Cancer Chemother Pharmacol (1992) 29: 305–308

Cancer Chemotherapy and Pharmacology

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Phase II trial of PALA in combination with 5-Fluorouracil in advanced pancreatic cancer*

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Received 15 July 1991/Accepted 10 September 1991

Summary. Phosphonacetyl-L-aspartate (PALA), an inhibitor of aspartate transcarbamylase that depletes uridine nucleotide pools, selectively potentiates the antitumor activity of 5-fluorouracil (5-FU) in preclinical models. Due to the promising results we obtained using PALA/5-FU in colorectal cancer, we performed a phase II trial in patients presenting with advanced pancreatic cancer. PALA was given intravenously at 250 mg/m^2 on day 1, followed 24 h later by 2,600 mg/m^2 5-FU given by 24-h infusion. Treatments were repeated weekly. A total of 41 patients who had not previously undergone chemotherapy were entered in the trial; of these, 35 were evaluable for response. Toxicity was generally mild to moderate; neurotoxicity (13/35) and diarrhea (8/35) predominated. Among the 35 patients, 1 achieved a complete response and 4, a partial remission, for an overall response rate of 14%. The median survival was 5.1 months. Pretreatment with PALA alone was not sufficient to enhance the activity of 5-FU in pancreatic cancer.

Introduction

5-Fluorouracil (5-FU) is the most active single agent for the treatment of advanced pancreatic cancer. However, the response rates are low, and the impact on survival is minimal. In empirical combinations with nitrosoureas, streptozotocin, and mitomycin C, variable response rates have been reported, but survival has not been increased [3].

Biochemical modulation of 5-FU has recently been investigated as a means of reversing drug resistance. One such approach is to deplete cells of the natural uridine nucleotides that compete with fluorinated nucleotides at various sites of action [6]. PALA (phosphonacetyl-L-aspartate), an analog of the transition state intermediate in the de novo pathway of pyrimidine biosynthesis, inhibits aspartate carbamyl transferase (ACTase) and depletes pyrimidine nucleotide pools in tumors [10, 14, 15]. PALA has exhibited antiproliferative effects in cell culture [19, 20] and antitumor activity in several murine tumors in vivo [7] but has not shown clinical activity in phase II trials. The ability of PALA to disrupt intracellular pyrimidine metabolism suggested that it might act synergistically with antimetabolites. It was shown to increase the cytotoxicity of 5-FU in in vitro models and to enhance its antitumor activity in vivo. This effect was associated with the enhanced incorporation of 5-FU into tumor RNA. Potentiation was also schedule-dependent in that a 24-h pretreatment interval maximally depleted pyrimidine nucleotide pools and increased 5-FU's incorporation into RNA [1, 18]. Caspar et al. [4] demonstrated that the biochemical effects of low-dose (250 mg/m^2) PALA were comparable to those observed at higher doses. In a phase I trial of 250 mg/m^2 PALA followed 24 h later by a 24-h infusion of 5-FU, full doses of 5-FU could be given without resulting in untoward toxicity [2]. We conducted a phase II trial of this regimen in colorectal cancer and obtained a 43% response rate [16]. These encouraging data prompted us to carry out a phase II trial of PALA and 5-FU in patients with advanced pancreatic cancer.

Patients and methods

A total of 41 patients were entered into this study between May 1987 and October 1990. Eligibility criteria included a diagnosis of histologically documented recurrent or metastatic adenocarcinoma of the pancreas with bidimensionally measurable lesions; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; a life expectancy of at least 12 weeks; and normal bone marrow (WBC, $\geq$4,000/mm^3, platelet count, $\geq$100,000/mm^3), kidney (serum creatinine, $\leq$1.5 mg/dl), and liver (bilirubin, $\leq$2 mg/dl; SGOT, $\leq$2 times the uppper limit of normal) function. Patients who had previously undergone cytotoxic chemotherapy

* Supported in part by grant CA 06927 from the National Cancer Institute

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Table 1. Demographic characteristics of treated patients

Characteristic	Number
Patients entered	41
Sex (M/F)	23/18
Median age (range)	66 (38–79) years
Performance status:	
0	11
1	23
2	7
Metastatic sites:	
Liver	24
Lung	2
Bone	1
Peritoneum	8
Other	5

Table 2. Toxicity encountered in evaluable patients

	Toxicity grade				
	0	I	II	III	IV
Ataxia	22	2	4	7	0
Mucositis	26	4	5	0	0
Diarrhea	27	5	2	1	0
Leukopenia	29	4	2	0	0
Anemia	25	7	2	1	0
Anorexia	28	6	1	0	0
Alopecia	33	1	1	0	0
Conjunctivitis	31	3	1	0	0
Hand-foot syndrome	30	3	1	1	0

were excluded from the study. All subjects gave their written informed consent in accordance with federal, state, and institutional guidelines.

PALA was given by rapid intravenous infusion on day 1; 24 h thereafter, a 24-h continuous infusion of 5-FU at 2,600 mg/m^2 was initiated. Through the use of subcutaneously implanted venous access ports and portable infusion pumps, all patients were treated in the outpatient setting. Treatment was repeated weekly. Modification of doses was based on toxicity, which was graded using the 1988 Common Toxicity Criteria of the National Cancer Institute (Bethesda, Md.). At WBC counts of 1,000–1,900/mm^3 or platelet counts of 25,000–75,000/mm^3, the dose of 5-FU was reduced by 50%. A WBC count of <1,000/mm^3 or a platelet count of <25,000/mm^3 was an indication for the discontinuation of both PALA and 5-FU. The 5-FU dose was reduced by 50% when grade II nonhematologic toxicity was observed, whereas both 5-FU and PALA were withheld when grades III and IV toxicity were noted. The occurrence of mucositis or diarrhea of any grade was an indication for the discontinuation of treatment with both drugs for 1 weeks. Ataxia resulted in treatment's being withheld with retreatment beginning at 50% of the 5-FU dose following the resolution of symptoms.

Pretreatment evaluation included a history and physical examination, a complete blood count, a serum chemistry panel, determinations of electrolyte and creatinine levels and X-rays and scans that were appropriate for disease measurement. A complete blood count was obtained weekly for 8 weeks and every other week thereafter. The history and physical examination, serum biochemistry screen, and X-rays and scans were repeated every 4 weeks. Patients who went off-study underwent a long-term follow-up for adverse events.

Response definitions were standard: a complete response (CR) was defined as the complete disappearance of all objective evidence of disease (clinical and radiologic) for a minimum of 4 weeks; a partial remission (PR) was defined as a decrease of ⩾50% in the sum of the products of the perpendicular diameters of measurable lesions; a minor response represented a decrease of 25–50% in the sum of the products of the perpendicular diameters of measurable lesions; and stable disease was defined as either a response amounting to less than a minor response or progression comprising less than progressive disease for a minimum of 6 weeks and the appearance of no new lesions [12]. Progressive disease was defined as an increase of ⩾25% in the size of any measured lesion or the appearance of any new lesion. Response was assessed separately by the treating physician and investigator and was independently audited by external reviewers. Survival duration was measured from the first day of treatment until the day of death. Response was measured from the 1st day of a documented response until relapse. The survival curve was plotted using the technique of Kaplan and Meier [9].

Table 3. Responses observed in evaluable patients

Patients entered	41	
Patients evaluable	35	
Complete remission	1	14%
Partial remission	4	
Minor response	3	
Stable disease	13	
Progressive disease	14	

Results

A total of 41 patients were entered, including 23 men and 18 women. Six subjects were not considered to be evaluable for response (one suffered a myocardial infarction; one developed a pulmonary embolus; one exhibited a primary colon tumor; one received PALA only; one received only 12 h 5-FU infusion, which was stopped due to possible toxicity; and one refused further treatment after undergoing two courses). The demographic characteristics of the patients entered in this study are shown in Table 1.

An analysis of the toxic effects experienced by our patients is shown in Table 2. No subject developed significant leukopenia of worse than grade 2, but one experienced grade III anemia. Mucositis and diarrhea occurred in approximately half of the patients. Neurologic toxicity, mainly in the form of ataxia, was the most frequent and most severe toxic effect, with grade III toxicity occurring in 20% of cases. When ataxia occurred, it usually did so at 8–12 weeks after the start of treatment. Symptoms resolved in every patient following the discontinuation of drug administration. Dose reductions were required in 15 of 35 evaluable patients (43%). Neurologic toxicity (principally ataxia) was the cause in 8/15 subjects; other causes included diarrhea ($n = 2$), mucositis ($n = 4$) and dermatitis ($n = 1$).

Dose intensity was analyzed in the 35 evaluable patients. The median dose intensity was 2,600 mg/m^2 5-FU weekly (range, 1,733.33–2.600 mg/m^2 weekly; mean, 2,376 mg/m^2 weekly). This value compares favorably with that achieved in the phase II trial of this regimen in colorectal cancer (mean, 2032 mg/m^2 weekly). Clearly, at this dose and on this schedule, PALA and 5-FU were well tolerated by our patients. Among the 35 subjects who were evaluable for response, 1 achieved a CR and 4, a PR, for a total response rate of 14% (95% confidence

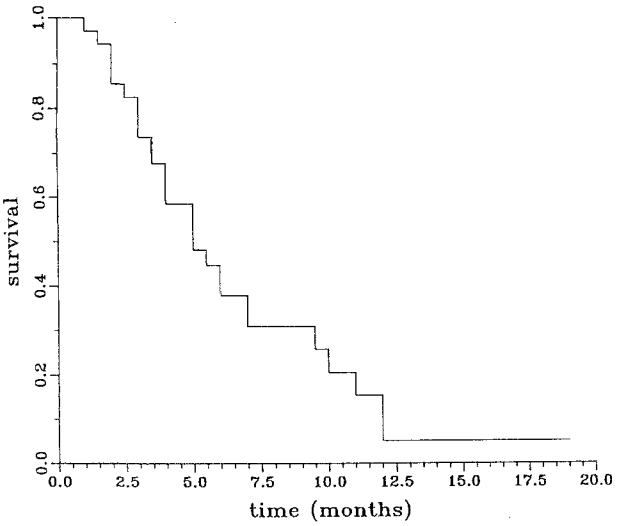

Fig. 1. Kaplan-Meier survival curve for all patients entered ($n = 41$)

limits, 3%–26%; Table 3). The duration of response ranged from 2 to 8 months; the median survival for the entire group was 5.1 months. The Kaplan-Meier survival curve for all patients is shown in Fig. 1.

Discussion

5-FU remains the most active agent in advanced pancreatic cancer, but it has no impact on the survival of patients suffering with this disease. A synergistic interaction between 5-FU and PALA that depletes cells of uridine nucleotide pools by inhibiting the enzyme aspartate carbamyl transferase [9, 14] has been noted in both in vitro and in vivo studies [6, 19, 20]. Previous phase I and II studies had also suggested that the combination of low-dose PALA and 5-FU could be used safely and with encouraging response rates in colorectal cancer. The combination is currently being evaluated in randomized clinical trials in this disease. Extension of the favorable results obtained in colorectal cancer to pancreatic cancer was the goal of this phase II study.

The 14% response rate obtained in 35 evaluable patients demonstrates that pretreatment with PALA alone is not sufficient to potentiate markedly the activity of 5-FU in this disease. The addition of leucovorin to 5-FU has previously been shown to be ineffective in enhancing response rates in pancreatic cancer [5]. Although 5-FU is substantially less active in pancreatic than in colorectal cancer, the mechanisms of cytotoxicity are not known to differ between these diseases. Additonal work to define mechanisms of resistance in human pancreatic carcinoma lines is needed to indicate new directions for therapeutic development [17].

Morrell et al. [13] recently reported the results of a phase II trial of this regimen in advanced pancreatic cancer. In this cooperative group study, the response rate was 1 PR among 21 patients (5%), and toxicity was severe (8 instances of grade IV toxicity). This high level of unacceptable toxicity undoubtedly contributed to the low response rate observed and emphasizes the need for careful selection of patients for phase II trials in this disease [13]. However, other than the wider range in allowable hepatic enzyme abnormalities that was used in the study of Morrell et al., the eligibility criteria and demographics were identical to those of the present investigation.

Although the combination of PALA and 5-FU appears to be generally well tolerated and has yielded a significant response rate in advanced colorectal cancer, there appears to be no advantage for this combination in advanced pancreatic carcinoma. However, further modulation of 5-FU may prove to be beneficial, and in the absence of effective regimens for the treatment of this disease, this continues to represent a rational area of investigation.

Acknowledgements. The authors gratefully acknowledge the expert secretarial assistance of Ms. C. Thompson.

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