First-Line Treatment for Advanced Pancreatic Cancer


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Summary
Pancreatic adenocarcinoma remains a treatment-refractory cancer. Although pancreatic adenocarcinoma is only the 10th most common cause of new cancer in the United States, it is the fourth most common cause of cancer-related death. Most cases are not suitable for resection and a majority is metastatic at presentation. Gemcitabine, with or without erlotinib, has been the standard chemotherapy in this setting but the benefit is only modest. Because gemcitabine has been considered a standard treatment for advanced pancreatic cancer for the past decade, several randomized trials have tested the combination of gemcitabine plus a second agent, including platinum based agents, topoisomerase inhibitors, taxanes, bevacizumab and cetuximab, as biologically "targeted" agents. At large this approach has not been successful and novel strategies are clearly needed. In this article, the authors summarizes the data from the 2011 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, including: Abstract #175 (review of survival data in a large cohort); Abstract #286 (rapid change in prescriber patterns after the suggestion of benefit of a new regimen, FOLFIRINOX); Abstracts #238, #277, #304, and #315 (phase II trials looking at combinations that utilized EGFR blockade); Abstracts #221, #266, and #284 (phase I/II trials including VEGF blockade, anticoagulation, and traditional Chinese medicines).

What Did We Know Before the 2011 ASCO GI Cancer Symposium?
In 2010 [1] there were an estimated 43,140 new cases and 36,800 deaths from pancreatic cancer in the United States. This represents the 10th most common cause of cancer but the 4th most common cause of cancer death in 2010, highlighting the disproportionate mortality associated with this diagnosis. Additionally, unlike most of the more frequent causes of cancer mortality (lung, colon, prostate and breast) whose death rates are declining, the death rate for pancreatic cancer is relatively stable. Data from 2000-2007 in the Surveillance, Epidemiology and End Results (SEER) registry [2] indicate that at diagnosis the majority of pancreatic cancer is advanced (50.5% metastatic vs. 8% localized, 25.9% regional spread, and 15.5% unstaged.) Thus a majority of patients are unresectable at presentation and treatments are needed to reduce the morbidity and mortality of this disease. Historically, 5-FU was utilized though associated with poor response overall. Gemcitabine was compared to 5-FU/leucovorin in randomized trials in the 1990s and was approved as a first line agent on the basis of a pivotal phase III trial [3] which demonstrated improvement in median overall survival and 1-year survival compared to 5-FU (5.7 months vs. 4.4 months and 18% vs. 2%, respectively). Despite the response rate of 5% and the modest overall survival benefit, gemcitabine was quickly adopted as the standard of care in first-line therapy of advanced pancreatic cancer. Five-year survival related to pancreatic cancer has improved significantly in the chemotherapy era; however, the absolute improvement is small: 3% to 6% (5-year survival from 1975-77 to 1999-2005). Data from the California Cancer Registry from 1998-2005 were reviewed by Gubens et al. and presented at the 2011 ASCO GI Cancer Symposium (Abstract #175). Notably of all cases reported in this timeframe (54,475), the median overall survival of all patients was 3.5 months with only 5.2% alive at 3 years [4]. Despite promising results from phase II trials, numerous phase III trials with gemcitabine
combinations have failed to demonstrate clear survival benefit [5]. Recently there have been two regimens that demonstrated improvement over gemcitabine. In 2007, Moore et al. demonstrated improvement in survival from (6.24 months vs. 5.91 months) when the combination of gemcitabine and erlotinib, a small-molecule tyrosine kinase inhibitor that targets and blocks EGFR, was compared to gemcitabine alone [6]. Despite the relatively small magnitude of this survival benefit, this was the first agent that had significant benefit in combination with gemcitabine in a phase III trial and this trial raised significant interest in targeting the EGFR pathway in metastatic pancreatic cancer. At the ASCO Annual Meeting in June 2010, preliminary data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) 11 trial which compared gemcitabine to oxaliplatin and irinotecan plus fluorouracil and leucovorin (FOLFIRINOX) was presented. This study demonstrated [7] significant improvements in progression free survival and median overall survival with FOLFIRINOX (6.4 months vs. 3.3 months and 11.1 months vs. 6.8 months, respectively) Perhaps most striking, the objective response rate was 31% for the FOLFIRINOX arm which compares to 9% in the gemcitabine arm. However, there was a significant increase in treatment-related toxicity with FOLFIRINOX and there is a need to identify which patients will ultimately benefit from this more aggressive approach.

Updates from the 2011 ASCO GI Cancer Symposium

At the 2011 ASCO GI Cancer Symposium, several abstracts were presented regarding first line treatment of advanced pancreatic cancer. The findings of these studies are summarized in Table 1 and discussed here. *EGFR Inhibition*

Given the small but significant benefit seen with the addition of erlotinib to gemcitabine, several trials tested the hypothesis that agents targeting the epidermal growth factor receptor would demonstrate activity in metastatic pancreatic cancer. In Abstract #238 [8], Kim et al. reported on a randomized phase II trial that looked to evaluate the role of dual EGFR inhibition by the addition of a monoclonal EGFR antibody. In addition to gemcitabine and erlotinib, 81 patients with metastatic pancreatic cancer were randomized to receive panitumumab, or placebo. The authors reported that panitumumab plus gemcitabine and erlotinib was well tolerated in the initial portion of

<table>
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<tr>
<th>Abstract/Design</th>
<th>Enrolled patients</th>
<th>Treatment</th>
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<th>Results</th>
<th>Side effects</th>
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<tr>
<td>Randomized, phase II GE vs. PGE</td>
<td>93 patients</td>
<td>Erlotinib: 100 mg daily</td>
<td>Dual EGFR inhibition (small molecule and antibody)</td>
<td>Median PFS: GE 2.0 months PGE 3.5 months</td>
<td>Rash more common in PGE (85% vs. 65%)</td>
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<tr>
<td>Single arm, phase II</td>
<td>32 patients with MPC</td>
<td>Caepectitabine: 1,000 mg/m² bid</td>
<td>Small molecule EGFR inhibition</td>
<td>RR: 6.3%</td>
<td>Rash, asthenia, hand-foot</td>
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<td>Single arm, phase II</td>
<td>62 patient, 46 with MPC</td>
<td>Gemcitabine: 1,500 mg/m²; over 150 min every week</td>
<td>Small molecule EGFR inhibition</td>
<td>Overall RR: 13%</td>
<td>Increased grade 3/4 hematologic toxicity</td>
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<tr>
<td>Single arm, phase II</td>
<td>9 patients with MPC</td>
<td>Lapatinib: 1,250 mg/day</td>
<td>Small molecule EGFR inhibition</td>
<td>Overall RR: 0% (0/9)</td>
<td>Study was terminated</td>
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<td>Single arm, phase II</td>
<td>43 patients with MPC, 30 evaluable for response</td>
<td>Gemcitabine: 1,000 mg/m²; days 1,8,15; every 28 days</td>
<td>Dual EGFR/VEGF inhibition</td>
<td>PR: 7% (2/30)</td>
<td>Grade 4 included bowel perforation, gastrointestinal bleed, and sepsis</td>
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<td>LA or MPC</td>
<td>Gemcitabine: 1,000 mg/m²; days 1,8,15; every 28 days</td>
<td>Factor Vila inhibition</td>
<td>Phase II dose: 1.2 mg/kg bid</td>
<td>Grade 3 hemato logic toxicity</td>
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<tr>
<td>Randomized, phase II</td>
<td>80 patients, 76% MPC</td>
<td>Gemcitabine: 1,000 mg/m²; days 1,8,15; every 28 days</td>
<td>Extract of dried toad skin glands</td>
<td>Overall RR: 6%</td>
<td>No difference in toxicity or outcomes between arms</td>
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</table>

ECOG: Eastern Cooperative Oncology Group; GE: gemcitabine plus erlotinib; GH: gemcitabine plus huachansu; LA: locally advanced; MPC: metastatic pancreatic cancer; OS: overall survival; PFS: progression free survival; PGE: panitumumab plus gemcitabine and erlotinib; PR: partial response; PS: performance status; RR: response rate; TTP: time to tumor progression.

* Gemcitabine plus huachansu vs. gemcitabine: P NS
the study with only fatigue as a dose-limiting toxicity. The randomized phase II portion was initiated and has completed accrual; survival data is still not mature and was not presented. The authors did report a difference in progression free survival (3.3 months for panitumumab plus gemcitabine and erlotinib vs. 2.0 months for gemcitabine and erlotinib), though they did not report if this achieved statistical significance.

In Abstract #277 [9], Folger et al. reported an open-label phase II trial that utilized erlotinib with capecitabine as first line treatment in metastatic pancreatic cancer. Capecitabine has shown activity in metastatic pancreatic cancer when added to gemcitabine with improved response rate and progression free survival and a trend to improvement in overall survival [10]. This study reported that 32 patients received first line treatment for metastatic pancreatic cancer with erlotinib and capecitabine and demonstrated a partial response in two patients (6.3%) and median progression free survival and overall survival of 2.1 months and 4.3 months, respectively. The combination of erlotinib with capecitabine was generally well tolerated with no grade 4 toxicity reported in this cohort.

In Abstract #315 [11], McDermott et al. described a single arm phase II trial that looked at the combination of capecitabine and lapatinib, a small-molecule, reversible tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor and HER-2. This combination is effective in the treatment of metastatic HER-2 positive breast cancer [12] and preclinical work suggested that this combination may have synergistic activity in metastatic pancreatic cancer. This study was terminated prematurely when 7 of the 9 patients enrolled did not achieve survival at 6 months. There were no responses among the 9 patients treated.

In Abstract #304 [13], Llarena et al. looked at the feasibility of fixed-dose-rate infusion of gemcitabine in combination with erlotinib in first line treatment. They included 46 patients with metastatic disease and reported progression free survival and overall survival for this cohort and concluded that this regimen is feasible but associated with increased hematologic toxicity, as expected based on our experience with Eastern Cooperative Oncology Group (ECOG) 6201 study.

**Vascular Endothelial Growth Factor (VEGF)**

Sorafenib, in addition to VEGF receptor inhibition, inhibits the raf-1 kinase and the platelet-derived growth factor receptor (PDGFR) tyrosine kinase, and may have enhanced activities compared to bevacizumab which only inhibits VEGF receptor. Therefore, the combination of gemcitabine with sorafenib was tested in patients with metastatic pancreatic cancer.

In Abstract #266 [14], Cohen et al. reported on a single arm phase II trial evaluating the addition of sorafenib, a tyrosine kinase inhibitor that targets VEGF (among other pathways), to the standard regimen of gemcitabine plus erlotinib in metastatic pancreatic cancer. Compared to historical data this did not result in robust improvement over standard therapy with gemcitabine plus erlotinib.

**Anticoagulation**

Thrombosis is a common finding in malignancy, especially in pancreatic cancer where the incidence of thrombotic events is reported to range from 17% to 57% [15]. The pathogenesis of this hypercoagulability is complex but higher expression of tissue factor, the initiator of coagulation, is associated with increased VEGF expression and thrombotic episodes [16], and worse prognosis [17].

In Abstract #221 [18], Ramanathan et al. reported the phase I results of an ongoing phase I/II trial of PCI-27483 in combination with gemcitabine. PCI-27483 is an inhibitor of factor VIIa which interacts with tissue factor in the coagulation pathway and is linked to coagulation and possibly up-regulation of VEGF and angiogenesis. A tolerable dose was determined and the phase II component of this study is ongoing.

**Traditional Chinese Medicine**

In Abstract #284 [19], Meng et al. looked at the activity of an extract of wild toad venom which has been used in traditional Chinese medicine. The addition of this extract to standard gemcitabine was evaluated in a randomized phase II study of advanced pancreatic cancer of 76 patients of which 58 (76%) were metastatic. Response rate, time to tumor progression, and median overall survival were not significantly different in the two arms suggesting that this extract provides no additional benefit compared to standard therapy.

**Discussion**

Despite declines in cancer-related mortality over the last decade, progress in pancreatic cancer has remained exceedingly slow and disappointing. The most patients are diagnosed with advanced disease and have a median survival with treatment of about 6 months. The underlying etiology for such poor outcome is attributable to many factors, including multiple molecular aberrations, intense desmoplastic stroma, hypoxia, and others.

Late stage clinical trials have generally failed to demonstrate improvement in outcome in metastatic pancreatic cancer, as evidenced by the 5.2%, 3-year survival in pancreatic cancer reported in the California registry data (Abstract #175) [4]. In new trials, combination chemotherapy with erlotinib showed modest benefit when combined with capecitabine (Abstract #277) [9] but not when combined with lapatinib (Abstract #315) [11]. The most exciting results in this category resulted from addition of panitumumab to gemcitabine plus erlotinib for dual EGFR inhibition (Abstract #238) [8]. Despite the failure of a large phase III trial of EGFR blockade with cetuximab [20] (Southwest Oncology Group; SWOG S0205), there was activity of dual inhibition in...
increasing progression free survival. Survival data from this trial are not reported and will be highly anticipated, if this indicates benefit it will form the basis for a phase III trial. Fixed-dose-rate infusion of gemcitabine was demonstrated to be feasible with erlotinib but as in a previous large phase III trial (E6201) [21], the hematologic toxicity is concerning.

Both a traditional Chinese medication (Abstract #284) [19] and sorafenib (Abstract #266) [14] failed to demonstrate benefit compared to standard treatment in phase II trials. Despite the benefit seen from VEGF inhibition in a variety of tumors, previous studies have failed to find benefit in pancreatic cancer (Cancer and Leukemia Group B; CALGB 80303) [22]. Metastatic pancreatic cancer is unique in that there is a deficiency of vasculature in the stromal environment and this is thought to limit drug delivery and confer poor response to anti-VEGF therapy [23]. Finally, another avenue of research targets the prominent role of thrombosis in pancreatic cancer and a phase I study demonstrated a tolerable dose of PCI-27483 and will be continued in a phase II trial (Abstract #221) [18].

Further evidence of the need for novel therapies is the rapid adoption of the FOLFIRINOX regimen by oncologists on the basis of preliminary phase III results. Bendell et al. (Abstract #286) [24], looked at prescribing patterns of a sample of U.S. oncologists in August, 2010 (following the June 2010 report of benefit with FOLFIRINOX). They found that compared to the same period in 2009, oncologists adopted this new regimen for 18% of their patients with metastatic pancreatic cancer and performance status equal to 1. This mostly substituted gemcitabine plus erlotinib regimen in this population (which declined from 44% to 35%).

In summary, these abstracts presented at the 2011 ASCO GI Cancer Symposium highlight the difficulty in improving outcomes in metastatic pancreatic cancer but also point to potential areas of interest including dual EGFR inhibition and anti-coagulation. This continues to be a field of intense interest and regimens that conclusively show benefit in this disease are likely to generate enthusiasm and rapid adoption into clinical practice.

Conflict of interest The authors have no potential conflict of interest

References
19. Z. Meng, L. Liu, Y. Shen, et al. A randomized phase II study of gemcitabine (G) plus the cardiac glycosate huachansu (H) in the treatment of patients with locally advanced (LAPC) or metastatic pancreatic cancer (MPC). J Clin Oncol 2011; 29(Suppl. 4);Abstract 284.

