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Original Paper

Phase II Trial of Topotecan as a 21-day Continuous Infusion in Patients with Advanced or Metastatic Adenocarcinoma of the Pancreas

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The aim of this study was to determine the efficacy and toxicity of topotecan administered as a 21-day continuous intravenous infusion in patients with advanced or metastatic adenocarcinoma of the pancreas. 26 previously untreated patients with advanced or metastatic pancreatic adenocarcinoma received topotecan at a dose of 0.5 mg/m^2/day or 0.6 mg/m^2/day as a continuous intravenous infusion for 21 days. Courses were repeated every 28 days. 26 patients were assessable for response and toxicity on an intent-to-treat basis. The initial 8 patients at a starting dose of 0.6 mg/m^2/day experienced unacceptable myelosuppression and dose delays. The subsequent 18 patients, therefore began therapy at a dose of 0.5 mg/m^2/day. The major toxicity of topotecan at this dose and schedule was myelosuppression, which was reversible and non-cumulative. There were no complete responses and two partial responses for a total response rate of 8% (95% confidence interval, 1–25%). Response durations were 17 and 45 weeks. Stable disease was seen in 3 patients. The median time to progression for all patients was 8 weeks and the median survival was 20 weeks. Topotecan given as a 21-day continuous intravenous infusion has a similar response rate and median survival to our previously reported study of the 5-day short infusion regimen in pancreatic carcinoma. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

ADENOCARCINOMA OF the pancreas is expected to be the fourth leading cause of cancer death in the U.S.A. in 1997, with incidence and mortality rates being nearly equal [1]. Therapy remains inadequate, and surgical resection in early stage disease offers the only reasonable chance of cure, although the majority of patients are unresectable at the time of presentation. Long-term survival rates of 20% have been reported in patients undergoing resection, but overall 5-year survival rates are only 1–4% [2]. Most studies employing 5-Fluorouracil (5-FU) based chemoradiation demonstrated a survival advantage in locally advanced, unresectable disease, but only patients with good performance status benefitted from therapy [3]. Distant failure in the form of hepatic metastases occurs in 50–70% of patients following combined-modality therapy, emphasising the need for better systemic agents.

As a single agent, 5-FU has produced response rates of up to 20% in advanced disease, with little impact on survival [4]. Combination chemotherapy has not proven superior to single-agent therapy and is more toxic [5]. A partial response rate of 11% to gemcitabine (2′,2′-difluorodeoxycytidine) was demonstrated in one phase II trial [6]; improvements in pain, performance status and weight were observed, even in non-responders, with 23% of patients alive at 1 year. These findings were confirmed in a phase III trial in which gemcitabine was demonstrated to be superior to 5-FU, which led to the approval of gemcitabine for use as single-agent therapy in

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advanced pancreatic cancer [7]. In this randomised trial, clinical benefit was reported in 23.8% of gemcitabine-treated patients compared with 4.8% of 5-FU-treated patients; median time to disease progression and survival were significantly prolonged in gemcitabine-treated patients. However, these gains are modest, and new agents for the treatment of pancreatic cancer are urgently required.

Topotecan (9-dimethylaminomethyl-10-hydroxycamptothecin, Hycamtin®) is a topoisomerase inhibitor which has demonstrated a broad spectrum of activity in human tumour cell lines [8] and xenografts [9, 10], and phase I trials have investigated a number of dosing schedules [11].

Myelosuppression, in the form of reversible, non-cumulative granulocytopenia was the dose-limiting toxicity at all schedules tested. Anaemia and thrombocytopenia were seen with prolonged infusions. Non-haematological toxicities included nausea, fatigue, and diarrhoea, but were mild and not dose limiting [11]. The 5-day 30-min infusion schedule repeated every 21 days was recommended for broad phase II testing, and we have recently reported the results of a phase II study in pancreatic cancer using this regimen [12].

Preclinical studies have suggested that prolonged administration of topotecan may be more effective and provide a superior therapeutic index [8, 9]. A previous phase I study of 21-day continuous topotecan infusion demonstrated reversible leucopenia and thrombocytopenia to be dose limiting at a dose of 0.7 mg/m^2/day [13]. We, therefore, conducted a phase II trial to determine the efficacy and toxicity of topotecan when administered as a continuous intravenous infusion for 21 days repeated every 28 days in patients with advanced or metastatic adenocarcinoma of the pancreas.

PATIENTS AND METHODS

Eligibility criteria

Patients were enrolled onto this study between March 1994 and September 1996. All were at least 18 years of age and had histologically confirmed pancreatic adenocarcinoma with distant metastases (stage IV) or stage III disease not suitable for combined-modality therapy. Patients had not received prior chemotherapy and were not candidates for curative surgical resection. An Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, and a life expectancy ≥ 3 months were required. Patients were required to have bidimensionally measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) scan, chest X-ray, or ultrasound with at least one diameter ≥ 2 cm. Prior radiotherapy, surgery or immunotherapy was allowed if the interval was ≥ 4 weeks. Eligibility further required adequate bone marrow function (neutrophils $\geq 2.0\times10^9$/l and platelets $\geq 100\times10^9$/l), creatinine ≤ 1.5 mg/dl, serum bilirubin ≤ 2.0 mg/dl, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels ≤ 2 times the upper limit of normal, or in the presence of liver metastases, ≤ 5 times the upper limit. All patients were given information on the purpose and conduct of this study, and signed written informed consent in accordance with federal, state, and institutional guidelines.

Treatment schedule

Topotecan, initially dosed at 0.6 mg/m^2/day, was administered as a 21-day continuous intravenous infusion repeated every 28 days. After accrual of 8 patients, a protocol amendment changed the starting single infusion dose to 0.5 mg/m^2/day as a result of unacceptable myelosuppression and subsequent dose delays. Topotecan (Hycamtin; SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania, U.S.A.) was supplied in vials as a light yellow, lyophilised cake, containing 5 mg of the free base, and reconstituted with 2 ml of sterile water with preservative prior to dilution. The appropriate volume of solution was transferred to the cassette. Final dilution to a total volume of 50 ml was made at a concentration such that the total daily dose was contained in 6 ml of solution. The cassette was inserted in a CADD-PLUS ambulatory infusion pump (Pharmacia-Deltec, St Paul, Minnesota, U.S.A.) adjusted at a flow rate of 6 ml/24 h and connected via a Hickman line or medi-port device. This topotecan solution is stable for at least 8 days under the conditions used in the study. The cassette and batteries were changed every week.

Dose modifications

Treatment cycles were repeated as scheduled if the neutrophil count was $\geq 2.0\times10^9$/l, haemoglobin ≥ 9.0 g/dl, and platelet count $\geq 100\times10^9$/l. The dosage of topotecan was reduced by 0.1 mg/m^2/day if myelosuppression persisted beyond day 28 or if the previous cycle of topotecan was stopped prematurely because of grade 4 neutropenia or grade 3 or 4 thrombocytopenia. For grade 3 or 4 non-haematological toxicity, the dosage was reduced by 0.1 mg/m^2/day. If toxicity was $\leq$ grade 2 during the previous two courses, the topotecan dosage was increased by 0.1 mg/m^2/day. The minimum single infusion dose was 0.2 mg/m^2/day. The maximum single infusion dose was 0.7 mg/mg^2/day.

Pretreatment and follow-up study scheme

Pretreatment evaluation consisted of a history and physical examination, complete blood count, serum chemistry, electrolytes and creatinine, urinalysis, chest X-ray, CT or MRI scan of the chest and abdomen, CT or MRI scan of the head (to rule out brain metastases), and assessment of ECOG performance status. Complete blood counts were performed weekly during each cycle, or twice weekly if haematological toxicity $\geq$ grade 2 was noted. A history and physical examination, assessment of performance status, complete blood count, serum chemistry, urinalysis and assignment of toxicity according to the NCI common toxicity criteria (CTC) were performed prior to each subsequent treatment course [14]. Measurable lesions identified at baseline were reviewed before each alternate course.

Criteria for evaluation

Responses were evaluated according to WHO criteria [15]. Response was assessed by the treating physician and the investigator separately. Survival duration was measured from the first day of treatment until the day of death. Response duration was measured from the time of the initial documented response to the first sign of progression. Time to progression was the time from the first infusion to the time of initial documented progression. The survival curve was plotted using the technique of Kaplan and Meier [16].

RESULTS

Patient characteristics

26 patients were entered into the study, and all were assessable for response. There are no patients remaining on study. Only intent-to treat analyses were performed, so all

Table 1. *Patient characteristics*

Characteristics	No. of patients
No. entered	26
Assessable	26
Ineligible	0
Sex	
Male	16
Female	10
Age (years)	
Mean	61
Range	39–80
Performance status	
0	5
1	20
2	1
Stage of disease	
III	1
IV	25
Prior treatment	
Surgery	6
Radiotherapy	0
Chemotherapy	0

patients were included in toxicity assessment and survival analysis. A total of 5 patients (19%) were withdrawn from the study: 2 patients were withdrawn from the study for adverse experiences, 1 patient for a decrease in performance status, 1 because of refusal to continue treatment, and 1 patient was lost to follow-up. The demographic characteristics of the patients entered are shown in Table 1.

Toxicity

Haematological toxicity. Haematological toxicity predominated, mainly in the form of reversible neutropenia (Table 2). Grade 3/4 neutropenia occurred in 7 patients at the 0.6 mg/m^2/day dose level, and in 6 patients who received 0.5 mg/m^2/day. 13 patients developed grade 3/4 anaemia (4 at 0.6 mg/m^2/day and 6 at 0.5 mg/m^2/day), and 9 patients developed grade 3/4 thrombocytopenia (4 at 0.6 mg/m^2/day and 3 at 0.5 mg/m^2/day). Granulocyte-colony stimulating factor (G-CSF) was administered to 4 patients. 14 patients required packed red blood cell transfusions for anaemia and 4 patients required platelet transfusions. Twenty six of a total of 53 treatment courses were delayed and the topotecan dose was reduced in 20 courses because of a haematological toxicity. There were three episodes of documented sepsis in 2 patients and four episodes of fever $\geq$ grade 2 associated with grade 4 neutropenia. No patient with grade 4 neutropenia experienced sepsis, and there were no deaths as a result of infection or sepsis in the setting of neutropenia.

Non-haematological toxicity. All patients experienced some form of non-haematological toxicity, but the majority of these toxicities were mild (grade 1/2; Table 2). No grade 3/4 stomatitis occurred. 3 patients experienced grade 3/4 hyperbilirubinaemia, and gastrointestinal haemorrhage occurred in 3 patients; 1 of which was associated with thrombocytopenia. All the most common non-haematological toxicities occur frequently in the setting of advanced or progressive pancreatic cancer, and it is, therefore, difficult to determine if these were solely treatment related.

Dose intensity. The overall median dose intensity obtained for the 26 patients entered was 2.10 mg/m^2/week (range 0.86–3.04 mg/m^2/week).

Table 3. *Responses*

	No.	(%)
Entered into study	26	
Total responses	2	(8)
Complete responses	0	(0)
Partial responses	2	(8)
Stable disease	3	(12)
Progressive disease	19	(73)
Not evaluable	2	(8)

Responses

There were no complete responses, but there were two partial responses in the 26 patients entered into the study, for a total response rate of 8% (95% confidence interval, 1–25%) (Table 3). 3 patients (12%) maintained stable disease for at least 8 weeks.

The 2 patients who exhibited partial responses were still alive at completion of the study. There was a partial response documented for 1 patient at week 33 that lasted for 45 weeks. This patient progressed at 78 weeks but was alive at 102 weeks when the study ended. The other response was

Table 2. *Drug-related toxicity per patient* ($n = 26$)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3–4 (%)
Haematological (0.6 mg/m^2/day ($n = 8$)					
Neutropenia	0	1	3	4	88
Anaemia	1	2	4	0	50
Thrombocytopenia	2	1	1	3	50
Haematological (0.5 mg/m^2/day ($n = 18$)					
Neutropenia	2	3	2	4	33
Anaemia	3	7	8	1	50
Thrombocytopenia	7	1	1	4	28
Non-haematological (all doses)					
Nausea	7	9	0	0	0
Fatigue	7	4	3	0	12
Diarrhoea	8	3	0	2	8

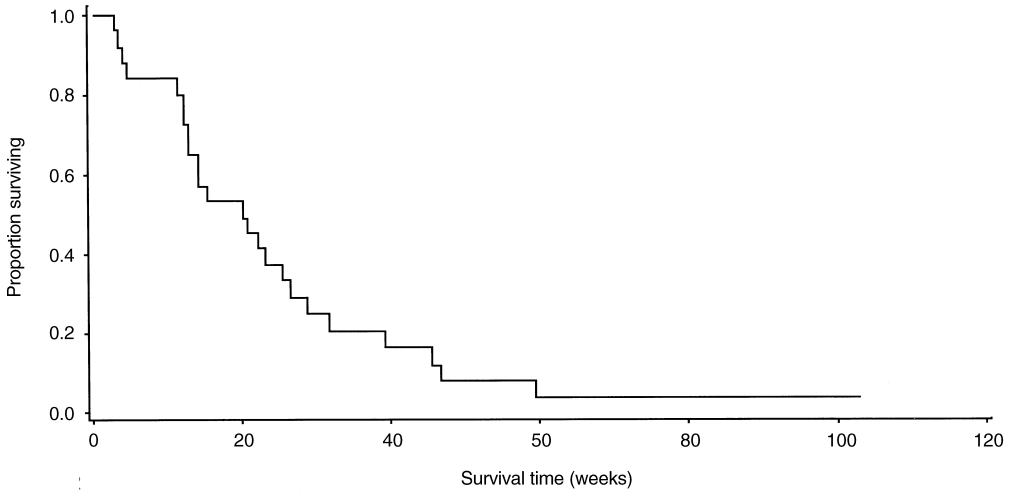

Figure 1. Kaplan–Meier survival estimate for the 26 patients entered into this trial.

documented at week 7 and lasted 17 weeks, with the patient still alive at 25 weeks.

The median time to progression for all patients was 8 weeks. Kaplan–Meier survival estimates are plotted in Figure 1. The estimated median survival for all patients was 20 weeks.

DISCUSSION

The treatment of advanced pancreatic adenocarcinoma remains problematic. The refractory nature of this malignancy to standard chemotherapeutic agents emphasises the need to identify more effective systemic agents in the clinic. Recent studies have focused on improvements in symptoms and quality of life as measures of efficacy [7], and where this has been observed, an advantage in time to progression and survival has also been evident.

Topotecan displayed significant activity against human cancer cell lines and xenografts during preclinical testing, specifically colorectal, breast, non-small cell lung, ovarian and renal cell cancers, as well as paediatric rhabdomyosarcoma and osteosarcomas. It also emerged that continuous exposure to topotecan was significantly more active than short-term incubation, although recent data suggest that this schedule dependency may not be true for all tumours [8, 17]. Whereas the daily $\times 5$ short infusion was selected for broad-phase II testing, activity and tolerability of topotecan when administered as a 21-day continuous infusion was demonstrated in one phase I trial [13]. The principal toxicity in this trial was myelosuppression, with more anaemia and thrombocytopenia than with short infusion regimens. Our study confirms this finding, as more patients experienced grade 3/4 anaemia and thrombocytopenia than in our previous study of the 5-day regimen in pancreatic cancer [12]. Non-haematological toxicities were similar in the two studies.

Reports of trials using prolonged continuous infusion of topotecan have been few to date. One recently reported phase II trial of 21-day continuous topotecan infusion in metastatic colorectal cancer demonstrated a 10% response rate, and 43% of patients maintained stable disease [18]. In another phase II trial in small cell lung cancer [19], a 30% partial response rate was reported in patients with responsive disease (relapsed more than 3 months after a partial response). More promising data have been reported in ovarian cancer: a phase I trial of topotecan administered as a 14-day continuous infusion in combination with paclitaxel every 21 days demonstrated activity in patients with ovarian and non-small cell lung cancers, and is presently ongoing [20].

Two of three previously reported phase II trials of topotecan in advanced pancreatic cancer demonstrated no responses with the 5-day short infusion regimen [21, 22]. In our own study, 10% of the patients responded, and the median survival was 19 weeks [12]. The partial response rate of 8% and the median survival of 20 weeks in this trial with 21-day continuous infusion suggests that topotecan has low but detectable activity in this disease. The time to progression and median survival reported here are similar to those observed with gemcitabine in a randomised trial [7]. Also, 28% of patients in the gemcitabine arm of that study had stage II or III disease; survival in these patients is significantly longer than those with stage IV disease, which was the stage of 25 of 26 patients entered into this study.

The hypothesis proposed by this study was that continuous infusion of topotecan might be more effective than a 5-day regimen in pancreatic cancer. Since response rates and survival were not strikingly better with the continuous infusion, the alteration in schedule has not resulted in a useful increment in activity. As in the 5-day study, however, we observed evidence of the activity of this drug, and combination studies with a number of other promising novel agents are in progress.

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