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Bisantrene, an Active New Drug in the Treatment of Metastatic Breast Cancer[1]

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ABSTRACT

Forty-four patients with metastatic breast cancer who had previously received extensive conventional systemic therapy, including combination chemotherapy with doxorubicin, were treated with Bisantrene, a new anthracene derivative. The dose schedule was 250 to 300 mg/sq m body surface administered as a 1- to 2-hr i.v. infusion. Of 40 evaluable patients, there were nine partial responses, and 18 patients had stable disease. Responses were seen in all major sites of organ involvement with a median time to progression of 28 weeks. Moreover, responses were seen among patients who had either failed to respond or had demonstrated refractoriness to prior therapy with doxorubicin, suggesting an apparent lack of cross-resistance between doxorubicin and Bisantrene. Except for myelosuppression and one incidence of acute anaphylactoid reaction, Bisantrene was generally well tolerated by most patients. We believe that Bisantrene may ultimately have a major role in the effective treatment of metastatic breast cancer, and further clinical trials are warranted.

INTRODUCTION

The anthracene derivatives have been developed in an attempt to find a group of compounds similar to the anthracyclines with a broad spectrum of antitumor activity but without the potential for cardiotoxicity (3, 4). Dihydroxyanthracenedione (Mitoxantrone) is the first of these compounds to be studied clinically and has been found to have activity against several human tumors, including breast cancer (1, 14). Unfortunately, recent data have indicated that dihydroxyanthracenedione may be cardiotoxic. Since doxorubicin has a major role as the initial therapeutic regimen in the treatment of many cancers, the potential for cardiac toxicity, especially in patients treated previously with doxorubicin, is likely to limit the usefulness of dihydroxyanthracenedione.

Bisantrene (CL 216,942; anthracenedicarboxaldehyde dihydrochloride) is the second anthracene compound recently introduced for clinical investigation. It has demonstrated significant antitumor activity in experimental tumor systems, including L1210 leukemia, P388 leukemia, Liberman plasma cell tumor, B16 melanoma, Ridgeway osteogenic sarcoma, and colon tumor 26 in mice (4). Although the precise mechanism of action of Bisantrene has not been well defined, preliminary evidence suggests that it is a DNA-reactive agent, producing RNA and DNA inhibition in mouse lymphoma L5178Y tissue culture. When compared to doxorubicin, Bisantrene is a more potent inhibitor of [^{3}H]uridine incorporation into RNA and [^{3}H]thymidine incorporation into DNA. Moreover, unlike doxorubicin, available experimental data to date have shown no evidence of cardiotoxicity (1, 8).

In 1980, Phase I clinical trials were initiated to determine the maximum tolerated dose with different schedules of drug administration (9, 12, 13). A maximum tolerated dosage for patients with solid tumors was found to be 260 mg/sq m given as a single dose repeated at 21- to 28-day intervals, 80 mg/sq m daily for 5 days repeated every 28 days, or 150 mg/sq m weekly for 3 weeks followed by a 2-week rest period. The dose-limiting toxicity of Bisantrene was myelosuppression, essentially granulocytopenia, which was of short duration and rapidly reversible. No evidence of hepatic, renal, or cardiotoxicity has been observed. Because of its good tolerance by patients and excellent *in vitro* antitumor activity (11), a number of Phase II trials of Bisantrene have been initiated recently. In this paper, we describe our experience with Bisantrene in the treatment of refractory metastatic breast cancer.

MATERIALS AND METHODS

Forty-four patients with metastatic breast cancer were entered in study. The median age was 62 years, with a range of 29 to 74 years. All patients had measurable or evaluable metastatic disease and had been treated previously with conventional chemotherapeutic agents including combination chemotherapy with doxorubicin. The median duration of prior systemic therapy was 27 months, with a range of 3 to 73 months. The number of prior therapeutic regimens ranged from 1 to 8, with a median of 3. All patients treated had a performance status (Zubrod's) of 3 or better, with a median of 1. The distribution of dominant disease site was soft tissue 7, bone 10, and visceral 23; the median number of organ sites involved was 2, with a range of 1 to 5.

A single dose schedule of 250 mg/sq m administered every 3 weeks was chosen based upon a Phase I study conducted by Von Hoff *et al.* (12). Patients who were considered poor risk (poor bone marrow reserve and/or bilirubin >2 but <5 mg%) were given 220 mg/sq m. Each dose of Bisantrene was mixed in 250 to 500 ml 5% dextrose water or 0.9% NaCl solution and infused over at least 1 hr via an indwelling subclavian venous catheter, except in 7 patients where the drug was given directly into a peripheral vein. Because the myelosuppression associated with 250 mg/sq m was mild to moderate, the starting dose of Bisantrene was subsequently escalated to 300 mg/sq m for the last 14 patients in the study. Prior to therapy, all patients had adequate blood cell counts (absolute granulocyte count greater than or equal to 1500/cu mm and platelet counts greater than 100,000/cu mm). Informed consent was obtained from all patients. Blood cell counts, differential counts, and platelet counts were obtained before therapy and repeated at weekly intervals. Blood chemistry profiles (including serum creatinine, blood urea nitrogen, and liver function tests), tumor measurements, and appropriate radiological and radionuclide studies were obtained prior to therapy and were repeated at

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least every 3 to 9 weeks. Partial response was defined as a 50% or greater decrease in the sum of the product of the diameters of all measured lesions without simultaneous increase in the size of any lesions or the appearance of new lesions. Response in the bone had to include evidence of blastic repair of previously known lytic lesions. A partial response in liver consisted of either a 50% reduction in the summation of the liver enlargement below the costal margin in both midclavicular and epigastric lines or a ≥50% decrease or a substantial improvement (in the absence of measurable lesions) in liver scanning, ultrasound, or computerized axial scan. Stable disease was a steady state of response less than partial response or progression less than increasing disease for a minimum of 8 weeks. There could be no appearance of new lesions for this category. Increasing disease was defined as an unequivocal increase of at least 25% in the size of any major lesions or the appearance of new lesions.

RESULTS

Of the 44 patients with metastatic breast cancer entered in this study, 4 were considered inevaluable for response; one patient died unexpectedly within the first 14 days of initiation of chemotherapy from a presumed pulmonary embolism, and 3 patients had inadequate trials. All 3 patients had received only one course of therapy and did not return for reevaluation. Among the 40 evaluable patients, there were 9 partial responses, giving a response rate of 22% (95% confidence limits, 10.8 to 38.4). Eighteen patients had stable disease while 13 had tumor progression in spite of treatment. In responding patients, the median time to progression from onset of therapy to evidence of progressive disease was 28 weeks (range, 22 to 39+ weeks). This is significantly better ($p = 0.02$) than that of patients with stable disease who had a median time to progression of 16 weeks (range, 8 to 26+ weeks). The median time to progression for all patients in the increasing disease category was 6 weeks. Responses were seen in all major sites of organ involvement, including chest wall (7 of 16), lymph node (3 of 8), bone (4 of 20), liver (1 of 8), and lung (1 of 12). Responses to Bisantrene occurred rapidly, with a median time to response of 6 weeks (range, 3 to 12 weeks).

The influence of prior doxorubicin therapy in response to Bisantrene is shown in Table 1. Patients with prior response to doxorubicin therapy and patients who were not known to be refractory (progressive disease developed more than 12 months after cessation of doxorubicin therapy) to prior doxorubicin therapy were more likely to respond to Bisantrene. Patients known to be refractory to doxorubicin (progressive metastatic disease during or within 6 months following cessation of doxorubicin therapy) and patients who had failed previously to exhibit a response to doxorubicin also had responses to Bisantrene chemotherapy indicating a lack of cross-resistance between Bisantrene and doxorubicin.

Myelosuppression (Table 2), principally granulocytopenia, was the most frequent toxic effect. Other side effects included mild nausea and vomiting in 20 to 30% of patients. General malaise and low-grade fever occurred in 20% of patients, with documented urinary infection and catheter site infection in one patient each. Phlebitis was encountered in all 7 patients who received the drug via peripheral veins, and in all but one patient placement of indwelling central venous catheters was subsequently performed for the continuation of therapy.

Acute anaphylactoid reaction probably related to Bisantrene was seen in one patient. This patient achieved a significant response in her soft tissue disease following therapy with

Table 1

Bisantrene response by prior Adriamycin experience

Previous Adriamycin experience	Response to Bisantrene			
	Total	Partial	Stable	Progressive disease
Prior Adriamycin response				
Complete	8	5	3	0
Partial	12	2	7	3
Stable	10	1	4	5
Progressive	5	1	1	3
Unknown	5	0	0	5
Prior Adriamycin refractoriness				
Refractory	23	2	10	11
Not refractory	14	7	6	1
Unknown	3		3	

Table 2

Bisantrene in breast cancer hematological toxicity

Dose (mg/sq m)	Lowest counts/cu mm × 10^3			Median day	
	WBC	Absolute granulocyte	Platelet	Lowest count	Recovery
250	2.3 (0.8–4.6)	0.9 (0.3–3.3)	227 (29–422)	9	16
300	2.1 (0.3–4.1)	0.8 (0–1.7)	204 (73–350)	10	16

Bisantrene. Prior to the onset of what appeared to be an acute anaphylactoid reaction, the patient had had 2 preceding episodes of acute shortness of breath and confusion during her infusion with Bisantrene. On both of those occasions, she responded well to therapy with diuretics and Benadryl without evidence of cardiovascular, respiratory, or neurological sequalae. On the day of her acute adverse reaction, the patient received premedication with Benadryl and Torecan. Immediately, following a few drops of infusion with Bisantrene 450 mg (dissolved in 250 ml 5% dextrose in water), the patient complained of burning sensation in both ears. Drug infusion was discontinued immediately, but she became short of breath, began wheezing, and subsequently had a respiratory arrest; she was resuscitated successfully. Unfortunately, she died subsequently from infectious complications resulting from her tracheostomy site which was performed during her respiratory arrest.

DISCUSSION

Based on our results, Bisantrene appears to be a very active single antitumor agent for the treatment of pateints with metastatic breast cancer. The 22% response rate and a 28-week median duration of time to progression observed in 40 heavily pretreated patients (median duration of prior chemotherapy, 27 months) indicates the significant activity of Bisantrene in breast cancer. The extent of prior systemic therapy has a definite impact on the rate of response to most of the major chemotherapeutic drugs commonly used for advanced breast cancer (6, 9, 15). Doxorubicin, the most active single agent, has a response rate of 40% in previously untreated patients and 20% in previously treated patients (5, 6, 7, 10). Thus, the response rate with Bisantrene is identical to that obtained with doxorubicin under similar circumstances. Furthermore, there was apparent lack of cross-resistance between Bisantrene and doxorubicin; response to Bisantrene was seen in patients who had failed to respond previously to doxorubicin or in whom the disease had already become refractory to doxorubicin.

Unlike our previous Phase II evaluation of dihydroxyanthracenedione, congestive cardiac failure has not been observed to date in our patients treated with Bisantrene. Furthermore, animal cardiotoxicity studies had been performed in beagle dogs comparing doxorubicin (36 mg/sq m) with Bisantrene (64 or 128 mg/sq m) once every 3 weeks for 31 weeks. Myocardial lesions that progressed with time were seen only in the sequential endocardial biopsies obtained from dogs receiving doxorubicin and were not seen in dogs that received Bisantrene (8). Thus, it is perhaps not surprising that Bisantrene does not appear to be cardiotoxic, and this may further improve the therapeutic potential of this new antitumor agent.

The major toxicity of Bisantrene was myelosuppression, essentially granulocytopenia, with prompt recovery. Otherwise, the most common complaint by our patients was general malaise accompanied at times by a flu-like illness with low-grade fever. This usually occurred after the second or third course of therapy, and each episode lasted for about 3 to 4 days. On the whole, the drug was well tolerated and relatively free of acute toxicity, especially when compared to doxorubicin. The development of an acute anaphylactoid reaction in one patient was unfortunate but does not outweigh the therapeutic benefit of this agent. We would, however, recommend that all patients receiving Bisantrene should be kept under close observation with appropriate precautions taken to prevent any serious or fatal complications resulting from an acute anaphylactoid reaction. Nevertheless, the observed antitumor activity in this group of heavily pretreated patients makes Bisantrene a provocative and important new antitumor agent in the chemotherapeutic armamentarian for the treatment of advanced breast cancer.

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