also used in combination with oxaliplatin in a phase II trial of 33 patients. The response rate was 23%, and overall survival was approximately 26 weeks. Toxicities included neuropathy as well as GI and hematologic effects.

Riess et al reported promising results at the annual ASCO meeting in 2007. Patients were randomized to 5-FU at 2 g/m² and leucovorin at 200 mg/m² on days 1, 8, 15, and 22 (FF regimen) vs FF plus oxaliplatin, 85 mg/m², on days 8 and 22. The preliminary overall survival result favored the oxaliplatin arm.

In trials using platinum compounds, many did not report any data about quality-of-life measures during and after treatment. In the study by Reni et al, 71% of patients completed a quality-of-life questionnaire and more than a 40% improvement was observed in health-care satisfaction, body image, fear for future health, and pain. These measures, however, were not specifically validated to reflect quality of life in this population. In another study combining liposomal cisplatin with gemcitabine in previously treated patients with pancreatic cancer, authors reported clinical benefits in 33% of patients for a median of 3 months.
Capecitabine

A prodrug of 5-FU, capecitabine has been studied extensively in the second-line treatment of pancreatic cancer. In the United States, capecitabine is probably one of the most commonly used second-line agents after gemcitabine failure but with limited data. Given its oral administration, capecitabine is more convenient for patients, and it has shown activity as a first-line treatment in patients with metastatic pancreatic cancer, with a response rate of 24%.[17]

Capecitabine was tested in phase II trials in different combinations at doses ranging from 800 to 1,500 mg/ m$^2$/d. When combined with docetaxel (Taxotere),[18-20] results were inconsistent, with response rates ranging from 0% to 27% and overall survivals of 5 to 13 weeks. Grade 3/4 toxicities were common and included leukopenia, significant GI toxicity, and hand-foot syndrome.

Capecitabine has also been tested in combination with other agents such as erlotinib and celecoxib (Celebrex) in small phase II studies.[21,22] The combination of two oral agents might be an attractive option for some patients; however, the overall objective radiologic response rate in these studies was 10%, with a median survival duration of 6.5 months.[22] The most common grade 3/4 toxicities were diarrhea, hand-foot syndrome, rash, and stomatitis (see Tables 1 and 2). Assessments of clinical benefits and quality-of-life were not performed in any of the studies discussed above. Given the large financial burden these agents will put on patients and the health-care system, cost-effectiveness and cost-benefit should be evaluated, especially in the palliative setting.

Camptothecins

Camptothecins have limited activities in pancreatic cancers. In the second-line setting, irinotecan and rubitecan as single agents showed disappointing results,[23-25] with response rates of 7% to 14%, a median overall survival of 20 weeks, and significant GI and hematologic toxicity (see Tables 1-3 for more detail). In a phase II study using rubitecan as a single agent,[24] patients were considered as experiencing clinical benefit if they had a ≥ 50% reduction in pain intensity (Memorial Pain Assessment Card) or a 20-point or greater improvement in Karnofsky performance status for a period of at least 4 consecutive weeks. Sufficient data to assess clinical response were available for only 35 patients, and only 3 patients showed evidence of clinical benefit according to the above criteria.

When camptothecins were used in combination with other agents such as raltitrexed, 5-FU/leucovorin, mitomycin, docetaxel, and irinotecan (MDI regimen), the response rate ranged from 0% to 24% and the median overall survival was between 14 and 26 weeks.[26-28] In the study comparing raltitrexed with irinotecan vs raltitrexed alone,[26] pain intensity and analgesic consumption was reduced compared to baseline in 1 of 11 patients in the raltitrexed-only arm vs 3 of 12 patients in the combination arm. Improvement in pain was accompanied by an improvement in
performance status in the patient in the raltitrexed arm, and in two cases in the combination arm. No weight gain was reported in either group.

More promising results were seen in combining irinotecan with gemcitabine, 5-FU, leucovorin, and cisplatin.[29] This combination produced a 24% response rate with a median overall survival of 40 weeks. However, grade 3/4 toxicities were substantial, and the regimen was poorly tolerated. Quality-of-life assessments were not done in this study.

Taxanes

Taxanes have been investigated as a second-line treatment in gemcitabine-resistant pancreatic cancer patients. In a small study, weekly paclitaxel treatment in 18 patients with recurrent disease produced a response rate of 6% and a median overall survival of 17.5 weeks. Treatment was well tolerated, with mild GI and hematologic toxicities.[30] In two small studies using a combination of docetaxel and gefitinib (Iressa), the median overall survival was about 12 weeks. Fatigue and diarrhea were the most reported side effects.[31,32]

Capecitabine was also combined with docetaxel, with response rates ranging from 0% to 12% and a median overall survival of 13 weeks.[18,19] In a study of 15 patients, the combination of docetaxel with mitomycin and irinotecan produced no responses, and the median overall survival was 24 weeks.[28] Clinical benefits were not reported in any of these studies.

Multitarget Antifolates

Multitarget antifolates such as pemetrexed (Alimta) and raltitrexed were tested in gemcitabine-refractory pancreatic cancer. When any of these agents were used alone,[26,33] the response rate was minimal (0%–3.8%) and the overall survival was 18 to 20 weeks. When these agents were tested in combination with oxaliplatin or irinotecan,[12,26] they produced modest overall survival improvements of 21 and 26 weeks, respectively. Grade 3/4 toxicities were common.

Targeted Therapy

Targeted therapy had promising effects in the front-line treatment of pancreatic cancer, which encouraged investigators to test these agents in second-line treatment. Of these agents, gefitinib was studied in combination with docetaxel in the salvage setting and produced no response in one study,[31] and 12-week survival in another.[32] Erlotinib was studied in combination with capecitabine in the same setting, and led to a median overall survival of 29 weeks. Grade 3/4 GI and skin toxicities were common.[34]

Novel Treatment

Novel treatment with pox virus–based therapeutic antitumor vaccines was tested in a phase I trial in patients with gemcitabine-refractory pancreatic cancer.[35] The results were promising, with a 1-year median overall survival of about 33%. Based on this, a phase III trial using the same vaccine is underway.

Other agents such as flutamide[36] and arsenic trioxide (Trisenox)[37] were tested in phase II trials and were found to be ineffective in second-line therapy for patients with pancreatic adenocarcinoma.

With better understanding of the pathophysiology of cancer as well as targeted and pathway-specific agents, the investigation of new agents in pancreatic cancer can become more important. Oral agents or agents with reasonable administration schedules and limited toxicity profiles should be considered in second-line treatment. Currently, multiple clinical trials are testing new agents or new combinations such as docetaxel with flavopiridol, AZD6244 vs capecitabine, and gulfosfamide vs best supportive care. The results of these trials are awaited.

Discussion

In the past decade, gemcitabine has been established as the treatment of choice in the first-line setting for advanced pancreatic cancer based on clinical benefits. Currently, gemcitabine is also being used more frequently as adjuvant chemotherapy after pancreatic resection as a single agent or in combination with 5-FU and radiation, based on data from the CONKO[6] and Radiation Therapy Oncology Group (RTOG 9704) studies.[38] Growing evidence suggests that sequential polychemotherapy can extend median survival by up to 16 months in selected patients.[39] Therefore, the role of second-line chemotherapy needs to be better defined in patients.
with gemcitabine-refractory metastatic pancreatic cancer and those who have failed adjuvant gemcitabine therapy. Given the fact that gemcitabine was approved for metastatic pancreatic cancer on the basis of clinical benefits, second-line trials should evaluate outcomes other than response rate or survival. For a well-designed study, researchers should consider using clinical benefits such as quality of life, symptom control, analgesic use, and weight gain as primary endpoints, and a valid, reliable scale for clinical benefit in this population. However, since the US Food and Drug Administration may not approve another drug for pancreatic cancer based on clinical benefits, most pharmaceutical companies will shy away from using such parameters as endpoints. Cancer therapies are very expensive and provide modest benefits in second-line treatment for pancreatic cancer. Therefore, an economic evaluation should also be undertaken, and any benefit in favor of new therapy should be balanced by the additional cost. Development of predictive or prognostic markers in pancreatic cancer can help us determine who may benefit from second-line treatment. Performance status, serum level of C-reactive protein, and peritoneal dissemination were identified as important prognostic factors in patients with gemcitabine-refractory pancreatic cancer.[40] These factors should be considered in determining the treatment following first-line chemotherapy. In an Italian/Swiss multicenter retrospective survey,[41] multivariate analysis in 160 gemcitabine-resistant pancreatic cancer patients revealed that performance status at the beginning of second-line therapy and response to first-line treatment are important determinants of survival in second-line chemotherapy. Excision repair cross-complementation 1 (ERCC1) expression in platinum-treated patients was also highly predictive of better survival. More research on molecular markers or certain metabolic enzymes that can predict clinical outcome would be helpful as well. For example, data presented in the annual GI ASCO meeting in 2007 showed that certain polymorphic variants of gemcitabine can predict sensitivity to gemcitabine-based therapy.[42]

**Gemcitabine-Refractory Pancreatic Cancer in the Metastatic Setting**

It is unclear at this time what percentage of patients who fail gemcitabine-based therapy for metastatic pancreatic cancer will go on to receive second-line chemotherapy. In some trials, up to 57% of patients who progress on gemcitabine subsequently receive second-line treatment.[5] The data on second-line chemotherapy compared to best supportive care is lacking in pancreatic cancer. Only one small randomized trial showed a benefit of second-line chemotherapy compared to best supportive care. In this trial, patients with gemcitabine-refractory pancreatic cancer who received oxaliplatin, 5-FU, and leucovorin had a longer median survival compared to best supportive care.[7] Further studies are needed to compare cytotoxic chemotherapy to palliative measures such as celiac axis block, stenting of blocked ducts, or palliative radiation and best supportive care. Since progression-free and overall survival in second-line treatment of pancreatic cancer is usually short, cost-effectiveness should also be considered in the analysis. Current phase II and III trials in this setting are using either 5-FU or capecitabine in their standard-treatment arm, most likely because of the difficulty of randomizing patients with good performance status to best supportive care only.
In this article, we have reviewed small phase I and II studies that have been reported primarily in abstract form. Most of these studies suffer from similar deficiencies secondary to small patient numbers and heterogeneous populations. The reports provide limited details about patients enrolled, their treatment history, and their response to first-line therapy, all of which is important in predicting overall survival in general.[12] Some of the patients in these trials received gemcitabine as an adjuvant treatment, while others received it in the metastatic setting, and authors have used different definitions of refractory disease. Most studies used response rate as a primary endpoint without taking into consideration clinical benefits or costs. Based on these data, it is difficult to draw a valid conclusion regarding standard second-line therapy in the metastatic setting.

**Gemcitabine-Refractory Pancreatic Cancer in the Adjuvant Setting**

As noted above, gemcitabine is commonly used in the adjuvant setting as a single agent or in combination with 5-FU and radiation, based on data from the CONKO[6] and Radiation Therapy Oncology Group (RTOG 9704) studies.[38] Unfortunately, the majority of patients will experience disease progression. Progression-free survival was 13.4 months in the treatment arm of the CONKO trial, and overall survival was 18.8 months in the gemcitabine arm in the RTOG trial. Therefore, we need to establish a better therapeutic guideline for patients who fail gemcitabine as an adjuvant treatment. The term “refractory to gemcitabine” in the adjuvant setting for pancreatic cancer is not clearly defined, compared to colon cancer where patients are considered refractory to the FOLFOX regimen (5-FU, leucovorin, oxaliplatin) if they relapse within 1 year of treatment.

From the clinical trials in this review, it is unclear what percentage of patients received gemcitabine as an adjuvant treatment. The main difference in the adjuvant setting is that patients who relapse after adjuvant gemcitabine therapy often have good performance status and will be able to receive further chemotherapy. The data for rechallenging these patients with gemcitabine are very limited.

**Conclusions**

For pancreatic cancer patients whose disease is refractory to gemcitabine, second-line therapy has not been clearly shown to affect survival. There are still many questions that need to be answered: Does the patient suffer from treatment-related toxicities without any survival or clinical benefit, and at what cost? Are we giving patients false hope and creating suffering by giving them chemotherapy? Why are we combining chemotherapeutic agents in the second-line setting when there is no survival or clinical benefit from single agents? In conclusion, more randomized studies formally investigating the role of second-line therapy in advanced pancreatic cancer are warranted, since more patients will now be receiving gemcitabine as an adjuvant treatment. Stratification based on an ideal prognostic system before randomization will be crucial to the success of such studies. Development of novel therapeutic agents is important in the second-line setting, but we first need to answer the fundamental question: Do patients gain anything from active treatment? Ideally, studies should compare active treatment against best supportive care, but these studies may be difficult to accomplish in the United States. Incorporating clinical benefits as primary endpoints along with cost-effectiveness analysis should be part of future clinical trials as well. With better patient selection and better endpoints, we can hopefully improve clinical outcomes for those with advanced pancreatic cancer in second-line settings, without giving patients false hope.

**Disclosures:** Financial Disclosure: The authors 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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