Phase II study of troxacitabine in chemotherapy-naïve patients with advanced cancer of the pancreas

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Background: Troxacitabine (Troxatyl®) is a novel L-enantiomer nucleoside analog with activity in pancreatic cancer xenograft models.

Patients and methods: Troxacitabine 1.5 mg/m² was administered by 30-min infusions daily ×5 every 4 weeks to 54 patients with advanced pancreatic cancer. Patients were evaluated for objective tumor response, time to tumor progression (TTP), changes in tumor marker CA 19-9, survival, safety, pain, analgesic consumption, Karnofsky performance status and weight change.

Results: Median TTP was 3.5 months (95% CI 2.0–3.8), median survival 5.6 months (95% CI 4.9–7.4), and the 1 year survival rate 19%. Best responses were stable disease in 24 patients with eight patients having stable disease for at least 6 months (15%). A 50% or greater decrease in CA 19-9 was seen in seven of 44 assessed patients (16%). Grade 3 and 4 neutropenia were observed in 37% and 30% of patients with one episode of febrile neutropenia. The most common drug-related non-hematological toxic effects reported were cutaneous, with 22% and 6% of patients reporting grade 2 and 3 skin rash, respectively and 4% grade 2 hand–foot syndrome.

Conclusion: Troxacitabine administered by a bolus daily ×5 monthly regimen has modest activity in advanced pancreatic adenocarcinoma.

Key words: nucleoside analog, pancreatic cancer, phase II, troxacitabine

Introduction

Pancreatic adenocarcinoma is diagnosed in approximately 32 000 new patients in North America each year [1]. The mortality rate virtually parallels the incidence rate, and pancreatic adenocarcinoma is the fifth most common cause of cancer-related death. Gemcitabine has been approved for first line treatment of patients with pancreatic carcinoma following the demonstration of a modest survival advantage relative to 5-fluorouracil [2]. However, the reported median survival time following gemcitabine therapy is approximately 6 months with a 1 year survival rate of around 20% [2]. Given such a poor therapeutic outcome, the therapy of advanced pancreatic cancer remains a significant unmet need.

Naturally occurring nucleosides and nucleoside analogs developed to date as anticancer therapeutics, such as gemcitabine, are in the D stereocchemical configuration. Until recently, corresponding unnatural L-enantiomers have largely been considered to be unrecognizable by cellular enzymes and therefore biologically inactive. However, the discovery that the L-DddC (2′-deoxy-3′-thiacytidine; lamivudine; 3TC®) stereoisomer was more potent than its corresponding D-enantiomer against human immunodeficiency [3] and hepatitis B [4] viruses led to the identification of L-OddC (2′-deoxy-3′-oxacytidine; troxacitabine; Troxatyl®), a nucleoside analog with significant preclinical anticancer activity [5]. The different isomeric configurations confer to troxacitabine different mechanistic properties relative to gemcitabine: its cellular membrane permeation is non-carrier mediated [6] and it is resistant to deamination [5], phosphorylated from diphosphate to triphosphate by 3-phosphoglycerate kinase [7] and excised from DNA by human apurinic/apyrimidinic DNA endonuclease [8]. Troxacitabine causes chain termination after it is incorporated into DNA since it lacks a hydroxyl group and is a potent inhibitor of DNA polymerases [9]. Troxacitabine has significant activity in pancreatic cancer xenograft models, where it was more active than gemcitabine in the Panc-01 model and has moderate activity in the gemcitabine refractory MiaPaCa model [10].
Three phase I studies of troxacitabine using different bolus administration schedules (every 3 weeks; daily ×5 monthly and weekly ×3 every 4 weeks) were carried out in patients with solid tumors and a fourth phase I study using the daily ×5 schedule was carried out in acute leukemia [11–15]. Granulocytopenia and skin rash were dose-limiting in the solid tumor studies and stomatitis and hand–foot syndrome in the acute leukemia trial. The pharmacokinetics of troxacitabine were linear and consistent across the phase I trials with urinary excretion of unchanged troxacitabine accounting for most drug elimination [11, 12, 14]. Pilot solid tumor phase II clinical trials were carried out in prostate, colorectal, pancreatic, renal cell [16], non-small-cell lung cancer [17] and malignant melanoma. In the pancreatic cancer trial, one of the seven patients with no prior chemotherapy had a partial response. There was no evidence of troxacitabine activity in eight patients previously treated with gemcitabine. The most commonly observed toxic effects in the phase II studies were hematological (neutropenia) and cutaneous (skin rash, dry skin, pruritus and hand–foot syndrome).

On the basis of the preclinical and clinical results and the activity of other nucleoside analogs in pancreatic adenocarcinoma, it was decided to study the activity of troxacitabine in advanced pancreatic cancer in patients with no prior chemotherapy using the daily ×5 every 4 weeks schedule.

**Patients and methods**

**Patient eligibility**

Eligible patients had a cytological or histological diagnosis of unresectable or metastatic adenocarcinoma of the pancreas. Patients with clinically significant ascites (i.e. requiring paracentesis) were not eligible. Analgesic usage had to be stable for 5 days before study enrollment. Patients were at least 18 years of age, had an estimated life expectancy of at least 12 weeks, a performance status of ≥50 on the Karnofsky scale and measurable disease. Prior radiation treatment of local disease could have been administered provided that the treatment was completed at least 3 months before registration. No prior chemotherapy was allowed other than as a radiosensitizer. Patients had to have adequate hematological (ANC ≥1.5 × 10^9/l; platelet count ≥100 × 10^9/l), renal (serum creatinine within the normal range or an estimated creatinine clearance of ≥45 ml/min) and hepatic (total bilirubin ≤1.5× upper limit of normal (ULN); AST and ALT ≤3× ULN unless liver had tumor involvement) functions. The institutional ethics committee approved the protocol at each site, and written informed consent was obtained from all patients.

**Study design and treatment**

This was a phase II, single-arm, open-label, multicenter study of troxacitabine administered as a 30-min infusion at 1.5 mg/m² daily ×5 every 4 weeks. The primary objective was to determine the progression-free survival of chemotherapy-naive patients treated with troxacitabine. Secondary objectives were overall survival, objective response rate, toxicity and assessment of pain, analgesic consumption, Karnofsky performance status and weight change. Doses were reduced for hematological and other toxic effects, as graded using the NCI Common Toxicity Criteria (CTC) version 2.0. If patients experienced grade 2 or higher skin rash, treatment was delayed until the skin rash had recovered to at least grade 1. Retreatment was carried out at the same dose but administered with prednisone at 25 mg orally daily for the first 5 to 7 days, starting the first day of treatment. Treatment was delayed in the event of grade 2 or 3 hand–foot syndrome until recovery to at least grade 1 with subsequent cycles administered at a 25% dose reduction. Study treatment was continued until there was evidence of disease progression, unacceptable toxicity, the patient requested discontinuation of study treatment, or the investigator felt the patient could not benefit from further treatment. Treatments administered after patients progressed and went off therapy were not documented.

**Evaluation**

Progression-free survival was defined as the time from the first day of treatment to the first documentation of clinical or radiological tumor progression. Overall survival was calculated from the first day of treatment until the date of death. Assessment of measurable lesions was based on computed tomography or magnetic resonance imaging scans. Imaging studies were carried out at baseline and following every two cycles of treatment. Objective tumor responses were evaluated according to WHO Response Criteria. CA 19-9 levels were measured at baseline and every two cycles using commercially available assays at each participating institution. Baseline was defined as the last measurement within 7 days before day 1 of cycle 1. Percent reduction was the minimum per cent change value in all evaluated study cycles from baseline for each patient.

Pain and analgesic consumption were assessed weekly and Karnofsky performance status and weight change assessed monthly. Each patient participated in a 2–7 day lead-in period before receiving study drug in order to stabilize and characterize analgesic consumption and pain intensity. To establish a baseline measurement before study drug administration, assessments of Karnofsky performance status by the investigator and weight were taken within 72h before day 1 of cycle 1. For pain intensity, the patient baseline status was the mean pain intensity score of day 1 of cycle 1 using the Memorial Pain Assessment Card (MPAC) visual analog scale (assessed before troxacitabine administration) and the scores from the last 2 days of the pain stabilization period (i.e. days −2 and −1 before day 1 of cycle 1). For analgesic consumption, the patient’s baseline status in morphine mg equivalents was determined from the last 2 days of the pain stabilization period (i.e. days −2 and −1 before day 1 of cycle 1). Each patient was classified as positive, stable or negative for pain intensity, analgesic consumption and performance status evaluation and globally as achieving overall clinical benefit as previously described [2]. Safety data from physical examinations, laboratory evaluations, and adverse events were assessed according to the revised NCI CTC version 2.0. Complete blood counts were carried out at baseline and weekly thereafter whereas, after baseline, renal and hepatic function tests were repeated on day 1 of each treatment cycle. CA 19-9 tumor marker levels were obtained at baseline and on day 1 of every second cycle thereafter.

**Statistical methods**

All patients who received at least one dose of troxacitabine were evaluated for toxicity and efficacy. Overall survival and progression-free survival were derived by Kaplan–Meier curves. After the first 25 patients were entered, the 2-month progression-free rate was assessed with a null hypothesis that the proportion of patients free of progression was 20% versus an alternative hypothesis of a proportion of 40%. The study would have been stopped if eight patients or less out of 25 were free of progression at 2 months. This stopping rule provided 72.6% power at a significance level of 0.047. Treatment administration, adverse events and laboratory abnormalities were summarized descriptively.
Table 1. Patient demographics (n = 54)

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>Sites of metastases</th>
<th>Karnofsky PS</th>
<th>Gender</th>
<th>Median age, years (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>Liver</td>
<td>Median (range)</td>
<td>F/M</td>
<td>61 (41–78)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Lymph nodes</td>
<td>90 (60–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>6 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>48 (89%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subcutaneous</td>
<td>27 (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F, female; M, male.

Results

Patient characteristics

Fifty-five patients from eight clinical sites in Canada and the UK were enrolled into the study between August 2000 and September 2001. The modified intention-to-treat population used for study analysis is 54 patients since one patient never received study drug. Data were collected through September 2002, providing a minimum of 12 months of follow-up. Patient characteristics are listed in Table 1. Two (4%) patients had a prior Whipple’s resection. One patient had prior chemoradiation to the pancreatic cancer primary. Six (11%) patients had locally advanced unresectable disease confined to the pancreas and all others (89%) had metastatic disease.

Toxicity

The median number of treatment cycles administered was 2 (range, 1–15). Five patients (9%) received one cycle of therapy, 25 (46%) two cycles, 4 (7%) three cycles, 12 (22%) four cycles, 4 (7%) six cycles, 1 (2%) eight cycles and another 3 (6%) 14 or more cycles. Nineteen patients (35%) had dose reductions and 9 (17%) dosing delays during the study. All 54 treated patients were assessed for safety according to version 2.0 of the NCI CTC. Grade 3 or 4 neutropenia, assessed at the previous cycle nadir, occurred, respectively in 37% and 30% of patients, with one episode of febrile neutropenia. Grade 3 thrombocytopenia occurred in 6% of patients with no episodes of grade 4, and grade 3 and 4 anemia in 9% and 2% of patients, respectively. Non-hematological toxic effects are summarized in Table 2. The most common drug-related non-hematological toxic effects reported were cutaneous, with 22% and 6% of patients reporting grade 2 and 3 skin rash, respectively. No prophylactic prednisone was administered in this study. Grade 2 hand–foot syndrome was reported in two (4%) patients, with no grade 3 event reported. Most toxic effects were grades 1 and 2. Reported grade 3 toxic effects included abdominal pain (7%), constipation (15%), nausea (4%), vomiting (2%), fatigue (6%), pyrexia (2%) and pruritus (4%). No toxic deaths were observed in this study. Three serious adverse effects were reported as being at least possibly troxacitabine-related: one episode of neutropenic sepsis and two episodes of vomiting.

Efficacy

Median time to progression was 3.5 months (95% confidence interval 2.0–3.8 months), median survival 5.6 months (95% CI 4.9–7.4 months), and the 1 year survival rate 19%. According to investigator assessments, best responses were stable disease in 24 patients and radiological or clinical progressive disease in 30. Eight patients had stable disease for at least 6 months (15%) with three patients remaining stable for 14 months or longer, including one still on therapy after 16 months. Tumor status was also examined in terms of changes in the serum tumor marker CA 19-9. Baseline and follow-up data were available in 44 patients (81%) with elevated CA 19-9 serum levels at study entry. CA 19-9 decreased by ≥50% during therapy in seven (16%) patients.

Thirty-one patients (57%) had a minimum analgesic consumption of 10 mg morphine equivalents per day at baseline and four of the 27 with follow-up data (15%) decreased their analgesic use by ≥50% for at least 4 weeks. Median pain score at baseline was 14 mm. Twenty-eight patients (52%) had a minimum pain score of ≥20 at baseline and three of the 24 (13%) with follow-up data decreased their pain intensity score by ≥50% for at least 4 weeks. Eight patients out of 53 with baseline data (15%) had a Karnofsky score <80 and none of these had a ≥20-point improvement during the trial. Forty-one patients (77%) had either a Karnofsky performance status PS <80, a minimum analgesic consumption of 10 mg morphine equivalents per day or a minimum pain score of

Table 2. Incidence of most common treatment emergent adverse effectsa (n=54)

<table>
<thead>
<tr>
<th>Toxidity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>2 (4%)</td>
<td>13 (24%)</td>
<td>4 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (11%)</td>
<td>9 (17%)</td>
<td>8 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (9%)</td>
<td>6 (11%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (28%)</td>
<td>19 (35%)</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (28%)</td>
<td>11 (20%)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (11%)</td>
<td>19 (35%)</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (15%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9 (17%)</td>
<td>5 (9%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (9%)</td>
<td>3 (6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin rashb</td>
<td>20 (37%)</td>
<td>12 (22%)</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>6 (11%)</td>
<td>2 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (6%)</td>
<td>6 (11%)</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>8 (15%)</td>
<td>2 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

aTreatment emergent adverse effects are defined as adverse events that started after the first dose of study medication, or adverse events that were seen before the start of study medication but increased toxicity grade during the treatment period or within 30 days after treatment; patients are counted only once within each system organ class and preferred term at the greatest severity.

bInclusive of all reported events listed as dermatitis exfoliative, dermatitis, erythema, rash macular and rash pruritic.
≥20 at baseline and were thus eligible for clinical benefit response evaluation. Four of the 34 (12%) with available follow-up data had a positive clinical benefit response. Two additional patients who were not sufficiently symptomatic to meet the criteria for clinical benefit response evaluation increased their weight by >7% on the study while receiving eight and 14 cycles of therapy, respectively.

Discussion

Troxacitabine is a novel cytosine analog with an unnatural stereochemical orientation that confers on it some unique mechanistic characteristics relative to the natural stereoisomer analog gemcitabine. Its superior activity profile in human pancreatic adenocarcinoma xenografts relative to gemcitabine [10] and the observation of response in an earlier study led to the initiation of this trial. The primary goal of this study was to obtain more information on the activity of troxacitabine in pancreatic cancer and compare it with published gemcitabine trials. Objective tumor response rate was not chosen as the primary end point for this study since tumor responses can be very difficult to assess in pancreatic cancer. Furthermore, verifiable response rates have been very low both for gemcitabine and comparator drugs in a number of published randomized trials [2, 18–23]. Progression-free survival, 1 year and overall survival have been remarkably consistent, however, following gemcitabine therapy in these trials and seemed to offer a better benchmark against which to compare troxacitabine’s activity. Progression-free survival was chosen as the study’s primary end point since it enabled us to stop the study at an interim analysis if troxacitabine had significantly underperformed compared with gemcitabine. Historical comparisons between clinical trials are hazardous, however, since patient populations can vary. For example, the gemcitabine pivotal trial [2] only enrolled symptomatic patients and 72% of them had metastatic disease, whereas 77% of patients in this study would have had sufficient baseline symptoms to qualify for entry in the pivotal trial but 89% had metastatic disease. With these considerations in mind, progression-free survival, 1 year survival and overall survival obtained following troxacitabine therapy in this study appeared to be comparable overall to those reported with gemcitabine [2, 18–23]. The activity of troxacitabine in pancreatic adenocarcinoma was also evidenced by the observation that 16% of patients had a ≥50% decrease in CA 19-9 levels, a result comparable to that achieved with gemcitabine [24].

The incidence of hematological toxicity was low with a single episode of febrile neutropenia observed and, as in previous studies, the most prevalent non-hematological toxic effects were cutaneous [16]. However, the severity of observed skin rashes and hand–foot syndrome appeared lower than reported with the every 3-week schedule [16].

Troxacitabine and cytarabine have been shown to have additive effects in vivo in a human acute leukemia xenograft model [25]. Recently, troxacitabine and gemcitabine were also demonstrated to be synergic in vitro in four human pancreatic adenocarcinoma cell lines and to be at least additive in an in vivo model [26]. The mechanisms of additivity/synergy has not yet been elucidated but may involve different mechanisms of cellular drug uptake [6] and DNA repair [8]. A phase I trial is currently examining the feasibility of a troxacitabine/gemcitabine combination and early results indicate that both drugs can be safely combined at effective doses [27].

This study indicates that bolus administration of troxacitabine daily ×5 has modest activity in pancreatic adenocarcinoma, with survival data comparable to those reported with single-agent gemcitabine.

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References


