JOP. J Pancreas (Online) 2007; 8(4):365-373.

EDITORIAL

Pancreatic Cancer: Is This Bleak Landscape Finally Changing?

Highlights from the '43rd ASCO Annual Meeting'. Chicago, IL, USA. June 1-5, 2007

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Summary

Pancreatic cancer remains a major therapeutic challenge in 2007. Most patients with advanced pancreatic cancer experience pain and must limit their daily activities because of tumor-related symptoms. Single-agent gemcitabine remains the standard treatment for advanced pancreatic cancer , which has shown improvement in disease-related symptoms and a modest benefit in survival. Recent phase III trials using gemcitabine in combination with other chemotherapeutic agents have failed to show improvements in survival, although the gemcitabine/oxaliplatin and gemcitabine/capecitabine combinations have shown some promise. The combination of gemcitabine with erlotinib, though showed a statistically significant prolongation of survival, may not be clinically significant. Encouraging results in two separate phase II trials of gemcitabine in combination with bevacizumab and cetuximab respectively led to two major randomized comparative trials of the combination (Cancer and Leukemia Group B, CALGB 80303; Southwest Oncology Group, SWOG S0205). The results of these studies presented at the 43rd American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA (June 1-5, 2007) showed no benefit of the combination. 'How can we change this bleak landscape?'. Probably by truly targeting our therapy with the epidermal growth factor receptor (EGFR) agents as well as other biologic agents by identifying those patients who are most likely to derive benefit and achieve meaningful responses. This is particularly crucial in a disease such as pancreatic cancer that has such a short life expectancy that the 'window' for any given treatment may be quite small. Consequently, further study should include the development of more predictive assays and improved exploitation of surrogate biomarkers of response. We need to study locally advanced pancreatic cancer patients separate from advanced pancreatic cancer patients. Role of multiple-targeted agents is also warranted. It's also time to investigate gemcitabine-free regimens. Two recent studies presented at ASCO showed that irinotecan/docetaxel or FOLFIRINOX (5-fluorouracil/leucovorin, irinotecan and oxaliplatin) can offer comparable results to gemcitabine when used as first-line treatment for advanced pancreatic cancer. Development of novel agents and approaches, are urgently needed in conjunction with improvement in access to clinical trials for patients.

Introduction

Pancreatic cancer remains a devastating and poorly understood malignancy. The incidence is increasing worldwide. Cancer of the exocrine pancreas is the fourth most common malignancy in the United States. The annual incidence rate is almost identical to the

mortality rate with approximately 25,000 new cases diagnosed each year in the United States and 24,800 deaths. It is estimated that there will be 37,170 new cases diagnosed in USA and 33,370 deaths due to pancreatic cancer in 2007 [1]. Pancreatic cancer is the forth cause of mortality in men and women and five-year survival rate remains less than 5%. Poor prognosis had been attributed to inability to diagnose while tumor is resectable and its propensity towards early vascular disseminat-ion and spread to regional lymph nodes. Up to 60% of patients have advanced pancreatic cancer at the time of diagnosis. Median survival of these patients is dismal with 3 to 6 months [2].

Gemcitabine: Concept Of Clinical Benefit Response

5-fluorouracil (5-FU) was the first agent to be widely used in the treatment of advanced pancreatic cancer but response rates were less than 20% and it was not known to provide significant palliative benefits. Gemcitabine, the current standard of care in first line treatment, was approved based on a relatively dramatic improvement in clinical benefit response but median survival was only modestly improved. In this study, one hundred twenty-six patients with advanced pancreatic cancer were randomized to receive either gemcitabine 1,000 mg/m^2 weekly for 7 weeks followed by one week of rest, then weekly for 3 weeks every 4 weeks thereafter (63 patients), or to 5-FU 600 mg/m^2 once weekly (63 patients) [3]. The primary efficacy measure was clinical benefit response, which was a composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. Clinical benefit required a sustained (equal to, or greater than, 4 weeks) improvement in at least one parameter without worsening in any others. Other measures of efficacy included response rate, time to progressive disease, and survival. Clinical benefit response was experienced by 23.8% of gemcitabine-treated patients compared with 4.8% of 5-FU-treated patients (P=0.0022). The median survival durations were 5.65 and 4.41 months for gemcitabine-treated and 5-FU-treated patients, respectively (P=0.0025). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients.

Interestingly, the dose and schedule used for 5-FU without leucovorin was not a standard one but since gemcitabine was more effective than 5-FU in alleviation of some disease-related symptoms in patients with advanced pancreatic cancer (in spite of a modest survival advantage) was accepted by FDA as well as the oncologist to become the new standard of therapy for advanced pancreatic cancer. After the approval of gemcitabine in 1997, many cytotoxic and targeted agents have been pitted against, or combined with gemcitabine in randomized phase III trials. No drug was shown to be superior to single-agent gemcitabine.

Combination of Gemcitabine with Other Cytotoxic Agents

Platinates

Gemcitabine plus oxaliplatin (GemOx) showed encouraging results in phase II trial and led to randomized trials comparing it to gemcitabine monotherapy. GERCOR/GISCAD intergroup study compared standard gemcitabine monotherapy versus GemOx in patients with locally advanced pancreatic cancer and advanced pancreatic cancer. GemOx showed longer progression-free survival (5.8 *vs*. 3.7 months; P=0.04) than that of gemcitabine [4]. GemOx also rendered better response rates (27% *vs*. 17%; P=0.04). There was a trend towards median survival benefit (9.0 *vs*. 7.1 months; P=0.13). Toxicities from both arms were acceptable while GemOx was more myelosuppressive and caused more peripheral neuropathies. The major criticism for this study was that it compared a 30-minute infusion with a fixed dose rate infusion in GemOx regimen.

Therefore, US intergroup trial ECOG 6201 trial compared standard 30-minute gemcitabine *versus* fixed dose rate gemcitabine *versus* GemOx. Preliminary data from this study presented at the annual

meeting of ASCO 2006 failed to show significant advantages of GemOx to gemcitabine monotherapy [5]. Other gemcitabine platinum combinations, such as gemcitabine and cisplatin also gave rise to a trend toward benefits. Heinemann *et al*. also showed 2.2 months prolongation of progression-free survival (P=0.53) by addition of cisplatin to gemcitabine [6].

Pooled analysis of two randomized trials, the GERCOR/GISCAD intergroup study and a German multicenter study was presented at the annual meeting of ASCO, 2006 [7]. For progression-free survival, the pooled univariate analysis indicated a hazard ratio (HR) of 1.34 (95% CI: 1.11-1.63, P=0.0030; median progression-free survival: 5.5 *vs*. 3.5 months) in favor of the gemcitabine-platinum combination. The benefit of the gemcitabine-platinum combination was greatest in the subgroup of patients with performance status equal to 0: progression-free survival (HR: 1.56; P=0.13) and overall survival (HR: 1.38; P =0.063) and patients with locally advanced pancreatic cancer (overall survival: 10.1 *vs*. 5.8 months).

Fluoropyrimidines

While phase III randomized trials did not show benefit of adding 5-FU (infusional or bolus) to gemcitabine [8, 9], addition of oral fluoropyrimidine, capecitabine, to gemcitabine (GemCap) showed promising results. A multinational randomized trial by Herrmann *et al*. reported no advantage of adding capecitabine, however subgroup analysis showed the benefit for GemCap in patients with good performance status (HR: 0.76; P<0.03) [10]. Another phase III randomized trial by Cunningham *et al*. that compared single agent gemcitabine with gemcitabine weekly for 3 weeks plus capecitabine 1,660 mg/m^2 daily for 21 days every 28 day cycle [11]. Addition of capecitabine doubled response rate (14% *vs*. 7%; P=0.008) and improved overall survival (HR: 0.80; P=0.026). Myelosuppression was higher in incidence with combination arm and hand-foot syndrome was only noted in combination arm. There have been three negative phase III trials of gemcitabine plus a fluoropyrimidine: "Why is this one positive?". The final results of the study are anxiously awaited to answer this question.

Addition of S-1, a novel oral fluoropyrimidine pro-drug combined with dihydropyrimidine dehydrogenase (DPD) inhibitor, to gemcitabine in patients with advanced pancreatic cancer showed promising activity in a phase II study [12]. Although no complete response was seen, a partial response was achieved in 24 patients, resulting in an overall response rate of 44% (95% CI: 30.9-58.6%). Twenty-six patients (48%) had stable disease. The median progression-free survival was 5.9 months (95% CI: 4.1-6.9 months) and the median overall survival was 10.1 months (95% CI: 8.5-10.8 months) with a 1-year survival rate of 33% with acceptable toxicity profile. A randomized phase III trial is being undertaken.

Exhausted with Cytotoxic Agents: Entering the Era of Targeted Agents

Based upon biology of pancreatic cancer, following classes of targeted agents are being investigated actively: EGFR inhibitors, vascular endothelial growth factor (VEGF) receptor inhibitors, farnesyl transferase inhibitors, matrix metalloproteinase inhibitors, and cyclooxygenase-2 (COX-2) inhibitors.

Ras-Farnesyltransferase Inhibitors and Matrix Metalloproteinase Inhibitors

Ras-farnesyltransferase inhibitors and matrix metalloproteinase inhibitors were shown to be ineffective against advanced pancreatic cancer as single agents as well as in combination in various phase III trials [13].

EGFR Inhibitors

National Cancer Institute of Canada randomized patients with locally advanced pancreatic cancer and advanced pancreatic cancer to gemcitabine/erlotinib and gemcitabine/placebo. The addition of erlotinib resulted in a statistically significant benefit in

survival (HR: 0.81; 95% CI: 0.67-0.97; P=0.025). Improvement of median survival was from 5.9 to 6.4 months, and 1-year survival rate improved from 17 to 24% [14]. This study led to the approval of erlotinib by FDA (the first biologic as well as gemcitabine combination that showed benefit after the efforts of a decade). Rash was the most common toxicity associated with erlotinib and correlated with outcome as expected.

Cetuximab, an anti-EGFR chimeric monoclonal antibody, in combination with gemcitabine showed promising activity in a phase II trial by Xiong *et al*. [15]. Forty-one patients with locally advanced pancreatic cancer and advanced pancreatic cancer were treated with this regimen and showed 12.2% response rate, median overall survival of 7.1 months, and 1-year survival rate of 31.7 %. Cetuximab was dosed with 400 mg/m^2 loading followed by 250 mg/m^2 weekly dose. Gemcitabine was given 1,000 mg/m^2 for 7 weeks on and one week off schedule. This regimen was well tolerated with the most common side effects being neutropenia (39%) and asthenia (22%).

In an effort to confirm this result, Phase III randomized trial was conducted by the Southwest Oncology Group [16]. Eligibility included locally advanced pancreatic cancer and advanced pancreatic cancer, adequacy of organ function, performance status 0-2, no prior EGFR therapy, no prior systemic chemotherapy except for adjuvant chemotherapy and submission of tumor for EGFR immunostaining. The primary endpoint was overall survival. Secondary endpoints included objective response, time to progression, pain control, and quality of life. Assuming 6-month median survival, the study was designed to detect a median improvement to 8 months (HR: 1.33) with 90% power, based on a one-sided 0.0125 test, and 704 eligible patients. Primary analyses used a Cox regression model, stratified for factors used in the randomization. Gemcitabine was given at a dose of 1,000 mg/m^2/week for seven weeks out of 8, then 3 weeks on and one week off. Cetuximab was given as a loading dose of 400 mg/m^2 on week 1 and then 250 mg/m^2 weekly. Seven-hundred and thirty five patients were enrolled between January 2004 and April 2006. Of those, 51% were males, 21.5% had locally advanced pancreatic cancer, and 13% had performance status of 2. The median survival was 6 months in the gemcitabine arm and 6.5 months in the gemcitabine plus cetuximab arm for an overall HR of 1.09 (95% CI: 0.93-1.27; P=0.14). The corresponding progression-free survival was 3.0 and 3.5 months, for gemcitabine and gemcitabine-cetuximab arms, respectively (HR: 1.13; 95% CI: 0.97-1.30, P=0.058). The unconfirmed responses yielded 14% in the gemcitabine arm and 12% in the gemcitabine-cetuximab arm.

Kullmann F *et al*. recently presented an abstract, at 2007 Gastrointestinal Cancers Symposium, of phase II trial testing first line GemOx plus cetuximab (GemOxCet) in metastatic pancreatic cancer patients [17]. Addition of cetuximab to GemOx was well tolerated and exhibited high response rate (38%). Myelosuppresion and rashes were commonly noted toxicities with this regimen.

GISCAD performed a multicenter, randomized two-arm phase II trial: gemcitabine 1,000 mg/m^2 day 1 and day 8 and cisplatin 35 mg/m^2 day 1 and day 8 every 21 days alone or in combination with cetuximab 250 mg/m^2 weekly after a loading dose of 400 mg/m^2. Cetuximab did not seem to enhance the activity of gemcitabine/cisplatin combination in terms of activity especially concerning time to progression (5 *vs*. 5 months) [18]. Although toxicity was not increased by cetuximab, this combination should not be assessed in a phase III trial.

VEGF Inhibitors

Based on the encouraging results of a phase II study, gemcitabine plus bevacizumab, recombinant humanized monoclonal antibody to VEGF, was tested in a phase III randomized trials by CALGB [19]. A total of 602 patients with advanced pancreatic cancer were randomized to gemcitabine (1,000 mg/m^2 days 1, 8, and 15) plus bevacizumab (10 mg/kg days 1 and 15) and gemcitabine

plus placebo (dosing schedule identical to the bevacizumab arm). Eligible patients had no prior therapy for advanced disease, performance status 0-2, no tumor invasion of adjacent organs, no increased bleeding risk. The primary endpoint was overall survival. The study was designed to have 90% power to detect a difference in median overall survival of 6.0 *vs*. 8.1 months. Six-hundred and two patients were enrolled between June 30th, 2004 to April 14th, 2006. Based on a protocol-specified interim analysis with 64% of information on overall survival, the CALGB Data Safety Monitoring Board released study data in June 2006 because a futility boundary was crossed. Patients on treatment were notified and unblinded. The demographic characteristics (gemcitabine plus bevacizumab: 302 patients; *vs*. gemcitabine plus placebo: 300 patients) were: males: 58 *vs*. 51%; median age: 63.8 *vs*. 65.0 years; performance status equal to 2: 9 *vs*. 9%; stage IV: 85 *vs*. 84%; prior external radiation therapy 11 *vs*. 11%. As of December 12th, 2006, 436 patients (224 *vs*. 212) have died (93% of total expected deaths at planned final analysis). Median overall survival was 5.7 *vs*. 6.0 months (95% CI: 4.9-6.5 *vs*. 5.0-6.9 months) and progression-free survival of 4.8 *vs*. 4.3 months, respectively (95% CI: 4.3-5.7 *vs*. 3.8-5.6 months). Objective response rates were as follow. Complete response rate: 1.9 *vs*. 3.0%; partial response rate: 11.2 *vs*. 8.3%; stable disease: 40.7 *vs*. 35.7%. Frequency of grade 3-4 toxicity in the gemcitabine plus bevacizumab group *vs*. gemcitabine plus placebo group were: neutropenia 33 *vs*. 30%; thrombocytopenia 12 *vs*. 12%; anemia 5 *vs*. 8%; hypertension 8 *vs*. 2%; proteinuria 4 *vs*. 1%; cerebrovascular accident: 2 *vs*. 2%; venous thrombosis: 9 *vs*. 9%; perforation: 0.4 *vs*. 0%; gastrointestinal bleed: 3 *vs*. 2%. Conclusion of this study was that addition of bevacizumab to gemcitabine did not improve survival in advanced pancreatic cancer.

Of note, more patients with ECOG performance status of 0 were enrolled in the phase II study than in the phase III study; all patients had advanced pancreatic cancer in the phase III study *versus* advanced pancreatic cancer and locally advanced pancreatic cancer in the phase II study; 23% had prior radiotherapy among phase II patients *versus* 11% in the phase III study.

GemOx plus bevacizumab combination, in phase II trial including 82 patients with advanced pancreatic cancer , showed 6-month survival of 65.0% (95% CI: 53.5-75.3%), median survival of 8.1 months (95% CI: 6.5-9.3 months) and median time to progression of 5.7 months (95% CI: 4.4-6.4 months) [20].

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 a small phase II trial with patients with advanced pancreatic cancer [21]. Sorafenib was dosed at 400 mg twice daily for 28 days along with gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 with a 28-day cycle. In this small study of 17 patients, the combination regimen was well tolerated but was inactive. There were no objective responses; 3 patients (23%) had stable disease and one of these patients with stable disease remains on treatment after 12 cycles. Median overall survival was 4.0 months (95% CI: 3.4-5.9 months).

Can We Use a Non-Gemcitabine Chemotherapy Regimens in Advanced Pancreatic Cancer ?

After the approval of gemcitabine (compared against bolus 5-FU), many cytotoxic and targeted agents were compared against gemcitabine in randomized phase III trials. No such single agent was shown to be superior to single-agent gemcitabine [22, 23, 24, 25] (Table 1).

In addition to our efforts, there needs to be a change in regulatory environment. Gemcitabine *vs*. drugs “X” plus “Y” wins no FDA approval and may never be able to happen. It is time to investigate gemcitabine-free regimens. Two such studies tested in the first-line treatment for advanced pancreatic

Table 1. Single-agents that have not improved survival when compared to gemcitabine in phase III randomized trials.

Drug	Median survival		P value
	Single-agent	Gemcitabine	
Exatecan [22]	4.95 months	6.46 months	0.993
SCH 66336 [23]	3.3 months	4.4 months	-
Marimastat [24]	3.5-4.1 months	5.6 months	-
BAY 12-9566 [25]	3.2 months	6.4 months	0.0001

cancer were presented at ASCO: irinotecan/docetaxel (ECOG) or FOLFIRINOX (5-FU/leucovorin, irinotecan and oxaliplatin) [26, 27]. FOLFIRINOX induces a response rate greater than 30% with manageable toxicity in ECOG 0-1 patients with advanced pancreatic cancer. ECOG study of weekly irinotecan/docetaxel plus/minus cetuximab also showed median survival of 6.5 months for irinotecan/docetaxel and 7.4 months for irinotecan/docetaxel plus cetuximab. These two studies indicate that non-gemcitabine containing therapy is active in advanced pancreatic cancer.

Is This Bleak Landscape Finally Changing?

Pancreatic cancer persists as a major therapeutic challenge largely characterized by chemotherapy-refractory disease and poor responses to currently available treatments. Thus far EGFR targeted therapies have demonstrated promising results with favorable toxicity profiles. Nonetheless, even dual therapy with gemcitabine and erlotinib, which was the first combination therapy in pancreatic cancer to ever demonstrate statistically significant benefits in overall survival, did so with modest results. Randomized studies of other targeted agents (bevacizumab and cetuximab) have been disappointing. Concomitant administration of the monoclonal antibodies and tyrosine kinase inhibitors together and with combination chemotherapeutic agents may both augment their therapeutic activity as well as offset mechanisms of resistance.

Although we have made incremental progress in the treatment of pancreatic cancer, the prognosis of patients with this disease remains extremely poor. This bleak landscape finally changed “but with modest success” after two large randomized phase III studies in advanced pancreatic cancer have demonstrated the superiority of a gemcitabine-containing combination over single-agent gemcitabine: capecitabine plus gemcitabine (GemCap) and erlotinib plus gemcitabine. Gemcitabine plus/minus erlotinib or capecitabine are considered the standard of care for advanced pancreatic cancer patients in North America. In pilot studies of modern combination chemotherapy responses may exceed single agent gemcitabine, but with added toxicities.

Table 2. What actions need to be taken to change?

Study design
- Locally advanced pancreatic cancer and advanced pancreatic cancer patients need to be studied separately

Appropriate trial size
- Study of gemcitabine plus cisplatin may have been underpowered?
- Study of gemcitabine plus erlotinib may have been overpowered?

Advocacy input needs to be sought early
- How much benefit is enough to a patient?
- How much toxicity is too much for a patient?

Regulatory environment
- Gemcitabine *vs*. drugs “X” plus “Y” wins no FDA approval and may never be able to happen
- Focus on 2nd line replace treatment as most 1st line negative in the last decade

What Actions Need to Be Taken to Change? (Table 2)

We need to improve our knowledge on pancreatic cancer cells, relationships between tumoral, endothelial and stromal cells, and pancreatic cancer patients. We should develop separate strategies and studies in advanced pancreatic cancer and in locally advanced pancreatic cancer patients [28]. Role of prophylactic anticoagulation needs to be further investigated. It is also time to investigate gemcitabine-free regimens. Perhaps more importantly will be to truly target our therapy with the EGFR agents as well as other biologic agents by identifying those patients who are most likely to derive benefit and achieve meaningful responses. This is particularly crucial in a disease such as pancreatic cancer that has such a short life expectancy that the "window" for any given treatment may be quite small. Already we have seen changes in treatment paradigms for EGFR therapy with increasing evidence that EGFR over-expression in colorectal cancer is not essential for response and there is conflicting data in lung cancer with regard to the significance of tyrosine kinase mutations. Consequently, further study should include the development of more predictive assays and improved exploitation of surrogate biomarkers of response such as the development of skin rash or re-analysis of downstream markers of EGFR inhibition early in the course of treatment. We also need to need to study genomics and proteomics for individualized strategies. We definitely need to identify surrogates for survival. In addition the oncologists need to change their attitudes towards clinical trials (Figure 1). Development of novel agents and approaches are urgently needed in conjunction with improvement in access to clinical trials for patients.

Keywords bevacizumab; capecitabine; cetuximab; Cisplatin; Drug Therapy; Epidermal Growth Factor; erlotinib; Fluorouracil; gemcitabine; gemcitabine-oxaliplatin regimen; oxaliplatin; Pancreatic Neoplasms; Receptor, Epidermal Growth Factor; sorafenib; Vascular Endothelial Growth Factor A

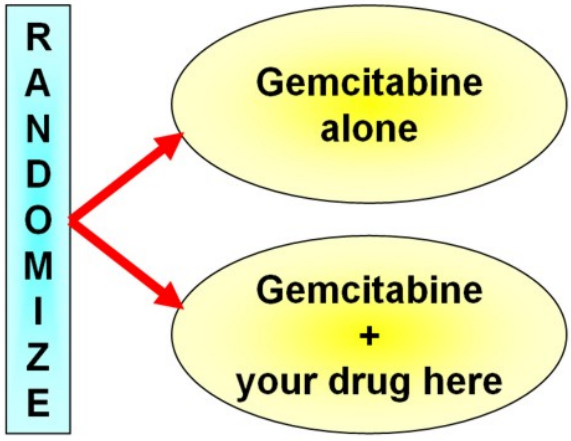

Figure 1. Can oncologists change?

Abbreviations ASCO: American Society of Clinical Oncology; CALGB: Cancer and Leukemia Group B; COX-2: cyclooxygenase-2; DPD: dihydropyrimidine dehydrogenase; ECOG: Eastern Cooperative Oncology Group; FOLFIRINOX: 5-FU/leucovorin, irinotecan and oxaliplatin; GemCap: gemcitabine plus capecitabine, GemOx: gemcitabine plus oxaliplatin; GemOxCet: gemcitabine plus oxaliplatin plus cetuximab; GERCOR: Groupe d'Etude et de Recherche en Cancreologie Onco-Radiotherapic; GISCAD: Italian Group for the Study of Gastrointestinal Tract Carcinomas; PDGFR: platelet-derived growth factor receptor

Conflict of interest The author has no potential conflicts of interest

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Document URL: http://www.joplink.net/prev/200707/15.html

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