



Sofia Cáceres. *Descartes (Discardings)*. Installation; mixed media, 74" × 86".

Despite much effort, continued research is needed to develop more effective regimens to manage patients with pancreatic cancer.

Cancer of the Pancreas: Are We Making Progress? A Review of Studies in the US Oncology Research Network

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Background: Pancreatic cancer is the fourth leading cause of cancer deaths in the United States. In 2008, approximately 37,680 people will be diagnosed with pancreatic cancer and 34,290 will die of this disease.

Methods: The authors reviewed the literature on treatment of pancreatic cancer with an emphasis on studies conducted in the US Oncology Research (USOR) Network.

Results: Although much research has been conducted to develop improved systemic therapies of pancreatic cancer, gemcitabine as a single agent remains the current standard of care. Combinations with other chemotherapeutic drugs or biological agents have resulted in limited improvement.

Conclusions: Despite aggressive efforts to improve treatment for patients with pancreatic cancer, limited progress has been made. It is hoped that new studies being planned and conducted will improve outcomes for patients with this disease.

Introduction

Pancreatic cancer is the fourth leading cause of cancer deaths in the United States. In 2008, an estimated 37,680 people will be diagnosed with pancreatic cancer in the United States, and 34,290 will die of the disease.¹ Only 23% of patients with cancer of the exocrine pancreas will survive for 1 year, while about 4% will survive for 5 years.

Risk factors for cancer of the pancreas include age (50 years and older), male sex, race (black), smoking, a diet high in meats and fat, presence of diabetes or chronic pancreatitis, exposure to chemicals in the workplace, and a family history.

Most cases of pancreatic cancer are advanced at the time of diagnosis. Usually by the time symptoms are present, pancreatic tumors are typically unresectable, and there are no curative options. Only about 10% to 15% of patients who present with pancreatic cancer are considered eligible for resection. The tumor must be localized and not invade adjacent vascular structures such as the portal vein, celiac axis, superior mesenteric artery or vein, or the hepatic artery. Determination of resectability typically involves a computed tomography (CT) scan of the abdomen and pelvis as well as endoscopic retrograde cholangiopancreatography (ERCP)

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Abbreviations used in this paper: USOR = US Oncology Research.

with endoscopic ultrasound (EUS). Staging laparoscopy has been used recently and may help to identify patients with unsuspected peritoneal metastases.

For the majority of patients who present with pancreatic cancer, palliative therapy with a gemcitabine-based chemotherapeutic regimen or localized radiation therapy with chemotherapy remains the only option. This article focuses on the chemotherapeutic option for these patients and reviews new and ongoing clinical trials within the US Oncology Research (USOR) Network.

The US Oncology Research Network

USOR is a national network that encompasses community-based practices with over 1,100 physicians involved in patient care and ongoing research activities. Currently, nearly 15% of all patients diagnosed with cancer are treated by USOR-affiliated physicians. To date, over 35,000 patients have been enrolled on clinical trials conducted by USOR — 3,050 patients in 2007 alone. At any given time, more than 70 research trials are open and accruing. USOR has conducted multiple trials in pancreatic cancer, some of which are reviewed in this article.

Single-Agent Chemotherapy

Gemcitabine

The US Food and Drug Administration approved gemcitabine for first-line treatment of patients with locally advanced (nonresectable stage II or III) or metastatic (stage IV) adenocarcinoma of the pancreas in 1997. This was based on a relatively small randomized phase III study of 126 patients.² This study compared gemcitabine 1,000 mg/m² weekly \times 7 followed by 1 week of rest, then weekly \times 3 every 4 weeks thereafter (63 patients) to fluorouracil (5-FU) 600 mg/m² once weekly (63 patients). The primary efficacy measure was clinical benefit response, a composite measurement of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. Clinical benefit required a sustained improvement (4 weeks or more) in at least one parameter without worsening in any others. Clinical benefit response was experienced by 23.8% of patients treated with gemcitabine compared with 4.8% of patients treated with 5-FU ($P = .0022$). The median survival duration was 5.65 months for patients treated with gemcitabine and 4.41 months for those treated with 5-FU ($P = .0025$). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients.

This study demonstrated that gemcitabine was more effective than 5-FU in alleviating disease-related symptoms in patients with advanced symptomatic pancreatic cancer and that gemcitabine conferred a modest survival advantage over treatment with 5-FU.

Fixed-Dose-Rate Gemcitabine

Preclinical data suggest that giving gemcitabine at a fixed-dose-rate may improve its clinical usefulness. The

rationale for fixed-dose-rate is based on the availability of higher levels of the active metabolites. Tempero et al³ conducted a small randomized phase II trial of fixed-dose-rate gemcitabine compared with standard gemcitabine. This study showed an improvement in time to progression and overall survival for patients in the fixed-dose-rate arm. Based on these data, a phase III trial was conducted by the Eastern Cooperative Oncology Group (ECOG 6201) to assess fixed-dose-rate gemcitabine.⁴ E6201 compared three treatment arms. GEM (arm A) consisted of gemcitabine 1,000 mg/m² given as a 30-minute infusion weekly for 7 weeks with 1 week of rest, followed by gemcitabine 1,000 mg/m² given as a 30-minute weekly for 3 weeks followed by 1 week of rest. FDR-GEM (arm B) consisted of fixed-dose-rate gemcitabine 1,500 mg/m² given as a 150-minute infusion weekly for 3 weeks followed by 1 week of rest. GEMOX (arm C) consisted of gemcitabine 1,000 mg/m² given as a 100-minute infusion on day 1 and oxaliplatin 100 mg/m² given as a 120-minute infusion on day 2 every 14 days.

The median overall survival times for patients were 4.9 months for arm A (95% CI = 4.5, 5.6), 6.0 months for arm B (95% CI = 5.4, 6.9), and 5.9 months for arm C (95% CI = 5.1, 6.8). The 1-year survival rates for these arms were 17%, 21%, and 21%, respectively. Neither experimental treatment succeeded in achieving the hazard ratio (HR) goal of $\leq .75$ or the required $P = .25$. The authors concluded that neither the FDR-GEM arm nor the GEMOX arm was significantly (statistically) better than the standard GEM arm. The survival outcome for standard GEM was slightly shorter than the 5- to 6-month survival reported by other large studies. Neither the FDR-GEM arm nor the GEMOX arm had survival durations that were as long as those reported in smaller studies.

Gemcitabine in Combination Trials

Since single-agent gemcitabine was established as the standard of care in advanced pancreatic cancer, efforts to improve its efficacy have focused on adding a second agent to gemcitabine. Table 1 lists randomized phase III trials of gemcitabine combined with a second agent.^{4,17} Results among the studies were similar; the addition of a chemotherapeutic agent to gemcitabine did not improve overall survival or quality of life compared with single-agent gemcitabine, with the possible exceptions of gemcitabine plus capecitabine and gemcitabine plus a platinum agent.

Gemcitabine Plus Capecitabine

Capecitabine has been studied as a single agent in advanced or metastatic pancreatic cancer by Cartwright et al.¹⁸ This combination showed clinically significant beneficial effects in tumor-related symptoms and produced some objective responses.

Herrmann et al^{16,19} conducted a phase III trial of gemcitabine plus capecitabine (GEM/CAP) that included 316 patients who were randomized to two arms: (1) GEM/CAP as oral capecitabine 650 mg/m² daily on days 1 through 14 plus gemcitabine 1,000 mg/m² on days 1 and 8 of every 3 weeks or (2) gemcitabine alone. The overall survival was 8.4 months in the GEM/CAP arm vs 7.2 months in the gemcitabine alone arm. The study failed to reach statistical significance. In a subgroup of patients with good performance status, the median overall survival was improved significantly in the GEM/CAP arm.¹⁶

In another randomized phase III trial, this gemcitabine/capecitabine combination demonstrated a significant improvement in overall survival. Cunningham et al¹⁷ have presented this study only in abstract format at the 2005 European Cancer Conference. A total of 533 patients were randomized to two treatment arms: gemcitabine alone or gemcitabine at 1,000 mg/m² weekly × 3 plus capecitabine 1,660 mg/m² for 21 days with a 7-day rest period. The initial presentation of this trial showed a median survival of 6 months for the gemcitabine alone arm and 7.4 months for the combination arm, with 1-year survival rates of 16% and 26%, respectively ($P = .026$). The final results of this study are anxiously awaited.

Gemcitabine Plus Platinum Compounds

Gemcitabine combinations with a platinum have shown synergistic activity in vitro. However, similar to the gemcitabine/fluoropyrimidine combination, gemcitabine/platinum combinations have shown mixed results.

As previously noted, the ECOG 6201 conducted by Poplin et al⁴ was a negative trial. However, one study did show a trend toward positive results. Heinemann et al⁶ treated 195 patients with advanced adenocarcinoma of the pancreas. They were randomly assigned to receive either gemcitabine 1,000 mg/m² and cisplatin 50 mg/m² on days 1 and 15 of a 4-week cycle or gemcitabine alone at a dose of 1,000 mg/m² on days 1, 8, and 15 of a 4-week regimen. The primary endpoint was overall survival; secondary endpoints were progression-free survival, response rate, safety, and quality of life. Baseline characteristics were well balanced between treatment arms. The gemcitabine/cisplatin arm was associated with a prolonged median progression-free survival (5.3 months vs 3.1 months; HR = 0.75; $P = .053$). Also, median overall survival was superior for patients treated in the combination arm (7.5 months) compared with the gemcitabine alone arm (6.0 months), an advantage that did not reach statistical significance (HR = 0.80; $P = .15$).

Colucci et al²⁰ conducted a prospective, randomized phase III trial to determine whether the addition of cisplatin to gemcitabine compared with gemcitabine

Table 1. — Randomized Phase III Trials of Gemcitabine Plus a Second Agent in Pancreatic Cancer

Study	Progression-Free Survival/ Time to Progression (mos)	Overall Survival (mos)
Gemcitabine + bevacizumab ¹¹	4.9	5.8
Gemcitabine + cetuximab ¹²	3.5	6.4
Gemcitabine ± marimastat ¹⁰	NA	5.5
Gemcitabine ± tipifarnib ⁹	3.7	6.4
Gemcitabine ± exatecan ¹³	3.7	6.7
Gemcitabine ± irinotecan ⁷	3.4	6.3
Gemcitabine ± pemetrexed ⁸	3.3	6.2
Gemcitabine ± 5-FU bolus ⁵	3.4	6.7
Gemcitabine ± capecitabine ¹⁴	5.7	9.0
Gemcitabine + capecitabine ¹⁶	NA	8.4
Gemcitabine + capecitabine ¹⁷	NA	7.4
Gemcitabine ± 5-FU/leucovorin ¹⁵	4.9	5.9
Gemcitabine ± cisplatin ⁶	5.3	7.5
Gemcitabine ± oxaliplatin ⁴	5.8	5.9

alone improved the time to progression (TTP) and the clinical benefit rate (CBR) in patients with advanced pancreatic adenocarcinoma. Standard-dose gemcitabine (arm A, 54 patients) was compared to cisplatin 25 mg/m² per week given 1 hour before standard-dose gemcitabine (arm B, 53 patients). On day 22 in arm B, only gemcitabine was administered. The median TTP was 8 weeks in arm A and 20 weeks in arm B ($P = .048$). The tumor growth control rate (ie, complete responses, partial responses, and stable disease) was 42.6% (95% CI = 29%, 57%) in arm A and 56.6% (95% CI = 42%, 70%) in arm B. The median overall survival was 20 weeks for arm A and 30 weeks for arm B ($P = .43$). The addition of cisplatin to gemcitabine significantly improved the median TTP and the overall response rate compared with gemcitabine alone. Median overall survival favored arm B, although the difference was not statistically significant. The authors concluded that the combination of cisplatin/gemcitabine may be considered as a treatment for patients with locally advanced and/or metastatic adenocarcinoma of the pancreas.

Multiple trials are ongoing with gemcitabine and other chemotherapy. Two promising drugs involve nab-paclitaxel²¹ and S-1.²²

Gemcitabine and Targeted Therapy Combinations

Gemcitabine Plus Erlotinib

The epidermal growth factor receptor (EGFR) pathway appears to be critical in a variety of cancers, including pancreatic cancer. Pancreatic tumors often overexpress human epidermal growth factor receptor type 1 (HER1/EGFR), and this is associated with a worse prognosis. Erlotinib, a small molecule inhibitor of the EGFR pathway, was initially approved for the treatment of non-small cell lung cancer.

Table 2. — Summary of the CAN-NCIC PA.3 Phase III Trial: Gemcitabine Plus Erlotinib vs Gemcitabine Alone in Advanced Pancreatic Cancer

	Gemcitabine Plus Erlotinib	Gemcitabine Alone	Hazard Ratio	P Value
No. of patients	285	284		
Response rate	8.6%	8.0%		
Median survival	6.24 mos	5.91 mos	0.82	.038
1-yr survival rate	23%	17%		
Progression-free survival	3.75 mos	3.55 mos	0.77	.004
Data from Moore et al. ^{23,24}				

A phase III trial conducted by Moore et al^{23,24} showed that the addition of erlotinib to gemcitabine produced a statistically significant improvement in median survival over single-agent gemcitabine (Table 2). Overall survival, based on an intent-to-treat analysis, was significantly prolonged on the erlotinib/gemcitabine arm (HR = 0.82; 95% CI = 0.69, 0.99; *P* = .038, adjusted for stratification factors; median 6.24 months vs 5.91 months). The 1-year survival rate was also greater on the erlotinib/gemcitabine arm (23% vs 17%; *P* = .023). Progression-free survival was significantly longer with the erlotinib/gemcitabine combination, with an estimated HR of 0.77 (95% CI = 0.64, 0.92; *P* = .004). Objective response rates were not significantly different between the arms, although more patients on the erlotinib/gemcitabine arm had disease stabilization, and this combination was associated with only modest increases in toxicity and no improvement in quality of life.

Due to the small improvement in median survival and the assessed toxicity, the clinical significance of this combination is unclear. Still, this study was the first demonstration of a benefit of EGFR tyrosine kinase inhibitors in combination with chemotherapy.

Gemcitabine Plus Monoclonals

Although phase II trials combining gemcitabine and monoclonal antibodies have shown some initial promise and have generated considerable interest, larger studies have not confirmed the initial findings.

Gemcitabine Plus Cetuximab

Cetuximab targets the EGFR. Xiong et al²⁵ conducted a phase II study of cetuximab in combination with gemcitabine to determine the response rate, time to disease progression, survival duration and rate, and toxicity of the combination in EGFR-expressing advanced pancreatic cancer. The cetuximab/gemcitabine combination showed promising activity against advanced pancreatic cancer. Five patients (12.2%) achieved a partial response, and 26 (63.4%) had stable disease. The median time to disease progression was 3.8 months, and overall survival was 7.1 months.

At the 2007 American Society of Clinical Oncology Annual Meeting, Philip et al¹² presented the results of the phase III Southwest Oncology Group (SWOG) S0205 study. The efficacy of cetuximab plus gemcitabine in the phase III setting was studied. Tumor samples were submitted for EGFR immunostaining. The median survival was 6 months in the gemcitabine alone arm and 6.5 months in the combination arm, for an overall HR of 1.09 (95% CI = 0.93, 1.27; *P* = .14). The corresponding progression-free survival was 3 months for the gemcitabine alone arm and 3.5 months for the combination arm (HR = 1.13; 95% CI = .97, 1.3; *P* = .058). The confirmed response probabilities were 7% in each arm, and inclusion of unconfirmed responses yielded 14% in the gemcitabine alone arm and 12% in the gemcitabine plus cetuximab arm. This study failed to demonstrate a clinically significant advantage of the addition of cetuximab to gemcitabine for overall survival, progression-free survival, or response in advanced pancreatic cancer.

Gemcitabine Plus Bevacizumab

Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor. This agent, which was initially approved in the treatment of advanced carcinoma of the colon, shows promising activity in a number of other malignancies. Bevacizumab is of interest in pancreatic cancer as vascular endothelial growth factor (VEGF) is overexpressed in pancreatic cancer and high VEGF expression correlates with advanced stage and decreased survival. An initial phase II study of gemcitabine plus bevacizumab²⁶ showed promising results leading to a randomized phase III trial of gemcitabine plus bevacizumab vs gemcitabine plus placebo. In a subsequent phase III trial of gemcitabine plus bevacizumab (arm 1) vs gemcitabine plus placebo (arm 2) in patients with advanced pancreatic cancer, Kindler et al¹¹ reported a median overall survival of 5.7 months in arm 1 and 6.0 months in arm 2 months (95% CI = 4.9, 6.5 vs 5.0, 6.9). Median failure-free survival was 4.8 months vs 4.3 months (95% CI = 4.3, 5.7 vs 3.8, 5.6) (Table 3). Response rates (including unconfirmed responses) were

Table 3. — Phase III Trial of Bevacizumab Plus Gemcitabine in Patients With Advanced Pancreatic Cancer: Median Overall and Progression-Free Survival

	Gemcitabine + Bevacizumab	Gemcitabine + Placebo	P Value	Hazard Ratio
Median overall survival (95% CI)	5.7 mos (4.9, 6.5)	6.0 mos (5.0, 6.9)	0.40	1.09
Progression-free survival (95% CI)	4.8 mos (4.3, 5.7)	4.3 mos (3.8, 5.6)	0.99	1.0
Data from Kindler et al. ¹¹				

as follows: complete 1.9% vs 3.0%, partial 11.2% vs 8.3%, and stable disease 40.7% vs 35.7%. Disease control rates (complete responses, partial responses, stable disease) were 54% vs 47%. The authors concluded that the addition of bevacizumab to gemcitabine did not improve survival in patients with advanced pancreatic cancer. Additionally, they believed that the distribution of patients with good prognostic factors likely accounted for the differences between Cancer and Leukemia Group B (CALGB) 80303 and the prior phase II trial, and they confirmed the need for randomized trials in this disease.

Nongemcitabine Regimens and Second-Line Treatments

USOR and non-USOR investigators have also studied nongemcitabine combinations, with negative results (Table 4). The ECOG 8200 study of docetaxel and irinotecan with or without cetuximab was also a negative trial.²⁷ USOR investigators have also assessed second-line treatment for advanced pancreatic cancer, again with negative results (USOR #9866 RFS 2000 [9-nitrocamptothecin, 9-NC] vs 5-FU who have progressed following gemcitabine).

Table 4. — Nongemcitabine Studies in the USOR

USOR Study No.	Title
9847	Phase II trial of MGI 114 [irofulvene] in patients with advanced pancreatic adenocarcinoma
98007	Phase I/II trial of UFT, leucovorin, and carboplatin in patients with metastatic pancreatic cancer
01122	Phase II trial of CG 8020 and CG 2505 in patients with nonresectable or metastatic pancreatic cancer
02008	Phase II multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of anti-TNF α monoclonal antibody, infliximab, to treat cancer-related cachexia in subjects with pancreatic cancer
02020	Randomized phase II study of TNFerade biologic with 5-FU and radiation therapy for first-line treatment of unresectable locally advanced pancreatic cancer

Table 5. — Ongoing Phase I Gemcitabine Studies in the USOR

USOR Study No.	Title
06162	Phase Ib/II study to evaluate the safety and efficacy of AMG 655 in combination with gemcitabine as first-line therapy for metastatic pancreatic cancer
06123	Phase I open-label dose-finding study of intravenous BI 2536 administered in repeated 4-week cycles as repeated doses on day 1 and day 15 in combination with gemcitabine administered on day 1, day 8 and day 15 in patients with locally advanced or metastatic pancreatic cancer
06150	Randomized phase I/II study with gemcitabine (Gemzar) and RTA 402 or Gemzar and placebo for patients with unresectable pancreatic cancer

Future Treatments

USOR and non-USOR investigators are conducting phase I trials and planning future phase II and III studies in pancreatic cancer with a variety of new agents. Ongoing phase I trials are presented in Table 5.

Conclusions

The USOR organization has been involved in studying pancreatic cancer for almost 15 years and has participated in key clinical trials that have led to the current standard of treatment of advanced pancreatic cancer. At the current time, gemcitabine, either alone or in combination with erlotinib, remains the only approved treatment. Other combination chemotherapy regimens, such as gemcitabine plus capecitabine or a platinum, have shown promise, but improvement has been limited. Multiple trials are planned that will employ new and novel targeted and biological agents. It is hoped that these studies will lead to improvements in patient care.

Disclosures

Dr Cartwright is a consultant for and receives honoraria from Amgen Inc and F.Hoffmann-La Roche Ltd. The other authors report no significant relationship with the companies/organizations whose products or services may be referenced in this article.

The authors have disclosed that this article discusses unlabeled/unapproved uses of the drug capecitabine for the treatment of pancreatic cancer.

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