HIGHLIGHT ARTICLE

First-Line Treatment for Advanced Pancreatic Cancer

Highlights from the "2011 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 20-22, 2011

Paul E Oberstein, Muhammad Wasif Saif

Columbia University College of Physicians and Surgeons at New York Presbyterian Hospital. New York, NY, USA

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 new 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

Key words Drug Therapy; erlotinib; gemcitabine; Pancreatic Neoplasms

Abbreviations FOLFIRINOX: 5-fluorouracil, leucovorin, irinotecan and oxaliplatin

Correspondence Muhammad Wasif Saif
Columbia University College of Physicians and Surgeons; New York Presbyterian Hospital; MHB, 6N-435; New York, NY 10032; USA
Phone: +1-212.305.4954; Fax: +1-212.3050.3035
E-mail: mws2138@columbia.edu

URL http://www.serena.unina.it/index.php/jop/article/view/3331/3578

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) were 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 1. Summary of first-line treatment in metastatic pancreatic cancer.

Abstract/ Design	Enrolled patients	Treatment	Targeted mechanism	Results	Side effects
#238 [8] Randomized, phase II GE vs. PGE	93 patients ECOG PS: 0-1	Erlotinib: 100 mg daily Gemcitabine: 1,000 mg/m^2; every week Panitumumab: 4 mg/kg every 2 weeks	Dual EGFR inhibition (small molecule and antibody)	Median PFS: GE: 2.0 months PGE: 3.3 months	Rash more common in PGE (85% *vs*. 65%)
#277 [9] Single arm, phase II	32 patients with MPC	Capecitabine: 1,000 mg/m^2 *bid* Erlotinib: 1,500 mg daily	Small molecule EGFR inhibition	RR: 6.3% Median PFS: 2.10 months Median OS: 4.3 months	Rash, asthenia, hand-foot
#304 [13] Single arm, phase II	62 patient, 46 with MPC	Gemcitabine: 1,500 mg/m^2; over 150 min every week Erlotinib: 100 mg daily	Small molecule EGFR inhibition	Overall RR: 13% In MPC patients: Median PFS: 2.5 months Median OS: 7 months	Increased grade 3/4 hematologic toxicity
#315 [11] Single arm, phase II	9 patients with MPC	Lapatinib: 1,250 mg/day Capecitabine: 2,000 mg/m^2/day; days 1-14; every 21 days	Small molecule EGFR inhibition	Overall RR: 0% (0/9) Median OS: 4 months	Study was terminated
#266 [14] Single arm, phase II	43 patients with MPC, 30 evaluable for response ECOG PS: 0-1	Gemcitabine: 1,000 mg/m^2; days 1,8,15; every 28 days Erlotinib: 150 mg daily Sorafenib: 400 mg *bid*	Dual EGFR/VEGF inhibition	PR: 7% (2/30) Median TTP: 111 days Median OS: 195 days	Grade 4 included bowel perforation, gastrointestinal bleed, and sepsis
#221 [18] Phase I dose escalation, phase II randomized, controlled	LA or MPC 8 patients, 5 evaluable ECOG PS: 0-1 Normal coagulation	Gemcitabine: 1,000 mg/m^2; days 1,8,15; every 28 days PCI-27483- s.c. *bid* (0.8 to 1.2 to 1.5 mg/kg)	Factor VIIa inhibition Possible down-regulation of VEGF	Phase II dose: 1.2 mg/kg *bid* 4/5 patients with stable disease at 16 weeks	Grade 3 hematologic toxicity Phase II is ongoing
#284 [19] Randomized, phase II GH *vs*. gemcitabine	80 patients, 76% MPC	Gemcitabine: 1,000 mg/m^2; days 1,8,15; every 28 days Huachansu: 20 mL/m^2 i.v. daily; days 1-21	Extract of dried toad skin glands	Overall RR: 6% Median TTP: 102 *vs*. 103 days [a] Median OS: 154 *vs*. 134 days [a]	No difference in toxicity or outcomes between arms

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

[a] 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 FOLFIRNOX 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

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60:277-300. [PMID 20610543]

2. Surveillance Epidemiology and End Results (SEER). U.S. Cancer Statistics: 1999-2007 Incidence and Mortality Report. Available at http://www.seer.cancer.gov/publications/uscs.html (Accessed January 31, 2011).

3. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15:2403-13. [PMID 9196156]

4. Gubens MA, Kunz PL, Fisher GA, Ford JM, Lichtensztajn D, Clarke CA. Long-term survivorship in pancreatic adenocarcinoma. J Clin Oncol 2011; 29(Suppl. 4):Abstract 175.

5. Stathis A, Moore MJ. Advanced pancreatic carcinoma: current treatment and future challenges. Nat Rev Clin Oncol 2010; 7:163-72. [PMID 20101258]

6. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007; 25:1960-6. [PMID 17452677]

7. Conroy T, Desseigne F, Ychou M, Ducreux M, Bouche O, Guimbaud R, et al. Randomized phase III trial comparing FOLFIRINOX (F: 5FU/leucovorin (LV), irinotecan (I), and oxaliplatin (O)) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): Preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial. J Clin Oncol 2010; 28(15 Suppl.):Abstract 4010.

8. Kim GP, Foster NR, Salim M, Flynn PJ, Moore DF Jr, Zon R, et al. Randomized phase II trial of panitumumab (P), erlotinib (E), and gemcitabine (G) versus erlotinib-gemcitabine in patients with untreated, metastatic pancreatic adenocarcinoma. J Clin Oncol 2011; 29(Suppl. 4):Abstract 238.

9. Candamio Folgar S, Méndez Méndez C, Jorge Fernández M, Romero Reinoso C, Quintero-Aldana G, Salgado Fernández M, et al. A phase II study of capecitabine in combination with erlotinib as first-line therapy in patients with metastatic pancreatic cancer (stage IV). J Clin Oncol 2011; 29(Suppl. 4):Abstract 277.

10. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009; 27: 5513-8. [PMID 19858379]

11. McDermott RS, Calvert P, Parker M, Webb G, Moulton B, McCaffrey J. A phase II study of lapatinib and capecitabine in first-line treatment of metastatic pancreatic cancer (ICORG 08- 39). J Clin Oncol 2011; 29(Suppl. 4):Abstract 315.

12. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355:2733-43. [PMID 17192538]

13. Munoz Llarena A, Mane J, Lopez-Vivanco G, Ruiz de Lobera A, Sancho A, Iruarrizaga E, et al. Gemcitabine (G) fixed-dose-rate infusion (FDR) plus erlotinib (E) in patients with advanced pancreatic cancer (APC). J Clin Oncol 2011; 29(Suppl. 4):Abstract 304.

14. Cohen DJ, Leichman LP, Love E, Ryan T, Leichman CG, Newman E, et al. Phase II study of sorafenib with gemcitabine and erlotinib (GES) in first-line advanced pancreatic cancer. J Clin Oncol 2011; 29(Suppl. 4):Abstract 266.

15. Khorana AA, Frine RL. Pancreatic cancer and thromboembolic disease. Lancet Oncol 2004; 5:655-63. [PMID 15522652]

16. Khorana AA, Ahrendt SA, Ryan CK, Francis CW, Hruban RH, Hu YC, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. Clin Cancer Res 2007; 13:2870-5. [PMID 17504985]

17. Nitori N, Ino Y, Nakanishi Y, Yamada T, Honda K, Yanagihara K, et al. Prognostic significance of tissue factor in pancreatic ductal adenocarcinoma. Clin Cancer Res 2005; 11:2531-9. [PMID 15814630]

18. Ramanathan RK, Gressler V, Shah S, Loury D, Hamdy A, Khorana A. Phase I/II study of PCI-27483, a coagulation factor VIIa (FVIIa) inhibitor in patients with advanced pancreatic cancer receiving treatment with gemcitabine. J Clin Oncol 2011; 29(Suppl. 4):Abstract 221.

19. Meng Z, Liu L, Shen Y, Yang P, Cohen L, Huo Y, et al. A randomized phase II study of gemcitabine (G) plus the cardiac glycoside 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.

20. Philip PA, Benedetti J, Fenoglio-Preiser C, Zalupski M, Lenz H, O'Reilly E, et al. Phase III study of gemcitabine (G) plus cetuximab (C) versus gemcitabine in patients (pts) with locally advanced or metastatic pancreatic adenocarcinoma (PC): SWOG S0205 study. J Clin Oncol 2007; 25(18 Suppl.):Abstract LBA4509.

21. Poplin E, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009; 27:3778-85. [PMID 19581537]

22. Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol 2010; 28:3617-22. [PMID 20606091]

23. Van Cutsem E, Vervenne WL, Bennouna J, Humblet Y, Gill S, Van Laethem JL, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 2009; 27:2231-7. [PMID 19307500]

24. Bendell JC, Britton S, Green MR, Willey J, Lemke KE, Marshall J. Immediate impact of the FOLFIRINOX phase III data reported at the 2010 ASCO Annual Meeting on prescribing plans of American oncology physicians for patients with metastatic pancreas cancer (MPC). J Clin Oncol 2011; 29(Suppl. 4):Abstract 286.