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Phase II Trial of Pyrazoloacridine in Children With Solid Tumors: A Pediatric Oncology Group Phase II Study

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Abstract

Purpose—Pyrazoloacridine (PZA), a rationally synthesized deoxyribonucleic acid (DNA) binding agent that preferentially inhibits ribonucleic acid rather than DNA synthesis, is active against hypoxic and noncycling tumor cells and has greater in vitro activity against a broad range of human solid tumor lines than against the L1210 murine leukemia line. The Pediatric Oncology Group conducted a phase II study to determine the activity of PZA administered as a 3-hour infusion.

Patients and Methods—The activity of PZA was evaluated in patients with a variety of childhood solid tumors including rhabdomyosarcoma, Ewing sarcoma/peripheral neuroectodermal tumor, neuroblastoma, osteogenic sarcoma, Wilms tumor, or other solid tumors (excluding brain tumors). In addition to a standard three-stage design to test the drug's activity in each tumor type, a global stopping rule was used such that if no complete or partial responses (CR or PR) occurred in the first 35 patients (pooled across all strata except "other"), the study would be closed.

Results—A total of 47 patients were entered into the study. Myelosuppression was the primary toxicity. Severe nonhematologic toxicity was uncommon. Only one patient exhibited grade 3 neurologic toxicity (anxiety). No CRs or PRs were observed.

Conclusion—Use of the global stopping criterion permitted early identification of lack of activity of PZA against childhood solid tumors.

Keywords

Pyrazoloacridine; PZA; Children; Cancer; Phase II trial; Global stopping criterion

Pyrazoloacridine (PZA) is a rationally synthesized deoxyribonucleic acid (DNA) binding agent that preferentially inhibits ribonucleic acid (RNA), rather than DNA, synthesis, and is

active against hypoxic and noncycling tumor cells. It has greater in vitro activity against a broad range of human solid tumor lines than against the L1210 murine leukemia line (1–3). Pyrazoloacridine retains activity in vitro and, to a lesser extent, in vivo against multidrug-resistant cell lines (4). In a phase I trial in children and young adults, PZA was well-tolerated on a 1-hour infusion schedule. Myelosuppression was the dose-limiting toxicity. The recommended phase II dose was 640 mg/m² (5).

The Pediatric Oncology Group investigated the activity of PZA against a variety of childhood solid tumors in a phase II study. Because neurotoxicity, presumed to be related to high-peak plasma PZA concentrations, was dose-limiting in adult phase I trials when PZA was administered as a 1-hour infusion (6, 7), the drug was administered as a 3-hour infusion in the phase II trial. In addition, a novel phase II design was used in this trial in which we included a global stopping rule to limit overall accrual if the drug was found to be inactive in traditionally drug-sensitive tumor types.

PATIENTS AND METHODS

Patients

Patients younger than 21-years-old with a histologically confirmed diagnosis of rhabdomyosarcoma, Ewing sarcoma/peripheral neuroectodermal tumor, neuroblastoma, osteogenic sarcoma, Wilms tumor, or other solid tumors (excluding brain tumors) refractory to conventional treatment or for which no effective therapy is known, were eligible for this trial. Patients were also required to have measurable disease and limited previous treatment (less than two previous chemotherapy regimens). Other eligibility criteria included: a) life expectancy of 8 weeks, Eastern Cooperative Oncology Group performance status 0 to 2, and no severe uncontrolled infection; b) adequate organ function (peripheral absolute neutrophil count [ANC] 1,000/mm³ and platelet count 100,000/mm³; bilirubin 1.5 mg/dL; alanine aminotransferase [ALT] <3 times normal; creatinine normal for age or creatinine clearance or glomerular filtration rate 60 mL/min/1.73 m²); c) recovery from toxicity of all previous chemotherapy; and d) no concurrent anticancer therapy. Informed consent was obtained from the patient or legal guardian before patient enrollment according to institutional guidelines.

Drug Administration and Study Conduct

Pyrazoloacridine was supplied by the Division of Cancer Treatment, National Cancer Institute as an orange-red lyophilized powder with sodium hydroxide added for pH adjustment and was reconstituted with sterile water. The final dose of 640 mg/m² was then diluted with 5% dextrose in water to a final volume of 100 mL and administered as a 3-hour infusion every 3 weeks. Before the next course, patients must have recovered from all previous course toxicity and have an ANC 1,000/mm³ and platelets 100,000/mm³. Patients with clearly progressive disease after 3 weeks of therapy were removed from study. Patients with stable disease or better response were permitted to continue on therapy as long as they received clinical benefit, for a maximum of 12 courses of therapy. Toxicities were graded using the National Cancer Institute Common Toxicity Criteria (8). For patients with ANC <500/mm³ for more than 1 week, granulocyte colony-stimulating factor was added for

subsequent courses. For other organ toxicity greater than grade 3, subsequent doses were decreased by 25%. Patients with grade 4 or irreversible grade 3 nonhematologic toxicity were removed from the study.

Patient histories, physical examination, and laboratory studies as defined previously were obtained before study entry and at specified intervals during treatment. Blood counts were obtained at least weekly. Appropriate tumor imaging was obtained at baseline, after the first or second cycle, and then every two cycles as clinically indicated. Standard tumor response criteria were used.

A three-stage design was used to assess antitumor activity as defined by complete or partial response (CR or PR) in each tumor type. In this design, in stage one, 12 patients are initially accrued to each stratum (rhabdomyosarcoma, Ewing sarcoma/peripheral neuroectodermal tumor, neuroblastoma, osteogenic sarcoma, or Wilms tumor). If CR or PR occurs once at most, the stratum is closed and the drug declared inactive. If CR or PR occurs in four or more patients, the stratum is closed and the drug declared active. If CR or PR occurs in two to three patients, the study proceeds to stage two. In stage two, 10 more patients are accrued to the stratum. If CR or PR occurs two or three times among all 22 patients, the stratum is closed and the drug declared inactive. If CR or PR occurs in six or more of the 22 total patients, the stratum is closed and the drug declared active. If CR or PR occurs in four to five of the 22 total patients, the study proceeds to stage three. In stage three, eight more patients are accrued to the stratum. If CR or PR occurs four to six times among all 30 patients, the drug is declared inactive; if CR or PR occurs seven or more times among all 30 patients, the drug is declared active. This design has a *P*-value of 4.3% for testing the null hypothesis that the true response rate is 10%, and 82% power when the true response rate is 30%.

In addition to the three-stage design to determine PZA activity in each tumor type, we used a global stopping strategy. With this strategy, if no CR or PR occurs in the first 35 patients (pooled across all strata except “other”), the study is closed. This permits the conclusion that the global response rate is less than 10% with 97.5% confidence.

RESULTS

Forty-seven patients were enrolled in the study. Patient characteristics are listed in Table 1.

Response

No CRs or PRs were observed. Only five patients received more than three cycles of chemotherapy.

Toxicity

Myelosuppression was the primary toxicity. Most patients experienced grade 3 or 4 neutropenia. However, clinically significant infection was rare, with only two patients having greater than grade 3 infection. Grade 3 and 4 anemia and thrombocytopenia were also common. Severe nonhematologic toxicity was uncommon. Two patients had grade 3 vomiting, one patient had grade 3 transaminase elevations, and one patient had grade 3 skin

toxicity (phlebitis after PZA administration via a peripheral catheter). Of note, only one patient exhibited grade 3 neurologic toxicity, manifested as anxiety during and immediately after drug infusion.

DISCUSSION

Pyrazoloacridine is inactive in children with solid tumors at the dose and schedule administered in this phase II trial. However, because there is no preclinical or clinical evidence of schedule-dependent activity for this agent (1–4, 9–11), further investigation in children using PZA as a single agent on different schedules is not warranted. Furthermore, because the phase I trial in children demonstrated that PZA concentrations that inhibit tumor growth in vitro were achieved in the plasma of all patients who received a dose of 640 mg/m² of PZA (5), it is unlikely that underdosing of drug resulted in the lack of activity noted in this trial.

Use of the global stopping rule limited accrual on this trial to 47 patients, whereas recent previous Pediatric Oncology Group phase II studies accrued approximately 150 patients each. In part, the larger accrual in previous studies occurred because CRs or PRs required additional patient entry in particular disease strata to define more accurately the drug activity rate in that disease. In addition, in the phase II study of topotecan, despite the lack of CR/PRs, an unusually high rate of prolonged stable disease was noted in the neuroblastoma stratum, prompting further patient accrual (12). However, even in the absence of any CR/PRs, the PZA study would have had to accrue at least 25 more patients to meet the first-stage goal of 12 patients in each tumor stratum. Thus, the use of the global stopping criterion prevented a substantial number of children from being treated with an inactive agent.

Two potential drawbacks of using the global stopping rule must be considered. First, drug activity in some tumor types may not be adequately tested, particularly if a given disease stratum is slow to accrue. For example, the Wilms tumor stratum on this protocol only accrued two patients before the stopping rule was invoked. It appears unlikely, however, that an anticancer agent will be active in one childhood cancer while producing an overall response rate of <10% when tested in a group of sentinel tumors that are generally considered chemosensitive. However, CRs or PRs were observed within the subset of the first 35 patients with “sensitive” tumor types accrued in both the topotecan (12) and the paclitaxel (M. Harris, personal communication) Pediatric Oncology Group phase II studies. Thus, neither of these studies would have been closed prematurely using the global stopping criterion. Indeed, the criterion is quite conservative, as indicated by the ultimately poor activity shown by paclitaxel, despite its having passed the initial global stopping threshold (13). The second potential drawback is that the global stopping design as used in our study is intended to identify agents with a high rate of activity. However, in tumors for which there is little effective therapy, such as brain stem gliomas, a response rate of 10% to 15% may be indicative of a clinically important drug. Such a drug may be “missed” in a trial that accrues relatively few patients.

The identification of active new anticancer agents remains a major challenge in oncology. Improved selection of agents for anticancer drug development, by improvements in drug

design and preclinical testing strategies, may mean that fewer inactive drugs will enter into clinical trials in the future. Meanwhile, given the limited numbers of new agents that can be evaluated in the pediatric population, and the ethical mandate to treat as few patients as possible with an inactive agent, the global stopping rule provides a common sense approach to phase II drug testing in children with cancer.

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APPENDIX. Participating institutions

Institution	Grant number
Cross Cancer Institute	
Baylor College of Medicine	CA 03161
Boston Floating Hospital	
Children's Hospital (San Diego)	
Dana-Farber Cancer Institute	CA 41573
Duke University	
West Virginia University-Morgantown	
Mount Sinai Medical School (New York)	CA 69428
University of Maryland	
University of Massachusetts	
Yale University	
Emory University	
Tampa Children's Hospital	
Hospital for Sick Children	
Johns Hopkins University	CA 28476
McMaster University	
Oklahoma University	
Oschner Clinic	
POG Operations Office	CA 30969
POG Statistical Office	CA 29139
Sainte-Justine	
St. Louis University/Cardinal Glennon Children's Hospital	
University of Kansas	
University of Miami	
University of Mississippi Medical Center	CA-28383
University of Virginia	
UC-San Diego	CA-28439
UT-San Antonio	
Washington University	CA-05587

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TABLE 1

Patient characteristics

Number of patients	47
Number evaluable for response	46
Median (range) age (years)	14 (6 mos–21 yrs)
Male/female	28/19
Previous therapy	
Chemotherapy	47
Radiation	24
Diagnosis	
Rhabdomyosarcoma	8
Ewing sarcoma/PNET	10
Neuroblastoma	7
Osteogenic sarcoma	8
Wilms tumor	2
Other	12