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Original article

Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC early clinical trials group study

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Summary

Background: CPT-11 (irinotecan) is a semi-synthetic derivative of camptothecin and exerts its activity by inhibiting DNA topoisomerase I. A phase II study of this drug was performed in patients with pancreatic cancer.

Patients and methods: Eligibility criteria included advanced non-chemotherapy-pretreated pancreatic cancer. CPT-11 was administered as a 30-minute i.v. infusion at a dose of 350 mg/m^2 diluted in 250 ml normal saline every 3 weeks.

Results: Thirty-four eligible patients were enrolled in the study, thirty-two of them were evaluated, and three achieved partial responses (9%; 95% C.I. = 3%–25%). The duration of response was 7.2, 7.5 and 7.8 months, respectively. Thirteen patients had no change, fourteen patients had progressive disease and two had early progressive disease. The median duration of survival for all patients treated was 5.2 months. The main toxicities (CTC grade ⩾ 3) were diarrhea, leukocytopenia, asthenia, nausea and vomiting in, respectively, 7%, 16%, 8%, 6%, 4% of the courses. These toxicities were reversible and manageable with anti-emetics and prophylactic or curative antidiarrheal agents.

Conclusion: CPT-11 is an interesting moderately effective drug in pancreatic cancer.

Key words: CPT-11, irinotecan, pancreatic cancer

Introduction

In recent decades the incidence of pancreatic cancer has increased all over the world. Despite tremendous efforts in early diagnosis and therapy the prognosis is still dismal. Over 99% of the patients will die of their disease within 5 years. The main reason is that in approximately 90% of the cases the tumor is diagnosed late and in an advanced stage, when effective surgery is no longer possible. The median survival of patients with locally advanced disease is approximately 3–5 months and the survival of patients with distant metastases about 2 months [1, 2].

Pancreatic cancer is considered a chemoresistant tumor. The activity of most cytotoxic drugs is disappointingly low. The reported objective response rates in patients with measurable disease usually do not exceed 10%, with the possible exception of 5-fluorouracil, the anthracyclines, mitomycin C, ifosfamide, cisplatin and streptozotocin. There is thus a great need for active new drugs.

Recently a great deal of attention has been paid to DNA toposimerases as novel targets for cancer chemotherapy. The DNA topoisomerases are essential nuclear enzymes which control and modify the topologic states of DNA and are involved in the processes related to cell division and growth. They have been classified into types I and II, which are believed to alter the topology of single- and double-stranded DNA, respectively.

The new semi-synthetic camptothecin derivative, CPT-11 (irinotecan (INN), 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy camptothecin hydrochloride trihydrate) is a topoisomerase I inhibitor. It has very low intrinsic in vitro activity and requires metabolic activation to SN-38. It has greater antitumor activity and less toxicity than camptothecin itself in animals [3, 4]. Data from phase I clinical trials with CPT-11 conducted in France suggested that a dose of 350 mg/m^2 every 3 weeks was the optimal dose [5].

CPT-11 is undergoing clinical testing and has shown definite antitumor activity against small-cell lung cancer [6], non-small-cell lung cancer [7], leukemia [8], lymphoma [9], colorectal cancer [9–11], gastric cancer [12] and gynecologic cancers [13, 14].

We have performed a phase II study with the drug in patients with non-pretreated advanced pancreatic cancer.

Patients and methods

All patients entered into this trial had histologically or cytologically proven pancreatic cancer. Inclusion criteria included the following: locally advanced, unresectable or metastatic disease, with uni- or bidimensionally measurable lesions. If the primary tumor was considered as a measurable lesion it had to be unequivocally demarcated by appropriate technology: CT scan with intravenous and gastrointestinal contrasts or endoscopic ultrasonography. The primary lesion had to measure at least 3 cm. Liver metastases were accepted as criteria of response if they are measurable on CT-scan or ultrasonography and if they fulfil the following conditions: a single lesion must measure at least 2.5 cm in diameter and pathologic proof of malignancy was required when multiple liver metastases were present: one lesion must measure at least 2 cm in diameter. No proof of malignancy was required in these cases. The age should be $\geq$ 18 and $\leq$ 75 years, WHO performance status $\leq$ 2; life expectancy > 3 months; adequate baseline organ function defined as WBC $\geq 4 \times 10^9$/l, granulocytes $\geq 2 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, creatinine $\leq$ 140 µmol/l, liver function: in absence of hepatic metastases: serum bilirubin $\leq 1.25 \times$ N (normal), ASAT and ALAT ≤ 2 N, if liver metastases were present: serum bilirubin $\leq$ 1.5 N, ASAT and ALAT $\leq$ 4 N. Informed consent had to be obtained according to local rules. Criteria for exclusion were: prior chemotherapy or radiotherapy, brain or leptomeningeal disease, other concomitant malignant disease, active infection, overt pulmonary or cardiac disease and chronic enteropathy or important diarrhea.

Administration and evaluation

CPT-11 was provided by Rhône-Poulenc Rorer (Neuilly sur Seine, France) in 2 ml and 5 ml vials at a concentration of 20 mg/ml. CPT-11 was administered as a 30-minute i.v. infusion at a dose of 350 mg/m^2 diluted in 250 ml normal saline every 3 weeks.

If diarrhea $\geq$ grade 3 occurred during or following the infusion, the infusion time had to be extended to 90 minutes for the next administration. The recommended anti-diarrheal agents were atropine s.c. 0.25 mg or loperamide 4 mg orally every 2 to 6 hours as prophylactic treatment or as curative treatment if diarrhea occurred. It was intended for at least 2 courses of CPT-11 to be administered.

In instances of granulocytes less than 1.5, WBC less than 3×10^9/l, or a platelet count less than 100×10^9/l, chemotherapy was withheld for 7 days. If the nadir count of granulocytes at days 8 or 15 was less than 0.5×10^9/l or platelet count less than 25×10^9/l the dose of the next course was adjusted to 300 mg/m^2. If the nadir of granulocytes after 300 mg/m^2 was less than 0.5×10^9/l or platelets less than 25×10^9/l the dose of the next course was reduced to 260 mg/m^2.

Follow-up studies included weekly complete blood cell counts and serum creatinine (the latter only in case of diarrhea), and 3 weekly serum ionogram, bilirubin, ASAT, ALAT, alkaline phosphatase, total protein and albumin.

The end points of this study were response rate and toxicity. The tumor evaluation was performed after the first two cycles and repeated every 3 courses thereafter.

Complete response (CR) was defined as the disappearance of all known disease as determined by 2 observations not less than 4 weeks apart. Partial response (PR) was defined, in instances of bidimensionally measurable disease, as a decrease of at least 50% in the sum of the products of the greatest perpendicular diameters of all measurable lesions for 4 weeks. For unidimensionally measurable disease, PR was defined as a reduction of at least 50% in the sum of the largest diameters of all lesions as determined by 2 observations not less than 4 weeks apart. No change (NC) was defined as a less than 50% reduction or less than a 25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions, without appearance of new lesions. Progressive disease (PD) was defined as a greater than 25% increase in the size of all measurable lesions or the appearance of new lesions.

Toxicities were graded according to the Common Toxicity Criteria for cancer clinical trials.

Results

From July 1992 to December 1993, 38 patients with previously untreated non-resectable pancreatic cancer were entered into the study (Table 1). Four patients were not considered eligible: 1 had received prior chemotherapy, 1 had no measurable lesion, 1 had an active infection at the start of the treatment and 1 had no histologically or cytologically proven pancreatic carcinoma. Two patients were not evaluable, because they went off study after 1 course: one patient refused further treatment and the others died of a lung embolism.

The pancreas was involved in 33 of 34 eligible patients. In 25 patients the primary tumor was the target lesion. Liver involvement was present in 22 patients, lung metastases in 5, lymph node metastases in 12, soft tissue involvement in 3 patients and spleen localisation in 1 patient.

At the time of evaluation 156 courses had been given to 34 patients. One patient is still on study. CPT-11 was well tolerated. The most frequently occurring side effect was diarrhea. It was seen to be drug-related during 105 courses (67%) and in 31 patients (91%). It was of CTC grade $\geq$ 3 during 7% of the courses and in 21% of the patients (Table 2). The median number of stools per day was 3 with a range of 1–9. During 4 courses there was only diarrhea during the first 24 hours, in 72 courses the diarrhea continued after the first 24 hours and in 29 courses the diarrhea started after 24 hours. Most patients were treated with loperamide. In 11 patients also atropine was given during 53 courses.

For subsequent courses there was no significant difference in the occurrence of diarrhea between patients who had taken prophylactic antidiarrheal agents and those who had not.

Malaise was seen in 8% of the cycles and nausea in 6%. The reported neurological grade 3 side effect consisting of weakness with impairment of function of the left leg is probably related to the disease and not to CPT-11.

The grade 3 and 4 hematological toxicities are listed in Table 3. Grade 3 and 4 leukocytopenia occurred in 16% of the cycles and 50% of the patients. Conversely,

Table 1. Patient characteristics (n = 34).

Sex	
Male	22
Female	12
Age, years	
Median	56
Range	43–76
Stage	
II (locally advanced)	6
III (distant metastases)	25
Unknown	3
Performance status	
Median	1
Range	0–2
Previous surgery	15

Table 2. Non-hematological toxicity. Common toxicity criteria.

	Per patient				Per course			
	Grade		No.		Grade		No.	
	3	4	Pts	(%)	3	4	Crs	(%)
Asthenia/ malaise/ fatigue	9	2	11	(32)	11	2	13	(8)
Diarrhea	3	4	7	(21)	7	4	11	(7)
Nausea	10		10	(29)	10		10	(6)
Vomiting	5	2	7	(21)	5	2	7	(4)
Alopecia	1		1	(3)	2		2	(1)
Anorexia	1		1	(3)	1		1	(<1)
Pain		1	1	(3)		1	1	(<1)
Constipation	1		1	(3)	2		2	(1)
Infection	1		1	(3)	1		1	(<1)
Neurological	1		1	(3)	1		1	(<1)
Sialorrhoea	1		1	(3)	1	1	2	(1)

Table 3. Hematological toxicity. Common toxicity criteria.

	Per patient				Per course			
	Grade		No.		Grade		No.	
	3	4	Pts	(%)	3	4	Crs	(%)
Anemia	2		2	(6)	2		2	(1)
Leucopenia	13	4	17	(50)	21	4	25	(16)
Neutropenia	5	12	17	(50)	16	12	28	(18)
Thrombo-cytopenia		1	1	(3)		1	1	(<1)

grade 3 and 4 thrombocytopenia was seen in fewer than 1% of the cycles and 3% of the patients.

Dose reduction was necessary in 29 of 156 cycles (in 4 patients only) for the following reasons: Hematologic toxicity in 2, sepsis in 1 and diarrhea in 1 patient.

Three patients achieved partial responses (9%, 95% confidence interval 3–25%), lasting 7.2, 7.5 and 7.8 months. The target lesions in these patients were the primary tumor in 1, pancreas tumor, liver and lymph node metastases in 1 and lymphnode involvement in 1 patient. All responses were confirmed by independent review. Thirteen patients had NC. The median duration of the NC was 4 months (range $2^1/_2$–22 months).

One patient had a primary tumor of 45 × 45 mm which did not change significantly during 22 months, but the patient became clinically non-symptomatic and the CA 19-9 decreased from 1505 to 82 U/ml. Fourteen patients had PD and 2 patients EPD.

The median survival for all patients treated was 5.2 months (0.4-22+ months).

Discussion

The low response rate of CPT-11 presumably does not accurately reflect the real efficacy of the drug, because even with newer imaging techniques evaluation of a response in pancreatic cancer remains rather unreliable. To assess the value of a drug in advanced pancreatic cancer survival data are of more importance. The overall median survival time was 5.2 months (range 0.4-22+), whereas a survival of approximately 2.6 months was to be expected based on the staging of the patients [1, 2].

In addition it was recently shown by Abigerges et al. [15, 16] that the recommended dose of CPT-11 for phase II studies with proper antidiarrhea prophylaxis with loperamide exceeded 500 mg/m^2 every three weeks. Thus the dose in our study may have been too low.

Because CPT-11, like the other camptothecin derivatives, exerts its antitumor activity in a way that is distinct from that of all other anticancer compounds in current use, and because there is still a dearth of effective cytostatic drugs in pancreatic cancer it seems appropriate also to test this higher dose in pancreatic carcinoma. This is supported by the findings of Sakata et al. [17], who established the effectiveness in advanced pancreatic cancer of 100 mg/m^2 CPT-11 once a week or 150 mg/m^2 once every week.

Despite the rather low response percentage of CPT-11 in this phase II trial in metastatic pancreatic cancer, it is an interesting agent.

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