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Phase II Trial of Pyrazoloacridine (NSC#366140) in Patients with Metastatic Breast Cancer

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Abstract

Purpose—Pyrazoloacridine (PZA) is an investigational nucleic acid binding agent that inhibits the activity of topoisomerases 1 and 2. We conducted a phase II clinical study to determine the efficacy and toxicities of PZA in patients with metastatic breast cancer (MBC).

Experimental Design—In this phase II multicenter study, patients who were treated with no more than one prior chemotherapy for MBC were treated with 750 mg/m2 of PZA given as a 3-hour intravenous infusion every 3 weeks. Treatment cycles were continued until disease progression or unacceptable toxicities. The study was designed to distinguish between a response rate of <15% vs >30% (alpha=0.10, beta=0.10) using Simons optimal 2-stage design. At least 2 responses were required in the first 12 patients in the 1st stage and 6 of 35 in the 2nd stage to recommend the agent for further study.

Results—Two patients in the first stage had a response allowing accrual to second stage. A total of 15 patients (out of 35 planned) were treated on the study prior to premature closure. Three patients had a partial response (20%) lasting 4.5–6 months. Two patients had stable disease for 3 and 5 months. The dose limiting toxicity was granulocytopenia with ten patients requiring dose reduction or dose delay for grade 4 neutropenia. Other grade 3 and 4 toxicities include vomiting (n=2), nausea (n=2), neurotoxicity (n=1), fatigue (n=1), anemia (n=1), dyspnea 9n=1) and renal (n=1).

Conclusions—Pyrazoloacridine demonstrated modest activity in patients with metastatic breast cancer.

Keywords

pyrazoloacridine; metastatic breast cancer; Phase II

INTRODUCTION

Metastatic breast cancer is a highly heterogeneous disease which still remains incurable. Treatment is palliative with the goal to prolong life with agents that have low toxicity and able to maintain good quality of life. Treatment strategies depend on several criteria including tumor biology, tumor burden, performance status and prior treatment. Factors that predict response to chemotherapy include high proliferative index, performance status,

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tumor burden and age. In general cytotoxic agents are not likely to show high activity against low-growth fraction tumors. Solid tumors such as breast cancer exhibit varying proliferative rates and it is the quiescent cells that are resistant to conventional chemotherapy and can be recruited back into the cell cycle. The inability of many cytotoxics to kill the noncycling cells is the major determinant of chemotherapeutic failure. Hence there is a need for an agent that has activity against hypoxic and quiescent cells and can overcome drug resistance.

Pyrazoloacridine (PZA) is the first of a new class of rationally synthesized acridine derivatives. The postulated mechanism of anti-tumor activity is interference with the normal function of both topoisomerase I and II that is distinct from the commercially available topoisomerase I and II –targeting agents[1]. Other mechanisms of PZA cytotoxicity include DNA intercalation and RNA synthesis[1]. Moreover preclinical data showed several unique properties of PZA uncharacteristic to most cytotoxic agents including activity against hypoxic cells, cytotoxicity against noncycling cells, and ability to overcome multi drug resistance in tumor cell lines[2,3]. PZA demonstrated cytotoxicity against broad spectrum of human tumor cells line in vitro and in vivo including mammary cell lines[4–6].

Phase I clinical trials recommended 600–750 mg/m2 dose administered over 3 hours for further evaluation in phase II studies[7,8] Multiple phase II clinical trials evaluated efficacy of PZA against broad spectrum of metastatic tumors. Despite promising preclinical data no anti-tumor activity was seen in gastrointestinal malignancies[9,10], cervical cancer[11] solid tumors in children[12], germ cell tumors[13], transitional cell carcinoma[14], renal cell carcinoma[15] and advanced non-small cell carcinoma of the lung[16]. In contrast, 1 of 17 patients with hormone refractory prostate cancer was a reported to have a 96% decrease in the PSA level accompanied by improvement in the bone scan[17]. The Gynecologic Oncology Group (GOG) performed a phase II study of single agent PZA in patients with platinum-resistant ovarian cancer and reported that out of 24 evaluable patients there was one complete response and one partial response.[18,19] The GOG also performed a Phase II study of PZA in cervical cancer and reported that among 24 evaluable patients, 1 pt had a transient complete response in the palpable supraclavicular lymph node, but had progression in the lung within a month[11]. Hence single agent activity of PZA has been negligible in solid tumors.

We conducted a multi-center phase II trial of PZA at a dose of 750 mg/m2 every three weeks as first- or second-line therapy in metastatic breast cancer that was prematurely closed due to loss of continued financial support. We report here the results from the study enumerating the toxicities and responses seen in patients with breast cancer.

PATIENTS AND METHODS

Phase II Research Consortium at the Ohio State University Medical Center in collaboration with the University of Michigan and the Central Baptist Hospital performed a phase II clinical trial to assess the clinical response and toxicity of PZA in patients with metastatic breast cancer.

PATIENT ELIGIBILITY

Patients with a histologically confirmed metastatic breast cancer, bi-dimensionally measurable disease, and treated with no more than one prior chemotherapy for recurrent or metastatic breast cancer were eligible. Hormone therapy in the adjuvant or metastatic setting was permitted. Patients must have been off hormonal therapy for at least 3 weeks. Prior radiotherapy had to be limited to < 25% bone marrow and had to be completed at least 4 weeks prior to registration. Patients were required to have Southwest Oncology Group

(SWOG) performance status of 2 or less, and life expectancy of 6 months or more. The following organ function was required: platelets ≥ 100,000 cells/dl absolute neutrophil count ≥ 1,500 cells/dl; serum creatinine < 1.5 mg/dL or creatinine clearance > 60ml/min; AST ≤ 2.5 times institutional ULN and bilirubin ≤ 2.0 mg/dl. Patients with brain metastases, a seizure disorder or anticonvulsant therapy were excluded from the study given the known potential neurotoxicity of PZA. Patient with a history of congestive heart failure, MI within 6 months, ventricular arrhythmia or ischemic heart disease requiring medications were not eligible. The Institutional Review Board of each institution approved the study protocol, and written informed consent was obtained from each patient.

TREATMENT PLAN

PZA was provided by Cancer Therapy Evaluation Program, the National Cancer Institute, Bethesda, MD as an orange-red lyophilized powder with sodium hydroxide added for pH adjustment in flint vials. Sterile vials contained 100 mg or 500 mg of drug. Eligible patients received 750 mg/m2 of PZA on day 1 of a 21 day cycle. PZA was diluted in 100 ml of D5W and was intravenously infused over 3 hours. The use of granulocyte colony stimulating factor (Neupogen®, G-CSF) or erythropoietin (Procrit®) was permitted at the discretion of the treating physician. Patients received treatment until disease progression, or unacceptable toxicity defined as a drug-related grade ≥ 3 toxicities that did not resolve to grade ≤ 1 within 2 weeks and/or recurred despite dose reduction, or patients' decision to withdraw from study. Toxicity assessments and complete blood counts with differential were obtained on days 1, 8, 15, and 21. Physical examination and serum chemistry studies were obtained on day 1 of each treatment cycle. Toxicities were assessed according to NCI-CTC version 2.0

DOSE MODIFICATIONS

Each cycle of PZA was initiated if granulocyte count was ≥ 1500/dl and platelet count ≥ 100,000/dl. Dose modification was based upon nadir counts and interim non-hematologic toxicities of the preceding cycle. PZA dose was reduced to 600 mg/m^2 for an episode of febrile neutropenia requiring hospitalization in the previous cycle or for neutropenia that lasted for >14 days. PZA was held for ≥ grade 2 hepatic or renal toxicity or for ≥ grade 3 non-hematologic toxicity except alopecia, nausea or vomiting. The drug was restarted at 600 mg/m^2 dose following recovery to grade 0. Patients were removed from the study if either hepatic and/or renal toxicity reaches grade 4.

RESPONSE EVALUATION

All patients had imaging studies and/or physical exam measurements for assessment of tumor sites within 28 days before starting treatment. The same imaging modalities were used for response evaluation after every 2 cycles. The definitions of response were as follows: complete response (CR) is the complete disappearance of all measurable and evaluable disease for a minimum of 4 weeks; partial response (PR) is a ≥ 50% decrease in the sum of products of the longest perpendicular diameters of all measurable lesions lasting at least 4 weeks and no new lesions; stable disease (SD) is present when findings do not qualify for CR, PR or progression; and progressive disease (PD) is a ≥ 50% increase or an increase of 10 cm^2 (whichever is smaller) in the sum of products of measurable lesions over smallest sum observed, or reappearance of any lesion which had disappeared, or clear worsening of any evaluable disease, or appearance of any new lesions, or failure to return for evaluation due to deteriorating condition..

STUDY DESIGN

The primary objective of this non-randomized, two-stage phase II trial was to evaluate the objective response rate of PZA in patients with metastatic breast cancer. The study utilized a two-stage accrual design of Simon with $\alpha = 0.10$ and $\beta = 0.10$ involving a maximum of 35 patients, with an interim review after 12 patients had been registered. If one or no responses were seen in the first 12 response-evaluable patients, the study would be terminated. If two or more responses were seen in the first 12 patients, an additional 23 patients would be treated. The 35 patients would allow us to estimate the frequency of response with a confidence interval of 16.6%. The drug would be recommended for further study if the true response rate is 30 % or greater (p_1).

The efficacy analysis was based on the intent-to-treat population.

RESULTS

Patient Characteristics

Fifteen patients from three institutions were entered into this study. After two responses were seen in the first 12 evaluable patients, additional patients were enrolled in the study. The study was prematurely terminated after total of 15 patients were treated due to loss of financial support. Patient characteristics are shown in Table 1. The median age of the study population was 48 years, range (30–80), 14 (93%) patients had SWOG performance status ≤ 1. Seven (46%) patients had ER/PR positive tumor, and 3 had unknown ER/PR status. Thirteen (86%) patients received prior adjuvant chemotherapy, and 13 (86%) patients were treated with 1 prior regimen of palliative chemotherapy for metastatic disease. Fourteen patients (93%) had received prior anthracyclines. Majority of patients had visceral organ involvement. The lungs were the most common site of metastases in 10 (66%) patients.

Response Data

Fourteen patients were evaluable for response. One patient withdrew from the study without completing the first infusion of PZA after she developed severe pruritus. Fourteen patients received a total of 45 cycles of PZA, the median number of cycles was 2 (range1–8). There were no complete responses. Three patients (20%) had partial response lasting for 6, 5.5, and 4.5 months respectively. Two responding patients had ER/PR negative and one had ER/PR positive breast cancer. Additional two patients had stabilization of their disease lasting for 5 and 3 months, one ER/PR positive and one negative. The overall response rate was 20% with tumor growth control rate (PR +SD) seen in 33% of patients. Median time to progression was 7 weeks, range (2–26 wks)

Toxicity

Fifteen patients were evaluable for toxicities and the worst grade experienced by the patients for each toxicity is listed in Table 2. Ten patients (67%) had a dose reduction or dose delay due to grade 4 neutropenia. Similar to other studies the predominant toxicity was hematologic in this population. No patients on this study had thrombocytopenia. Other toxic side effects included neurotoxicity in the form of agitation, anxiety, twitching and paranoia during infusion of the drug. These were transient in nature. In general most gastrointestinal toxicities were mild (grade1–2). Only two patients (13%) had grade 4 vomiting.

DISCUSSION

Pyrazoloacridine is a rationally synthesized acridine derivative to undergo clinical testing as an anticancer agent. PZA is a dual topoisomerase inhibitor and is unique due to its direct

enzyme inhibition. PZA had much promise as an anticancer agent during the preclinical development demonstrating activity against a wide spectrum of tumors, activity against hypoxic cells and cytotoxicty in noncycling cells. Unfortunately this agent did not hold its promise with lack of clinical activity in various solid tumors including genitourinary, lung, glioma and ovarian cancers. Therefore, further development of this agent was unfortunately aborted.

To our knowledge this is the first study that has reported a durable response to PZA in patients with solid tumors. Three patients (RR 20%) had partial response lasting for 6, 5.5, and 4.5 months respectively. Additionally, tumor growth control lasting for more than 5 months was seen in 1 patient with stable disease. Although when compared to historical controls, this RR may be considered uninteresting, this is the only tumor type in which PZA has shown such a response. Our study also confirmed that grade ≥ 3 neutropenia is the most common toxicity occurring in 87 % of patients. Ten patients required dose reduction or dose delay due to grade 4 neutropenia.

Although this drug is no longer in development we believe that reporting this data is important in principle to show that agents targeting topoisomerases are active in breast cancer. We speculate that although this agent lacks activity in solid tumors as a single agent perhaps using some rational combination of this drug with other cytotoxics may have improved responses. Breast cancer is a disease that is characterized by late recurrences which suggest that perhaps non-cycling dormant tumor cells escape therapy and result in late metastases. PZA was designed to target such cells and overcome drug resistance and designing similar compounds and combining them at low doses with other cytotoxics in the treatment of early breast cancer may be a rational option.

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Table 1

Patients Demographics

Clinical Parameter	N=15
Median Age (range)	48 (30–80)
SWOG performance status	
0	7
1	7
2	1
Race	
White	13
African-American	2
Receptor status	
ER or PR-positive	7
ER/PR-negative	5
ER/PR unknown	3
Prior therapy	
Adjuvant chemotherapy	13
Metastatic	13
Radiation therapy	8
Site of metastatic disease	
Skeleton	10
Liver	7
Lung	10
Lymph nodes	8

Abbreviations: Estrogen receptor (ER); Progesterone receptor (PR);

Table 2

Toxicity

Toxicity	Grade 1–2 N=15	Grade 3 N=15	Grade 4 N=15
Hematological			
Neutropenia	2	3	10
Anemia	6	1	0
Thrombocytopenia	0	0	0
Gastrointestinal			
Nausea	7	2	0
Vomiting	2	0	2
Neurologic Constitutional	6	1	0
Fatigue	5	1	0
Pain	3	1	0
Others			
Skin discoloration	3	0	0
Dyspnea	0	0	1
Renal	1	0	1
Infusion reaction	2	0	0

Table 3

Efficacy

Best Response	N=15 (%)
CR	0
PR	3 (20)
SD	2 (13)
Tumor growth control rate (SD+PR)	5 (33)
PD	4 (26)
NE	1

Abbreviations: Complete response (CR); partial response (PR); stable disease (SD);