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Phase II study of pyrazoloacridine in patients with advanced colorectal carcinoma

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Abstract *Purpose*: Pyrazoloacridine (PZA) is an acridine derivative selected for clinical development because of broad preclinical antitumor activity and solid tumor selectivity. Phase I evaluations with PZA have demonstrated predictable toxicity and suggested clinical efficacy. A phase II trial in patients with previously untreated advanced colorectal cancer was conducted. *Methods*: PZA was administered at a dose of 750 mg/m^2 intravenously over 3 h every 21 days to patients who received a total of 31 courses of PZA. *Results*: In 15 patients evaluable for response, no responses were observed (0% response rate, 95% confidence interval 0–22%). Toxicity to PZA consisted of myelosuppression and neurotoxicity that was treatment-limiting in several instances. *Conclusion*: PZA at this dose and schedule of administration is inactive in patients with colorectal cancer.

Key words Pyrazoloacridine · Colorectal cancer

Introduction

Colorectal carcinoma is responsible for more than 50 000 deaths annually in the United States [7]. While 5-fluorouracil-based adjuvant therapy has improved disease-free survival for patients with locoregional disease, similar success has not been achieved in patients with metastatic disease [3]. The identification of new cytotoxic agents with activity in this common disease is needed.

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Pyrazoloacridine (PZA) is one of a series of acridine derivatives selected for clinical development because of its broad preclinical antitumor activity, solid tumor selectivity, activity against hypoxic cells, and activity in multidrug-resistant tumor systems [2, 5]. PZA demonstrates in vitro activity against the colon 38 cell line, as well as significant in vivo activity against both early and "upstaged" colon 38 tumors [5]. The mechanism of cytotoxicity of PZA is believed to be related to DNA intercalation, although inhibition of both topoisomerase I and II have recently been reported [1, 2]. In phase I trials PZA demonstrated neurotoxicity and myelosuppression as dose-limiting toxicities [4, 9]. In one of these trials, a partial response in ovarian cancer as well additional minor responses in ovarian, cervical and colon cancer were observed [9]. A dosage of 750 mg/m^2 infused over 3 h every 21 days was recommended for phase II trials [9]. These preclinical and clinical observations prompted a phase II study with PZA for patients with advanced colorectal cancer.

Patients and methods

Patients with a histologic diagnosis of metastatic or unresectable colorectal carcinoma were eligible for this study. Prior chemotherapy was limited to an adjuvant 5-fluorouracil-based regimen. Further eligibility criteria included measurable disease, Zubrod performance status of 2 or better, life expectancy of >8 weeks, age $\geq$18 years, CT scan of brain negative for metastasis, and adequate bone marrow function (absolute granulocyte count $>2000/mm^3$, platelet count $>100\ 000/mm^3$), hepatic function (total bilirubin <2.0 mg/dl), and renal function (creatinine <1.5 mg/dl). All patients were informed of the investigational nature of the study and provided written informed consent.

Treatment consisted of PZA 750 mg/m^2 infused over 3 h through a central venous catheter. Cycles were repeated at 21-day intervals. Dose escalation to 820 mg/m^2 was permitted if less than grade 2 toxicity was observed. Doses were to be reduced to 600 mg/m^2 for grade 3 toxicities or higher. PZA was provided by the Division of Cancer Treatment, National Cancer Institute (Bethesda, Md.).

A two-stage design was used in this phase II study. The initial accrual goal was 15 response-evaluable patients. If between one and three responses were observed an additional 15 patients were to

be accrued. Standard response criteria were used [6]. Responding patients were to be treated for 1 year or 6 months beyond best response achieved, whichever was shorter. Patients were removed from study for tumor progression, unacceptable toxicity, or patient request.

Patients were considered evaluable for toxicity if at least one treatment was administered. Patients were considered evaluable for response if two cycles of treatment were given, or if one cycle of treatment were given followed by obvious progression of disease. Response duration was defined as the time from documentation of response to progression. Survival was measured from the time of initiation of therapy until death or lost to follow-up.

Results

Between August 1994 and October 1995, 17 eligible patients were registered to this study (Table 1). There were ten men and seven women, nine Caucasian and eight African American. The median age of the patients entered into the trial was 65 years, and the median performance status was 1. The primary site of disease was colon in 12 patients and rectum in 5 patients. Each of the patients with rectal cancer had received adjuvant radiation and chemotherapy, and four of the patients with primary colon cancer had received adjuvant chemotherapy. In the nine patients treated adjuvantly, the median interval between completion of adjuvant therapy and recognition of metastatic disease and trial entry was 7 months (range 1 to 27 months). Metastatic disease was present in the following sites; intraabdominal/retroperitoneal (6), lung and liver (4), lung (4), and liver (3). One patient refused treatment after registration and was not evaluable for either toxicity or response.

Toxicity

Sixteen patients received 31 cycles of PZA, and the median number of cycles received was 2 (range 1–4 cycles). All patients were evaluable for toxicity and the worst grades of each toxicity experienced by the patients are shown in Table 2. The major toxicity was myelosuppression and neurologic toxicity which was similar to the dose-limiting toxicities described in phase I trials.

Following the first dose of PZA, grade 3 and 4 neutropenia and leukopenia occurred in 87% and 50% of patients treated, respectively. Of the 11 patients treated with a second cycle, 4 required dose reductions and 2 delay for myelosuppression. The dose was escalated in only one patient. Grade 4 thrombocytopenia occurred in two patients without bleeding complications. Anemia was present in most patients and was probably due to the underlying disease process rather than PZA toxicity.

Three patients experienced neutropenic fever, two of whom had documented bacteremia. An additional patient experienced grade 4 infection from *Klebsiella* bacteremia complicated by septic shock, 13 days after the second cycle of PZA. Three additional patients experienced infection while on study, a patient with reappearance of chronic osteomyelitis, a patient with urinary retention and urosepsis and a patient with a mild upper respiratory tract infection.

Neurotoxicity was observed in five patients. Two patients experienced mild anxiety, restlessness and agitation near the end of the 3-h PZA infusion which resolved shortly after completion of the infusion. One patient complained of mild irritability that lasted for 3 to 4 days following chemotherapy. Two patients experienced more severe neurologic symptoms. One patient, while receiving a second cycle of PZA, developed muscle spasms, electric shock sensation in his legs, severe agitation and restlessness 2.5 h into the infusion requiring cessation of treatment. These symptoms resolved spontaneously and no further doses of PZA were given. A second patient experienced severe and disabling anxiety following the first cycle of PZA which persisted for approximately 5 days. A second cycle, given with a dose reduction, resulted in mild anxiety controllable with lorazepem. This patient declined further therapy after three cycles primarily because of subjective anxiety.

Nausea and vomiting were absent to mild in all cases. Alopecia was not seen. One patient developed subclavian vein thrombosis on the side of the vascular access device.

Table 1 Patient characteristics

	No. of patients
Gender	
Male	10
Female	7
Age (years)	
Median	65
Range	31–85
Racial group	
Caucasian	9
African American	8
Performance Status	
0	8
1	3
2	6
Primary Site	
Colon	12
Rectum	5
Previous therapy	
Chemotherapy	4
Chemotherapy + radiotherapy	5

Table 2 Numbers of patients with worst grade of each toxicity experienced (NCI common toxicity criteria)

	Grade			
	0	1–2	3	4
Leukopenia	1	7	5	3
Neutropenia	1	1	5	9
Thrombocytopenia	10	4	0	2
Anemia	1	12	3	0
Neurologic	11	3	2	0
Infection	9	1	5	1
Catheter	15	0	1	0

Response

Of the 16 treated patients, 15 were evaluable for response. A patient with grade 3 neurologic toxicity was not evaluated for response and expired 8 months after study entry. No objective responses were observed (0% response rate, 95% confidence interval 0–22%). Two patients had stable disease after two and three cycles of therapy but were removed from study because of chronic osteomyelitis and patient refusal to continue therapy because of subjective impact on quality of life, respectively. The remaining 13 patients developed progressive disease after 1 (5), 2 (7), or 4 (1) cycles. The median survival of patients on study was 4 months (0–17 + months).

Discussion

The lack of efficacy of PZA in this trial in patients with colorectal cancer was disappointing. While therapy was generally well tolerated, antitumor activity was not observed. The dose of PZA was adequate as evidenced by the level of myelosuppression observed. Despite a 3-h infusion, neurotoxicity remained treatment-limiting in two patients.

The poor therapeutic results might be explained in part by the patient population treated. The performance status of a third of the patients on trial was 2, the pattern of metastatic disease was unusual with the liver not dominating, and the number of patients progressing clinically after one cycle (5) coupled with the short median survival of the study population (4 months) suggest that this group of patients was somewhat unusual for untreated metastatic colorectal cancer. Nevertheless, all patients were eligible. Additionally, one of five patients subsequently treated with 5-fluorouracil had a partial response to that therapy. The results of our trial are similar to those reported from the Cleveland Clinic with PZA in colon cancer [8]. Together, these two trials suggest that PZA in the dose and schedule studied is inactive and does not warrant further investigation in colorectal cancer.

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