

Treatment update for metastatic pancreatic cancer

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The treatment of metastatic pancreatic cancer continues to be a major unresolved health problem and a therapeutic challenge, with a poor median survival averaging 3–6 months. Disappointing response rates to standard single-agent therapy have led to a search for more effective agents. Early study results with gemcitabine indicate a potential survival benefit in these patients, which is illustrated here in a case report of a 75-year-old man with metastatic pancreatic adenocarcinoma who has defied the odds. Chemotherapy with GEMOX (gemcitabine and oxaliplatin) was initiated, and the patient has enjoyed a good quality of life, with long-term disease control (stable disease 21 months after diagnosis).

Pancreatic cancer is the fourth most common cause of cancer death in men and the fifth most common cause of cancer death in women in the United States. In 2006, an estimated 33,730 new cases of pancreatic cancer and 32,300 deaths due to the disease are expected in the United States.¹ Only 1%–4% of patients diagnosed with this neoplasm are alive 5 years after diagnosis. Due to their anatomic location, pancreatic tumors typically do not produce specific signs or symptoms until they are significantly enlarged. As a result, most patients with pancreatic cancer have locally advanced or metastatic disease at the time of presentation. Unfortunately, the median survival of those with metastatic disease averages 3–6 months.

Case history

A 75-year-old man had a history of diet-controlled diabetes for several decades. Nine months prior to presentation, he initiated insulin therapy due to worsening control of his diabetes. He also reported mild mid-thoracic back pain and a 10-pound weight loss about 3 months prior to presentation. Other than diabetes, his medical history is notable for a myocardial infarction and coronary artery bypass surgery. He has a remote history of tobacco use and consumes alcohol in moderation.

Computed tomography of the chest and abdomen revealed multiple pulmonary lesions (measuring up to 2.5 cm) and a poorly defined mass in the body of the pancreas (Figures 1 and 2). A fine-needle aspirate of the pancreatic mass revealed groups of atypical glandular cells. A lung wedge biopsy demonstrated a moderately differentiated metastatic adenocarcinoma. Immunohistochemical stains of this tissue were

positive for CK7 and CK20 and negative for TTF-1 (thyroid transcription factor-1, expressed in epithelial cells of the thyroid gland and the lung), favoring a gastrointestinal primary tumor. The CA 19-9 level was elevated at 276 U/mL (normal, 0–37 U/mL).

On initial physical examination, he was afebrile, with a blood pressure of 138/65 mm Hg and a pulse of 72 beats/min. He weighed 144 pounds at 5'6" tall and had mild temporal wasting. There was no evidence of scleral icterus. Cardiac examination revealed a normal S1 and S2. His lungs were clear to auscultation, and his abdominal examination was normal. There was no palpable lymphadenopathy. His Eastern Cooperative Oncology Group (ECOG) performance status was 1.

After his initial presentation, chemotherapy with GEMOX (gemcitabine [Gemzar], 1,000 mg/m² over 100 minutes on day 1, plus oxaliplatin [Eloxatin], 100 mg/m² over 2 hours on day 2, both administered every 2 weeks) was started. Two months after starting therapy, imaging studies revealed regression of the pancreatic mass and stable pulmonary disease. The CA 19-9 level decreased to within normal limits (36 U/mL). Although the patient tolerated therapy well, after 12 cycles of treatment, he developed grade 2 neuropathy of his hands and feet. As a result, oxaliplatin was discontinued, and the neuropathy decreased to grade 1; over the next several cycles, however, the CA 19-9 level elevated slightly to 60 U/mL. He was maintained on a fixed dose rate of gemcitabine every 14 days.

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One year after his initial diagnosis, the treatment course was interrupted for 4 weeks while he underwent a herniorrhaphy. During that time, the CA 19-9 level rose to 121 U/mL, and the pulmonary lesions worsened. Postoperatively, a fixed dose rate of gemcitabine was restarted, and he has been maintained on this chemotherapy since then. The most recent CA 19-9 level was 97 U/mL, and imaging studies revealed stable disease, 21 months after diagnosis. Clinically, the patient is doing well and reports only mild diarrhea.

Standard treatment

Single-agent chemotherapy has been the primary treatment of metastatic pancreatic cancer. However, the response rates associated with single-agent therapy, typically < 10%, have been disappointing.

5-Fluorouracil (5-FU) has been available since the late 1950s and remains the foundation of treatment for most gastrointestinal tumors. Its administration, both as a single agent and in conjunction with modulators, has been extensively studied over the past 50 years. Unfortunately, the most recent studies of leucovorin-modulated 5-FU in pancreatic cancer suggest a low response rate (0%–9%) using infusional as well as bolus administration schedules and a median survival ranging from 10 to 24 weeks.^{2,3}

Use of gemcitabine

The early clinical trials of gemcitabine took a novel approach to determine benefit in metastatic disease. In 1996, a phase II study was conducted in patients with metastatic pancreatic cancer refractory to gemcitabine.⁴ The primary endpoint was alleviation of cancer-related symptoms, not overall survival or tumor response. In this trial, 27% of patients derived a clinical benefit from therapy (ie, improvement in pain, performance status, or weight), whereas only 11% of patients derived an objective tumor response. This study led to US Food and Drug

Administration (FDA) approval of single-agent gemcitabine for the treatment of metastatic pancreatic cancer.

A follow-up trial to assess clinical benefit and survival included previously untreated patients with unresectable pancreatic cancer who were randomly assigned to receive weekly 5-FU or gemcitabine.⁵ Although the study design had several flaws, including lack of blinding to those determining clinical response and failure to administer leucovorin with 5-FU, gemcitabine was associated with a significantly better clinical response (24% vs 5%) and 1-year survival (18% vs 2%).

Pharmacokinetic data suggested that longer infusion times of gemcitabine may have an advantage over shorter infusion times, since the activation of gemcitabine to gemcitabine triphosphate by deoxycytidine kinase is saturated at infusion rates of approximately 10 mg/m² per minute.⁶ Based on these findings, a phase II study was conducted in which patients with advanced disease were randomly assigned to receive gemcitabine at 1,500 mg/m² over 150 minutes (fixed dose rate) or 2,200 mg/m² over 30 minutes (constant dose rate).⁷ The fixed dose rate was associated with a significantly better median survival (8 months vs 5 months) and 1-year survival (29% vs 2%) than the constant dose rate.

To improve upon the benefit provided by gemcitabine alone, various doublet regimens have been proposed. Gemcitabine has been combined with both bolus and infusional 5-FU. Several clinical trials have failed to show any advantage in overall survival with the combination compared with gemcitabine alone.^{8,9}

Gemcitabine has also been combined with oxaliplatin. A multicenter trial of 326 patients with unresectable pancreatic cancer (GERCOR) randomly assigned patients to receive gemcitabine (30-minute infusion) versus GEMOX (gemcitabine [1,000 mg/m² over 100 minutes on day 1] plus oxaliplatin [100 mg/m² over 2 hours on day 2], admin-



FIGURE 1 Abdominal CT scan demonstrating atrophy of the pancreatic tail with prominence of the pancreatic duct which is related to a poorly defined mass in the body of the pancreas.

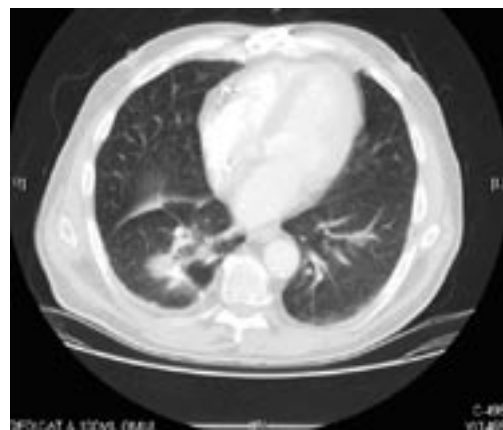


FIGURE 2 Chest CT scan demonstrating a mass in the right lower lobe. Wedge resection of this mass revealed metastatic adenocarcinoma consistent with a gastrointestinal primary.

istered every 2 weeks).¹⁰ The GEMOX study arm was associated with significantly higher response rates (27% vs 17%) and progression-free survival (5.8 months vs 3.7 months). Although there was a trend toward improved median survival (9 months vs 7 months), it was not statistically significant ($P = 0.13$).

One criticism of this study is the nonuniform administration of gemcitabine between the study arms. Patients receiving GEMOX were given a fixed-dose-rate gemcitabine, whereas those receiving gemcitabine alone were given a constant dose rate. As a result, it is not clear whether the benefit seen in the GEMOX arm was at least partly due to the differences in administration of gemcitabine. To answer this question,

Resources

Pancreatic Cancer Action Network
www.pancan.org

For a listing of clinical trials go to:
www.pancreatica.org

MedlinePlus
www.nlm.nih.gov/medlineplus/
pancreaticcancer.html

a phase III ECOG trial was conducted (ECOG 6201) which compared fixed-dose-rate gemcitabine (1,500 mg/m² over 150 min) with and without oxaliplatin (100 mg/m²) to standard infusion gemcitabine (1,000 mg/m² over 30 minutes).¹¹ The patients who received fixed-dose-rate gemcitabine and GEMOX had an increase in overall survival (6.0 months and 5.9 months respectively) compared with standard infusion gemcitabine (4.9 months); however, this increase was not statistically significant.

Radiation therapy

Currently, there is no proven role for the use of radiation therapy in the treatment of metastatic pancreatic cancer. However, in patients with locally advanced, unresectable disease, radiation therapy with and without chemotherapy has been explored to help extend overall survival in these patients. These trials have failed to show a survival advantage of chemoradiotherapy over chemotherapy alone.^{12,13} Importantly, one of these trials revealed that while gemcitabine is a potent radiosensitizer, the toxicity associated with combined gemcitabine and radiation is significant and not tolerable. It is not yet clear if 5-FU plus radiation is superior to gemcitabine alone or a combination regimen in patients with locally advanced disease.

Biologic agents

The success of biologic agents in the treatment of metastatic colon cancer offers hope for similar outcomes in the treatment of metastatic pancreatic cancer. Pancreatic tumors frequently express receptors for epidermal growth factor (EGFR)¹⁴ and vascular endothelial growth factor (VEGF)¹⁵; therefore, agents that target these re-

ceptors are of particular interest.

Erlotinib (Tarceva), an EGFR tyrosine kinase inhibitor, has already shown efficacy in the treatment of metastatic pancreatic cancer. A recent phase III study in which patients with unresectable or metastatic pancreatic cancer were randomized to receive gemcitabine or gemcitabine plus erlotinib (100 mg/d) revealed a statistically significant survival benefit in the combination arm.¹⁶ Although the survival benefit was modest (median survival, 6.4 months vs 5.9 months; 1-year survival, 24% vs 17%), this study led to FDA approval of erlotinib in combination with gemcitabine for unresectable or metastatic pancreatic cancer.

There are several ongoing trials studying the role of bevacizumab (Avastin) and cetuximab (Erbix) in combination with chemotherapy for metastatic pancreatic cancer. These results are anxiously awaited, and we hope these agents will provide benefit to our patients with this devastating disease.

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