

HIGHLIGHT ARTICLE

First-Line Treatment of Metastatic Pancreatic Cancer

Highlights from the "2012 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA.
January 19-21, 2012

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Summary

Metastatic pancreatic cancer is an aggressive malignancy that is difficult to treat. Gemcitabine monotherapy has been used first line and many contemporary treatment approaches have focused on gemcitabine plus experimental agents. The 2012 ASCO Gastrointestinal Cancers Symposium Abstract #213 is a study of gemcitabine with IPI-926, a novel hedgehog pathway inhibitor. Abstract #227 is a study of gemcitabine with ⁹⁰Y-hPAM4 radioimmunotherapy with yttrium labeled anti-mucin humanized antibody. Abstract #296 is a study of gemcitabine with temsirolimus, an mTOR inhibitor. Gemcitabine and erlotinib has shown slight advantages to gemcitabine alone. Abstract #253 takes this one step further and evaluates gemcitabine and erlotinib with apicoxib, a COX-2 inhibitor. FOLFIRINOX has shown superiority to gemcitabine; however, doing so at the cost of significantly greater toxicity. Abstract #199, is a study which examines the cost effectiveness of first line FOLFIRINOX approaches. Another cost effective study is portrayed in Abstract #372, a study evaluating the survival of unresectable pancreatic cancer patients treated with gemcitabine and the disease course is followed clinically without radiographic follow-up.

Introduction

Forty-four thousands people in the United States each year develop pancreatic cancer [1], which ranks fourth as the leading cause of cancer death in both sexes [1]. Incidence rate is 8.8 per 100.000 in the general population; however, the disease is rarely seen in patient younger than 45 [2]. Surgery is the only cure, but unfortunately this is an option in about a fifth of patients only. Two-fifths present with locally advanced unresectable disease, and another two-fifths present with metastatic disease.

Palliative chemotherapy with 5-fluorouracil has been a historical benchmark and studies reveal results of a radiographic objective response rate of 0-9% and in a median survival of 2.5 to 6 months [3, 4, 5]. In 1997, gemcitabine was compared to 5-fluorouracil in 126 patients [6]. There were no significant differences in objective response rate; however, gemcitabine group

did result in a superior clinical benefit response (23.8% vs. 4.8%), which was as a quality of life measurement that factored pain, weight, and Karnofsky performance status. The gemcitabine group also had a slight improvement in median overall survival (5.65 vs. 4.41 months) and 1-year survival rates (18% vs. 2%). This led to the acceptance of gemcitabine as a first line treatment.

Pancreatic cancers often express epidermal growth factor receptors (EGFR); the addition of molecular targeted therapy to gemcitabine has been investigated as well [7]. In 2007, gemcitabine was compared to gemcitabine plus erlotinib, an EGFR inhibitor [8]. There were no significant differences in objective response rate; however, the gemcitabine plus erlotinib group did have improvements in median overall survival (6.24 vs. 5.91 months), and 1-year survival rates (23% vs. 17%). These improvements came with increased toxicities in the gemcitabine plus erlotinib group. This study led to the U.S. approval of gemcitabine plus erlotinib as an option metastatic pancreatic cancer; however, the statistically significant and subtle improvement in median overall survival of 0.33 months (about 10 days) comes with the substantial monetary expense of erlotinib. In 2010, gemcitabine was compared to gemcitabine plus cetuximab, a monoclonal antibody to EGFR [9]. There were no statistically significant differences in median overall survival, progression free survival, or objective response rate.

Key words 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-1H-pyrrole; gemcitabine; IPI-926; MUC-1 monoclonal antibody; Pancreatic Neoplasms; Radioimmunotherapy; temsirolimus

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

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In 2011, FOLFIRINOX, a combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin, was compared to gemcitabine in metastatic pancreatic disease [10]. The FOLFIRINOX group had improvements in objective response rate (32% vs. 9%), median progression free survival (6.4 vs. 3.3 months), and overall survival (11.1 vs. 6.8 months). Unfortunately, superiority of FOLFIRINOX was at the cost of greater toxicities, but with this trade-off in mind, FOLFIRINOX has been accepted as the preferred first line treatment in patients with a good performance status.

Updates from the 2012 ASCO Gastrointestinal Cancers Symposium

Gemcitabine Chemotherapy Until Symptomatic Disease Progression in Advanced Pancreatic Cancer: A Retrospective Analysis (Abstract #372 [11])

A single center retrospective analysis of 50 patients with unresectable pancreatic cancer (21 locally advanced and 29 metastatic) treated first-line with gemcitabine from January 2008 to December 2009. Disease response and progression were followed clinically and not radiographically. Their results found an overall median survival of 10.4 months; more specifically the median survival in locally advanced disease was 11.3 months and in metastatic disease was 7.2 months.

Cost-Effectiveness of FOLFIRINOX for First-Line Treatment of Metastatic Pancreatic Cancer (Abstract #199 [12])

A cost effective analysis of first line FOLFIRINOX treatment compared to first line gemcitabine treatment of metastatic pancreatic cancer was conducted in Canada. Costs included first and second line treatments, monitoring, adverse events and end of life costs. Using a Markov model of disease state and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) 11 trial results of overall survival and progression free survival, the study examined the cost effectiveness of two different treatment approaches.

One approach was first line FOLFIRINOX followed by second line gemcitabine compared to first line gemcitabine followed by second line platinum based regimen. Granulocyte colony stimulating factor (G-CSF) was allowed. Another approach was first line FOLFIRINOX followed by second line gemcitabine compared to first line gemcitabine followed by best supportive care. Granulocyte colony stimulating factor was not allowed.

Both approaches found that using FOLFIRINOX first line had more overall life years and quality adjusted life years when compared to first line gemcitabine.

A phase Ib trial of IPI-926, a Hedgehog Pathway Inhibitor, Plus Gemcitabine in Patients with Metastatic Pancreatic Cancer (Abstract #213 [13])

A phase Ib study of the addition of oral daily IPI-926 (a novel hedgehog pathway inhibitor) to intravenous

weekly 1 g/m² gemcitabine (3 weeks on, 1 week off) in 16 patients with untreated metastatic pancreatic cancer with Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1. Results found radiographic partial response rate in 5 patients (1 of 3 patients in the 110 mg dose cohort, 2 of 6 patients in the 130 mg cohort, and 2 of 7 patients in the 160 mg cohort). Median progression free survival was greater than 7 months, and 74% were alive at 6 months. No serious IPI-926 toxicities were reported and the most common toxicities were fatigue (total 75%; grade 3, or greater, 6%), thrombocytopenia (total 63%; grade 3, or greater, 25%), and anemia (total 56%; grade 3, or greater, 13%).

Activity of Fractionated Radioimmunotherapy (RAIT) with ⁹⁰Y Clivatuzumab Tetraxetan (⁹⁰Y-hPAM4) Plus Gemcitabine (Gem) in Advanced Pancreatic Cancer (APC): Final Results from a Two-Part Study (Abstract #227 [14])

A phase I and II study of weekly (weeks 2-4 per 28 day cycle) intravenous ⁹⁰yttrium-labeled anti-mucin humanized antibody (⁹⁰Y-hPAM4) plus weekly intravenous gemcitabine in 90 patients with untreated advanced pancreatic cancer, stage 3 and 4. In phase I, 38 patients were separated into 4 dose cohorts of ⁹⁰Y-hPAM4, all with low dose 200 mg/m² gemcitabine. Cycles were repeated 1 to 3 times in 13 patients. Grade 3 or 4 thrombocytopenia or neutropenia was reported in 20 of 38 patients after cycle 1 and in all patients in repeated cycles. There were 3 febrile neutropenia cases and 4 intravenous antibiotic requiring infections. No major bleeding was reported. CT Response Evaluation Criteria in Solid Tumors (RECIST) criteria found 6 patients (16%) with a partial response and 16 patients (58%) with stabilization. After the first cycle, 13 of 25 (52%) PET avid disease patients became negative or had a 25% SUV reduction. Also after the first cycle, 9 of 27 (33%) patient with elevated CA 19-9 had a 50% reduction. Median overall survival was 7.7 months, and for retreated patients 11.8 months. In phase II, 52 patients were separated into 3 dose cohorts of gemcitabine (n=17 in 200 mg/m²; n=8 in 600 mg/m²; and n=27 in 1 g/m²), all with the same dose of ⁹⁰Y-hPAM4. Preliminary results indicated no advantage to cohorts with increased gemcitabine doses.

Apricot-P: A Randomized Placebo Controlled Phase II Study of COX-2 Inhibitor Apricoxib or Placebo in Combination with Gemcitabine and Erlotinib in Advanced or Metastatic Adenocarcinoma of the Pancreas (Abstract #253 [15])

A phase II study of the addition of oral daily apricoxib (a COX-2 inhibitor) to oral daily erlotinib and weekly (3 weeks treatment, 1 week off) intravenous 1 g/m² gemcitabine in 109 patients (n=70 in treatment group; n=39 in the control group) with locally advanced or metastatic pancreatic cancer. Results reported the primary end point of objective progression free survival was not met. Most common toxicities were

rash (69%), diarrhea (59%), nausea (59%), and fatigue (57%). Severe toxicities including gastrointestinal bleeding, myocardial infarction, and cerebrovascular accident were more common in the apricoxib group.

A phase I Study of Temozolomide in Combination with Gemcitabine in Previously Untreated Metastatic Pancreatic Cancer (Abstract #296 [16])

A phase I study of the addition weekly temsirolimus (an mTOR inhibitor) to every other week intravenous 800 mg/m² gemcitabine in 8 patients with untreated metastatic pancreatic cancer with a performance status of 1. The study found significant toxicities including 2 grade 4 neutropenia, and multiple grade 3 cytopenias. Five of the 8 patients were withdrawn due to significant adverse reactions and no patients were enrolled after this first cohort. Median time on the study was 22 days; however, one patient demonstrated stable disease and received 6 cycles until he developed grade 3 neutropenia requiring dose delay and subsequent 20% dose reduction of both temsirolimus and gemcitabine. No partial or complete responses were reported.

Discussion

The 2012 ASCO Gastrointestinal Cancers Symposium Abstract #199 [12] has shown that much like the therapeutic benefits, the cost effectiveness of first line FOLFIRINOX is also superior to gemcitabine. In addition, Abstract #372 [11] suggests that clinical decision making alone without radiographic follow-up can be used to guide advanced pancreatic cancer patients through gemcitabine monotherapy with survival results similar to historic controls.

Abstracts #213 [13], #227 [14], #296 [16] are all phase I studies with the intention of improving over gemcitabine monotherapy. Abstract #213 [13] assessed a novel hedgehog pathway inhibitor, IPI-926, and results reveal its activity and toxicity profile, prompting future phase II studies to follow. Abstract #296 [16] evaluated temsirolimus, an mTOR pathway inhibitor, and the study was curtailed after its toxicity was too great. Abstract #227 [14] was a phase I and II study, which evaluated radioimmunotherapy with ⁹⁰Y-hPAM4. Its results suggested anti-tumor activity with the addition of ⁹⁰Y-hPAM4, even at lower doses of gemcitabine (200 mg/m² and 600 mg/m²). Future studies could examine the efficacy of radioimmunotherapy with gemcitabine to gemcitabine monotherapy.

Abstract #253 [15] was a phase I study that focused on improving the subtle benefit that erlotinib adds to gemcitabine monotherapy by the addition of a COX-2 selective inhibitor, apricoxib. Results failed to meet the primary end point of progression free survival. It was mentioned that data suggested a trend towards improvement of overall survival, but future investigations need to also consider the increased incidence of gastrointestinal bleed, myocardial

infarction, and cerebrovascular accident in the apricoxib arm.

Conflict of interest The authors have no conflicts of interest

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