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Weekly high-dose 5-fluorouracil and folinic acid in metastatic pancreatic carcinoma: a phase II study of the EORTC GastroIntestinal Tract Cancer Cooperative Group

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Abstract

The aim of the study was to assess the response rate and toxicity of high-dose 24 h infusion of 5-fluorouracil (5FU) in metastatic adenocarcinoma of the pancreas. Patients with measurable disease, performance status 0–2, and no prior chemotherapy were registered to receive cycles of leucovorin (LV) 500 mg/m^2 (or l-LV 250 mg/m^2 over 1 h followed by 5FU 2.6 g/m^2 over 24 h, weekly for 6 weeks, followed by a 2-week rest. The main endpoints were the response rate and toxicity. From 37 patients, 36 were the analysed for toxicity, and 33 were eligible and analysed for response. The median age was 59 years (range 28–74 years), and the median performance status was 1. Partial response was observed in three patients (9%) (95% Confidential Interval (CI): [2–24]%). Main grade 3/4 National Cancer Institute (NCI) common toxicity criteria toxicities (patients) were diarrhoea ($n = 3$), vomiting ($n = 2$) and hand–foot syndrome ($n = 5$). Median time to progression was 7 weeks (95% CI: [6.4–11.7] weeks) and median survival 19 weeks (95% CI: [12–35] weeks). In conclusion, high-dose 5FU and folinic acid is well tolerated, but has only modest activity in pancreatic cancer.

Keywords: Pancreatic neoplasms/drug therapy; Fluorouracil; Leucovorin

1. Introduction

Pancreatic cancer is the fourth most common cause of death from malignant disease in Western countries. These tumours account for 3% of all malignancies, but for 5% of all cancer deaths. The disease carries a poor prognosis, the median survival of all patients with tumours of the exocrine pancreas being only 4–6 months. Only a few patients are candidates for surgical resection, which is the only possibility for cure [1]. All other patients may be considered for palliative chemotherapy or radiotherapy, the modality of treatment primarily being dependent on the stage of the disease. A large number of chemotherapeutic agents have been investigated in pancreatic cancer, but the results of both single-agents and combination chemotherapy in terms of response rate and overall survival have been disappointing [2,3]. The European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Cooperative Group (GITCCG) previously initiated studies with cisplatin, ifosfamide, epirubicin and epirubicin-based combination chemotherapy [4–8].

Especially in patients with metastatic pancreatic cancer, the toxicity of chemotherapy is of concern, as a decreased performance status and concomitant liver-,

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lung-, and cardiac disease are frequently present and may preclude a course of intensive therapy. When chemotherapy for pancreatic cancer is considered, single-agent 5-fluorouracil (5FU) and gemcitabine are probably the most frequently used regimens. Both bolus injections and prolonged infusions of 5FU, either alone or in combination with leucovorin, have been investigated [9–14]. The response rate in these studies varied between 0% and 19%. In a meta-analysis of randomised studies comparing bolus injections of 5FU with prolonged infusion in colorectal cancer, both the response rate and the survival times were significantly higher with prolonged infusions [15]. For the present study, aimed at assessing the activity of prolonged administration of 5FU in metastatic pancreatic cancer, a schedule using weekly administration of leucovorin followed by 5FU infusion over 24 h was selected. The schedule allows the delivery of a high dose-intensity, is associated with a favourable toxicity profile, and may achieve responses even in patients previously exposed to bolus 5FU [16,17].

2. Patients and methods

2.1. Study population

Patients eligible for the study were required to have histologically or cytologically confirmed adenocarcinoma of the pancreas, a performance status 0–2, an estimated life expectancy of 3 months or more, and bidimensionally measurable metastatic disease outside previously irradiated areas. Target lesions qualifying for measurable disease included lung metastases $\geqslant 1$ cm and liver, soft tissue or lymph node metastases $\geqslant 2$ cm. Lymph node and skin metastases $\geqslant 1$ cm were only allowed if their metastatic nature was proven by fine-needle aspiration. Prior chemotherapy was not allowed. Other eligibility criteria included age $\geqslant 18$ years, no other malignancy except adequately treated basal carcinoma of the skin, no overt cardiac disease or active infection, and no signs or symptoms of Central Nervous System (CNS) or leptomeningeal involvement. Excluded were major organ dysfunctions, indicated by white blood cell (WBC) $<3.5 \times 10^9$/l, platelet count $<100 \times 10^9$/l, serum creatinine >120 μmol/l, and serum bilirubin >30 μmol/l. All patients had to be available for follow-up and to have given informed consent.

2.2. Treatment

Treatment consisted of weekly administration of racemic folinic acid 500 mg/m^2 over 1 h immediately followed by 5FU 2600 mg/m^2 as a 24-h infusion. The replacement of racemic folinic acid by L-folinic acid 250 mg/m^2 was allowed. Treatment was administered for 6 weeks, followed by a 2-week rest. This 8-week period was called a cycle.

Dose delays or adjustments were foreseen for toxicities. The grading of toxicities followed the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) guidelines. Treatment was skipped in case of WBC $<3 \times 10^9$/l or platelet count $<100 \times 10^9$/l at the day of scheduled retreatment. The dose of 5FU was reduced by 25% in subsequent courses in case of grade 3/4 leucopenia or thrombocytopenia, or when courses had to be delayed for one week or more due to insufficient recovery of the WBC or platelet count. The dose of 5FU was also reduced by 25% in case of grade $\geqslant 2$ mucositis, dermatitis, or diarrhoea, and was withheld in case of CTC organ toxicity >2, other than alopecia, nausea and vomiting. Pyridoxine was recommended for patients developing hand–foot syndrome. Treatment was administered until disease progression or unacceptable toxicity. Response assessment was planned every 8 weeks. In patients with stable disease, the continuation of treatment was left to the investigator's discretion.

2.3. Response assessment

Standard World Health Organisation (WHO) response criteria were used. A clinical complete response was defined as the disappearance of all clinically measurable and evaluable disease, and a partial response as a reduction of all measurable lesion of more than 50%, for a duration of at least 4 weeks. When measurable lesions increased less then 25% or decreased less than 50% for a duration of at least 6 weeks, this was called stable disease. Progressive disease was defined as an increase of measurable lesions more than 25% or the occurrence of new lesions. Early death was defined as death during the first 6 weeks after commencement of chemotherapy without severe toxicity, and a toxic death any death where drug toxicity was thought to have made a major contribution.

2.4. Statistics

The Simon one sample minimax design [18] was applied, with P_0 taken as 5%, P_1 (true response rate) as 20%, α as "0.1" and β as "0.1". The trial was to be prematurely closed if no responses were observed after 18 patients had been enrolled. Otherwise, accrual would continue until 32 eligible patients had been entered. If four or more responses were observed, the regimen would warrant further investigation.

3. Results

Thirty-seven patients from nine institutions were enrolled between December 1996 and August 1998. Thirty-

Table 1
Patient characteristics ($n = 37$)

Median age (range)	59 years (28–74)
WHO performance status	
0/1/2	11/20/6 pts
Male/Female	25/12 pts
Location of primary tumour	
Head/body/tail	21/9/7 pts
Prior surgery	13
Prior radiotherapy	0
Analgesic use	
None	9 (24%)
Nonopoids	8 (22%)
Weak opoids	9 (24%)
Strong opoids	11 (30%)

WHO, World Health Organisation ; pts, patients.

Table 2
Activity outcome ($n = 33$)

Partial response	3 (9%)	95% CI: [2–24]
No change	7 (21%)	
Progression	15 (46%)	
Early death	5 (15%)	
Not assessable	3 (9%)	
Median time to progression	7 weeks	95% CI: [6.4–11.7]
Median survival	19 weeks	95% CI: [12–35.2]

CI, confidence interval.

three patients were eligible and analysed for response, four patients were ineligible, three patients because of unsuitable target lesions and one patient due to enrollment after the treatment start. All patients enrolled were analysed for toxicity. Patient characteristics are summarised in Table 1. The median age of the patients was 59 years (range 28–74 years) and the median performance status was 1. Seventy-five percent of the patients used analgesics at study entry, evenly divided between nonopoids (usually non-steroidal anti-inflammatory drugs (NSAIDs)), weak opoids and strong opoids. Altogether 67 cycles of 8 weeks duration were administered. Twenty-four patients received 1 cycle, eight patients received 2 cycles, and five patients received 3 or more cycles, with a maximum of 13 cycles being given. The major reason for discontinuation of treatment was disease progression in 31 patients. Three patients stopped because of toxicities, namely angina pectoris, severe diarrhoea, and hand–foot syndrome, and three for other reasons.

Response to treatment is summarised in Table 2. Three patients (9%) achieved a partial response, and another 7 patients had stable disease. The median time to progression was 7 weeks, and the median survival 19 weeks (Fig. 1). Table 3 summarises the main non-haematological toxicities. The Grade 3 and 4 toxicities consisted of hand–foot syndrome (14%), diarrhoea (8%), lethargy (5%), nausea (5%), and stomatitis (3%). No leucocytopenia or thrombocytopenia in excess of grade 1 was observed, but mild to moderate anaemia occurred in 92% of patients.

4. Discussion

Over the years, a variety of administration schedules of 5FU have been explored, in which the drug was given either as a bolus injection or as a prolonged infusion, with or without biomodulation with leucovorin or other agents. Meta-analyses from the Advanced Colorectal Cancer Meta-analysis Project comparing various therapeutic strategies versus bolus 5FU showed a significantly

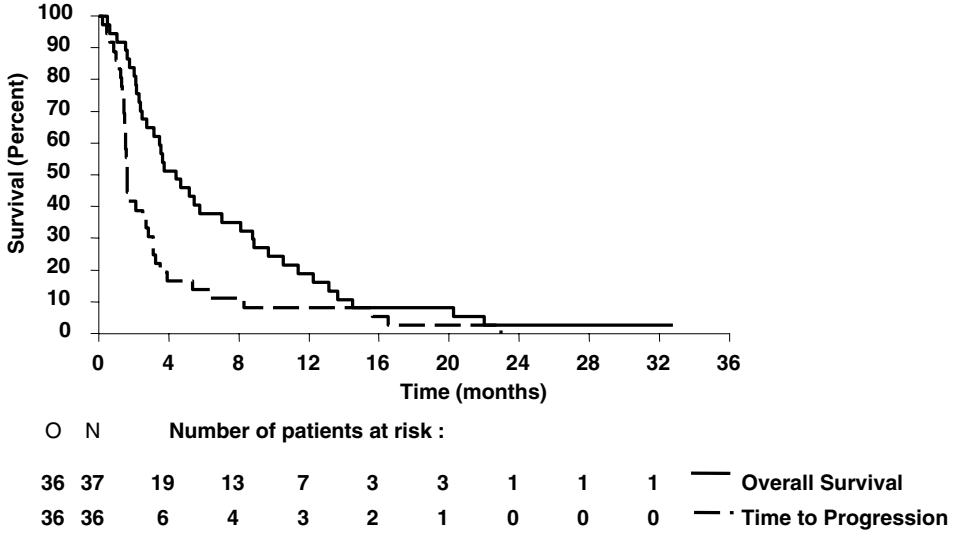

Fig. 1. Progression-free survival and overall survival of patients treated with high-dose 5-fluorouracil and leucovorin in metastatic pancreatic cancer. O, observed; N, number.

Table 3
Toxicities (worst adverse event)

Toxicity	Grades 1–2	Grade 3	Grade 4
Diarrhoea	13 (36%)	3 (5%)	1 (3%)
Nausea	26 (71%)	0	
Vomiting	13 (35%)	2 (5%)	
Hand–foot syndrome	3 (8%)	4 (11%)	1 (3%)
Stomatitis	11 (30%)	1 (3%)	
Lethargy	11 (31%)	2 (5%)	
Anaemia	34 (92%)	0	

improved response rate of leucovorin-modulated regimens (22.5% vs 11.1%) and continuous infusion schedules (22% vs 14%) in comparison with single-agent bolus 5FU [15,19]. Moreover, in colorectal cancer, responses have been observed with both low-dose continuous infusion and high-dose intermittent infusion over 24 h in patients previously treated with bolus injections [17,20,21]. In addition, toxicities of bolus and continuous infusion regimens differ. Leucocytopenia and mucositis are more frequently associated with bolus injections, hand–foot syndrome is more common in continuous infusion schedules [22]. This is also reflected in the toxicity pattern of the present trial. Leucocytopenia and thrombocytopenia were virtually absent, but hand–foot syndrome and stomatitis were regularly observed.

The improved response rate of protracted infusion that exists in colorectal cancer is not evident in pancreatic cancer. Typically, bolus injections are associated with a response rate of 0–17% [10–12]. Low-dose continuous infusion of 5FU 300 mg/m^2/day produced a response rate of 8.4% and a median survival time of 5.1 months in patients with locally advanced and metastatic disease [14]. More recently, a high-dose weekly infusion of 5FU has also been investigated in pancreatic cancer. The present trial showed a disappointing low response rate of 9%, which was below the preset level of interest (20%) of this schedule.

When considering the results of this trial, it should be taken into account that only patients with metastatic disease were eligible. In addition, the criteria for measurability were stringent, and deliberately required relatively large lesions in order to improve the accuracy of repeated measurements. Locally advanced disease was excluded, because the pancreatic primary was not considered a target for response assessment, as such lesions may contain a considerable amount of fibrosis. A set of studies using the gemcitabine and fluorouracil combination to treat pancreatic cancer show that the median survival increases with an increasing proportion of locally advanced disease. Median survival was 4.4, 6.7, 7, and 11 months, respectively, for proportions of patients with 0%, 11%, 46% and 64% of locally advanced disease [23–26]. The median survival of 19 weeks, as observed in the present study, is in agreement with what can be expected in a population of patients who all have metastatic disease. In another study of patients with locally advanced and metastatic disease treated with high-dose weekly 5FU, the response rate was 8%, and the median survival approximately 8 months [27]. The proportion of patients experiencing benefit from the treatment was larger and correlated with those patients who had stabilisation of their disease. These data are comparable to results achieved with single-agent gemcitabine, which is easier to administer. The high-dose weekly schedule might be useful in combination regimens, as it is associated with limited haematological toxicity.

In conclusion, the activity of high-dose infusional 5-FU/LV by itself to treat metastatic pancreatic cancer is insufficient. Whether improved results can be obtained by high-dose infusional 5-FU/LV in combination with other agents, such as CPT-11, oxaliplatin or the taxanes, will require further study.

Conflict of interest

None.

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