Anti-Cancer Drugs 1996, **7**, pp. 410–414

A phase II trial of topotecan in patients with previously untreated pancreatic cancer

Seamus O'Reilly, Ross C Donehower, Eric K Rowinsky, Sarah Ord and Louise B Grochow
Division of Pharmacology and Experimental Therapeutics, Rm 1-121, The Johns Hopkins Oncology Center, 600 North Wolfe Street, Baltimore, MD 21287-8934, USA. Tel: (+1) 410 955-8902; Fax: (+1) 410 550-5499.

Because currently available chemotherapeutic agents are largely ineffective in the treatment of pancreatic cancer, novel treatments are urgently needed to improve outcomes in this disease. The purpose of this phase II study was to evaluate the anti-tumor activity of topotecan, a hydrophilic camptothecin analog that has demonstrated a wide range of anti-tumor activity in preclinical and phase I studies. Topotecan was administered as a 30 min infusion at a dose of 1.5 mg/m^2/day for five consecutive days every 3 weeks, to chemotherapy-naive patients with advanced pancreatic cancer. Neutropenia was the principal toxicity of topotecan on this dosing schedule. No significant anti-tumor responses were observed in 27 patients with measurable disease. The median time to disease progression was 7 weeks and the median survival duration was 17.5 weeks. Thus, topotecan, administered on this schedule, is ineffective for patients with pancreatic carcinoma.

Key words: Pancreatic cancer, topotecan.

Introduction

Pancreatic cancer is the fifth most common cause of adult cancer-related death in the US.[1] At presentation, 80% of patients with pancreatic cancer will have unresectable or metastatic disease and only 3% will be alive 5 years after diagnosis.[2–4] Chemotherapy has shown only minimal activity against this disease and 5-fluorouracil is currently the only agent whose upper 95% confidence limit of response exceeds 20%.[3] Although aggressive multi-agent regimens have achieved preliminary response rates of up to 40%, only two randomized trials have shown any survival advantage with chemotherapy.[5,6] These dismal results suggest that approaches aimed at improving treatment efficacy for patients with pancreatic cancer must include the identification of novel targets for anti-cancer agents.

The enzyme topoisomerase I (topo I) modulates the topology of chromatin DNA by introducing transient breaks in DNA and removing excessive supercoils.[7] Although the levels and activity of topo I are only slightly increased in cells or tissues that are stimulated to proliferate,[8,9] topo I levels are significantly increased in both surgical tumor specimens and several human tumor xenografts.[10,11] Sodium camptothecin, the first topo I targeting agent to be evaluated clinically,[12,13] demonstrated unpredictable toxicity and a perceived lack of anti-tumor activity and so was excluded from further clinical trials. After topo I was identified as the target enzyme for the captothecins, however, analogs were developed, with topotecan being the first of the camptothecin analogs to enter clinical trials. In both preclinical[14] and phase I testing,[15–18] topotecan demonstrated a broad range of anti-tumor activity. Dose-related reversible neutropenia has been the principal toxicity of topotecan in all schedules evaluated to date; nevertheless, the broad spectrum of this agent's anti-tumor activity and its excellent toxicity profile argued for its evaluation in chemotherapy-naive patients with unresectable pancreatic cancer.

Patients and methods

Eligibility

Only patients with histologically or cytologically documented, bidimensionally measurable, unresectable adenocarcinoma of the pancreas of the ductal or undifferentiated variety were candidates for this study. Those patients with a consistent clinical syndrome (weight loss, early satiety, epigastric pain, painless jaundice and a pancreatic mass) and histologically documented adenocarcinoma without evidence of another likely primary tumor were eligible. Prior to enrollment, any patient with symp-

Supported by grant CA 63437 from the National Institutes of Health, Bethesda, MD.

Correspondence to LB Grochow

tomatic, localized, unresectable disease was given a multimodality evaluation including consultation with radiation therapy. Further eligibility criteria for the study included: (1) age > 18 years; (2) an Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 (ambulatory and capable of self-care); (3) a life expectancy of at least 12 weeks; (4) adequate hematopoietic function [absolute neutrophil count (ANC) $< 1500/\mu l$ and platelet count $> 100\,000/\mu l$); (5) adequate hepatic (total bilirubin ≤ 2.0 mg/dl) and renal (creatinine ≤ 2.0 mg/dl) functions; (6) no prior chemotherapy or radiation therapy to sites of measurable disease; (7) no major surgery within 21 days or wide-field radiation therapy within 28 days of entering the protocol; (8) no co-existing medical problems of sufficient severity to prevent full compliance with the study; and (9) no history of another malignancy (other than basal or squamous skin carcinoma or carcinoma *in situ* of the cervix) within 5 years of study entry Before receiving treatment, all patients gave written informed consent according to institutional and federal guidelines.

Dosage

The starting dose of topotecan was 1.5 mg/m^2 administered as a 30 min infusion daily for five consecutive days.[15–18] Dosages were adjusted based on myelosuppression, i.e. the dose of topotecan was increased to 2.0 mg/m^2/day if the ANC nadir during the prior course was $> 1000/\mu l$ and the platelet nadir was $> 75\,000/\mu l$. A second incremental escalation of dose to 2.5 mg/m^2 was permitted, if these identical criteria were satisfied. If the ANC nadir was $< 500/\mu l$ or the platelet nadir was $< 50\,000/\mu l$, the dose of topotecan was reduced to 1.0 mg/m^2/day.

Drug administration

Topotecan (SK&F 104864; SmithKline Beecham, King of Prussia, PA) was supplied by the Division of Cancer Treatment, National Cancer Institute (Bethesda, MD), in vials containing a lyophilized mixture of 5 mg topotecan and 100 mg mannitol, with the pH adjusted to 3–4 with hydrochloric acid or sodium hydroxide. Topotecan was reconstituted in our pharmacy with 2 ml sterile water, diluted in 100 ml of 5% dextrose solution and then administered i.v. over 30 min in the outpatient clinic.

Pretreatment and follow-up studies

Interval histories, physical examinations and routine laboratory studies were performed before treatment and every 3 weeks. Pretreatment and laboratory studies performed weekly included complete blood cell and differential white blood cell counts, electrolytes, urinalysis, and renal and liver function tests. Complete blood counts were obtained on days 8, 10 and 15, or if the ANC decreased to $\leq 1000/\mu l$ every 2 days. Electrocardiograms were obtained before treatment began. Toxicities were evaluated according to the NCI Common Toxicity Criteria.[19] Formal tumor measurements were performed after every two courses and treatment was continued if patients did not develop progressive disease or unacceptable toxicities. A *complete response* required a complete disappearance of all active disease on two measurements separated by a minimum period of 4 weeks. A *partial response* required a 50% or greater reduction in the sum of the product of the bidimensional diameters of all measurable lesions, as documented by two measurements separated by at least 4 weeks. A *minor response* required a decrease by less than 50% in the sum of the product of the bidimensional tumor measurements. *Response duration* was calculated from time of documented response until objective disease progression. *Survival time* was calculated from day 1 of topotecan treatment.

Statistical considerations

The primary objectives of this study were to determine the activity of topotecan in pancreatic cancer and to characterize the toxicities of topotecan in this patient population. Anti-tumor activity was defined as the proportion of patients with complete and partial responses. The study employed a two-stage design: if none of the first 14 patients had a partial or complete response, the trial was to be ended. If the true response rate was as high as 20%, the probability of incorrectly rejecting this treatment as ineffective was 5%.[20] If a major anti-tumor response was detected in any of the first 14 patients studied, an additional 13 patients were to be studied in a second stage of accrual to estimate more precisely the actual response rate. Survival and progression-free survival probabilities were calculated with the method of Kaplan and Meier[21]. Statistical analysis was performed by means of the Statistica W (StatSoft, Tulsa OK) software program.

Table 1. Patient characteristics

Characteristics	No. of Patients
Gender	
male	14
female	13
Mean age (range)	58 (41–80)
Performance status	
0	11
1	15
2	1
Prior therapy	
none	14
pancreas resection	3
palliative bypass	7
biliary stent	2
radiotherapy	1
Median duration in weeks between diagnosis and study entry (range)	9 (2–192)
Number of disease sites	
1	3
2	14
3	9
4	1

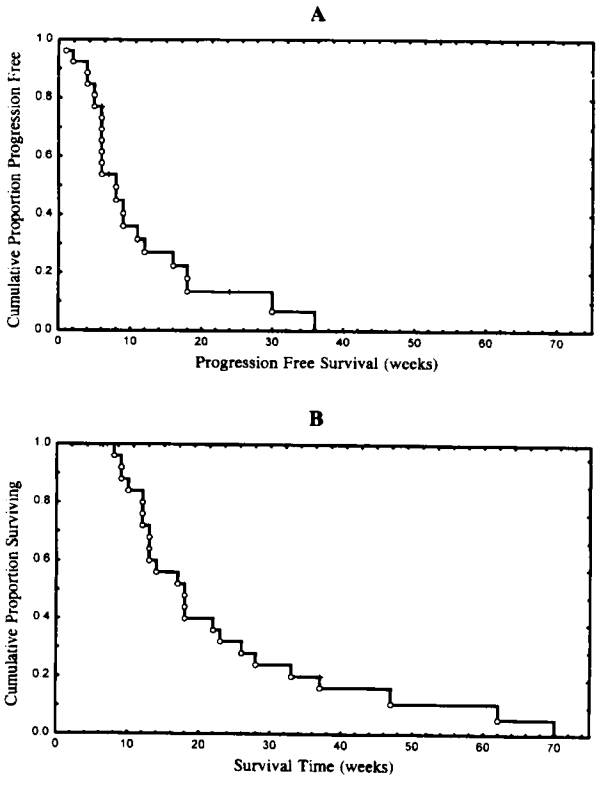

Figure 1. Kaplan–Meier plots illustrating (a) progression-free survival intervals (weeks) and (b) survival duration after study entry for all patients.

Results

Twenty-eight patients were enrolled in the study between July 1992 and April 1995. One patient, determined to have colon cancer following radiology review after cycle 1, was removed from the study The characteristics of the other 27 patients are listed in Table 1. One patient developed liver metastasis 4 years after his primary pancreatic tumor was resected by a Whipple's procedure. Another patient, who had soft-tissue metastasis involving the right leg, had received palliative radiotherapy to this area prior to study entry. Twenty-five of the 27 patients had either clinical or radiographic evidence of pancreatic disease; two patients developed metastatic disease after pancreatic resection. Twenty-six patients had extrapancreatic disease, including liver metastases (20 patients), lung metastases (four patients) and peritoneal carcinomatosis (seven patients).

Eighty-three courses of topotecan were administered in this study (median number of courses administered per patient = 2; range 1–12). Seven patients required dose reductions due to severe neutropenia (seven courses), neutropenic fever (two courses) or grade 3 diarrhea and neutropenia (one course). Two patients had their doses escalated once each and one patient had the dose escalated twice. Of the three patients who were treated with only a single course of topotecan, two developed biliary obstruction during or immediately after treatment, and the third developed severe dehydration due to nausea and subsequently developed neutropenic fever. This last patient was removed from the study because of these side effects, as well as a decline in performance status. Seven treatment courses were delayed for 1 week (three due to neutropenia, two to biliary obstruction or infection and two to intercurrent illness).

Toxicity

Neutropenia was the principal toxicity of topotecan in this phase II study. Neutropenic fever requiring hospitalization was reported in three patients during three courses of treatment. Grade 3 and 4 neutropenia occurred during 32 and 20 courses, respectively. Thrombocytopenia of grade 2 severity or greater was observed during 11 courses. No patient required platelet transfusions. Non-hematologic toxicities included nausea (29 courses), diarrhea (six courses), fever (four courses) and fatigue (six courses), but were predominantly transient, of grade 1 or 2 severity, and responsive to supportive treatment.

Anti-tumor response

No significant anti-tumor responses were observed in this study. One patient's response was initially categorized as partial because of a 60% reduction in the dimensions of the pancreatic mass after two cycles. However, a follow-up CT scan was not obtained until after cycle 5, by which time there was evidence of progression; the brevity of effect and the uncertainty of response duration precluded designating this response as partial. Eleven patients had periods of disease stabilization which lasted from 3 to 36 weeks (median, 21 weeks). Four patients could not be evaluated for response, and three of these four developed biliary obstructions after one cycle of treatment and had to be removed from the study. Median time to disease progression for all patients was 7 weeks (Figure 1a) and median survival time after study entry was 17.5 weeks (Figure 1b).

Discussion

Topotecan, administered at a dose of 1.5 mg/m^2/day for 5 days every 3 weeks, demonstrated no significant anti-tumor activity against pancreatic cancer. However, this dose of topotecan consistently produced levels of toxicity that necessitated dose reductions in seven patients because of severe neutropenia and associated sequelae. These results are similar to those of Sugarman *et al.* who reported no significant anti-tumor responses among 15 patients treated with topotecan 1.5 mg/m^2/day for 5 days.[22] The results of phase II studies with irinotecan, another water-soluble camptothecin analog, in advanced pancreatic cancer have thus far also been disappointing. Wagener *et al.*, administering irinotecan 350 mg/m^2 every 3 weeks, reported three partial responses among 32 previously untreated patients with advanced pancreatic cancer.[23] Similarly, Sakata *et al.* reported a preliminary 11.4% response rate in both previously treated and untreated patients with pancreatic cancer receiving either irinotecan 100 mg/m^2 weekly or 150 mg/m^2 every 2 weeks.[24] The schedule dependent activity of these topo I targeting agents raises the possibility that more prolonged schedules of administration might be more efficacious;[25] however, the lack of even a single major response among 41 evaluable, chemotherapy-naive patients treated in two phase II studies of topotecan to date suggests that alternate schedules are not likely to increase the magnitude of anti-tumor activity significantly.

A phase I study of topotecan in patients with hepatic dysfunction, which was defined by a serum bilirubin level of 2.0 mg/dl or greater, demonstrated that dosages of topotecan did not need to be reduced in this patient group.[26] In the current phase II study, four patients developed biliary obstruction during treatment with topotecan. Although one of these patients developed jaundice during chemotherapy administration, treatment was continued without a dose reduction and was well tolerated, providing further evidence that topotecan dose need not be reduced in patients with liver dysfunction.[26]

The ineffectiveness of the topo I inhibitors and of most of the other anti-cancer agents against pancreatic cancer underscores the need to identify the mechanisms of drug resistance in this tumor type. However, such studies have been hampered by the desmoplatic reaction generated by normal tissues surrounding the pancreatic tumor which makes obtaining tissue samples with a predominantly neoplastic component extremely difficult.[27] Because conventional cytotoxic anti-cancer agents have consistently failed to provide effective levels of anti-tumor activity in this disease, interest has increased in the potential ability of cytostatic anticancer agents to prevent local tumor invasion and metastasis.[28] In addition, recent insight into the molecular biology of pancreatic cancer, and in particular the importance of the *ras* oncogene,[29] has led to the identification of new targets for anti-cancer therapy. Preliminary results of gene therapy[30] and signal transduction[31] strategies directed against the *ras* oncogene are encouraging, and may improve the dismal prognosis of this disease.

Conclusion

Topotecan, administered on a daily times 5 days schedule, has no significant activity against pancreatic carcinoma. These results are consistent with those of other phase II trials of agents targeting topo I in patients with untreated pancreatic cancer. Therapeutic strategies targeting specific genetic alterations in pancreatic cancer are being developed and may improve the prognosis for patients with this disease.

Acknowledgments

We would like to express our gratitude to the medical and nursing staffs at The Johns Hopkins Oncol-

ogy Center who provided care and support for the patients in this study, and to Rod Graham for assistance with manuscript preparation.

References

1. Wingo PA, Tong T, Bolden S. Cancer statistics 1995. *CA Cancer J Clin* 1995; **45**: 8–30.
2. Warshaw AL, Fernandez-del Castillo C. Pancreatic carcinoma. *N Eng J Med* 1992; **326**: 455–65.
3. Kelly DM, Benjamin IS. Pancreatic carcinoma. *Ann Oncol* 1995; **6**: 19–28.
4. Williamson RCN. Pancreatic cancer: the greatest oncological challenge. *Br Med J* 1988; **296**: 445–6.
5. Mallinson CN, Rake MO, Cocking JB, *et al.* Chemotherapy in pancreatic cancer Results of a controlled, prospective randomized multicenter trial. *Br Med J* 1980; **281**: 1589–91.
6. Palmer KR, Kerr M, Knowles G, *et al.* Chemotherapy prolongs survival in inoperable pancreatic carcinoma. *Br J Surg* 1994; **81**: 882–5.
7. Pantazis P. Preclinical studies of water-insoluble camptothecin congeners: cytotoxicity, development of resistance, and combination treatments. *Clin Cancer Res* 1995; **1:** 1235–44.
8. Kaufman SH. Additional members of the rat liver lamin polypeptide family. *J Biol Chem* 1989; **264**: 13946–55.
9. Duget M, Lavenot C, Harper F, *et al.* DNA topoisomerases from rat liver: physiological variations. *Nucleic Acids Res* 1983; **11**: 1059–75.
10. Giovanella BC, Stehlin JS, Wall ME, *et al.* DNA topoisomerase I-targeted chemotherapy of human colon cancer. *Science* 1989; **246**: 1046–8.
11. Potmesil M. Camptothecins: from bench research to hospital wards. *Cancer Res* 1994 **54**: 1431–9.
12. Wall ME, Wani MC. Camptothecin and taxol: discovery to clinic—Thirteenth Bruce F Cain Memorial Award Lecture. *Cancer Res* 1995; **55**: 753–60.
13. Slichenmyer WJ, Rowinsky EK, Donehower RC, Kaufman SH. The current status of the camptothecin analogues as antitumor agents. *J Natl Cancer Inst* 1993; **85**: 271–91.
14. Kingsbury WD, Boehm JC, Jakes DR, *et al.* Synthesis of water soluble (aminoalkyl) camptothecin analogues: inhibition of topoisomerase I and anti-tumor activity. *J Med Chem* 1991; **34**: 98–107.
15. Rowinsky E, Grochow L, Hendricks C, *et al.* Phase I and pharmacologic study of topotecan: A novel topoisomerase I inhibitor. *J Clin Oncol* 1992; **10** 647–56.
16. Recondo G, Abbruzzese J, Newman B, *et al.* Phase I and pharmacokinetic trial of topotecan on a weekly 24hr infusion schedule. *Proc Am Ass Cancer Res* 1991; **32**: 206
17. Saltz L, Sirott M, Young C, *et al.* Phase I clinical and pharmacologic study of topotecan given daily for 5 consecutive days to patients with advanced solid tumors, with attempts at dose intensification using recombinant granulocyte colony stimulating factors *J Natl Cancer Inst* 1993; **85**: 1499–507.
18. van Warmerdam LJC, Verweij J, Schellens JHM, *et al.* Pharmacokinetics and pharmacodynamics of topotecan administered daily for 5 days every 3 weeks *Cancer Chemother Pharmacol* 1995; **35**: 237–45.
19. National Cancer Institute. *Guidelines for reporting of adverse drug reactions*. Bethesda, MD: Division of Cancer Treatment, National Cancer Institute 1988.
20. Gehan EA. The determination of the number of patients required in a follow-up trial of a new chemotherapeutic agent. *J Chronic Dis* 1961; **13**: 346–53.
21. Kaplan EL, Meier P Nonparametric estimation from incomplete observations. *J Am Statist Ass* 1958; **53**: 457–81.
22. Sugarman SM, Pazdur R, Daughtery K, *et al.* A phase II trial of topotecan for the treatment of unresectable pancreatic cancer *Proc Am Soc Clin Oncol* 1994; **13** 224.
23. Wagener DJTh, Verdonk HER, Dirix LY, *et al.* Phase II trial of CPT-11 in patients with advanced cancer, an EORTC early clinical trials group study. *Ann Oncol* 1995; **6**: 129–32.
24. Sakata Y, Wakui A, Nakao I, *et al.* A late phase II study of irinotecan in advanced pancreatic cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 211.
25. Hochster H, Liebes L, Speyer J, *et al* Phase I trial of low-dose continuous topotecan infusion in patients with cancer: an active and well tolerated regimen. *J Clin Oncol* 1994;**12**: 53–9.
26. O'Reilly S, Rowinsky EK, Slichenmyer W, *et al* Phase I and pharmacologic study of topotecan in patients with abnormal liver function. *J Natl Cancer Inst*, in press.
27. Seymour AB, Hruban RH, Redston M, *et al.* Allelotype of pancreatic cancer. *Cancer Res* 1994; **54**: 2761–4.
28. Kohn EC, Liotta LA. Molecular insights into cancer invasion: strategies for prevention and intervention *Cancer Res* 1995; **55**: 1856–62.
29. Hruban RH, van Mansfield ADM, Offerhaus GJA, *et al.* K-*ras* oncogene activation in adenocarcinoma of the human pancreas. A study of 82 carcinomas using a combination of mutant enriched polymerase chain reaction analysis and allele-specific oligonucleotide hybridization. *Am J Pathol* 1993; **143**: 545–54.
30. Aoki K, Yoshida T, Sugimara T, Masaaki T. Liposome mediated *in vivo* gene transfer of antisense K-*ras* construct inhibits pancreatic tumor dissemination in the murine peritoneal cavity. *Cancer Res* 1995; **55**: 3810–6.
31. Blaskovich M, Qian Y, Lerner E, *et al. Ras* CAAX peptidomimetics inhibit tumor growth in nude mice. *Proc Am Ass Cancer Res* 1995; **36**: 432.

(Received 2 February 1996; accepted 5 March 1996)