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Original Paper

A Phase II Study of High-dose Octreotide in Patients with Unresectable Pancreatic Carcinoma

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This report describes the results of a phase II trial to evaluate the safety, feasibility and response of patients with irresectable, histologically proven, stage II–IV adenocarcinoma of the pancreas receiving high-dose octreotide treatment. Octreotide was self-adminstered subcutaneously (3×2000 μg per day) by 49 patients. Therapy was discontinued after progression of the disease. Due to the subseqment diagnosis of bile duct carcinoma and stage I disease, 2 patients were excluded, leaving 47 evaluable patients with measurable disease. The median Karnofsky score was 80%. 3 patients had stage II (6%), 19 stage III (40%), and 25 (53%) stage IV disease. Octreotide treatment resulted in stable disease in 9 patients (19%) for more than 12 weeks. No complete or partial response was observed. The median overall survival was 21.4 weeks and the median progression-free survival 9.0 weeks. Therapy with high-dose octreotide is feasible, well tolerated and might prolong survival. In a placebo-controlled phase III study the effects of octreotide in patients with pancreatic cancer will be confirmed. © **1999 Published by Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THE PROGNOSIS of pancreatic carcinoma, with a 5-year survival rate of 3%, is one of the worst of all cancers. Despite the reports on curative radical surgery in small pancreatic tumours and the possible benefits of radiochemotherapy [1–4], there have been no significant advances in therapy of metastatic pancreas cancer.

It has become more evident in the early 1990s that some low-toxicity systemic regimens yield response rates as high as more toxic combinations [5–9]. Additionally, symptomatic palliation rates may exceed objective response rates [5, 7] and only very few trials have measured the quality of life. Using stringent criteria, the objective response rates did not exceed 20% [5].

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Experimental data suggest that somatostatin analogues work through a number of different mechanisms to exert an antitumoral effect. These include: an inhibition of IGF-1, TGF-β and EGF which have been shown to stimulate tumour growth; inhibition of angiogenesis; and a direct antiproliferative effect on certain tumour cells [10, 11]. In preclinical evaluations, the antiproliferative effects of octreotide were dose-dependent.

Based on the good tolerability of octreotide treatment in other indications, the dose-relationship for antiproliferative effects, and the data of pilot studies with high-dose octreotide (6000 μg/day) in advanced pancreatic cancer [10, 12], we designed a phase II trial to test the antitumoral effect of high-dose octreotide. The objective was to determine whether octreotide could increase tumour response rates and improve survival in patients with advanced pancreatic cancer.

PATIENTS AND METHODS

Patients with histological proof of unresectable adenocarcinoma of the pancreas, stages II–IV, were included in this prospective, open-label, non-randomised, multicentre trial with four participating institutions. The institutional ethics committees reviewed this study, and before treatment every patient gave written informed consent.

Patients who underwent surgical exploration and/or biopsy began octreotide treatment preoperatively at a dose of 100 μg subcutaneously (s.c.) every 8 h the day before surgery and continued at this dose level until the seventh postoperative day. If the pathology report confirmed malignancy the dose was escalated to 3×2000 μg/day. Eligible patients who did not undergo surgery received 3×1000 μg/day s.c. from day 1 to 3 and afterwards 3×2000 μg/day until discontinuation of treatment.

Within 2 weeks before study entry, each patient received a computed tomography (CT) scan. This investigation served as the baseline evaluation to determine tumour response. Radiological studies were performed every 12 weeks, or more frequently if clinically indicated, for tumour assessment. Physical and laboratory examinations were conducted every 4 weeks to monitor the patient's condition, the tolerability of the experimental treatment and to detect signs of tumour progression very early. These included a complete blood count with differential and platelet count, chemistry profile with total protein, albumin, glucose, blood urea nitrogen (BUN), uric acid, creatinine, calcium, phosphorus, bilirubin, alkaline phosphatase, lactate dehydrogenase LDH, aspartate transaminase (AST), alanine transaminase (ALT), carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19-9). Every 12 weeks a gallbladder ultrasound was performed.

All patients received individual diaries to record adverse events and to document compliance with the study regimen. Any adverse event occurring during the course of the study was evaluated according to severity, duration, and relationship to the administration of the test drug.

Response to treatment was judged as complete response (complete disappearance of all known disease), partial response (decrease of 50% or more in tumour size as compared with baseline), stable disease (no change or an increase in size less than 25% or decrease less than 50%) or progressive disease (appearance of any new lesions not previously identified or an increase of at least 25% in existing lesions).

The main objectives of the study were to determine whether the antitumour response rate of octreotide in patients with adenocarcinoma of the pancreas is at least 20%, to evaluate the survival probability and to determine the safety and tolerability of octreotide administered subcutaneously at a single dose level. For this study, a responder was defined as a patient who shows a complete response, partial response or stable disease for three consecutive months. Survival data were evaluated according to the Kaplan–Meier method. Descriptive statistics were used to display the safety and tolerance of octreotide.

RESULTS

49 patients were enrolled in this multicentre study. All patients had histologically proven adenocarcinoma of the pancreas with the exception of 1 patient who had a distal bile duct carcinoma. This patient, who was excluded from survival analysis, was treated with octreotide for 1 year, underwent a Whipple resection and was still alive more than 4 years after the start of octreotide therapy. Additionally, 1 patient was found to have stage I disease rather than advanced disease and was excluded from the analysis. Statistical evaluation involved 47 patients who had measurable disease.

The mean age of the entire group was 58.1 years (median 58.0 years, range 20–79 years). All patients were caucasian, 39 were male (83%) and 8 female (17%). Mean weight of patients before the start of octreotide therapy was 67.4 kg (mean height: 172.8 cm). The median Karnofsky score averaged 80.0% before the start of octreotide treatment.

All patients had unresectable disease according to laparotomy or CT-criteria. 3 patients (6%) had stage II, 19 (40%) stage III, and 25 (53%) stage IV disease (that is, proven distant metastases).

Treatment with octreotide was discontinued after progression of the disease, but for humanitarian reasons some patients continued octreotide therapy after disease progression. 9 patients (19%) responded to octreotide treatment with stable disease for more than 12 weeks. No partial or complete response was observed among the patients with pancreatic adenocarcinoma. One patient who had unresectable multiple histologically proven adenocarcinoma of the pancreas withdrew his consent after 12 weeks with stable disease. He underwent regional chemotherapy with consecutive total pancreatectomy at another institution and was still alive 24 months after the commencement of octreotide treatment. 7 patients survived more than a year (1-year survival rate 14.9%). The longest observed survival was a 46-year old male with stage III disease who survived 78 weeks (1.5 years).

The median overall survival was 21.4 weeks, the median progression-free survival 9.0 weeks (Figure 1a). The median survival for stage II/III patients was 34.3 weeks and for stage IV patients 13.0 weeks (Figure 1b).

In terms of other clinical parameters, such as pain intensity, analgesic consumption, Karnofsky performance status and weight change, which can be used to assess clinical benefit, no major changes could be detected between baseline, treatment period and the end of study.

The patients tolerated octreotide treatment by self-administration very well. In no case did the therapy have to be terminated because of serious adverse events. Side-effects that were, according to the investigators, 'possibly' linked to the study drug were reported for 22 patients (46.8%). The most frequent side-effects, which may also be linked to the underlying malignancy, were diarrhoea and steatorrhoea. In 1 patient gallstone formation was observed under high-dose octreotide therapy. Further adverse events observed in single cases were hyperglycaemia, diabetes mellitus, meteorism, abdominal tenderness, vomiting and fever (Table 1).

DISCUSSION

Pancreatic carcinoma is still the gastro-intestinal malignancy with the worst prognosis despite various attempts to increase surgical radicality or develop new systemic approaches [2, 4–6, 13, 14]. The most extensively studied drug for the chemotherapy of pancreatic carcinoma is 5-fluorouracil (5-FU). Objective response rates of approximately 15% with a median duration of response ranging between 3 and 6 months have been reported. No significant improvement in overall survival has been observed for populations treated with 5-FU [5, 6].

Combination chemotherapy has been extensively studied in pancreatic carcinoma, mainly using 5-FU-based combinations.

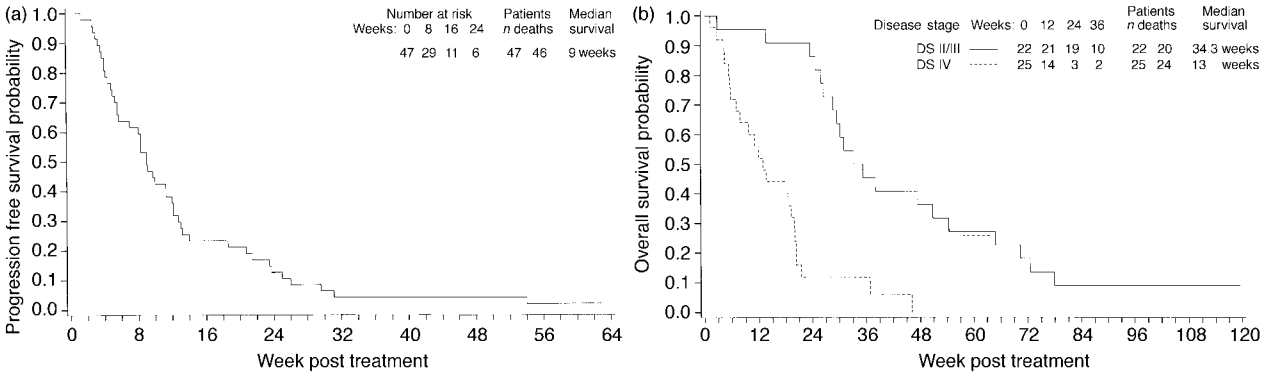

Figure 1. (a) Probability of progression-free survival after octreotide treatment in patients with unresectable pancreatic carcinoma. (b) Survival probability in patients with unresectable pancreatic carcinoma treated with octreotide according to stage of disease.

Despite promising figures in some single arm trials, phase III trials have failed to support the initial impression of patient improvement with combination chemotherapy. The North Central Cancer Treatment Group (NCCTG) compared 5-FU with 5-FU plus doxorubicin to the FAM (fluorouracil doxorubicin mitomycin C) regimen. In this trial survival was essentially identical for all three arms. In a preliminary assessment of quality of life, it was indicated that patients receiving 5-FU had less toxicity than those receiving combination chemotherapy. Similar results have been found with cisplatin-based combinations [5, 6].

These results place a special focus on the quality of life of patients with pancreatic carcinoma undergoing chemotherapy [7, 9, 14], since pancreatic cancer is usually a highly symptomatic disease with severe pain, and a broad spectrum of other systemic effects.

Gemcitabine is a novel pyrimidine antagonist with activity in a number of tumour types. Gemcitabine has been evaluated in phase II studies revealing antitumour activity, albeit to a modest degree of approximately 10% [14–16]. Objective tumour reductions have been seen, and improved symptom control has been reported. In a randomised phase III study comparing gemcitabine with weekly 5-FU chemotherapy, patients receiving gemcitabine achieved a higher response rate, had improved symptom control and had prolonged survival compared with those who received 5-FU [17]. Compared with gemcitabine, octreotide seems to be a well tolerated drug with potential to have beneficial effects in patients with disseminated pancreatic tumours [9, 10, 12, 18]. Our trial demonstrates that high-dose octreotide treatment with self-administration is feasible and well tolerated. The observed median survival in patients with advanced pancreatic cancer is comparable with previously reported results for single-agent chemotherapy in patients with stage III and IV tumours. Symptom control was not obvious in this study. Concerning side-effects related to octreotide, only minor impairments of the patient were observed. No patient was excluded from the study because of toxicity and all adverse events were consistent with the expected profile.

However, no complete or partial response (i.e. reduction in tumour size) was observed in our series among patients with pancreatic cancer. The only patient who displayed a complete

Table 1. *Summary of patients reporting adverse events considered related to octreotide*

	Number (%) of patients ($n = 49$)	Mild	Moderate	Severe
No adverse event	27 (55)	–	–	–
At least one adverse event	22 (45)	7	14	1
Gastro-intestinal system disorders	20 (41)	6	14	0
Diarrhoea	8 (16)	2	6	0
Steatorrhoea	8 (16)	2	6	0
Meteorism	6 (12)	1	5	0
Vomiting	2 (4)	1	1	0
Abdominal pain and tenderness	1 (2)	1	0	0
Metabolic and nutritional disorders	5 (10)	1	4	0
Hyperglycaemia	2 (4)	0	2	0
Diabetes mellitus	1 (2)	0	1	0
Enzyme abnormality	1 (2)	0	1	0
Hypokalaemia	1 (2)	1	0	0
Liver and bilary system disorders	2 (4)	1	0	1
Bile duct stricture	1 (2)	0	0	1
Cholelithiasis	1 (2)	1	0	0
Jaundice	1 (2)	0	0	1
Body as a whole	2 (4)	1	0	1
Fever	2 (4)	1	0	1

response and was resected in a second operation was shown to be suffering from a distal bile duct cancer. It has been shown that cholangiocarcinomas express somatostatin receptors and octreotide inhibits the growth of these tumour cells *in vitro* [19]. Based on these observations a trial investigating octreotide treatment in patients with bile duct carcinomas may be interesting.

Other hormonal treatment options have been evaluated recently. Most pancreatic adenocarcinomas were neurotensin receptor positive, whereas endocrine pancreatic cancers, chronic pancreatitis or normal pancreatic tissues, including pancreatic acini, ducts, and islets did not express neurotensin receptors. This selective and high expression of neurotensin receptors could form the molecular basis for successful clinical applications, such as chemotherapy with neurotensin receptor antagonists [20].

In conclusion, the results of this phase II trial have led us to start prospective, controlled phase III investigations comparing octreotide with 5-FU and placebo. Furthermore, regarding the favourable response rate and clinical benefit reported for gemcitabine, octreotide should be compared to this treatment modality in a phase III trial in future. It will be very interesting to evaluate if the observed effect of octreotide on tumour growth can be enhanced by a combination with other substances or treatment modalities, for example radiotherapy, gemcitabine, 5-FU or tamoxifen in patients with pancreatic cancer [9].

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