

HIGHLIGHT ARTICLE

Second Line Therapy for Advanced Pancreatic Adenocarcinoma: Where Are We and Where Are We Going?

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Summary

Most patients with adenocarcinoma of the pancreas present with locally advanced or metastatic disease. Although single agent gemcitabine is widely accepted as first-line therapy, there is no current standard of care for gemcitabine-refractory patients. Common second-line chemotherapy regimens included oxaliplatin and 5-FU/leucovorin (OFF), gemcitabine and oxaliplatin (GEMOX), oxaliplatin and capecitabine (XELOX), and irinotecan-oxaliplatin. At the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting, several new second-line chemotherapy regimens were presented, including gemcitabine and oxaliplatin with imatinib, single agent nab-paclitaxel, and the combination of high-dose capecitabine with oxaliplatin and sorafenib. These abstracts provide exciting new directions for the treatment of gemcitabine-refractory advanced pancreatic cancer.

Introduction

In 2009, 42,470 patients were diagnosed with pancreatic cancer in the United States, and pancreatic cancer remains the fourth leading cause of cancer related death among both men and women [1]. Although surgical resection remains the only potentially curative treatment for adenocarcinoma of the pancreas, only 15-20% of patients present with early-stage disease amenable to surgical resection. For patients with locally advanced or metastatic disease, first-line treatment with single agent gemcitabine has been shown to have a clinical benefit and a modest survival advantage over treatment with bolus 5-fluorouracil (5-FU) [2]. Very few patients who experience progression of disease with first-line gemcitabine chemotherapy have an adequate performance status to warrant the use of second line chemotherapy. As a result, there are very few randomized trials for gemcitabine-refractory patients, and there is no widely accepted standard of care.

What We Knew Prior to ASCO 2010

The use of second-line chemotherapy versus best supportive care was established with the preliminary

report of the CONKO-003 trial, in which patients were assigned to best supportive care with or without OFF chemotherapy (oxaliplatin, 5-FU, leucovorin) [3]. Patients receiving chemotherapy were found to have a longer median overall survival. The addition of oxaliplatin to infusional 5-FU and leucovorin has also been shown to result in an improved overall survival of 26 weeks vs. 13 weeks when compared with 5-FU and leucovorin alone [4]. The combination of gemcitabine and oxaliplatin has demonstrated efficacy as a second-line therapy in gemcitabine-refractory patients [5, 6]. A clinical benefit has also been seen with the use of irinotecan and oxaliplatin in patients previously treated with gemcitabine [7, 8]. XELOX, the combination of capecitabine and oxaliplatin, has also been used as second line therapy after gemcitabine failure [9]. Single agent paclitaxel has also shown to be an effective second-line chemotherapy agent with a low toxicity profile [10].

What We Learned at ASCO 2010

Three important abstracts were presented focusing on the use of gemcitabine and oxaliplatin plus imatinib, single agent nab-paclitaxel, and high dose capecitabine, oxaliplatin and sorafenib (Table 1).

Oxaliplatin-Based Regimens

Starling *et al.* presented a dose escalation study of gemcitabine plus oxaliplatin in combination with imatinib in patients with gemcitabine-refractory advanced pancreatic adenocarcinoma [11]. As discussed above, the combination of gemcitabine and oxaliplatin has activity in the first and second line treatment of advanced pancreatic adenocarcinoma. As

Key words 130-nm albumin-bound paclitaxel; capecitabine; gemcitabine-oxaliplatin regimen; Pancreatic Neoplasms

Abbreviations ASCO: American Society of Clinical Oncology; SPARC: secreted protein, acidic and rich in cysteine

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Table 1. Summary of 2010 ASCO Annual Meeting abstracts for second-line advanced pancreatic adenocarcinoma.

Abstract	Study design	Drugs	Overall survival (median)	Progression free survival (median)
#4155 Starling, <i>et al.</i> [11]	Dose escalation	Gemcitabine and oxaliplatin plus imatinib	5.7 months	4.6 months
#4120 Hosein, <i>et al.</i> [15]	Phase II	Nab-paclitaxel (abraxane)	7.3 months	1.6 months
#4143 Lubner, <i>et al.</i> [12]	Phase II	High-dose capecitabine, oxaliplatin, and sorafenib	Not reported	5.98 months

many pancreatic adenocarcinomas overexpress platelet-derived growth factor receptors (PDGFRs), the combination of imatinib with gemcitabine and oxaliplatin was thought to possibly enhance anti-tumor activity or chemotherapy delivery. Twenty-six patients with gemcitabine refractory locally advanced or metastatic pancreatic cancer were enrolled in the study. Doses of gemcitabine at 1,000 mg/m² (day 1) and oxaliplatin 85 mg/m² (day 2) with intermittently administered imatinib (400 mg) for 7 days were safely tolerated. The median number of cycles given was 4. Two patients showed a partial response, and eleven patients demonstrated stable disease. The median progression free survival and overall survival were 4.6 months (95% CI: 2.3-6.9 months) and 5.7 months (95% CI: 4.6 to 6.7 months), respectively.

Lubner *et al.* presented the results of the phase II portion of an open label phase Ib/II trial involving high dose capecitabine with oxaliplatin, and sorafenib [12]. As described above, the combination of capecitabine and oxaliplatin (XELOX) has demonstrated activity in second line therapy of patients with advanced pancreatic adenocarcinoma. In this study, 24 patients received sorafenib 200 mg *bid* with oxaliplatin 85 mg/m² i.v. on days 1 and 15, followed by high-dose capecitabine (2,250 mg/m² *po* every eight hours for six doses) also on days 1 and 15, every 28 days. Only one patient experienced grade 3 hand-foot syndrome. Two patients demonstrated a partial response, and thirteen patients demonstrated stable disease. Progression free survival was 5.98 months, and the median overall survival endpoint has not yet been reached, although the 6-month overall survival was 62%. Although further study is needed, this combination may prove efficacious in patients who cannot tolerate other forms of chemotherapy.

Novel Taxane Regimens

Secreted protein, acidic and rich in cysteine (SPARC) is a protein frequently expressed by stromal fibroblasts adjacent to pancreatic adenocarcinomas [13]. Previous research has demonstrated that a series of patients whose pancreatic cancer stromal fibroblasts expressed SPARC had a worse prognosis than patients whose tumor stroma did not express SPARC [13]. Nab-paclitaxel, a nanoparticle albumin-bound form of paclitaxel, is thought to increase tumor accumulation of paclitaxel through binding of albumin to SPARC [14]. A phase I/II study presented at the 2009 American Society of Clinical Oncology (ASCO) Annual Meeting demonstrated the safety and efficacy of the combination gemcitabine and nab-paclitaxel; SPARC positive status by immunohistochemistry was

associated with a higher response rate and longer progression free survival [14].

At 2010 ASCO Annual Meeting, Hosein *et al.* presented a phase II study evaluating the effectiveness of nab-paclitaxel monotherapy in patients with advanced pancreatic cancer who progressed on previous gemcitabine-based therapy [15]. Nineteen patients received nab-paclitaxel 100 mg/m² weekly for three weeks every 28 days. One patient demonstrated a partial response and six demonstrated stable disease. The median progression free survival and overall survival were 1.6 months (95% CI: 1.5-3.4 months) and 7.3 months (95% CI: 2.8-13.3 months), respectively. Five patients were alive at a median follow-up of 12.7 months. Immunohistochemical analysis of tissue samples is ongoing to determine the predictive value of SPARC expression in these patients.

Commentary

For patients with locally advanced or metastatic pancreatic adenocarcinoma refractory to gemcitabine monotherapy, options remain limited. For patients with adequate performance status, the CONKO-003 trial helped to establish the superiority of second line chemotherapy versus best supportive care [3]. The CONKO-003 trial also demonstrated an overall survival benefit with the addition of oxaliplatin to infusional 5-FU and leucovorin (OFF regimen) [4]. At the 2010 ASCO Annual Meeting, the combination of high-dose capecitabine with oxaliplatin and sorafenib was shown to be beneficial in selected patients [12]. Previous studies have also demonstrated the effectiveness of gemcitabine and oxaliplatin therapy in patients with gemcitabine refractory advanced pancreatic adenocarcinoma [5, 6]. At the 2010 ASCO Annual Meeting, a dose escalation study was presented involving the combination of gemcitabine and oxaliplatin with imatinib [11]. Small series have demonstrated a worse prognosis in patients whose pancreatic cancer stromal fibroblasts expressed SPARC [13]. These patients may respond to nab-paclitaxel, a nanoparticle albumin-bound form of paclitaxel which is thought to increase tumor accumulation of paclitaxel through binding of albumin to SPARC [14]. The efficacy of single-agent nab-paclitaxel was demonstrated at the ASCO 2010 Annual Meeting [15]. Although further phase III studies and longer follow-up data are needed, these abstracts build upon previous research and provide exciting new directions for the treatment of gemcitabine-refractory advanced pancreatic cancer.

Conflict of interest The authors have no potential conflicts of interest

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