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Combined Irinotecan and Oxaliplatin in Patients with Advanced Pre-Treated Pancreatic Cancer

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Key Words
Pretreated pancreatic cancer · Irinotecan · Oxaliplatin

Abstract
Objectives: This study evaluated the clinical activity and toxicity of combination chemotherapy with irinotecan and oxaliplatin in patients with advanced pancreatic cancer that had progressed despite ≥1 course of a gemcitabine-containing regimen. ***Methods:*** Thirty patients with metastatic pancreatic cancer and Karnofsky performance status ≥70 received oxaliplatin 60 mg/m^2 on days 1 + 15 and irinotecan 60 mg/m^2 on days 1 + 8 + 15 every 4 weeks. Patients were assessed on the basis of clinical benefit response, changes in serum tumour marker CA 19-9, objective tumour response, time to progressive disease (TTP), and survival. ***Results:*** Six patients (20%) had clinical benefit response (median duration of 7.2 months). CA 19-9 levels were reduced ≥50% from baseline in 8 patients (26%) and remained stable in 8 patients. CT scans revealed that 3 patients (10%) had a partial response and 7 (23%) had stable disease. Two patients (7%) were down-staged and underwent surgery. Median TTP was 4.1 months, median survival was 5.9 months and the 1-year survival rate was 23.3%. The most serious adverse events were grade 3–4 leukopenia in 2 patients (6%), grade 3 neuropathy in 2 (6%) and grade 3 diarrhoea in 1 (3%). ***Conclusion:*** Chemotherapy with irinotecan and oxaliplatin is an active and well-tolerated combination in patients with advanced pre-treated pancreatic cancer.

Introduction

Pancreatic cancer, which is estimated to be the fourth leading cause of cancer death in the United States [1], is rarely curable. This is partly because most patients present with unresectable locally advanced and/or metastatic disease [2]. Additionally, systemic chemotherapy characteristically has a negligible impact on the growth of pancreatic tumours, and, until recently, there has been no standard approach to the treatment of advanced disease [3].

The novel nucleoside analogue gemcitabine is now established as a standard first-line systemic approach to the treatment of pancreatic cancer [2, 4]. The first pivotal trial of gemcitabine in patients with advanced pancreatic cancer revealed a modest but significant survival advan-

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tage with gemcitabine compared with fluorouracil [5]. The trial also demonstrated the superiority of gemcitabine in terms of clinical benefit response, a composite parameter that includes measures of pain, functional status and weight loss. Clinical benefit response is an important indicator of the impact of treatment on disease-related symptoms that occur frequently and become increasingly debilitating as pancreatic cancer progresses. Trials investigating the activity of gemcitabine in combination with other chemotherapeutic agents are ongoing in an effort to find a combination that consistently improves upon the anti-tumour activity of single-agent gemcitabine [2, 4]. It has also been suggested that sequential polychemotherapy may improve the survival of patients with pancreatic cancer whose disease has progressed despite first-line therapy with a gemcitabine-containing cycle [6].

In vitro studies have shown cytotoxic synergism between oxaliplatin and the active metabolite of irinotecan [7], and this combination has also shown signs of anti-tumour activity in patients with pancreatic cancer [8, 9]. The aim of this phase II study was to determine whether combined therapy with oxaliplatin and irinotecan could have utility as a second- or third-line approach to the treatment of pancreatic cancer that had progressed after first-line treatment with a gemcitabine-containing regimen.

Patients and Methods

Patients

Eligibility criteria included a histologic or cytologic diagnosis of pancreatic adenocarcinoma, a Karnofsky performance status of ≥ 70, and previous treatment with ≥ 1 gemcitabine-containing cycle, during which there was evidence of disease progression documented by imaging, and clinical and biological markers. At least 3 weeks must have passed since the end of previous therapy. Patients were also required to have an adequate bone marrow reserve (leucocyte count >3,500/μl, platelet count >100,000 μl), a total bilirubin level <2.0 mg/dl and a serum creatinine level <1.5 mg/dl. Patients with clinically significant ascites or other third-space fluid collections were excluded.

The study protocol was approved by our Institutional Review Board, and informed consent was obtained from all patients.

Treatment

Patients received oxaliplatin 60 mg/m^2, administered as a 2-hour intravenous infusion on days 1 + 15, followed by irinotecan 60 mg/m^2, given as a 30-min intravenous infusion on days 1 + 8 + 15. Treatment cycles were repeated every 4 weeks. If a patient responded to therapy, treatment could be continued until there was evidence of toxicity or disease progression.

Drug doses could be reduced by 25% if grade 3–4 haematological toxicity or any grade 3 non-haematological toxicity occurred. Oxaliplatin was discontinued if a patient had progressive peripheral neuropathy or experienced any other severe neurotoxicity. Prior to administration of cytotoxic drugs, patients received 8 mg of ondansetron and 8 mg of dexamethasone as prophylaxis for nausea and vomiting. A prophylactic dose of atropine (0.25 mg) was also administered so as to avoid the cholinergic syndrome that can sometimes occur in conjunction with irinotecan infusion [10]. Patients were also provided with guidelines for the treatment of delayed diarrhoea, which specified a 2-mg dose of loperamide every 2 h until the patient was free of diarrhoea for ≥ 12 h. Treatment could be delayed for up to 2 weeks if diarrhoea persisted. Any patient who required more than 2 weeks in order to recover from adverse reactions was withdrawn from the study.

Evaluations

Staging was performed using abdominal sonography, total abdominal computed tomography (CT) and chest X-ray at baseline. Total abdominal CT scanning was also performed after 3 cycles of chemotherapy. Pain intensity was assessed via a combination of the visual analogue scale of the Memorial Pain Assessment Card (MPAC) [11] and analgesic consumption. Pain intensity, Karnofsky performance status, weight change and CA 19-9 levels were all evaluated at baseline and after each treatment cycle.

Assessment of Efficacy

Similarly to the first pivotal study of gemcitabine in patients with advanced pancreatic cancer by Burris et al. [5], the primary efficacy end point used in the current study was clinical benefit derived from measurement of pain, functional impairment and weight loss. Pain and functional impairment were the primary measures of clinical benefit. Weight change was considered a secondary measure. A positive change in pain intensity consisted of an improvement of $\geq 50\%$ from baseline on the MPAC 0–100 visual analogue scale, and a negative change was any worsening from baseline. A positive change in analgesic consumption was defined as a $\geq 50\%$ decrease from baseline, and a negative change was any increase from baseline. A positive change in Karnofsky performance status was defined as an improvement of ≥ 20 points from baseline, and a negative result was any worsening of ≥ 20 points. A positive weight change consisted of a $\geq 7\%$ gain from baseline, and any other result was non-positive. In order to achieve an overall rating of positive clinical benefit response, patients had to be positive for ≥ 1 parameter for ≥ 4 weeks without being negative for any of the other parameters. CA 19-9 levels were systematically monitored. Complete CA 19-9 response was defined as reduction of CA 19-9 to a level within the normal range (≤ 37 U/ml) [12]. Partial response was defined as a >50% decrease of CA 19-9 from the baseline value. Progressive disease was defined as any increase in CA 19-9 levels. Stable disease was recognized when the response did not meet any of the previous criteria.

CT scans were used to assess objective tumour response according to the standard World Health Organization criteria [13].

Other secondary efficacy end points included time to progression (TTP; calculated from the start of treatment to the time when the patient was classified as having progressive disease or was withdrawn from therapy), and overall survival (OS; calculated from the first day of study treatment until the day of death). OS from the time of original diagnosis was also evaluated.

Toxicity was assessed at each cycle according to WHO criteria.

Table 1. Baseline patient characteristics (n = 30)

Characteristics	n	%
Sex		
Male	20	67
Female	10	33
Median age, range	59.7	38/79
Metastatic disease	30	100
Site of metastases		
Liver	18	60
Peritoneal	7	23
Lung	2	7
Two or more sites	3	10
Karnofsky performance status		
70	9	30
80	12	60
90	9	30
Pain	19	63
Median baseline pain intensity score	39 mm	
Range	23 – 79 mm	
Prior chemotherapy		
GEM alone	17	57
Other GEM-based regimens	6	20
Two chemotherapeutic lines	7	23

GEM = Gemcitabine followed by an intra-arterial FLEC (5-fluorouracil, folinic acid, epirubicin, carboplatin) regimen after the first failure.

Statistics

The objective of this prospective, open-label phase II study was to evaluate the activity and safety of irinotecan combined with oxaliplatin in patients with pancreatic cancer progressing after gemcitabine. Since the study was open and non-comparative, power calculations to estimate the required sample size were not performed. A planned sample size of approximately 30 patients was chosen, a figure often used in this type of oncology study to demonstrate activity.

OS and TTP curves were analysed according to the Kaplan-Meyer method.

Results

Patient Characteristics

Between January 2000 and January 2003, 30 patients were registered to this study. Patient characteristics are summarised in table 1. All patients had metastatic disease with at least one measurable lesion on the CT scan. Eighteen patients had liver metastases, 7 patients had peritoneal metastases, 2 patients had lung metastases and 3 patients had more than one site of metastatic disease. Pain was present in 19 out of 30 patients, and the median baseline MPAC pain intensity score was 39. All patients had disease progression during prior chemotherapy. The most common prior treatment regimen consisted of first-line gemcitabine alone (n = 17). First-line combination therapy with gemcitabine + 5-fluorouracil had previously been administered to 6 patients. Disease had progressed in 7 patients despite first-line gemcitabine and second-line therapy with an intra-arterial FLEC (5-FU, folinic acid, epirubicin, carboplatin) regimen [14].

Efficacy

A positive clinical benefit response was observed in 6 of the 30 patients (20%). The median duration of this response was 7.2 months, with a range between 4 and 15.1 months. In terms of CA 19-9 levels, 8 patients (26%) had a partial response, and 8 (26%) were stable. Increases of CA 19-9 indicated progressive disease in 14 patients (47%). CT scans revealed a partial response in 3 patients (10%), stable disease in 7 (23%), and progression of disease in 10 (33%). Ten patients (33%) did not undergo a follow-up scan because of progressive disease.

Median survival from the start of the study was 5.9 months, and ranged between 0.7 and 34.2 months. The 1-year survival rate was 23%. Median TTP was 4.1 months (range 0.7–13.1 months). Median overall survival from diagnosis was 16.1 months with 1-year and 2-year survival rates of 57% and 29%, respectively.

Two patients were down-staged and underwent radical surgery of the primary tumour. One of these patients had liver and nodal relapses 6 months after histological disappearance of liver metastases, and died 21 months after the start of chemotherapy. The other patient had liver recurrences and was still alive 3 months after surgery.

As of April 2003, with a follow-up ranging between 1 and 34.1 months (median follow-up of 5.3 months), 27 patients (90%) have died of progressive disease.

Safety

A total of 97 cycles of chemotherapy were administered. No dosage modifications were required. There were 3-week delays because of transient peripheral neuropathy.

As shown in table 2, haematological toxicity was generally mild. WHO grade 1–2 anaemia was most common, occurring in 53% of patients. There was no grade 3 or 4 anaemia. Grade 3–4 leucopenia occurred in 6% of patients, and 30% had grade 1–2 leukopenia. Grade 3 thrombocytopenia occurred in 3% of patients and 16% had grade 1–2 thrombocytopenia. Grade 1 and 2 nausea/vomiting was the most common gastrointestinal adverse

Table 2. Highest grade of treatment-associated toxicity

	WHO grade			
	1	2	3	4
Leucopenia	6 (20%)	3 (10%)	1 (3%)	1 (3%)
Thrombocytopenia	4 (13%)	1 (3%)	1 (3%)	0
Anaemia	9 (30%)	7 (23%)	0	0
Nausea/vomiting	7 (23%)	4 (47%)	0	0
Diarrhoea	4 (13%)	11 (37%)	1 (3%)	0
Mucositis	1 (3%)	0	0	0
Asthenia	7 (23%)	3 (10%)	0	0
Fever	4 (13%)	4 (13%)	0	0
Alopecia	5 (17%)	1 (3%)	0	0
Peripheral neuropathy	3 (10%)	2 (6%)	2 (6%)	0

Results represent number and percentage of patients.

event, occurring in 70% of patients. There was no grade 3 or 4 nausea or vomiting. 50% of patients had grade 1–2 diarrhoea. There was 1 case of grade 3 diarrhoea. Grade 1–2 peripheral neuropathy occurred in 16% of patients, and there were 2 cases of a grade 3 peripheral neuropathy.

Discussion

In recent years, single-agent gemcitabine has been established as the standard first-line approach to systemic therapy in pancreatic cancer, and a number of promising combinations with gemcitabine have also been identified [2, 4]. There has, however, been relatively little research focusing on identification of combinations that may be beneficial in patients with advanced pancreatic cancer who have failed first-line therapy with a gemcitabine-containing regimen. In our experience, we have frequently observed patients with a good performance status, albeit with progressive disease, after chemotherapy with a gemcitabine-based regimen, leading us to hypothesise that such patients may benefit from second-line therapy with a completely different regimen. The results of the current study in patients with a Karnofsky performance status ≥ 70 and progressive pancreatic cancer despite previous therapy with a gemcitabine-containing regimen suggest that such patients do stand to benefit from second- or third-line therapy with combined irinotecan and oxaliplatin.

The camptothecan derivative irinotecan and the diaminocyclohexane platinum compound oxaliplatin have shown cytotoxic synergism in vitro and in vivo, with no overlapping toxicity [7, 8, 15]. Single-agent irinotecan has exhibited anti-tumour activity in patients with pancreatic cancer [16, 17], and single-agent oxaliplatin has shown cytotoxic activity against pancreatic cancer cell lines in vitro [18]. Such observations suggested that irinotecan and oxaliplatin would be an ideal combination to try as a second- or third-line approach to therapy in patients with advanced pancreatic cancer.

Patients in our study started therapy with oxaliplatin 60 mg/m^2 (days 1 and 15) and irinotecan 60 mg/m^2 (days 1, 8 and 15) every 4 weeks. These dosages are in line with the following recommendations from a study of irinotecan plus oxaliplatin as second-line therapy in previously treated patients with metastatic colorectal cancer with a reduced weekly dose of oxaliplatin from 40 mg/m^2/week to 30 mg/m^2/week [19]. The overall feasibility and acceptability of this combination at this dosage is highlighted by the fact that 19 of the 30 patients included in our study received ≥ 3 cycles of therapy, and by the fact that in no case was a dosage reduction necessary due to toxicity. In light of the excellent tolerability of this regimen, dosages could possibly be increased in future studies in an effort to boost response. It is relevant to note that, in a study in which patients with advanced colorectal cancer were treated with oxaliplatin 85 mg/m^2 (days 1 and 15) and irinotecan 80 mg/m^2 (days 1, 8 and 15) ± G-CSF support, 31% of patients required dose reductions because of toxicity [20].

Considering that many patients with advanced pancreatic cancer experience increasingly severe pain, nausea and vomiting, anorexia, weight loss and weakness, clinical benefit response is now established as a valid indicator of treatment success in this disease [5]. This underlies the primary intention behind chemotherapy in advanced pancreatic cancer, which is currently to provide palliation of symptoms. Positive clinical benefit was observed in 20% of the patients involved in the current trial, lasting between 4 and 15.1 months.

It has previously been demonstrated that changes in serum levels in the tumour marker CA 19-9 can be used as an adjunct to radiographic tumour evaluation in patients with pancreatic cancer [21]. It has also been suggested that such changes may represent a more sensitive indicator of tumor response to palliative therapy than imaging methods [9]. We accordingly decided to monitor CA 19-9 response to treatment in our trial, and found that CA 19-9 levels decreased by >50% from baseline in 26% of patients, and remained stable in another 26%. Partial response, as evidenced by CT scan, was only seen in 10%

of patients. CT scans indicated stable disease in 23% of patients.

The percentage of patients who experienced a clinical benefit (20%) is smaller than the rate of observed overall response rate (objective responses plus stable disease = 33%); this was expected and is probably due to the fact that patients with very advanced disease, treated in second or third line, may fail to gain a significant clinical benefit from any cytotoxic treatment.

Although it is important for palliative chemotherapy to ameliorate symptoms of disease, the hallmark of a truly successful systemic therapy for pancreatic cancer is an ability to prolong survival. Survival was included as a secondary end point in this trial. Median survival was 5.9 months from the start of study therapy and 16.1 months from the original time of diagnosis. The 6 patients who experienced a clinical benefit response had a median survival of 21 months, which points to the potential value of clinical benefit as a prognostic indicator. The longest follow-up has been for 34.1 months, and 27 of the 30 patients have now died.

Our trial was a preliminary investigation in a small group of patients. It is acknowledged that the small patient population and absence of a comparative control group do limit the clinical significance of our findings in this trial. We do, however, conclude that combination irinotecan plus oxaliplatin is a well-tolerated second- or third-line systemic treatment that shows evidence of being therapeutically beneficial, in patients with progressive metastatic pancreatic cancer who have a high performance status and progressive disease despite having previously been treated with a gemcitabine-containing regimen. Future studies should try higher doses of irinotecan and oxaliplatin in such patients.

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