Clinical Studies

Docetaxel Second-line Therapy in Patients with Advanced Pancreatic Cancer: A Retrospective Study

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Abstract. *Background: No therapeutic standard of care exists for patients who have progressed following first-line treatment with a gemcitabine-based regimen with advanced pancreatic cancer. Approximately half of the patients failing upfront treatment present with ECOG PS 1-2 and are willing to undergo further treatment. Docetaxel activity against pancreatic cancer is reported both in the preclinical and clinical setting. This study retrospectively evaluated the role of docetaxel as second-line therapy in patients with gemcitabine-refractory disease. Patients and Methods: Between January 2006 and November 2009, 17 patients (median age of 61 years) with advanced pancreatic adenocarcinoma, after receiving gemcitabine-containing chemotherapy as first-line median ECOG performance status 1 and with adequate organ function, were treated with either weekly docetaxel at 25 mg/m^2 or 3-weekly docetaxel regimen (docetaxel at 75 mg/m^2 or docetaxel-gemcitabine-capecitabine or docetaxel-gemcitabine) until progressive disease. Serum CA19-9 levels were measured every 3/4 weeks and CT scans performed after every eight/nine weeks. Results: Docetaxel dose intensity was 90% in the patients who received weekly docetaxel, 85% in docetaxel-erlotinib regimen and 65% in 3-weekly regimen (docetaxel-gemcitabine-capecitabine, docetaxel-gemcitabine). Only one objective response (6%) to treatment was obtained (docetaxel-gemcitabine), while 5 patients achieved stable disease (weekly docetaxel). Median progression-free survival was 8 weeks (range: 3-16 weeks) and median survival was 4.0 months (range: 2.0-6.5 months). No toxicity with grade >3 associated with docetaxel was observed. Conclusion: Docetaxel seems to have mild activity in the treatment of gemcitabine-resistant metastatic pancreatic cancer. Although some patients may benefit from the treatment, other dosing regimens and novel taxanes such as Nab-paclitaxel should be explored in this setting.*

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Pancreatic cancer affects more than 39,000 individuals in the United States each year and, stage for stage, is associated with the highest mortality of any solid cancer (1). The majority of patients are diagnosed at an advanced stage of disease, at which point systemic therapy becomes the mainstay of treatment. Since 1997, gemcitabine, remains the primary cytotoxic agent used in advanced pancreatic cancer, based on modest improvements in median survival compared to 5-FU (5.65 *vs*. 4.41 months, p=0.0025), one-year survival rate (18% *vs*. 2%) and clinical benefit response (2). Two recent randomized phase III trials have demonstrated small but statistically significant survival advantages with the addition of a second agent to gemcitabine, including the epidermal growth factor receptor inhibitor erlotinib (4) and the oral fluoropyrimdine prodrug capecitabine (4). Unfortunately, secondary to the poor functional status and rapid clinical deterioration of these patients, only 50% of patients who progress following first-line gemcitabine-based chemotherapy are eligible for further treatment (5). There are relatively few and small studies evaluating the effectiveness of second-line or salvage treatment in this setting (Table I) and no established standard of care exists at present (6).

After failing gemcitabine-containing regimen, over half of patients present with good performance status are willing to undergo further treatment. The choice of docetaxel, a semi-synthetic taxane, was based on activity against pancreatic cancer reported both in the preclinical (7) and clinical (8-11) setting (Table I). In addition, a phase II and phase III randomized trials conducted in breast and non-small lung cancers respectively, demonstrated that weekly docetaxel is an active regimen with comparable efficacy to 3-weekly docetaxel and a more favorable toxicity profile (12-15).

Therefore, the present study analysed retrospective data on patients with gemcitabine-refractory pancreatic cancer who were treated with docetaxel-based regimens as second-line treatment in order to evaluate the efficacy and toxicity of the treatment.

Table I. *Summary of clinical trials of taxanes in pancreatic cancer (references: 8-11).*

	Gemcitabine + Docetaxel (8) (n=18)	Docetaxel (9) (n=20)	Docetaxel GCSF (10) (n=33)	Docetaxel (11) (n=21)
ORR	5%	5%	6%	0%
OS (months)	5.4	5.9	8.4	3.9 (3.5-5.3)
TTP (months)	3	-	4.7	1.2

ORR: overall response rate; OS: overall survival; TTP: time to tumor progression; CI: confidence interval; PFS: progression free survival; GCSF: granulocyte stimulating factor.

Table II. *Patient characteristics at baseline.*

Patients enrolled	17
Age (years)	
Median	65
Range	59-73
Gender	
Male	6
Female	11
ECOG performance status	
1	6
2	11
Sites of metastases	
Liver	8
Lung	4
Peritoneum	5
Brain	1
Prior therapy	
Prior pancreatic surgery	3
Prior radiotherapy	2

Patients and Methods

Safety and toxicity data on patients at our institution with cytologically or histologically proven metastatic pancreatic adenocarcinoma were retrospectively reviewed. Based on institutional standards, all these patient had adequate bone marrow (absolute neutrophil count >1500 cells/mm^3; platelet count >1000,000 cells/mm^3 and hemoglobin >9 g/dl); kidney (serum creatine <1.5 mg/dl) and liver function (serum total bilirubin <1.5 mg/dl and serum transaminases <2.5 times the upper limit of laboratory normal) before receiving docetaxel-containing regimen. All patients had documented progressive disease after gemcitabine-based chemotherapy. Patients received either weekly docetaxel at 25 mg/m^2 or 3-weekly docetaxel regimen (docetaxel at 75 mg/m^2 or docetaxel-gemcitabine-capecitabine (GTX) or docetaxel-gemcitabine (GT)) as second-line treatment and continued until progressive disease. Docetaxel (Taxotere™) at 25 mg/m^2 was dissolved in 500 ml of 5% dextrose and administered over 1 hour by intravenous infusion once a week. GTX was given to two patients with the following dose: . One patient received GT due to prior history of severe toxicity to capecitabine (Xeloda™) when administered with radiation therapy (hand-foot syndrome; HFS, diarrhea, mucositis leading to hospitalization); the GT regimen included gemcitabine at 750 mg/m^2 and docetaxel at 35 mg/m2 weekly for 3 out of 4 weeks. Prophylactic treatment and antiemetics were given according to the institutional guidelines: dexamethasone 8mg PO BID starting 24 hours prior to chemotherapy and anti-t-hydroxytryptamine-3 as antiemetic.

Serum CA19-9 levels were measured every 3/4 weeks and CT scans performed after every eight-nine weeks until disease progression. Staging was performed according to the RECIST criteria (16). Complete blood, platelet and differential counts were done every week, while biochemistry profile was done on a bi-weekly or three-weekly basis. Toxicity was graded according to the NCI-CTC version 3.0 (17).

Progression free survival was calculated as the interval between the initiation of treatment and the occurrence of progressive disease (PD) or death; overall survival (OS) was measured from initiation of treatment to the date of death or to the last follow-up assessment.

Results

Demographics. Between January 2006 and November 2009, 17 patients with metastatic pancreatic adenocarcinoma after receiving gemcitabine-containing chemotherapy were treated at our institution with either weekly docetaxel at 25 mg/m^2 or 3-weekly docetaxel at 75 mg/m^2 until progressive disease (Table II). Weekly docetaxel was the most commonly used regimen based on the data described earlier suggesting a favorable safety profile. Gemcitibine-based first-line therapies were: Gem-ox (gemcitabine-oxaliplatin) for 7 patients, Gem-ox (gemcitabine-cisplatin) for 4 patients, Gem-ox (gemcitabine-capecitabine) for 2 patients, gemcitabine-erlotinib for 1 patient, gemcitabine-S1 for 2 patients and gemcitabine alone for 1 patient. Thirteen patients had an elevated CA 19-9 measurement at baseline and the other two had elevated CEA. Tumor markers were not available in two patients.

Dose intensity. Docetaxel dose intensity was 90% in the patients who received weekly docetaxel, 85% in docetaxel-erlotinib and 65% in the 3-weekly regimen (docetaxel-gemcitabine-capecitabine, docetaxel-gemcitabine). Duration of therapy with docetaxel ranged from 4 to 12 weeks (median: 8 weeks).

Efficacy. Two patients were not assessed for response due to early clinical progression (1 patient on weekly docetaxel) and poor tolerance (1 patient on docetaxel-gemcitabine-capecitabine). Only one objective response to treatment was obtained (docetaxel-gemcitabine) (6% response rate), while 5 patients achieved stable disease (weekly docetaxel). Stable disease lasted between 2.5 and 6.5 months (median: 3). Median progression-free survival (PFS) was 8 weeks (range: 3-16 weeks). The median survival (OS) was 4.0 months (range: 2.0-6.5 months); all patients died of progressive

Table III. *Characteristics and efficacy of patients on docetaxel as second-line therapy.*

Patient	First-line therapy	ECOG PS at time of starting second-line therapy	Ascites at time of starting second-line therapy	Second-line therapy	Radiographic response	CA19-9/CEA response
1	Gem-Ox	1	+	Wkly Doc	SD	↓
2	Gem-Ox	2	+	Wkly Doc	SD	↓
3	Gem-Ox	2	-	Wkly Doc	PD	↑
4	Gem-Ox	2	-	Wkly Doc	SD	↑
5	Gem-Ox	1	+	GT	PR	↓
6	Gem-Ox	1	-	Wkly Doc	PD	↑
7	Gem-Ox	2	+	Wkly Doc	PD	↑
8	Gem-Cis	2	-	Wkly Doc	SD	↔
9	Gem-Cis	2	-	Wkly Doc	PD	↑
10	Gem-Cis	2	-	Wkly Doc	PD	↓
11	Gem-Cis	2	-	Wkly Doc	PD	↑
12	Gem-Cap	1	+	Wkly Doc	PD	↔
13	Gem-Cap	2	-	GT	PD	↔
14	Gem-Erlotinib	1	+	GTX	PD	↔
15	Gem-S1	2	-	Wkly Doc	SD	↓
16	Gemcitabine-S1	1	+	Wkly Doc	PD	↑
17	Gemcitabine	2	-	Wkly Doc	PD	↔

Gem-Ox: Gemcitabine + Oxaliplatin; Gem-Cis: Gemcitabine + Cisplatin; Gem-Cap: Gemcitabine + Capecitabine; GT: Gemcitabine + Docetaxel; GTX: Gemcitabine + Docetaxel + Capecitabine; PS: performance status; PR: Partial response; SD: Stable disease; PD: Progressive disease; ↓: Decreased; ↑: Increased; ↔: Unchanged.

disease. CA 19-9 decreased by 50% in 1 patient and by 25% in 3 patients, while it remained stable in another 4 patients. CEA dropped by 20% in another 2 as shown in Table III.

Toxicity. No toxicity with grade >3 related to docetaxel was observed. Most common grade 1 and 2 toxicities included fatigue, nausea, abdominal pain, edema, alopecia and anemia. One patient developed grade 3 rash attributed to erlotinib. No patient developed a hypersensitivity reaction. One patient had to stop the gemcitabine-docetaxel combination due to grade 2 fatigue. Patients with ECOG performance status of 0-1, adequate baseline liver functions and absent or controlled ascites received the most benefit in the cohort.

Quality of life. Patients tolerated the weekly regimen better than the 3-weekly regimen, as less toxicity was encountered in the former regimen. However, convenience of every three week regimen was also a point of decision for choosing the regimen (Table IV).

Table IV. *Comparison of toxicity grade (≥G2).*

	Weekly docetaxel				Three-weekly docetaxel			
Grade	1	2	3	4	1	2	3	4
Neutropenia	1	0	0	0	0	3	0	0
Peripheral neuropathy	1	1	0	0	0	3	0	0
Nail changes	1	2	0	0	2	0	0	0
Fatigue	1	1	0	0	1	2	0	0
Thrombocytopenia	0	0	0	0	2	1	0	0
Anemia	2	0	0	0	2	1	0	0

Weekly docetaxel: 14 patients including 1 patient with docetaxel+erlotinib; Three-weekly docetaxel: 3 patients (GTX: 1, GT: 2).

Discussion

There is a relative paucity of published studies evaluating the safety and effectiveness of chemotherapy regimens in patients with advanced pancreatic cancer who have progressed following first-line therapy. This may be largely due to the fact that many such patients have a declining performance status and are no longer eligible to receive further systemic therapy.

Taxanes have demonstrated some activity in preclinical pancreatic cancer models. In 3 clinical trials docetaxel had an objective RR of 0-15% and in 3 clinical trials paclitaxel had an objective RR of 0-8% (8-11). Median OS in trials of the two drugs ranged from 4 to 8 months. The present study also revealed that docetaxel has a mild activity in the treatment of gemcitabine-resistant metastatic pancreatic cancer. It was found that weekly administration of single-agent docetaxel at 20 mg/m^2 as salvage therapy in patients with gemcitabine-refractory metastatic pancreatic cancer was tolerated with a dose intensity up to 90%. Single agent

docetaxel for chemotherapy-naïve patients with locally advanced or metastatic pancreatic cancer has been explored in few other trials, including schedules of docetaxel at 100 mg/m^2 intravenously every three weeks (8-10) or docetaxel 60 mg/m^2 every 3 or 4 weeks (11). Overall response rate ranged from 5% to 15% in trials administering docetaxel at 100 mg/m^2, while no response was observed in the lower-dose trial. Median survival duration for patients with docetaxel at 100 mg/m^2 ranged from 5.9 to 8.3 months. Stable disease was observed in 35% to 67% of patients. The median survival duration for the single study of docetaxel at 60 mg/m^2 was 3.9 months with 33% of stable disease patients. Thus, these results suggest that a greater planned dose intensity may be more effective.

However, the docetaxel dose intensity of 25 mg/m^2 weekly, used in the present study, was very similar to these studies. When tested in other solid tumors, docetaxel three-weekly administration seems to have similar efficacy to the weekly administration in both breast and non-small cell lung cancer (12-15), but superior efficacy in prostate cancer (18). The weekly schedule may have only a marginal role on tumor growth control perhaps by inhibiting tumor angiogenesis and no cytotoxic activity in pancreatic cancer as well (19, 20). Ouettle *et al*. reported a response rate of 6% including a complete remission using weekly paclitaxel, a different semisynthetic taxane, as salvage therapy in a small series of patients with advanced pancreatic cancer (21). As the authors acknowledged, the interesting results observed may have been partly due to a better selection of patients who had good performance status (median KPS of 80) and presented a median previous PFS >8 months (). Possible explanations to explain the lack of efficacy of taxanes in pancreatic cancer may include P170 multidrug resistance pump or an alteration in microtubulin composition. Since P-glycoprotein (P-gp) is often expressed in normal pancreatic tissue, P-gp mediated taxane resistance may have been found natively in pancreatic cancer or been readily induced by different substrates, such as gemcitabine-containing first-line chemotherapy (22).

It is worth noting that 6 patients had disease control including one partial response. It is uncertain whether this reflects the true efficacy of docetaxel or favorable tumor biology, as the patient numbers in the present study were too small to draw any firm conclusions one way or another. However, these findings do highlight the fact that a subset of patients with metastatic pancreatic cancer, even those refractory to first-line chemotherapy, can receive clinical benefit from appropriate therapeutic intervention. It was found that patients with ECOG performance status of 0-1, adequate baseline liver functions and absent or controlled ascites received the most benefit in the cohort. It is the identification of such patients *a priori*, along with the ability to make more judicious selection of effective therapeutic agents based on the clinical and molecular characteristics of patients and their disease, that represent key challenges facing cancer specialists in the future.

Although this was a retrospective study, this data is very important at present as a recent study has rekindled the importance of taxanes in pancreatic cancer (23). Pancreatic cancer cells and surrounding stroma are known to overexpress SPARC (secreted protein acid rich in cysteine), which is associated with poor clinical outcomes. Nanoparticle albumin-bound paclitaxel (Nab™-paclitaxel; ABI-007; Abraxane®) is a novel CrEL-free formulation of paclitaxel (24). This formulation increased tumor accumulation of paclitaxel through the binding of albumin to SPARC. In a pilot study, patients received Nab-P doses (100-150 mg/m^2) + gemcitabine at 1000 mg/m^2. Results presented at the annual meeting of ASCO 2009 showed that 2% had complete response, 24% had a partial response and 41 % had stable disease. Median progression-free survival increased from 4.8 months for SPARC- patients to 6.2 months for SPARC+ patients.

Lack of attention to second-line treatment strategy in advanced pancreatic cancer is due to the fact that there is still no first-line option available that renders true survival benefit. Therefore, development of novel therapeutic agents should be an obvious area of research focus in the future (6). However, the present study re-emphasizes the challenge in treating patients with metastatic pancreatic cancer who have progressed following first-line chemotherapy due to poor performance status and toxicities.

It is important that the study design is improved and phase II data are more rigorously scrutinized, before moving forward with large phase III randomized trials that require enormous resources. One solution would be a more frequent implementation of randomized phase II trials to test agents with encouraging activities before undertaking phase III trials. While it is still at a very early stage and it will take years before being applied clinically, pharmacogenomics in pancreatic cancer is an important area that may improve second-line treatment strategies in advance pancreatic cancer. Improvements are also possible through better patient selection. Thus, selected advanced pancreatic cancer patients with a good performance status should be considered for second-line chemotherapy after first-line gemcitabine failure.

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