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Mitoxantrone: A Phase II Study in the Treatment of Patients with Advanced Breast Carcinoma and Other Solid Tumours

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Summary. *A phase II study of mitoxantrone, an anthraquinone derivative with structural similarities to adriamycin, has been carried out in 34 patients with advanced breast carcinoma and other malignancies. The first 20 patients were treated with a starting dose of 12 mg/m^2 by IV infusion repeated every 3 weeks; this was escalated to 14 mg/m^2 in the subsequent 14 patients. Of the 29 patients with advanced breast carcinoma, 8 achieved a partial response and two further patients achieved a mixed response. There were no complete responses. Of the eight responding patients, five had received no prior chemotherapy. Response duration ranged from 3$^1/_2$ months to 10+ months. No responses were seen in the other five patients, three whom had small cell carcinoma of lung, one squamous cell carcinoma of the lung, and one colonic carcinoma. Neutropenia was the most frequently seen toxicity but was usually mild and transient; WBC fell to less than 2,000/mm^3 in eight patients and to less than 1,000/mm^3 in only two. Otherwise, the drug was well tolerated; nausea occurred in 35% of patients and vomiting in 21%; severe alopecia requiring a wig was never seen. Mitoxantrone appears to be a well-tolerated and clinically active agent against advanced breast carcinoma.*

Introduction

Mitoxantrone (1,4-dihydroxy-5,8-bis2-2-hydroxyethyl-amino-ethyl-amino 9,10-anthracenedione dihydrochloride) is a new anthraquinone derivative synthesised in the hope of providing a compound with good clinical anti-tumour activity but without cardiotoxicity. Its main structural difference from adriamycin is the absence of the amino sugar moiety [6]. Experimental studies have shown equal or superior activity to adriamycin against several animal tumours but without proven cardiotoxicity [2]. Our own unpublished studies have shown activity against four human breast carcinoma xenografts.

Phase I clinical trials have shown the dose-limiting toxicity to be leucopenia [1, 3, 6, 7, 9]. A starting dose of 12 mg/m^2 to 14 mg/m^2 every 3 weeks has been recommended for phase II studies [6].

We report here our initial experience with a phase II study of mitoxantrone in the treatment of patients with advanced breast carcinoma and other solid tumours.

Patients and Methods

Patients. Between November 1980 and September 1981, 34 patients with histologically proven metastatic malignant disease were entered into the study. Informed consent was obtained from all patients. Thirty-one were female and three male; the median age was 55 years (age range 34–76 years). Twenty-nine patients had breast carcinoma, three patients had small cell lung cancer, and one each had squamous cell carcinoma of the bronchus and colonic carcinoma.

Twenty-one of the breast carcinoma patients were postmenopausal, five were premenopausal, and three were perimenopausal (less than 2 years from last menstrual period).

Of the 34 patients, 21 had received prior chemotherapy, seven of these on an adjuvant basis.

Dose and Schedule. The first 20 patients were treated with a dose of 12 mg/m^2 repeated every 3 weeks. In five non-responding patients this was increased to 14 mg/m^2 after two courses. The subsequent 14 patients received 14 mg/m^2 from the onset, repeated every 3 weeks. The dose of therapy was decreased in two patients from 14 mg/m^2 to 12 mg/m^2 because of delayed recovery of the WBC in one and non-neutropenic infection in the other. Treatment was given as an infusion in 100 ml of 5% dextrose over 30 min.

Investigations. Full blood counts were carried out at weekly intervals in all patients during treatment. Before treatment and at 3-weekly intervals the following were also checked: plasma urea

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and electrolytes, serum creatinine, bilirubin, alanine transferase, alkaline phosphatase, total protein, albumin, gamma GT, calcium, urate, chest X-ray and electrocardiogram. Skeletal X-rays, isotope scans of bone and liver, and bone marrow aspiration were carried out as indicated.

Criteria for Assessment of Response and Toxicity. Patients who received a minimum of two courses of therapy or who showed clear evidence of disease progression after one course of therapy were considered evaluable for response. Response in patients with breast carcinoma was defined according to standard UICC criteria [4]. WHO criteria for response were used for patients with other tumours [8]. All patients, whether completing two courses or not, were assessed for toxicity.

Results

Response in Breast Cancer

Eight of the 29 patients with advanced breast cancer achieved a partial response; none achieved a complete response. Two further patients achieved minor responses in soft tissues, one with healing of a fungating chest wall ulcer, the other with decrease in size of recurrent primary tumour, but in both patients this was accompanied by progression of co-existing pulmonary and pleural disease. Five of the eight patients achieving partial response had received no prior chemotherapy. Response according to sites of disease is given in Table 1.

Response in Other Tumours

No responses were seen for any of the other tumours (three small cell lung cancer, one squamous cell lung cancer, and one colonic carcinoma).

Time to Achieve Response

Response was achieved within 3 weeks (one course) in three patients, 6 weeks (two courses) in two patients, 9 weeks (three courses) in two patients, and a full 12 weeks (four courses) in one patient.

Response Related to Dose

Of the eight responding patients, two achieved a response at a dose of 12 mg/m^2, two achieved a response when the dose was increased after two courses from 12 mg/m^2 to 14 mg/m^2, and four responded at an initial dose of 14 mg/m^2.

Duration of Response

Five of the eight responding patients remain in partial remission after 3 months, 4 months, 5 months, 8 months, and 10 months. The other three patients relapsed after 3½ months, 5½ months, and 9 months. The median duration of response for the group has not yet been reached, but will be in excess of 5 months.

Response in Adriamycin-Treated Patients

Seventeen of the 29 patients with advanced breast cancer were treated with adriamycin, either before or after treatment with mitoxantrone. One of nine adriamycin responders also responded to mitoxantrone; one of six adriamycin non-responders responded to mitoxantrone; six of 12 patients not yet treated with adriamycin responded to mitoxantrone (details in Table 2).

Haematological Toxicity

The major objective toxicity encountered during treatment was myelosuppression. Therapy was accompanied by a fall in peripheral WBC in all patients, but in the majority this was minor and transient, with a nadir between 1 and 2 weeks after treatment. The WBC fell to less than 2,000/mm^3 during 10 courses and to less than 1,000/mm^3 during two courses in a total of eight patients (details in

Table 1. Response by site of disease in patients with advanced breast cancer

	No. of patients	Responses
Soft tissue	18	5
Nodes	8	3
Lung	8	0
Pleura	3	1
Bone	7	3
Liver	8	3

Table 2. Response related to adriamycin response

	No. of patients	Response to mitoxantrone
Adriamycin responders[a]	9	1
Adriamycin non-responders[b]	6	1
Adriamycin adjuvant therapy	2	0
Adriamycin not given	12	6

[a] Six before mitoxantrone; three after mitoxantrone
[b] Two before mitoxantrone; four after mitoxantrone

Table 3. White blood count (WBC) nadir with mitoxantrone

Dose	Patients	Courses	WBC nadir/course			
			2,000–3,000/mm^3	1,000–2,000/mm^3	< 1,000/mm^3	Mean nadir
12 mg/m^2	21[a]	45	15	5	2	3,200/mm^3
14 mg/m^2	19[a]	50	23	5	0	3,200/mm^3

[a] Six patients treated at both dose levels

Table 4. Toxicity and side-effects in 34 patients treated with mitoxantrone

	No. of patients
Nausea	12 (35%)
Vomiting	7 (21%)
Mild hair loss	17 (50%)
Alopecia requiring wig	0[a]
Dry mouth	10 (29%)
Stomatitis	1 (3%)
Neutropenic infection	3 (9%)
Blue discoloration of urine	6 (18%)
Blue discoloration of skin	3 (9%)
Paraesthesiae	4 (12%)
Nocturia	2 (6%)
Loss of taste	1 (3%)

[a] Out of 26 patients (the remaining eight already had adriamycin-induced alopecia)

Table 3). Precipitating factors such as extensive prior chemotherapy or radiotherapy, advanced age, or extensive liver metastases were present in seven of these. In one patient with liver metastases and elevated serum bilirubin (29 μmol/l, normal less than 17 μmol/l) the white blood count fell to 800/mm^3 after the first course; with the second course, by which time the bilirubin had fallen to normal limits, the white blood count fell to only 1,800/mm^3.

The mean WBC nadirs for both dose levels were identical, but the only patients who received 14 mg/m^2 were those who showed lack of haematological toxicity at 12 mg/m^2 or those who had not received extensive prior chemotherapy or radiotherapy.

Treatment was delayed on one occasion in each of two patients because of delayed recovery of the WBC. There were three episodes of neutropenic infection, all successfully treated with antibiotics. Thrombocytopenia of less than 100,000/mm^3 occurred in only four patients, and platelet values never fell below 75,000/mm^3. Haemoglobin values remained stable throughout.

Other Toxicity

Details of other toxicity are given in Table 4. In general these were mild and caused little serious distress; for example, some hair loss was reported in 50% of patients but this was never serious enough to require a wig, even with prolonged treatment. Four of eight patients with pre-existing adriamycin-induced alopecia had regrowth during treatment. Similarly, 35% of patients experienced nausea, some with vomiting, but this was usually mild and of short duration. No clinical or electrocardiographic evidence of cardiotoxicity was seen in any patient. No patient had to discontinue treatment because of toxicity.

Discussion

This study shows that mitoxantrone is clinically active against advanced breast carcinoma, with a response rate and duration of response as good as those reported for most other single agents except perhaps adriamycin [5]. It should be noted, however, that five of the eight objective responses were achieved in patients who had not been previously treated with chemotherapy. The lack of response in other tumours was disappointing, although this may simply reflect the small number of patients studied.

An impressive feature of the drug was its low incidence of serious side-effects, and most patients tolerated treatment very well. It is reasonable to compare mitoxantrone with adriamycin in view of structural similarities; in contrast with adriamycin, socially unacceptable alopecia was not a problem, and so far we have seen no clinical or electrocardiographic evidence of cardiotoxicity; in terms of anti-tumour effect, we have found lack of cross-resistance in only one patient, who achieved a response to mitoxantrone after failing to respond to adriamycin.

These initial results justify further clinical study with this agent, particularly in the treatment of breast

carcinoma. The finding that neutropenia is so far the dose-limiting toxicity suggests that dose escalation studies may also be possible with appropriate antibiotic support if required.

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