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Metastatic Pancreatic Cancer 2008: Is the Glass Less Empty?

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Key Words. Metastatic pancreatic cancer • Gemcitabine • Oxaliplatin • Pancreatic enzyme replacement therapy • Erlotinib

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Editor’s Note

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ABSTRACT

Pancreatic cancer is the fourth most common cause of adult cancer death in the U.S. The high mortality rate from pancreatic cancer is a result of the high incidence of metastatic disease at the time of diagnosis, an often fulminant clinical course, and the lack of adequate systemic therapies. Unfortunately, only 5%–25% of patients present with tumors amenable to resection. The median disease-free survival interval following resection for operable pancreatic cancer is 13.4 months for patients treated with adjuvant gemcitabine and 6.9 months for untreated patients. A much higher percentage of patients present with metastatic disease (40%–45%) or locally advanced disease (40%), and have median survival times of 3–6 months or 8–12 months, respectively. The frustrating lack of significant clinical advancements in the treatment of metastatic pancreatic cancer remains one of medical oncology’s biggest disappointments. The past decade-long frustration has resulted in regulators, investigators, and practicing oncologists gradually lowering their standards/expectations with regard to interpreting clinical trials. Two of the more important examples of this include the approval of gemcitabine plus erlotinib and the use of a progression-free survival advantage to defend the use of gemcitabine plus oxaliplatin. Given the marginal benefit of systemic antineoplastics, a scholarly review inclusive of other palliative strategies will help oncologists optimize the care of pancreatic cancer patients. This article examines the existing evidence in support of a role for palliative therapy in metastatic pancreatic cancer, describes recent developments with newer chemotherapeutic and molecular-targeted agents, and explores future study designs. The Oncologist 2008;13:562–576

INTRODUCTION

Pancreatic cancer is the fourth most common cause of adult cancer death in the U.S.. In 2007, 37,170 people were expected to develop pancreatic cancer, with 33,370 anticipated deaths resulting from this disease [1]. The high mortality rate from pancreatic cancer is a result of the high
incidence of metastatic disease at the time of diagnosis, an often fulminant clinical course, and the lack of adequate systemic therapies. Unfortunately, only 5%–25% of patients present with tumors amenable to resection. Following resection for operable pancreatic cancer, the median disease-free survival interval is 13.4 months for patients treated with adjuvant gemcitabine and 6.9 months for untreated patients. Although the longer median disease-free survival time associated with adjuvant gemcitabine has not translated into a median overall survival (OS) advantage (22.1 versus 20.2 months), a trend toward a higher survival rate at 3 years (34% versus 20.5%) and 5 years (22.5% versus 11.5%; \( p = .06 \)) has been observed [2]. A much higher percentage of patients present with metastatic disease (40%–45%) or locally advanced disease (40%), and have median survival times of 3–6 months or 8–12 months, respectively [3].

The frustrating lack of significant clinical advancements in the treatment of metastatic pancreatic cancer remains one of medical oncology’s biggest disappointments. The past decade-long frustration has resulted in regulators, investigators, and practicing oncologists gradually lowering their standards/expectations with regard to interpreting clinical trials. Two of the more important examples of this include the approval of gemcitabine plus erlotinib and the use of a progression-free survival (PFS) advantage to defend the use of gemcitabine plus oxaliplatin. Given the marginal benefit of systemic antineoplastics, a scholarly review inclusive of other palliative strategies will help oncologists optimize the care of pancreatic cancer patients. This article examines the existing evidence in support of a role for palliative therapy in metastatic pancreatic cancer, describes recent developments with newer chemotherapeutic and molecular-targeted agents, and explores future study designs.

**TREATMENT OF METASTATIC Pancreatic CANCER**

Effective symptom palliation requires an integrated management strategy to improve both survival and quality of life (Table 1). Because patients often struggle with several weeks to months of progressive pain, weight loss, and a declining Karnofsky performance status (KPS) score prior to diagnosis, the initial oncology consultation should be accommodated as soon as possible. Patients’ pain and nutritional needs should be addressed at this first encounter along with a discussion of palliative chemotherapy options.

**PAIN CONTROL**

The treatment of pancreatic cancer pain includes pharmacotherapy, chemotherapy and/or radiotherapy, psychosocial support, celiac/splanchnic neurolytic blocks, and epidural or intrathecal infusion of medications [4]. Typically, the initial approach to characteristic pancreatic cancer–associated pain (constant midepigastric pain radiating through to the back or circumferentially and/or right upper quadrant pain resulting from hepatic metastases) is the initiation of long-acting narcotics such as extended-release oral morphine, oxycodone preparations, or transdermal fentanyl coupled with their immediate-acting counterparts to address breakthrough pain. Intermittent, postprandial epigastric discomfort, suggesting pancreatic enzyme insufficiency, may be successfully palliated with the initiation of pancreatic enzyme replacement therapy (PERT) alone. Lastly, reassuring the patient and his family that pain will be promptly and satisfactorily controlled helps soothe the fear and distress that this symptom causes.

Neurolytic celiac plexus block (NCPB) is typically reserved for tumor-associated pain that fails to respond adequately to systemic narcotic analgesics. NCPB is likely to have prompt and long-lasting analgesic efficacy for pancreatic cancer. A meta-analysis, composed mainly of retrospective studies, suggests that NCPB has durable (at least 3 months) partial or complete pain relief in approximately 90% of patients with pancreatic and other intra-abdominal cancers [5]. While the administration of NCPB is typically reserved for patients with ongoing significant pain despite optimized opioid therapy (maximum analgesia achievable without intolerable opioid-related adverse effects), a randomized, double-blind, controlled trial evaluated the implementation of NCPB while opioid therapy was being initiated or increased [6]. That study demonstrated that pain intensity was significantly less at 1 and 6 weeks following NCPB compared with sham injection. However, additional opioid consumption, the frequency of opioid-related adverse events, and quality of life were not different between interventions. Another study, which accrued patients from 1987 until 1991, demonstrated that a durable (up to 6 months) improvement in pain intensity could be achieved with intraoperatively placed alcohol NCPB compared with saline placebo [7]. In that trial, notably, both patients with and without pre-existing pain (preoperative pain) experienced a durable benefit from intraoperative alcohol NCPB.

**PERT**

Patients with pancreatic cancer are vulnerable to pancreatic enzyme deficiency and the associated malabsorption resulting from tumor-associated pancreatic duct obstruction as well as the tumor- or surgery-associated loss of normal pancreatic parenchyma (up to 25% of patients who have under-
gone a Whipple resection have pancreatic exocrine insufficiency) [8]. Furthermore, gastric and duodenal resection/bypass may be associated with decreased endogenous stimulation of pancreatic enzymes as well as a decreased mixture of chyme and pancreatic enzymes. Symptoms of exocrine insufficiency may include abdominal discomfort and/or distension, pain, excessive flatus, belching, diarrhea, steatorrhea, and weight loss. Standardly, restoration of normal digestion in pancreatic exocrine insufficiency can be achieved with 25–40,000 IU of lipase for a standard meal. Commonly prescribed preparations such as Pancrease (Ortho-McNeil Pharmaceutical, Inc., Titusville, NJ), Lipram (Global Pharmaceutical Corporation, Philadelphia), Protilase (Rugby, Inc., Rockville Centre, NY), Cotazym (Organon, Inc., Roseland, NJ), Zymase (Organon, Inc.), Ultrase (Axcan Scandinpharm, Inc., Birmingham, AL), Viokase (Axcan Scandinpharm, Inc.), and Creon (Solvay Pharmaceuticals, Inc., Marietta, GA) contain porcine pancreatin protected within acid-resistant microspheres. The dosage may be increased if steatorrhea or other evidence of malabsorption persists. Another important strategy demonstrated to optimize the efficacy of enteric-coated pancreatic enzyme extracts is the additional use of potent inhibition of gastric acid secretion by a proton pump inhibitor. Up to 50% of patients with pancreatic exocrine insufficiency are thought to also suffer with either inadequate secretion of pancreatic bicarbonate or increased gastric acid secretion, with either mechanism leading to an intestinal pH sufficiently low enough to inactivate PERT [9]. If a patient continues to have malabsorption symptomatology despite titration of PERT dosing and the use of concurrent proton pump inhibition then evaluation and empiric treatment of bacterial overgrowth, particularly in patients with prior gastric or intestinal resection, may be beneficial. Powder preparations should be considered in patients prone to accelerated gastric emptying, particularly patients with prior gastroenterostomies. While bovine-derived pancreatin preparations have inferior lipase content and may be difficult to obtain, they may represent an important option for patients who refuse ingestion of pork-based products based on a religious or other ethical basis.

ENDOSCOPIC STENTING OF BILIARY AND PANCREATIC OBSTRUCTION

Biliary tract obstruction may lead to jaundice, pruritus, abdominal discomfort, nausea, malabsorption, and hepatic dysfunction. In unresectable patients, obstructive jaundice is routinely managed by endoscopic placement of plastic or metal biliary stents [10]. In addition to the relief of jaundice and pruritus, biliary decompression has been shown to improve quality of life by increasing appetite and reducing indigestion [11, 12].

Expandable metal stents are typically chosen over plastic stents because of their superior patency. Typically, expandable metal stents remain patent for a median of 8 months, compared with 4 months of patency for plastic stents.
stents. As well, given a reduction in the need for recurrent endoscopic intervention, initial placement of metal stents has been shown to be cost-effective [13].

Pancreatic stenting may restore pancreaticoduodenal flow impaired by strictures. The main indication for pancreatic ductal stenting is “obstructive” pain related to meals in patients with a dilated main pancreatic duct beyond a stricture. However, this procedure is rarely used and the literature suggests that at most 15% of patients will have symptoms that may benefit from this intervention [14].

**CHEMOTHERAPY FOR METASTATIC Pancreatic Cancer**

The goal of systemic therapy for metastatic pancreatic cancer is to minimize disease-related symptoms and prolong survival. The superior survival outcomes achieved with 5-fluorouracil (5-FU)-based combinations compared with best supportive care (BSC) alone provided an initial validation of chemotherapy benefit for advanced pancreatic cancer patients. The median survival times associated with 5-FU were consistently in the 6-month range, as summarized in Table 2 [15–17]. However, in a meta-analysis, 5-FU combinations did not demonstrate a survival benefit when compared with 5-FU alone [17].

**Gemcitabine**

Because of its favorable toxicity profile and modest ability to palliate typical pancreatic cancer symptoms, single-agent gemcitabine has been the global reference regimen for this disease since its approval in 1996. Gemcitabine (2’-deoxy-2’ ,2’-difluorocytidine monohydrochloride [beta-isomer]) is a deoxycytidine analogue structurally related to cytarabine (cytosine arabinoside) originally investigated for its antiviral effects [18, 19]. It is a prodrug that requires cellular uptake and intracellular phosphorylation to gemcitabine di- and triphosphate, the active metabolites. Gemcitabine triphosphate competitively inhibits DNA chain elongation, leading to DNA fragmentation and cell death [18].

In the pivotal trial that helped gemcitabine gain regulatory approval in the U.S., 126 patients were randomized to receive either weekly gemcitabine (1,000 mg/ m² over 30 minutes) or weekly bolus 5-FU. The primary efficacy measure was clinical benefit response (CBR), a composite measurement of pain (analgesic consumption and pain intensity), KPS score, and weight. Clinical benefit required improvement for at least 4 weeks in one or more parameters without a worsening of the other parameters. CBR was observed in 23.8% of the gemcitabine-treated patients, compared with 4.8% of the 5-FU–treated patients (p = .0022). The median survival times for gemcitabine and 5-FU patients were 5.65 and 4.41 months, respectively (p = .0025). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients [20].

Myelosuppression is the main toxicity associated with gemcitabine. However, postmarketing surveillance has documented rare occurrences of acute lung, liver, and kidney injury. Therefore, gemcitabine-induced acute lung injury should be considered if new symptoms such as cough or dyspnea develop, and consistent monitoring of renal and hepatic function should be included in the follow-up of patients treated with gemcitabine.

Gemcitabine is a renally cleared drug. One phase I evaluation study in patients with hepatic or renal dysfunction showed that patients with baseline hyperbilirubinemia were at risk for liver function deterioration with gemcitabine. However, that study indicated that gemcitabine may be safely given to patients with elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (patients in the trial had baseline AST levels up to 530 U/l). Also observed in that trial was the fact that patients with impaired renal function were at risk for significant gemcitabine toxicity, including skin toxicity [21]. The authors of the paper conceded that the heterogeneity of the studied patients and

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n of patients</th>
<th>MS (months)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Meta-analysis [17]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU</td>
<td>262</td>
<td>6.38</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BSC</td>
<td>434</td>
<td>3.87</td>
<td></td>
</tr>
<tr>
<td>RCT [15]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAM</td>
<td>43</td>
<td>33 wks</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>BSC</td>
<td>15</td>
<td>15 wks</td>
<td></td>
</tr>
<tr>
<td>RCT [16]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mallinson regimen</td>
<td>40</td>
<td>LA/Met, 48/33 wks</td>
<td>LA/Met, 0.048/0.001</td>
</tr>
<tr>
<td>BSC</td>
<td>12/7 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-analysis [17]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU alone</td>
<td>428</td>
<td>5.23</td>
<td>.1</td>
</tr>
<tr>
<td>5-FU combinations</td>
<td>414</td>
<td>4.98</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; BSC, best supportive care; FAM, 5-FU, doxorubicin, and mitomycin-c; LA, locally advanced; Met, metastatic, stage 4 disease; MS, median survival; ORR, objective response rate; RCT, randomized controlled trial.
the small sample size (15 patients) did not permit specific dosing recommendations for patients with renal dysfunction. Indeed, a subsequent phase I trial of weekly gemcitabine in 18 patients showed no evidence of greater toxicity in patients with impaired creatinine clearance [22]. The currently available data suggest that gemcitabine may reasonably be offered to chemotherapy-naïve patients with compromised renal function, although initiating treatment at a lower weekly dose (800 mg/m²) with incremental increases to 1,000 mg/m², depending on patient tolerance, is a reasonable consideration.

Striving to Optimize Gemcitabine Efficacy
While the optimal dose and schedule of gemcitabine have not been identified, studies have shown that dosing intervals <1 week or infusion times ≥60 minutes are associated with substantially greater toxicity without clinical benefit. A phase I study evaluating the maximum-tolerated dose (MTD) of gemcitabine on a daily for 5 days schedule showed that patients developed intolerable, dose-related hypotension and severe flu-like symptoms at doses >10 mg/m² per day [23]. Phase I studies using a twice-weekly schedule reached MTDs of only 65 mg/m² (30-minute infusion) and 150 mg/m² (5-minute bolus). Thrombocytopenia and flu-like symptoms, particularly asthenia, were dose-limiting toxicities [24]. Lastly, a phase I study to assess the maximum-tolerated infusion time of gemcitabine identified ≥270 minutes for weekly doses of 300 mg/m² as the maximum-tolerated infusion duration [25].

Phase II and III trials evaluating fixed-dose rate (FDR) gemcitabine infusions of 10 mg/m² per minute were based on the fact that phosphorylation of gemcitabine by deoxycytidine kinase is the rate-limiting step in the accumulation of active diphosphate and triphosphate gemcitabine metabolites. Early phase I studies demonstrated that a gemcitabine plasma concentration of 20 μmol/l was associated with a maximized rate of gemcitabine triphosphate formation (in mononuclear cells). This plasma concentration and gemcitabine triphosphate accumulation were best achieved using dose rates approximating 10 mg/m² per minute [26, 27]. Also, preclinical data with cell lines, including pancreatic carcinoma, suggested a possible dose–response relationship [28, 29]. Therefore, a randomized phase II trial was designed to compare weekly high-dose (2,200 mg/m²) gemcitabine administered using a standard 30-minute infusion with weekly FDR gemcitabine (10 mg/m² per minute; 1,500 mg/m² over 150 minutes). Ninety-two patients were enrolled in this study; 91% had metastatic disease. Time to treatment failure, the primary endpoint, was comparable in the two treatment groups. The median survival times were 5.0 months in the standard arm and 8.0 months in the FDR arm (p = .013). For patients with metastases, the median survival times were 4.9 months in the standard arm and 7.3 months in FDR arm (p = .094). The 1-year survival rate was 28.8% versus 9% (p = .014) and the 2-year survival rate was 18.3% versus 2.2% (p = .007), favoring FDR [30]. However, in a confirmatory randomized phase III trial, the same FDR dose/schedule failed to show a statistically significant difference in the median OS time compared with the standard infusion schedule of gemcitabine at 1,000 mg/m² over 30 minutes weekly [31].

Phase III Combination Chemotherapy Trials
Because of its unique mechanism of action and favorable nonhematological toxicity profile, investigators have undertaken intense efforts to develop gemcitabine-based combinations that offer at least additive benefit for pancreatic cancer patients. Table 3 summarizes 13 randomized phase III trials that attempted to improve upon the survival outcomes achieved with gemcitabine alone, typically by adding a second cytotoxic agent [20, 31–42]. With the exception of the gemcitabine plus capcitabine experimental arm reported by Cunningham et al. [35] in abstract form only as of this review, these efforts have failed to identify a gemcitabine-based chemotherapy doublet that has produced significantly better median or 1-year survival outcomes.

One caveat in applying these data to clinical practice and research is to not dismiss a particular agent or class of drugs as inactive in pancreatic cancer simply because combining it with gemcitabine failed to produce superior clinical outcomes. The most relevant example of this is the role of oxaliplatin and 5-FU in patients with gemcitabine-refractory metastatic pancreatic cancer, detailed later in this manuscript.

Gemcitabine plus a Platinum Analogue: A Closer Look
Gemcitabine (1,000 mg/m² over 100 minutes on day 1) followed by oxaliplatin (100 mg/m² as a 2-hour infusion on day 2), the GemOx regimen, was administered every other week to 157 patients (experimental arm) in a phase III trial that accrued 313 patients [37]. GemOx was superior to gemcitabine in terms of response rate (26.8% versus 17.3%, respectively; p = .04), PFS time (5.8 versus 3.7 months, respectively; p = .04), and CBR (38.2% versus 26.9%, respectively; p = .03). The median OS times for GemOx and gemcitabine were 9.0 and 7.1 months, respectively (p = .13). GemOx was well tolerated, albeit with higher grade 3–4 per patient thrombocytopenia (14.0% versus 3.2%), vomiting (8.9% versus 3.2%), and neurosensory symptoms (19.1% versus 0%).
Table 3. Phase III gemcitabine-based combination chemotherapy trials

<table>
<thead>
<tr>
<th>n of patients</th>
<th>ORR</th>
<th>Disease control</th>
<th>TTP/PFS (mos)</th>
<th>OS (mos)</th>
<th>1-Yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine versus 5-FU [20]</td>
<td>126</td>
<td>23.8% versus 4.8%;</td>
<td>2.33 versus 0.92;</td>
<td>5.65 versus 4.41;</td>
<td>18% versus 2%</td>
</tr>
<tr>
<td>FDR gemcitabine versus gemcitabine + oxaliplatin [31]</td>
<td>833</td>
<td>7% versus 14%;</td>
<td>4.96 versus 6.01;</td>
<td>p = NS</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine versus exatecan bolus 5-FU [32]</td>
<td>327</td>
<td>5.6% versus 6.9%;</td>
<td>2.2 versus 3.4;</td>
<td>5.4 versus 6.7;</td>
<td>18% versus 2%</td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine + 5-FU/ folinic acid [33]</td>
<td>466</td>
<td>8.2% versus 10.2%;</td>
<td>6.2 versus 5.85;</td>
<td>p = .68</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine + capecitabine [34]</td>
<td>319</td>
<td>7.9% versus 10.1%;</td>
<td>4.0 versus 4.8;</td>
<td>7.3 versus 8.4;</td>
<td>p = .314</td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine + pemetrexed [35]</td>
<td>533</td>
<td>7% versus 14%;</td>
<td>6.0 versus 7.4;</td>
<td>HR, 0.8;</td>
<td>19% versus 26%</td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine + cisplatin [36]</td>
<td>190</td>
<td>8.2% versus 10.2%;</td>
<td>48.5% versus 70.4%;</td>
<td>p &lt; .001</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine + oxaliplatin [37]</td>
<td>313</td>
<td>17.3% versus 26.8%;</td>
<td>3.1 versus 5.3;</td>
<td>6.0 versus 7.5;</td>
<td>p = .15</td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine + irinotecan [38]</td>
<td>342</td>
<td>4.4% versus 16.1%;</td>
<td>3.7 versus 5.8;</td>
<td>p = .04</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine + irinotecan [39]</td>
<td>130</td>
<td>10% versus 15%;</td>
<td>7.1 versus 9.0;</td>
<td>p = .13</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine + exatecan [40]</td>
<td>349</td>
<td>10% versus 15%;</td>
<td>21.8% versus 24.3%;</td>
<td>p = .666</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine versus PEGF [41]</td>
<td>104</td>
<td>8.5% versus 38.5%;</td>
<td>3.3 versus 5.4;</td>
<td>p = .0033 (PFS)</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine + pemetrexed [42]</td>
<td>565</td>
<td>7.1% versus 14.8%;</td>
<td>3.3 versus 3.9;</td>
<td>p = .1109 (PFS)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; FDR, fixed dose rate; HR, hazard ratio; NS, nonsignificant; ORR, objective response rate; OS, overall survival; PEGF, cisplatin, epirubicin, gemcitabine, and 5-FU; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to disease progression.

Notably, second-line therapy may have muted a possible survival advantage of GemOx in that trial. While second-line chemotherapy was administered to 55% of the gemcitabine patients and to 55.4% of the GemOx patients, the majority of gemcitabine patients (74.0%) received a true crossover regimen containing oxaliplatin or a crossover-like regimen (with a platinum), whereas 31.1% of GemOx patients received a cisplatin-based regimen as second-line therapy [37].

A pooled analysis of individual patient data collected from two randomized trials comparing gemcitabine with either gemcitabine plus oxaliplatin or gemcitabine plus cisplatin suggests that pancreatic cancer patients with an excellent performance status may benefit from more intensive combination therapy [43]. Survival was better in patients treated with the combination (median, 8.3 versus 6.7 months; p = .031; hazard ratio [HR], 1.23; 95% confidence interval [CI], 1.02–1.49). Patients with an Eastern Cooperative Oncology Group (ECOG) PS score of 0 (40% of patients) may have had a greater benefit from combination therapy (HR, 1.38; 95% CI, 0.99–1.93; p = .063).

Capcitabine
Capcitabine has demonstrated activity similar to that of gemcitabine, as reported in a phase II trial in chemotherapy-
naïve patients with either locally advanced or metastatic pancreatic cancer. Forty-two patients were treated with oral capecitabine (1,250 mg/m²) administered twice daily for 14 days followed by a 1-week treatment holiday. While the number of patients with metastatic disease was not detailed in that small study, the 24% CBR and median OS duration of 6 months are comparable with outcomes with gemcitabine [44].

However, two phase III trials attempting to demonstrate at least additive activity between gemcitabine and capecitabine have produced conflicting results. One multicenter trial involving 319 patients, 79% with metastatic disease, randomized patients to either gemcitabine (1,000 mg/m² on days 1 and 8) plus capecitabine (650 mg/m² twice daily on days 1–14) with cycles repeated every 3 weeks or standard weekly gemcitabine. The median OS time was 8.4 months for the gemcitabine plus capecitabine patients and 7.3 months for the gemcitabine only patients (p = .314). A post hoc analysis showed that patients with a KPS score ≥90 attained a statistically significant longer median OS time of 10.1 versus 7.4 months (p = .014) [34]. A second randomized phase III trial involving 533 patients, reported in abstract form only as of this writing, evaluated gemcitabine plus capecitabine (GEMCAP) versus gemcitabine alone. GEMCAP was shown to produce a statistically significant longer median OS time, 7.4 months, versus 6.0 months (HR, 0.77; p = .014). One possible reason why the experimental arm in that trial attained better outcomes may be the fact that capecitabine was given on a more prolonged schedule: 1,660 mg/m² daily for 21 days repeated every 4 weeks [35].

Table 4. Phase III trials evaluating molecularly targeted therapies

<table>
<thead>
<tr>
<th>Gemcitabine + placebo versus gemcitabine + tipifarnib [45]</th>
<th>n of patients</th>
<th>ORR</th>
<th>Disease control (CR + PR + SD)</th>
<th>TTP/PFS (mos)</th>
<th>OS (mos)</th>
<th>1 Yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine versus BAY12–9566 [46]</td>
<td>277</td>
<td>5%</td>
<td>0.92%</td>
<td>3.5 versus 1.68; p = .001 (PFS)</td>
<td>6.59 versus 3.74; p = .001</td>
<td>25% versus 10%</td>
</tr>
<tr>
<td>Gemcitabine + placebo versus gemcitabine + marimastat [47]</td>
<td>239</td>
<td>16%</td>
<td>11%</td>
<td>5.4 versus 5.5; p = .95</td>
<td>17% versus 18%</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine + placebo versus gemcitabine + erlotinib [48]</td>
<td>569</td>
<td>8.0%</td>
<td>8.6%</td>
<td>3.55 versus 3.75; p = .004 (PFS)</td>
<td>5.91 versus 6.24; p = .038</td>
<td>17% versus 24%; p = .023</td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine + bevacizumab [49]</td>
<td>602</td>
<td>13.1%</td>
<td>11.3%</td>
<td>4.3 versus 4.8</td>
<td>6.0 versus 5.7</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine + cetuximab versus gemcitabine [50]</td>
<td>735</td>
<td>7%</td>
<td>7%</td>
<td>3.5 versus 3; p = .058 (PFS)</td>
<td>6.5 versus 6; p = .14</td>
<td></td>
</tr>
<tr>
<td>G17DT + gemcitabine versus placebo + gemcitabine [51]</td>
<td>383</td>
<td>11%</td>
<td>13%; p = .46</td>
<td>3.9 versus 3.9; p = .09 (TTP)</td>
<td>5.9 versus 6.7; p = .10</td>
<td></td>
</tr>
</tbody>
</table>

*Confirmed.

Abbreviations: CR, complete response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to disease progression.

TARGETED THERAPIES

Gemcitabine plus Erlotinib: Statistical Significance Versus Clinical Relevance

Molecularly targeted agents have a solid preclinical rationale as treatment for advanced pancreatic cancer. However, as summarized in Table 4, with the exception of erlotinib, the completed phase III trials have not confirmed an important clinical benefit [45–51].

Because of its observed overexpression in a high percentage of pancreatic cancers and its association with poor prognosis, the human epidermal growth factor receptor 1 (HER-1/EGFR) signaling cascade has been targeted for anticancer drug development. Erlotinib, an orally available molecule, interrupts HER-1/EGFR signaling by inhibiting the tyrosine kinase integrated in the intracellular receptor domain.

Based on a phase III randomized, placebo-controlled trial, erlotinib in combination with gemcitabine received U.S. Food and Drug Administration approval as treatment for chemotherapy-naïve locally advanced and metastatic pancreatic cancer in 2005 [48]. In total, 569 patients were randomly assigned in a 1:1 ratio to receive standard gemcitabine plus erlotinib (100 or 150 mg/day orally) or gem-
citabine plus placebo in a double-blind, international phase III trial. The primary endpoint of a longer OS time was achieved statistically with an HR of 0.82 (95% CI, 0.69–0.99; \( p = 0.038 \)) and a median survival duration of 6.24 versus 5.91 months. A 1-year survival advantage was also attained with erlotinib plus gemcitabine (23% versus 17%; \( p = 0.023 \)). The PFS time was significantly longer with erlotinib plus gemcitabine, with an estimated HR of 0.77 (95% CI, 0.64–0.92; \( p = 0.004 \)) and with a median PFS interval of 3.75 versus 3.55 months. Objective response rates were not significantly different between the arms, although more patients on erlotinib had disease stabilization.

When the statistically positive results of this trial were initially presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2005, two U.S. Cooperative Group trials in patients with advanced pancreatic cancer were approximately halfway through patient accrual. Both studies used standard gemcitabine as the control arm. The Cancer and Leukemia Group B (CALGB) 80303 trial compared gemcitabine plus placebo with gemcitabine plus bevacizumab and the Southwest Oncology Group (SWOG) S0205 trial compared gemcitabine alone with gemcitabine plus cetuximab. The fact that both of these trials continued brisk accrual after the announcement of the results of the National Cancer Institute of Canada Clinical Trials Group PA.3 trial can be interpreted as early evidence of hesitancy on the part of treating clinicians, clinical investigators, and patients to accept gemcitabine plus erlotinib as a reference regimen.

A review of toxicities may further discourage the use of gemcitabine plus erlotinib. Patients receiving erlotinib and gemcitabine experienced higher frequencies of rash (72%), diarrhea (56%), infection (43%), and stomatitis (23%), generally grade 1 or 2. The six protocol-related deaths were all in the erlotinib–gemcitabine arm. Two were attributed to treatment complications (interstitial pneumonitis and sepsis) and four were attributed to a combination of cancer and protocol treatment complications (interstitial pneumonitis, sepsis, cerebrovascular accident, and neutropenic sepsis). Interstitial lung disease was observed in seven patients receiving erlotinib plus gemcitabine and in one patient receiving placebo plus gemcitabine.

An unplanned analysis showed an association between the severity of rash and survival. Grade 0 rash (79 patients) and grade 1 rash (108 patients) were associated with median survival times of 5.29 and 5.75 months, respectively. Grade 2 rash was observed in 103 patients and was associated with a median survival time of 10.51 months. The concept of exploiting a possible erlotinib dose–related rash for therapeutic benefit in patients with metastatic pancreatic cancer has not been validated. Erlotinib as a single agent for the treatment of chemotherapy-resistant pancreatic cancer is just beginning to be evaluated [52].

Finally, a pharmacoeconomic analysis for years of life gained (YLG) using the January 2006 Centers for Medicare and Medicaid Services Drug Payment Table and Physician Fee Schedule does not support the addition of erlotinib to gemcitabine as cost-effective [53]. The addition of erlotinib increases the costs of treating advanced pancreatic cancer by $12,156 wholesale or $16,613 retail per patient. Factoring in 0.4-month longer median survival time compared with gemcitabine alone, the addition of erlotinib costs $364,680 per YLG wholesale and $498,379 per YLG retail. In order to be cost-effective, even at the $100,000/YLG level, 6 months of erlotinib would have to be reduced to 20% of the current retail cost (i.e., to $18.52 per tablet). The minimal additional clinical benefit, side effects, and financial impact have discouraged patients and clinicians when deciding on the inclusion of erlotinib in combination with gemcitabine as palliative treatment for metastatic pancreatic cancer.

**Gemcitabine plus Bevacizumab**

Vascular endothelial growth factor (VEGF) plays a key role in the growth and metastasis of many tumors, including pancreatic cancer [54]. Bevacizumab (Avastin®; Genetics, Inc., South San Francisco, CA) is a recombinant humanized anti-VEGF monoclonal antibody with clinical benefit in metastatic colon, breast, and non-small cell lung cancer. Kindler and colleagues reported the results of a phase II trial of bevacizumab plus gemcitabine in 52 patients with metastatic pancreatic cancer. Partial responses were observed in 21% of patients, the median survival time was 8.8 months, and the 1-year survival rate was 29% [55]. These data prompted the CALGB to conduct a double-blind, placebo-controlled randomized phase III trial of gemcitabine plus bevacizumab versus gemcitabine plus placebo in 590 advanced pancreatic cancer patients [49]. That trial was designed to detect, with 90% power, a difference in the median OS of 6 versus 8.1 months. Gemcitabine was given in the standard fashion and bevacizumab was given at a dose of 10 mg/kg on days 1 and 15 of each 28-day cycle. The median OS times were 5.7 months and 6.0 months for gemcitabine plus bevacizumab and gemcitabine plus placebo, respectively.

The CALGB 80303 trial included a higher percentage of poorer performance status patients (36%/53% with an ECOG PS score of 0/1) than the phase II gemcitabine–bevacizumab trial (60%/38% with an ECOG PS score of 0/1). While this fact almost certainly contributed to the inferior survival outcomes in the gemcitabine–bevacizumab arm in the CALGB 80303 trial, the arms in that trial were
well balanced with regard to patient and disease characteristics. Not surprisingly, an ECOG PS score of 0 was associated with a statistically significant longer median survival time of 8 months, compared with 4.8 months for patients with an ECOG PS score of 1. Pharmacogenetics as possible predictors of outcome were collected and will be reported as a separate study.

Further disappointment in the development of bevacizumab as treatment for pancreatic cancer occurred in AVITA [Study of Avastin (bevacizumab) added to a chemotherapeutic regimen in patients with metastatic pancreatic cancer], a Roche-sponsored randomized, double-blind, placebo-controlled trial comparing gemcitabine plus erlotinib with or without bevacizumab, which did not meet the primary endpoint for survival. Reports of a further analysis to define benefit regarding other endpoints and patient subsets is awaited.

Another antiangiogenic therapy that has not been shown to have activity in metastatic pancreatic cancer, when combined with gemcitabine at least, is sorafenib, an inhibitor of Raf-1 kinase and VEGF receptor 2. Among 17 evaluable patients in a phase II trial of standard-schedule gemcitabine plus sorafenib (400 mg orally twice daily), no responses were seen, the median survival time was 4 months, and the 6-month survival rate was 23% [56].

Antiangiogenesis will continue to be evaluated in pancreatic cancer in a randomized trial comparing gemcitabine with VEGF Trap (afiblercept; Regeneron Pharmaceuticals, Inc., Rensselaer, NY) with gemcitabine. Afiblercept is a fusion protein made of human VEGF receptor extracellular domains fused to the Fc portion of human IgG1, designed to bind and inactivate circulating VEGF. Also, another oral tyrosine kinase inhibitor of the VEGF receptor as well as the platelet-derived growth factor receptor, sunitinib, is being evaluated as a second-line treatment option by the CALGB in a phase II study (CALGB 80603).

**Gastin VACCINE—IMMUNOTHERAPY: GEMCITABINE PLUS**

**GEMCITABINE PLUS WITHOUT CETUXIMAB**—SWOG S0205

The SWOG and Clinical Trial Support Unit enrolled 766 patients (735 were eligible) with a median age of 64 years (range, 30–91) into this phase III trial between January 2004 and April 2006 [50]. Eligibility included locally advanced unresectable (21.5%) or metastatic pancreatic cancer and a PS score ≥2 (13% of patients had a PS score = 2), no prior EGFR therapy, and no prior palliative chemotherapy. The study was designed to detect a median improvement in survival to 8 months (HR, 1.33) with 90% power for the experimental arm. Patients were randomized to standard weekly gemcitabine alone or with cetuximab given as a loading dose of 400 mg/m² on week 1 and then 250 mg/m² weekly. The median survival times were 6 months in the control arm and 6.5 months in the cetuximab arm, for an overall HR of 1.09 (95% CI, 0.93–1.27; p = .14). The corresponding PFS times were 3 months and 3.5 months, for the control and cetuximab arms, respectively (HR, 1.13; 95% CI, 0.97–1.3; p = .058). The confirmed response rate was 7% in each arm.

**IMMUNOTHERAPY: GEMCITABINE PLUS GAHRIN VACCINE**

Immunotherapy, defined in the context of clinical oncology, involves the stimulation of a patient’s immune system to achieve antitumor activity. Non-specific strategies include the use of exogenous immunostimulants or cytokines, the transfer of nonspecific immune effector cells, and the inhibition of immunosuppressive pathways. Alternatively, specific immunotherapeutic strategies strive to enhance the response to defined tumor antigens or induce antitumor antibody activity, often via vaccination.

Gastrin was shown to demonstrate the necessary criteria for a potential immunotherapy target against pancreatic cancer. Gastrin receptors and precursor gastrin forms were shown to be broadly expressed, demonstrated in up to 90% of pancreatic cancer resection tissues. Also, gastrin demonstrated a possible pathogenic role, because in vivo gastrin had a proliferative effect on pancreatic cancer cells, and antigastrin antibodies raised against G17DT, an immunocjugate of gastrin-17, inhibited the proliferation of pancreatic cancer cells [57]. Early human studies of G17DT in patients with other forms of cancer demonstrated that G17DT was safe and well tolerated [58]. In a phase II study of G17DT in advanced pancreatic cancer, 67% of 30 patients produced an antibody response [59]. The 250-μg dose resulted in a significantly greater antibody response rate of 82%, compared with 46% for the 100-μg group (p = .018). The most significant side effects, seen in three patients, were local abscess and/or fever. The median survival time for the whole group measured from first immunization was 187 days; the median survival times were 217 days for the antibody responders and 121 days for the antibody non-responders (p = .0023).

However, a randomized, double-blind study of gemcitabine plus placebo versus gemcitabine plus G17DT in 383 chemotherapy-naïve advanced and metastatic pancreatic cancer patients did not demonstrate a survival advantage [51]. The median OS time for the group receiving G17 DT was 178 days; the median OS time for patients receiving placebo was 201 days (p = .1). The time to disease progression (TTP) was the same in both arms, 118 days (p = .09). Interestingly, titer responses in women were substantially weaker. Also, higher anti-G17 titer levels were associated
with longer survival both overall and in gender-specific analyses. Similar antibody–survival correlations have been seen in other studies of G17DT.

Future strategies to validate the efficacy of immunotherapy in the treatment of pancreatic cancer may include better selection of patients able to mount an antibody response or development of superior immunogens. One candidate immunogen is telomerase, expressed in 85%–90% of pancreatic cancers. Immunogenic telomerase peptides have been characterized and a phase I–I/I study investigating the safety, tolerability, and immunogenicity of a telomerase peptide vaccination, GV1001, in combination with GM-CSF enrolled 48 patients with unresectable pancreatic cancer [60]. GV1001 was well tolerated and immune responses were observed in 24 of 38 evaluable patients. The median and 1-year survival outcomes among 27 evaluable patients were 8.6 months and 25%, respectively. The TeloVac trial in the United Kingdom is a phase III evaluation comparing GV1001 given either concurrently or sequentially with gemcitabine and capcitabine with the same chemotherapy given alone. This three-arm trial is expected to accrue 1,100 patients through 2012. A second, 520-patient phase III multinational trial including U.S. sites will evaluate GV1001 plus GM-CSF followed by gemcitabine upon disease progression against gemcitabine monotherapy.

Investigators at Johns Hopkins have pioneered the development of lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene as immunotherapy for pancreatic cancer. This vaccine was first developed in their single-institution, phase II study of 60 patients with resected pancreatic adenocarcinoma. The first vaccine was administered 8–10 weeks following resection and patients were subsequently treated with 5-FU chemotherapy. Patients who remained disease free received up to four additional vaccines. With a median follow-up duration of 36 months, the median survival time is approximately 26 months, which compares favorably with recent phase III outcomes of adjuvant gemcitabine [61].

Johns Hopkins investigators are now developing this vaccine in combination with immune-modulating doses of cyclophosphamide and additional cetuximab in patients with advanced disease. Currently 47 of the planned 60 patients have been enrolled. The preclinical rationale supporting this combination is that monoclonal antibody therapy of epidermal growth factor (EGF) proteins will lead to better presentation of EGF proteins to the immune system (Laheru D, personal communication).

Planned development of immunotherapy at Johns Hopkins includes a trial of the allogeneic vaccine plus anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody. The hope is that anti–CTLA-4 antibody suppression of host immune suppression factors will optimize the efficacy of allogeneic pancreatic tumor cell vaccine therapy. Another trial that Johns Hopkins investigators hope to activate in 2008 involves the development of attenuated *Listeria* carrying mesothelin peptide. In two adjuvant and one palliative trials, the Johns Hopkins group has observed that responding patients were largely able to recognize mesothelin as opposed to nonresponders. *Listeria* is a very efficient bacterium in generating an immune response and is therefore hypothesized to be a very useful vector (Laheru D, personal communication).

### SECOND-LINE THERAPY

A significant advance in the care of metastatic pancreatic cancer patients is the recently reported Charite Onkologie (CONKO) 003 trial that has identified a much needed option for patients with disease progression during or shortly after first-line palliative therapy with standard gemcitabine [62]. Patients with advanced pancreatic cancer and confirmed disease progression with first-line gemcitabine were randomized to BSC with or without oxaliplatin (85 mg/m² on days 8 and 22) plus 5-FU (2 g/m² over 24 hours) with folinic acid (leucovorin; 200 mg/m² over 30 minutes on days 1–8 and 15–22), repeated every 42 days (the OFF regimen). After 46 of 165 planned patients were enrolled, the BSC alone arm was closed because an early efficacy analysis showed a significant survival benefit with OFF. The two arms of this trial were balanced with regard to age, tumor stage, gender, PS score, and median duration of first-line therapy gemcitabine (19.9 versus 20.7 weeks). The median survival time measured from the initiation of second-line therapy was 21 weeks versus 10 weeks (p = .0077), favoring treatment with OFF. The OS times measured from the initiation of gemcitabine were 39.6 weeks for OFF and 34.4 weeks for BSC (p = .0312). Given the fact that second-line OFF was shown to be feasible and effective, CONKO 003 was modified into a comparison of OFF with FF (same 5-FU/leucovorin program as in OFF). As of the ASCO 2007 Annual Meeting update, 76 and 89 patients were randomized to OFF and FF, respectively. The median TTP (12.3 versus 8 weeks) and OS time (45 versus 35.6 weeks, measured from the initiation of first-line gemcitabine) both favored the OFF regimen [63].

### MULTIDRUG REGIMENS

Given the frustrating outcomes from phase III trials of gemcitabine-based chemotherapy doublets, investigators began investigating three- and four-drug regimens. Only one of these regimens, PEFG, has been evaluated in a randomized phase III trial [41]. PEFG consists of cisplatin (40 mg/ m²), epirubicin (40 mg/ m² i.v. on day 1), gemcitabine (600
mg/m² given over 1 hour on days 1 and 8), and 5-FU (200 mg/m²) daily for the duration of chemotherapy. Cycles are repeated every 28 days. One hundred four patients were randomized to PEFG or standard gemcitabine. The treatment groups were balanced in terms of age, gender, PS score, and proportion of patients with metastatic disease (57% versus 56%). This study met its primary endpoint by demonstrating a greater 4-month PFS rate in PEFG-treated patients (60% versus 28%; p = .001). OS outcomes also favored PEFG, with an HR for death of 0.65 (p = .047).

Grade 3–4 neutropenia and thrombocytopenia favored the gemcitabine group; one patient treated with PEFG required hospitalization for febrile neutropenia. The 1- and 2-year survival rates for the PEFG group were 38.5% and 11.5%, respectively. Salvage therapy was received by 49% of PEFG-treated patients and by 60% of gemcitabine-treated patients (with 70% receiving true crossover therapy with PEFG).

Additional multiagent chemotherapy programs are summarized in Table 5 [41, 64–68]. Notable among these are two nongemcitabine regimens. The single-arm, phase II experience of FOLFIRINOX (5-FU/leucovorin, irinotecan, and oxaliplatin) included 35 patients with chemotherapy-naïve metastatic disease. The confirmed response rate was 26%, TTP was 8.2 months, and median OS time was 9.5 months [66]. These encouraging results prompted a randomized phase II–III study, the so called ACCORD (Actions Concertées sur les cancers COlo-Rectaux et Digestifs) 11 trial, which compared FOLFIRINOX with standard gemcitabine as initial therapy for metastatic pancreatic cancer. Forty-three patients treated with FOLFIRINOX were evaluable for toxicity and efficacy outcomes. The febrile neutropenia rate was 2%, grade 3–4 vomiting occurred in 23% of patients, and grade 3–4 neuropathy occurred in 23% of patients. The response rate and disease control rate were 31.8% and 59%, respectively [69]. This trial will transition into a phase III study. The ECOG characterized the toxicity and efficacy of weekly irinotecan plus docetaxel with or without cetuximab in a randomized phase II trial. That study was limited to patients with chemotherapy-naïve metastatic pancreatic cancer. Grade 3–4 toxicities were significant in both treatment arms: febrile neutropenia, 6% and 9%; diarrhea, 30% and 44%; both worse in the cetuximab arm. The cetuximab arm had a 4.4% death rate, compared with a 2.2% death rate in the noncetuximab arm. The median survival time was shorter in the cetuximab-containing arm, 5.3 months versus 6.5 months [67]. While this small dataset did produce survival outcomes similar to those seen with gemcitabine, the current iteration of this protocol appears prohibitively toxic. Lastly, capecitabine (750 mg/m² orally, twice daily on days 1–14), gemcitabine (750 mg/m² over 75 minutes), and docetaxel (30 mg/ m² on days 4 and 11) repeated every 21 days has demonstrated an encouraging median OS time of 11.2 months and a 20% survival rate at 2 years [64]. However, these results come from a small retrospective analysis of 35 patients.

**CHEMOTHERAPY PLUS LOW MOLECULAR WEIGHT HEPARIN: A PROSPECTIVE, RANDOMIZED TRIAL OF SIMULTANEOUS PANCREATIC CANCER TREATMENT WITH ENOXAPARIN AND CHEMOTHERAPY**

Approximately 20% of patients diagnosed with pancreatic adenocarcinoma develop venous thromboembolism, contributing to the poor prognosis of this disease. A small phase II trial suggested longer survival with the addition of low molecular weight heparin (LMWH) to chemotherapy [70]. In that study, 69 patients received standard gemcitabine with or without LMWH (nadroparine calcium, 2,850 IU/day until disease progression). Ten of 35 patients in the LMWH group and 10 of 34 patients in the chemotherapy-alone group had primary inoperable locally advanced disease and the rest of the patients had metastatic disease. The response rate (58.8% with an 11.7% complete response [CR] rate versus 12% with no CRs), TTP (7.3 months versus 4.0 months; p = .0001), and median OS time (13.0 versus 5.5 months; p = .0001) all favored the LMWH arm.

These encouraging outcomes prompted European investigators to evaluate primary venous thromboembolic prophylaxis with enoxaparin in a phase III trial, PROSPECT (Prospective, Randomized trial Of Simultaneous Pancreatic cancer treatment with Enoxaparin and Chemotherapy)-CONKO 004 [71]. In that trial, patients receive gemcitabine (1 g/m² over 30 minutes), cisplatin (30 mg/m² over 90 minutes), 5-FU (750 mg/m² over 24 hours), and leucovorin (200 mg/m² on days 1 and 8) every 3 weeks with or without enoxaparin (1 mg/kg daily s.c.). Patients with a KPS score <80% and an elevated creatinine plasma level (>1.3 mg/dl) will be assigned to treatment with gemcitabine alone (1 g/m² over 30 minutes on days 1, 8, and 15) every 28 days with or without enoxaparin (1 mg/kg per day s.c.). After 12 weeks of initial chemotherapy, all patients who have not progressed will continue treatment with single-agent gemcitabine weekly with or without enoxaparin (40 mg daily). Accrual to this trial is ongoing.

**FUTURE DRUG DEVELOPMENT**

Unfortunately, broad, empiric clinical testing of novel gemcitabine-based combinations has been disappointing. One strategy to improve the productivity of the phase III mechanism is to increase the rigor by which phase II trials are designed and interpreted. Future phase II results should be interpretable with specific regard to survival outcomes for
patients with measurable metastatic disease, because inclusion of patients with locally advanced, nonmetastatic disease proportionately improves survival outcomes by virtue of disease biology rather than treatment effect. Also, increasingly, the use of second-line palliative treatment data should be captured and used to interpret phase II results, especially if these data will be used to select regimens for phase III testing.

Identification of new pathogenic targets hopefully will have a clinical impact as well. One such candidate target, S100P, has recently been found to be overexpressed in pancreatic, breast, and lung cancer. Overexpressed S100P may increase tumor growth and metastasis and decrease patient survival. Pancreatic cancer cells with high endogenous levels of S100P have shown resistance to cytotoxic drugs in vitro and gemcitabine in vivo. Most recent studies have shown that the antiallergy drug cromolyn inhibits the interaction between S100P and the receptor for advanced glycation end products (RAGE). Cromolyn binds S100P, prevents activation of RAGE, inhibits tumor growth, and increases the effectiveness of gemcitabine in experimental models. However, further studies are necessary to determine the anticancer activity of cromolyn and cromolyn analogues [72, 73].

Beyond the broad testing of novel agents intended to have efficacy against most patients’ pancreatic cancer, advances in the treatment of pancreatic cancer may be achieved by identifying strategies to match an individual’s cancer with the most effective available drug. For example, preclinical testing has demonstrated that pancreatic cancers that develop in patients with a BRCA-2 germline mutation

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<td>Gemcitabine versus PEGF [41]</td>
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<td>Irinotecan + docetaxel versus irinotecan + docetaxel + cetuximab [67]</td>
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<td>G-FLIP [68]</td>
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*Retrospective analysis.

5-FU: bolus 5-FU, 500 mg/m² per day via rapid infusion, <1 hour, for five consecutive days with courses repeated every 4 weeks. 5-FU and cisplatin: 5-FU, 1,000 mg/m² per 24 hours for five consecutive days; cisplatin on day 1 or 2 over 2–3 hours, 100 mg/m²; cycles repeated every 4 weeks.

GTX: capecitabine, 750 mg/m² orally twice daily on days 1–14; gemcitabine, 750 mg/m² over 75 minutes; docetaxel, 30 mg/m² on days 4 and 11; cycles repeated every 21 days.

PEFG: cisplatin, 40 mg/m²; epirubicin, 40 mg/m², both given on day 1; gemcitabine, 600 mg/m² given i.v. over 1 hour on days 1 and 8; 5-FU, 200 mg/m² per day given by continuous infusion on days 1–28 of a 4-week cycle.

FOLFIRINOX: sequential oxaliplatin (85 mg/m²), irinotecan (180 mg/m²), and leucovorin (400 mg/m²) followed by bolus 5-FU (400 mg/m²) followed by 5-FU at a dose of 2,400 mg/m² as a 46-hour continuous infusion; cycles repeated every 2 weeks. Irinotecan plus docetaxel: docetaxel (35 mg/m²) over 1 hour followed by irinotecan (50 mg/m²) over 30 minutes weekly for four cycles, repeated every 6 weeks; patients assigned to arm B received the same docetaxel plus irinotecan program plus cetuximab (loading dose, 400 mg/m² on week 1 followed by weekly 250 mg/m² doses). G-FLIP: biweekly (once every 14 days) cycles of sequential gemcitabine (500 mg/m²), irinotecan (120 mg/m²) (phase II dose), bolus 5-FU (400 mg/m²), and leucovorin (300 mg) on day 1 followed by a 24-hour 5-FU infusion (1,500 mg/m²) followed by cisplatin (35 mg/m²) on day 2.

Abbreviations: 5-FU, 5-fluorouracil; CR, complete response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to disease progression.
are close to 1,000 times more sensitive to mitomycin-C than cancers from patients without this mutation. Approximately 7% of pancreatic cancers in the U.S. are associated with BRCA-2 mutations. At Johns Hopkins, pancreatic cancer patients with BRCA-2 mutations are being treated with mitomycin-C in a phase II trial with the 6-month survival rate as the primary endpoint. Another approach to effective drug selection would be prospective development and validation of in vitro chemotherapeutic sensitivity and/or resistance assays, of which details have been expertly discussed by others [74, 75]. A potential predictor of gemcitabine efficacy is human equilibrative nucleoside transporter 1 (hENT)-1, a gemcitabine transporter in human pancreatic adenocarcinoma cells. Studies have shown that overexpression of hENT-1 correlates with a longer OS time in patients who have been treated with gemcitabine [76].

**CONCLUSIONS**

With nearly 20 randomized phase III trials that have failed to produce a relevant improvement in survival outcomes since 1996, metastatic pancreatic cancer has confirmed its status as one of the most frustrating malignancies to investigate and treat. Given the modest palliative benefits associated with either gemcitabine or gemcitabine plus erlotinib and second-line 5-FU plus oxaliplatin therapy, oncologists should emphasize supportive care strategies in helping patients cope with this disease. For the majority of patients with metastatic disease, the current data support opting for sequential gemcitabine followed by 5-FU plus oxaliplatin as second-line treatment. First-line doublet therapy, for example, gemcitabine plus a platinum or GEMCAP, or entry into protocols evaluating three- or four-drug chemotherapy combinations may be appropriately reserved for select patients with both tumor volume–associated symptomatology and an ECOG/World Health Organization PS score of 0 or KPS score ≥0. Hopefully ongoing or planned trials will identify advancements relevant to our practice and research efforts. Ideally, however, technologies will emerge that will allow physicians to detect pancreatic cancer at a much earlier, more treatable stage.

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