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Clinical report

A phase II trial of piroxantrone in endometrial cancer: Southwest Oncology Group Study 8918

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A phase II trial of the new anthrapyrazole piroxantrone was carried out by the Southwest Oncology Group in patients with advanced metastatic or recurrent endometrial cancer. A two-stage statistical design targeted accrual of 20 eligible patients. The starting dose of piroxantrone was 150 mg/m^2 in patients without prior radiation therapy (RT) and 120 mg/m^2 in patients with prior RT. There were 15 eligible patients, six of whom had received prior hormonal therapy while nine patients had not received prior hormonal therapy. Eight patients had received prior RT while seven patients had not received any prior RT. One to seven cycles of piroxantrone were administered. Dose escalation was feasible in four patients. No grade 5 toxicity was experienced by any patients. Most of the grade 4 (granulocytopenia in one) and grade 3 (leukopenia in three, granulocytopenia in three, anemia in two and thrombocytopenia in one) toxicity was related to myelosuppression. Grade 3 non-hematologic toxicities were nausea, fatigue and SGOT elevation. There was one partial response for a response rate of 7% (95% CI 0.2–32%) and median survival was 11 months (95% CI 3–13 months). The study was prematurely terminated due to lack of patient accrual.

Key words: Advanced endometrial cancer, piroxantrone, recurrent endometrial cancer.

Introduction

Piroxantrone is one of a series of 5-[(amino alkyl)-amino]-substituted anthra[1,9-*c*,*d*]pyrazol-6(2H)-one compounds commonly known as anthrapyrozoles. These agents were developed in an effort to combine broad anti-tumor activity of the anthracyclines with decreased myocardial toxicity, by decreased semiquinone free radical formation.[1,2]

The mechanism of action of piroxantrone and other anthrapyrazoles is incompletely understood but most likely involves DNA binding, with induction of DNA strand breaks, and inhibition of DNA, RNA and protein synthesis.[3,4] Piroxantrone has a 20-fold more potent effect on DNA synthesis than on RNA synthesis. This was demonstrated in the L1210 cell line. Piroxantrone has been demonstrated to cause single-strand and to a lesser extent double-strand breaks. Single-strand breaks were repaired very slowly after piroxantrone was washed out and additional breaks occurred thereafter for at least 2 h. Collectively, these findings suggest an interaction with topoisomerase II.[4] Other investigators have noted a lack of cross-resistance to other DNA intercalators.[5]

Previous investigators have demonstrated that piroxantrone has antitumor activity in a wide spectrum of experimental systems against breast cancer, colon cancer, osteogenic sarcoma, melanoma and leukemia.[3,4,6] In two phase I clinical trials, major toxicity of piroxantrone administered as a single dose in a 1 h infusion scheduled very 21 days was myelosuppression.[7,8] Additional schedules have not been investigated due to lack of schedule dependency seen in preclinical investigations. The maximum tolerated dose in the Johns Hopkins study was 150 mg/m^2 in patients who had minimal or no prior therapy and a good performance status, and 120 mg/m^2 for patients outside of these categories.[9] Patients with extensive prior therapy

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demonstrated significant myelosuppresion with doses above 140 mg/m^2.[7] No cardiac toxicity was observed at standard doses in these phase I trials. In fact, no definite effect on ventricular ejection fraction could be confirmed for a total dose of up to 2000 mg of piroxantrone.

The apparent lack of cardiotoxicity and significant myelosuppression made piroxantrone potentially desirable in the management of endometrial cancer that occurs in patients with a median age of 75 years. Since doxorubicin is considered to be the single best agent in the treatment of advanced endometrial cancer, a phase II trial of piroxantrone was undertaken to test its antitumor activity in this modestly anthracycline sensitive tumor. This report presents the initial Southwest Oncology Group (SWOG) experience with piroxantrone in patients with advanced epithelial endometrial cancer.

Patients and methods

Eligible patients had metastatic or recurrent bidimensionally measurable and histologically proven epithelial endometrial carcinoma (Table 1). The study was initiated in September 1991 and terminated in May 1994. The histology was confirmed in all cases by central pathology review. Other eligibility criteria included in a performance status of 2 or less, a granulocyte count of at least 1500/μl, platelet count and serum bilirubin level within institutional normal limits. In addition, adequate renal function as demonstrated by normal serum creatinine and creatinine clearance 60 cm^3/min or above was required for participation in the study.

Table 1. Patient demographics: SWOG 8918

	Piroxantrone ($n=15$)	
Age (years)		
Median	65	
minimum	34	
maximum	75	
Race		
white	13	87%
black	2	13%
other	0	0%
Prior hormonal		
yes	6	40%
no	9	60%
Prior RT		
yes	8	53%
no	7	47%
Performance status		
0–1	11	73%
2	4	27%

Patients who had received prior hormonal therapy, no or one biologic response modifier therapy, surgery or radiation therapy were eligible. A 3 week interval from previous therapy and recovery from all nadirs was required prior to piroxantrone treatment. Patients with myocardial infarction within the preceding 6 months, a history of congestive heart failure or cardiac arrhythmia that required treatment were ineligible. Prior malignancies within the preceding 5 years, concomitant and prior cytotoxic chemotherapy were criteria for exclusion from the study. Pregnant or lactating women were excluded. Effective contraception was required for participants of the reproductive age group.

All patients were informed of the investigative nature of the study, and written consent was obtained in accordance with institutional and federal guidelines. History and physical examination, blood, and radiographic tests to determine eligibility and measurable disease were done within 14 days of enrollment and all other screening tests within 42 days.

All patients with no prior radiation therapy (RT) received piroxantrone (1 mg/ml) as an initial dose of 150 mg/m^2 in 5% dextrose, infused over 1 h, every 21 days. Patients with prior RT received an initial dose of 120 mg/m^2. Dose escalations to 180 mg/m^2 (150 mg/m^2 for patients with prior RT) and then to 210 mg/m^2 were permitted after the first cycle in a given patient, if the following criteria were met during the previous cycle: non-hematologic toxicity of grade 1 or less, nadir of platelets of 100 000/μl or above and nadir of granulocytes of 1500 /μl or above. No change in subsequent dose was made if the platelet and granulocyte nadir were 50 000–100 000 and 500–1500/μl, respectively. If the nadir of platelets was 25 000–49 999/μl or the granulocytes 250–499/μl the piroxantrone dose was reduced by 30 mg/m^2 from the previous dose. If either nadir was less than these levels, the dose was further decreased by 25%. The lower dose was used if dose modifications according to granulocytes and platelets were different. If the platelet count was less than 100 000/μl or the granulocyte count less than 1500/μl on the initiation of a cycle the piroxantrone was delayed on a weekly basis until these levels were exceeded. The nadir complete blood count and differential count were measured on day 15 of the 21 day cycle.

On day 1 of the subsequent cycle, a history and physical examination was done, and blood count and serum chemistries were measured. A MUGA scan was obtained after the fourth course of piroxantrone and prior to every third course, thereafter. Piroxantrone was discontinued if congestive heart failure developed at any time or if the ejection fraction dropped by more than 15% from baseline. Treatment was withheld for grade 2 or greater (SWOG standard toxicity criteria) hepatic or renal toxicity or for all other toxicity of grade 3 or greater until resolution to grade 1 or less. Treatment was then resumed at one dose level lower, except for patients with cardiac toxicity who were removed from the study. An adverse drug reaction would be reported for all grade 4 non-hematologic toxicity.

The extent of disease was assessed with physical examination at 3 week intervals and radiographs every 6 weeks. Response determinations were made according to SWOG standard response criteria.[8] Assessment of objective disease status was done every 6 weeks, i.e. prior to treatment and at least every other course. Treatment was continued until progression of disease, unacceptable toxicity or patient request to withdraw from the study. Additional treatment was then at the discretion of the primary physician. All patients were followed until death.

A two-stage statistical design was used to determine patient accrual. It was assumed that piroxantrone would not be of further interest if the true response rate was less than 5% and that it would be of interest for further testing if true response rate was 20% or above. Thus, initially, 20 eligible patients were targeted. If no response was seen, the study would be terminated. If at least one response was observed, an additional 20 patients would be accrued. Five or more responses out of 40 would justify further study of piroxantrone, provided other factors such as toxicity, duration of response and survival also appeared favorable. This design has a significance level (probability of falsely declaring an agent with a 5% true response probability, to be one warranting further study) of 3% and a power (probability of correctly declaring an agent with a 20% response probability, to warrant further study) of 92%.

Results

Of 22 patients registered in the first stage of accrual, 15 were invaluable. Six were ineligible due to ineligible pathology and one patient was ineligible as she had no evidence of measurable disease at prestudy. The study was terminated in May 1994 for lack of patient accrual. The median age for the 15 invaluable patients was 65 years (range 34–75). The SWOG performance status was 0–1 in 11 patients (73%) and 2 in four patients (27%). Six patients received one cycle; four, two cycles; one, four cycles; two, five cycles; and two, seven cycles, of piroxantrone.

Table 2. Response: SWOG 8918

	Piroxantrone	
Complete response	0	0%
partial response	1	7%
Stable/no response	2	13%
Increasing disease	11	73%
Early death	1	7%
Total	15	100%

All eligible patients were invaluable for response and toxicity. In the 15 patients evaluated for response, there was one (7%) partial response (Table 2). This patient discontinued therapy after seven courses of piroxantrone due to fatigue and alopecia. Progressive disease was documented 5 months after termination of therapy. Eleven (73%) patients had progressive disease during treatment without a period of stability, two

Table 3. Toxicity of piroxantrone grade 2 or greater: SWOG 8918

Type of toxicity	Grade of toxicity[a]	No. of patients
Alopecia	2	1
Anemia	2	3
	3	2
Constipation	2	1
Diarrhea	2	1
Dyspnea	2	1
Granulocytopenia	2	5
	3	3
	4	1
Incontinence	2	1
Leukopenia	2	7
	3	3
Malaise/fatigue/lethargy	2	3
	3	1
Nausea	2	5
	3	1
Stomatitis	2	1
Thrombocytopenia	3	1
Increased SGOT	3	1
Vomiting	2	2

[a] SWOG toxicity criteria.[8]

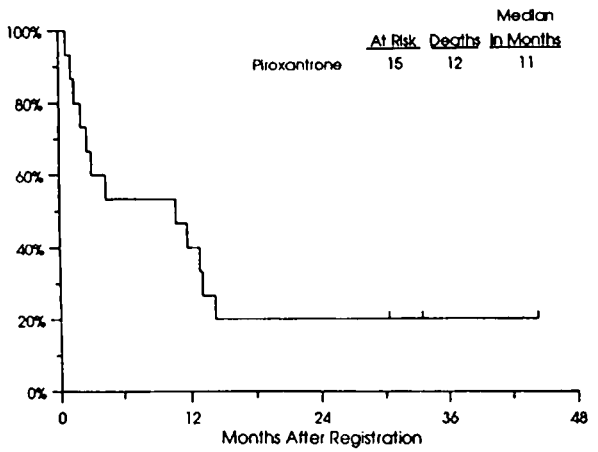

Figure 1. Overall survival: SWOG 8918.

(13%) patients had stable disease (3 and 7 months) and one died prior to response evaluation. The estimated response rate is 7% with an exact 95% confidence interval of 0.2–32%.

The toxicity data is reported in Table 3. Dose escalation was feasible in four of 15 patients. The grade 3 (leukopenia in three, granulocytopenia in three, anemia in two and thrombocytopenia in one) and grade 4 (granulocytopenia in one) events were related to myelosuppression. Grade 3 non-hematologic toxicity included nausea, malaise, fatigue and lethargy in one, and elevation of transaminases in another patient.

The median survival was 11 months (95% CI 3–13 months); 1 year survival was 45% and 2 year survival was 20% (Figure 1).

Discussion

This phase II trial establishes the safety of piroxantrone, but fails to answer the question of its effectiveness in patients with advanced previously untreated endometrial cancer. One partial response (for a duration of 7 months) was observed. The addition of colony stimulating factors (CSF), not permitted in the present study, could potentially allow the delivery of higher doses of piroxantrone. A recent phase I trial established that a doubling of the maximally tolerated dose of piroxantrone could be achieved with the use of granulocyte CSF.[9] However, in that study, seven of 38 patients developed symptomatic congestive heart failure at cumulative piroxantrone doses of 855–2475 mg. The role of piroxantrone in the etiology of heart failure is, therefore, unclear since six of these patients had received prior doxorubicin. Furthermore it was unclear from the study whether a steep dose–response curve existed for anthrapyrazoles. It is therefore unlikely that further dose escalation of piroxantrone would have been beneficial in our patients.

Conclusion

Although a small response rate (7% PR) was observed, premature termination of the study precludes any question of piroxantrone effectiveness in patients with recurrent or metastatic endometrial cancer.

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