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A phase II study of bisantrene in malignant lymphomas

A southwest oncology group study*

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Summary. Forty evaluable patients with malignant lymphoma (ML) were treated with bisantrene at a dose of 260 mg/m^2 every 3 weeks (18 patients) or 208 mg/m^2 every 3 weeks (22 patients). The initial dose rate was determined on the basis of expected myelosuppression. Patients were heavily pretreated and had advanced disease (92% had stage IV). The overall response rate was 10% and included 1 partial response (PR) in 17 patients with Hodgkin's disease (HD), 1 PR and 1 complete response (CR) in 5 patients with favorable histology in non-Hodgkin's lymphoma (NHL), and 1 PR in 18 patients with unfavorable histology in NHL. Neutropenia (WBC $\leq$ 3000 cells/μl) was the most common toxicity, occurring in 50% of patients. Phlebitis was a common side effect in patients treated with bisantrene administered by way of peripheral veins. Bisantrene has limited activity in heavily pretreated patients with HD or unfavorable histology in NHL. The role of bisantrene for treatment of NHL with favorable histology or for treatment at an earlier point in the natural history of ML is unknown.

Introduction

Bisantrene, 9,10-anthracenedicarboxaldehyde bis((4,5-dihydro-1H-immidazol-2-yl) hydrazone)dihydrochloride, is a newly synthesized anticancer drug, which has recently entered phase II clinical trials. Preclinical testing of human tumors indicates that bisantrene has in vitro activity against tumors with a variety of histological findings [1, 7]. Furthermore, in direct in vitro comparisons, bisantrene had activity equivalent or superior to that of doxorubicin [7]. Early phase I–II studies indicate that bisantrene is active against tumors with several histological findings in patients selected by in vitro drug screening [1]. Subsequent phase II trials have confirmed the activity of bisantrene in patients with breast cancer [5]. In addition, animal studies indicate an absence of myocardial lesions in bisantrene-treated dogs as against dogs receiving equally myelosuppressive doses of doxorubicin [6]. This apparent lack of myocardial toxicity in dogs and the possibility that bisantrene is more potent than doxorubicin make it an attractive choice for testing in patients with advanced malignant lymphoma (ML). The current phase II Southwest Oncology Group (SWOG) study reports the results of bisantrene in patients with ML having a variety of histological subtypes.

Patients and methods

Forty-four patients with ML were entered on study between April, 1982 and January, 1984. All patients had measurable disease, which was clinically resistant to standard treatment (chemotherapy and radiotherapy). Patients had an initial peripheral WBC $\geq$4000 cells/μl and a platelet count $\geq$125 000 cells/μl, or evidence of ML involving the bone marrow. Patients had a serum creatinine $\leq$2.0 mg%, a serum bilirubin $\leq$2.0 mg%, and a SWOG performance score $\leq$3 (partially bedridden). Patients who had previously received >400 mg/m^2 of doxorubicin and those who had a history of congestive heart failure, ischemic heart disease, or cardiac arrythmias were not eligible. Treatment with concomitant radiation, chemotherapy, or steroids was not allowed.

The histology of these patients was classified according to the Working Formulation [4]. No attempt was made to completely restage these heavily pretreated patients. Initially abnormal tests were repeated every 3 weeks to gauge response to bisantrene.

Bisantrene was diluted in 500 ml 5% dextrose in water and infused over 2 h through a peripheral vein or centrally placed Hickman catheter. The initial dose of bisantrene in this trial for patients with adequate bone marrow reserves was 260 mg/m^2 based on the phase I dosing study of Von Hoff et al. [8]. The initial dose was reduced to 208 mg/m^2 in patients older than 65 years, in patients with reduced peripheral blood counts due to bone marrow involvement by ML, and in patients who had received extensive prior radiotherapy to the bone marrow. Treatment was repeated every 3 weeks and the dose of bisantrene was modified on the basis of peripheral blood counts obtained at weekly intervals. The dose was increased by 10% with each course until there was evidence of myelosuppression (WBC$\leq$4000 cells/μl, platelets$\leq$125 000 cells/μl). The dose was reduced by 20% in patients with WBC 1000–1999 cells/μl or with platelets 25 000–49 999 cells/μl; and by

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50% in patients with life-threatening toxicity (neutropenia with sepsis, WBC $\leqslant 1000$ cells/μl, or platelets $\leqslant 25\,000$ cells/μl).

Standard definitions of response were used. A CR was defined as the resolution of all evidence of disease. A PR was defined as a 50% decrease in the product of the longest perpendicular diameters of each tumor mass. A minor response (MR) was defined as an objective decrease in the longest perpendicular diameters of each tumor mass by at least 25% but less than 50%.

Results

Forty-four patients with ML were entered on study. Four patients were not eligible for evaluation: two were subsequently found to have carcinoma instead of lymphoma after expert pathological review; and two patients died before receiving any treatment. The clinical characteristics of the forty evaluable patients are summarized in Table 1. There were 25 female and 15 male patients, ranging in age from 17 to 82 years (median = 53 years). In general, these patients had 'B' symptoms (70%) and advanced disease (92% in stage IV) and they were heavily pretreated. Patients had previously received treatment with 3–15 drugs (median = 7) or one to eight drug combinations (median = 3). Of the 40 patients 39 had previously developed progressive disease while receiving doxorubicin or a doxorubicin-containing drug combination.

The results of treatment are summarized in Table 2. Responses (CR or PR) were seen in 1 of 17 patients with

Table 1. Clinical characteristics of 40 evaluable patients with lymphoma treated with bisantrene

Clinical characteristics	Frequency	
	No. of patients	%
Histology		
Hodgkin's disease	17	42
Non-Hodgkin's lymphoma, favorable subtypes	5	12
Non-Hodgkin's lymphoma, unfavorable subtypes	18	45
Stage		
III_B	3	8
IV_A	12	30
IV_B	25	62
Performance status		
Asymptomatic and active	5	12
Ambulatory and symptomatic	27	68
Ambulatory but limited activity	6	15
Partially bedridden	2	5
Organ involvement		
Bone marrow	9	22
Liver	10	25
Prior treatment		
Radiotherapy	30	75
Doxorubicin-based combinations	39	98
Initial dose level		
260 mg/m²	18	45
208 mg/m²	22	55

Table 2. Results of treatment by histology

Histologic diagnosis	No. of patients	Response (duration in weeks)		
		Minor	Partial	Complete
Hodgkin's disease				
Nodular sclerosing	7		1 (16+)	
Mixed cellularity	7	2 (4, 8)		
Lymphocyte depleted	2			
Lymphocyte predominant	1			
NHL, favorable histology				
Follicular small cleaved	5		1 (4+)	1 (27)
NHL, unfavorable histology				
Diffuse small cleaved	9	2 (2, 26)	1 (6)	
Diffuse mixed cell	3	1 (6)		
Diffuse large cell	5			
Lymphoblastic	1			
Total malignant lymphomas	40	5	3	1

HD (6%), in 2 of 5 patients with NHL of favorable histology (40%), and in 1 of 18 patients with NHL of unfavorable histology (6%). These responses lasted from 6 to 27 weeks. Five additional patients had MR with bisantrene treatment. Three of four responding patients were treated with the reduced doses of bisantrene (208 mg/m^2).

Eighteen patients received 1–10 courses (median = 2) of bisantrene at a dose of 260 mg/m^2. Myelosuppression (a reduction in the peripheral WBC to $\leq$4000 cells/μl) was documented in 67% of these patients. Twenty-two patients received 1–21 courses (median = 2) of bisantrene at a dose of 208 mg/m^2. Myelosuppression was documented in 59% of these patients. Neutropenia was the most common toxicity. A decrease in the WBC to 2000–2999 cells/μl was seen in 12 of the 40 patients (30%); a decrease to 1000–1999 cells/μl in 6 (15%); and a decrease to $<$1000 cells/μl in 2 patient, 1 of whom died of sepsis. Thrombocytopenia with platelet counts between 50 000 and 99 999 cells/μl occurred in 3 patients (8%), and with platelet counts between 25 000 and 49 000 cells/μl in 2 patients. Pain and swelling in the injected arm were so common and severe that most investigators administered bisantrene through a centrally placed indwelling catheter. Hypotension (20-mm decrease in systolic blood pressure) was noted in 2 patients and resolved after a slower rate of drug administration was selected.

Discussion

Bisantrene appears to have only modest activity in heavily pretreated patients with HD or NHL of unfavorable histology This finding confirms a previous study, in which no objective responses were observed in 16 heavily pretreated patients with advanced intermediate and high-grade diffuse NHL [3]. The doses used in this study were adequate to cause myelosuppression and decreased the WBC to $<$4000 cells/μl in 25 of 40 patients. In a further 8 patients myelosuppression could not be determined, because of low initial peripheral blood counts. The degree of myelosuppression in these patients was probably the result in part of heavy prior treatment with chemotherapy and radiotherapy, the advanced stage of disease, and the bone marrow involvement with lymphoma. In patients without bone marrow involvement and without prior therapy, bisantrene has been shown to cause very modest myelosuppression at a dose of 250 mg/m^2 every 3 weeks [8]. However, there is no clear indication that a higher dose rate of bisantrene in patients with ML would result in a higher response rate, as 3 of the 4 objective responses in this study occurred in patients receiving a reduced dose rate of the drug (208 mg/m^2).

The role of bisantrene in the treatment of advanced NHL with favorable histology is not clear. Because of the small numbers of patients studied the actual response rate is unknown. However, in patients with NHL with favorable histology the goal of treatment is frequently to attenuate the symptoms of disease. Bisantrene cannot be administered easily, and either causes significant pain in the arm (lasting several days) or requires a centrally placed indwelling catheter. These problems make the current formulation of the drug unattractive for patients with indolent lymphomas.

In summary, bisantrene has limited activity in heavily pretreated patients with advanced HD and NHL of unfavorable histology. The drug may have greater activity in the indolent lymphomas, but difficulty in administration of the drug makes it less attractive for these patients. Myelosuppression is the dose-limiting toxicity of bisantrene.

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