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Phase II evaluation of piroxantrone in renal cell carcinoma

A Southwest Oncology Group Study

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Summary

The Southwest Oncology Group (SWOG) studied the response rate and toxicity of piroxantrone (150 mg/m^2 q 21 days) in patients with advanced metastatic renal cell carcinoma. Among 32 eligible patients, there were no partial nor complete responses. There were two mixed responses. Significant white cell toxicity, anemia, nausea, and vomiting were observed. Mild or moderate degrees of fever, malaise, and stomatitis occurred. No significant cardiac toxicity was noted. Piroxantrone does not have significant activity as a single agent in advanced renal cell carcinoma.

Introduction

Piroxantrone is an anthrapyrazole which was synthesized in an effort to combine the antitumor effect of related anthracycline compounds with decreased cardiotoxicity. Synonyms include NSC-349174, CI942, DuP 942, oxantrazole, and anthrapyrazole. It appears to cause cell death by DNA binding and subsequent strand breaks and inhibition of DNA, RNA, and protein synthesis [1,2]. Piroxantrone has demonstrated antineoplastic activity in several animal tumor systems, including: B16 melanoma; M5076 and Ridgeway sarcoma; L1210 and P388 leukemias; MX-1 and 16C mammary carcinoma. Some of these tumor models were resistant to doxorubicin and mitoxantrone [3,4].

Two separate phase I clinical trials have been published, both using a single-dose one hour infusion every 21 days [5,6]. Predictable, manageable toxicities were noted at dose levels around 150 mg/m^2. The most important of these was myelosuppression. No significant cardiac toxicity was seen. The Southwest Oncology Group (SWOG) studied piroxantrone in several different diseases; this report details the phase II results seen in patients with renal cancer. Study objectives were twofold: first, to assess the response rates and second, to assess the toxicities of piroxantrone administered every 21 days.

Materials and methods

Eligibility included a histologic confirmation of renal cell carcinoma, no prior chemotherapy, bidimensially measurable disease outside of previous radiation therapy ports, life expectancy of at least six weeks, performance status of 2 or better (SWOG criteria), and absence of a recent myocardial infarction (within six months) or history of congestive heart failure or significant cardiac dysrhythmia. Patients were to have recovered from prior surgery and radiation. Prior radiation must have included less than 25% of the bone marrow. Concomitant radiation was not allowed. While the patient may have received prior hormonal therapy

or cimetidine or coumarin, these could not be delivered concomitantly with the piroxantrone. Laboratory criteria for eligibility included a white blood cell count greater than or equal to 4,000/μl, platelet count greater than or equal to 100,000/μl, and serum bilirubin, SGOT (AST), and creatinine within institutional upper limits of normal. A radionuclide ventriculogram (gated-pool image; MUGA scan) prior to entry must have documented a left ventricular ejection fraction of at least 45%. All patients were provided information regarding the investigational nature of the study and were required to sign a written document of informed consent in keeping with institutional and FDA guidelines.

Patients received an initial dose of piroxantrone at 150 mg/m^2 in 5% dextrose, at a concentration of 1 mg/ml, infused over one hour and repeated every 21 days. Subsequent doses were administered at 21 day intervals and increased by 20% if the nadir granulocyte count was greater than 1,500/μl and platelet nadir exceeded 100,000/μl. For nadir granulocyte counts between 500–1500 or platelet counts between 50,000–100,000/μl, the dose remained the same. For nadir granulocyte counts less than 500/μl or platelet counts less than 50,000/μl, the subsequent dose of piroxantrone was decreased by 20%. Two downward and two upward dose adjustments were allowed.

Study patients underwent history and physical examination every three weeks, and serum chemistries were evaluated at the same interval. Blood counts were obtained weekly. Radionuclide ventriculograms were repeated after the fourth course of piroxantrone, and prior to every third course thereafter. Patients were removed from the study if their cardiac ejection fraction dropped by more than 10% from baseline. Tumor measurements were made every 42 days. Response criteria were standard for a phase II trial: complete remission (CR), which required disappearance of all clinically detectable disease for at least three weeks; partial remission (PR) which required a 50% shrinkage in the sum of the products of the perpendicular diameters of measured lesions for a minimum of three weeks, with no simultaneous increase in the size of any lesion or the appearance of any new lesions; progression, which required at least a 50% increase in the sum of products of measurable lesions, or appearance of a new lesion. Patients with progressive disease or unacceptable toxicity were taken off study.

Results

Piroxantrone was given to 34 patients. Two of these patients were ineligible due to inadequate baseline assessments. Of the remaining 32, one refused treatment after the first cycle, and two had inadequate follow-up. In reckoning response, these three patients were assumed to be non-responders. There were 28 males and 6 females. The median age was 60, with a range of 36 to 79. Four patients had received a biological response modifier, 2 had received hormonal treatment, and one had received both of these. One half of the patients (17) had a prior nephrectomy. Except for 10 patients all of those entered on the trial received two or more cycles of chemotherapy. Of these 10 patients, one refused further treatment due to toxicity. The others were taken off due to disease progression. No complete nor partial responses were seen. There were 2 mixed responses, in which marked shrinkage in lung lesions was noted at the same time that disease progressed elsewhere – in the central nervous system in one case, and in the kidney in the other case. One patient remains on the drug with stable disease, having received 14 cycles of chemotherapy for a cumulative dose of 1,933 mg/m^2. The stability of her disease could simply reflect the natural history of her particular disease; she had a hilar and a mediastinal mass which had progressed only minimally, without treatment, in the 6 months prior to going on study.

A median of 2.9 courses (range 1–14) of piroxantrone was given to the 32 eligible patients. The cumulative amount of piroxantrone administered per patient ranged from 150 mg/m^2 to 1,933 mg/m^2 with a median of 428 mg/m^2. There were 13 dose escalations and 6 dose reductions given per protocol criteria.

Toxicity is summarized in Table 1. Toxicity grading is by standard SWOG criteria. The major side

Table 1. Toxicities

Toxicities	Grade				
	(0) None	(1) Mild	(2) Mod	(3) Severe	(4) LT*
Granulocytopenia	23	1	3	3	4
Leukopenia	18	3	13	0	0
Anemia	19	4	6	4	1
Nausea	17	11	4	2	0
Vomiting	24	7	2	1	0
Alopecia	27	5	2	0	0
Fever without infection	28	2	4	0	0
Stomatitis	30	3	1	0	0
Hypercalcemia	33	0	1	0	0
Dysrhythmia	33	1	0	0	0

* LT = life-threatening

effect in this population, involving 65% of patients, was hematologic. Four patients experienced Grade 4 granulocytopenia. One of these patients inadvertently and inappropriately received an escalated dose with his second course of treatment. One patient experienced Grade 4 anemia. Severe (Grade 3) anemia was noted in 4 patients, severe nausea in 2 patients, and severe vomiting in 1 patient. One patient experienced palpitations with an irregular pulse before and three weeks after his fourth, and final, course of piroxantrone. This occurred at the same time that his hemoglobin had dropped to below 9.0. Other than this, no instances of acute nor chronic cardiac toxicity were noted. Alopecia was minimal. Other toxicities are noted.

One patient experienced extravasation of piroxantrone into the dorsum of her hand. She was hospitalized and observed overnight. The dorsum of her hand became swollen, tender, and dusky for approximately 48 hours, then normalized. There were no long-term sequelae.

The overall median survival was 5.4 months, with a median follow-up for censored cases of 4.3 months (range 1.3–8.9 months).

Discussion

Patients with advanced renal cell carcinoma remain relatively resistant to any form of systemic chemotherapy. This dose schedule of piroxantrone was reasonably well tolerated, although there was some significant white cell depression. While there is evidence that extravasated piroxantrone could have toxicity similar to doxorubicin, with potential for tissue necrosis, this did not occur with the patient who extravasated [7]. The finding that there were no responders among 32 eligible patients strongly suggests that piroxantrone in this dose schedule has no role in the treatment of patients with advanced renal cell carcinoma.

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References

1. Fry DW, Boritzki TJ, Besserer JA, Jackson RC: *In vitro* DNA strand scission and inhibition of nucleic acid synthesis in L1210 leukemia cells by a new class of DNA complexers, the anthra [1,9-cd] pyrazol-6(2H)-ones (anthrapyrazoles). Biochem Pharmacol 34:3499–3508, 1985
2. Leopold WR, Nelson JM, Plowman J, Jackson RC: Anthrapyrazoles, a new class of intercalating agents with high-level, broad spectrum activity against murine tumors. Cancer Res 45:5532–5539, 1985
3. Burchenal JH, Pancoast T, Elslager E: Anthrapyrazole and amsacrine analogs in mouse and human leukemia *in vitro* and *in vivo*. Proc Am Assoc Cancer Res 26:224, 1985
4. Sebolt JS, Havlick MJ, Hamelehle KL, Klohs WD, Steinkampf RW, Jackson RC: Establishment of adriamycin-resistant mammary adenocarcinoma 16/C *in vitro* and its sensitivity to the anthrapyrazoles CI-942 and C-937. Proc Am Assoc Cancer Res 26:339, 1985
5. Hantel A, Donehower RC, Rowinsky EK, Vance E, Clarke BV, McGuire MP, Ettinger DS, Noe DA, Grochow LB: Phase I study and pharmacodynamics of piroxantrone (NSC 349174), a new anthrapyrazole. Cancer Res 50:3284–3288, 1990
6. Ames MM, Loprinzi CL, Collins J, *et al.*: Phase I and clinical pharmacological evaluation of piroxantrone hydrochlo-

ride (oxantrazole). Cancer Res 50:3905–3909, 1990
7. Clarke BV, Harwood KV, Donehower R: Local toxicity of piroxantrone: an anthrapyrazole with irritant and vesicant properties similar to doxorubicin (letter). J Natl Cancer Instit 81:1331–1332, 1989

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