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Mitoxantrone for the Treatment of Advanced Breast Cancer: Single-agent Therapy in Previously Untreated Patients

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Abstract—*Mitoxantrone (dihydroxyanthracenedione) is a substituted anthraquinone with a similar spectrum of activity to adriamycin in experimental tumours. One hundred and thirty-four patients with advanced breast cancer and no prior chemotherapy for advanced disease were treated with mitoxantrone* (14 mg/m² *i.v. q* 3 weeks), *of whom* 99 *are presently evaluable for response and all for toxicity. Six patients achieved a complete response and* 29 *a partial response, the overall response rate being* 35% (95% *confidence limits,* 25–45%). *Median time to treatment failure was* >46 weeks. *Mitoxantrone was well tolerated, myelosuppression being the dose-limiting toxicity. The most frequent non-haematological toxicities were nausea and vomiting* (40%), *but these were rarely severe. Total alopecia occurred in only* 6 *patients. Four patients developed clinically significant evidence of cardiotoxicity after cumulative mitoxantrone doses of* 174–256 mg/m². *Mitoxantrone offers comparable efficacy and less acute toxicity than the most active currently available single agents in advanced breast cancer.*

INTRODUCTION

MITOXANTRONE (dihydroxyanthracenedione) is one of a series of anthracenedione derivatives synthesised as part of the search for compounds which retain the antitumour efficacy of the anthracycline compounds in current use but have less (or no) associated cardiotoxicity. In experimental tumours mitoxantrone has a spectrum of activity similar to that of adriamycin [1], while studies in beagle dogs have shown it to be markedly less cardiotoxic [2]. In phase I studies the compound was found to be well tolerated, being relatively free from side-effects such as nausea, vomiting and alopecia. Leucopenia was the dose-limiting toxicity.

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In phase II studies mitoxantrone has been shown to have significant activity in patients with advanced breast cancer [3, 4] and in patients with non-small cell lung cancer and melanoma [3]. Response rates of 20–25% have been reported in patients with breast cancer who had been heavily pre-treated, with relatively modest toxicity.

The purposes of the present study have been to establish the activity of mitoxantrone in patients with breast cancer who have received no prior chemotherapy for advanced disease, and to define further the acute and longer term toxicities of the drug. Parts of this study have been previously published [5] but this paper reports our collective experience in treating a large number of patients with mitoxantrone as their initial chemotherapy.

MATERIALS AND METHODS

One hundred and thirty-four women with locally advanced, recurrent or metastatic breast

cancer (histologically confirmed) were treated at one of six participating centres according to a common protocol. All had disease confined to one or more of the following sites: breast, skin, lymph nodes, lung (nodular disease), liver and bone. Patients with brain metastases, lymphangitic lung disease or severely deranged liver function tests were excluded. All the patients entered (see Table 1) were evaluable for toxicity. The 99 patients who were re-examined after two treatment cycles (minimum 42 days) have been evaluated for response (patient details—Table 2). At the time of this analysis 35 patients are non-evaluable, the reasons being shown in Table 3.

Previous endocrine therapy did not preclude inclusion in this study. Those patients who received tamoxifen, aminoglutethamide or prednisolone were eligible if their treatment stopped prior to commencing mitoxantrone. Patients receiving other forms of endocrine therapy were required to have discontinued treatment at least 4 weeks prior to entering the study. Recent or concomitant radiotherapy was permitted, the irradiated sites being then considered non-evaluable for response. No patient was entered in the study if she had received prior chemotherapy for advanced disease. Ten patients who had completed adjuvant chemotherapy >2 yr previously were considered eligible.

Table 1. Distribution of patients

Participating centre	No. of patients
Royal Marsden Hospital, London	35
Guy's Hospital, London	33
Western General Hospital, Edinburgh	22
University Hospital Clinic, Vienna	22
Finseninstitut, Copenhagen	17
University Ziekenhuis, Leiden	5
Total	134

Table 2. Pre-treatment characteristics of evaluable patients

No. of patients	99
Mean age	59 (Range 28–80)
Menopausal status:	
Post-menopausal	78
Pre-menopausal	3
Not recorded	18
Oestrogen receptor status:	
Unknown	74
1–29 fmol/l	12
30–100 fmol/l	8
>100 fmol/l	5
Performance status at entry (WHO):	
0	27
1	42
2	23
3	4
4	0
Not recorded	3
Sites of tumour spread prior to therapy:	
Primary tumour	28
Regional nodes	44
Skin	68
Bone	53
Lung	27
Liver	19
Metastatic nodes	21
Contralateral breast	8
Other	9

Table 3. Reasons for patients being considered non-evaluable for response to mitoxantrone

Too early	10
Early death due to malignancy	9
Inadequate documentation	7
Protocol violation	4 (concomitant non-study chemotherapy, radiotherapy to marker lesion, prior analogue, oestrogen withdrawal <4 weeks previously)
Less than 2 cycles	5
Total	35

Pre-treatment assessment included height, weight, performance status, physical examination with measurement of lesions and photography where possible, radio-isotope liver and bone scans and skeletal surveys as indicated, chest X-ray, full blood count and biochemical screen. Study inclusion criteria only permitted the entry of patients with pre-treatment white blood count $>4 \times 10^9/l$, platelet count $>120 \times 10^9/l$ and plasma urea and bilirubin values within the normal range of the laboratory at which they were measured unless the abnormality was attributable to proven involvement by tumour. Cardiac function had to be found normal by clinical, electrocardiographic and, where possible, ventricular ejection fraction measurements [estimated either by radioisotopic gated angiography or echocardiography (ECHO)]. Cardiac assessment was repeated after every four cycles of treatment.

Mitoxantrone was supplied by American Cyanamid at a concentration of 2 mg/ml. It was administered as an intravenous infusion over 30 min diluted in 100 ml 5% dextrose in water at a dose of 14 mg/m^2 every 21 days. Treatment was delayed as necessary to permit the recovery of the white blood count to $>4 \times 10^9/l$ and platelet count to $120 \times 10^9/l$, or to permit the resolution of any significant non-haematological toxicity.

Anti-emetics were prescribed in accordance with individual unit practice.

Toxicity was recorded employing WHO criteria and the criteria of response were those defined by the UICC. A complete response was defined as the complete disappearance of all identifiable tumours with no new lesions being noted. In the case of lytic bone metastases, these had to be shown to have calcified. A partial response required a reduction of >50% in the sum of the products of the longest perpendicular axes of measurable lesions and objective evidence of improvement in evaluable but non-measurable lesions, with no new lesions developing. It was not necessary for every lesion to have regressed to qualify as a partial response but no single lesion should have progressed. 'No change' indicated a <50% decrease or <25% increase in the sum of the products of the longest perpendicular axis of measurable lesions maintained for 8 weeks. Progression was defined as >25% increase in the product of the longest perpendicular axis of any lesion or the appearance of a new lesion. Durations of response and survival were calculated according to the method of Kaplan and Meier [6].

RESULTS

Patients were entered in this study between November 1980 and February 1983 from six participating centres. Ninety-nine patients are evaluable for response, and data on toxicity are available for 134 patients receiving a total of 732 courses of treatment.

Of the 99 evaluable patients, six demonstrated a complete response to mitoxantrone and 29 a partial response, giving an overall response rate of 35% (95% confidence limits, 25–45%). Disease progression was arrested (no change) in a further 20 patients (18%), while disease progressed during treatment in 44. Ten evaluable patients had received adjuvant chemotherapy >2 yr before entering the study. Of these, three achieved a complete response, three a partial response, one showed no change and three had progressive disease.

Oestrogen receptor status was known in only 25 of the 99 evaluable patients. Four out of thirteen patients with levels >30 fmol/l and 5/12 with levels <30 fmol/l achieved partial responses.

Response rate by pre-treatment performance status is shown in Table 4. Of fully evaluable patients 9/27 (33%) with performance status 0 responded to treatment, with two patients achieving a complete response. For performance status 1 and 2 patients the response rates were 50 and 30% respectively.

The response rates at different sites of disease are shown in Table 5. A total of 277 evaluable lesions were assessed of which 42 (15%) achieved a complete response and 66 (24%) a partial response. Regional lymph nodes showed the highest complete response rate (43%) while lung metastases showed the lowest response rate (4/27 partial responses).

Overall the median time to response was 9 weeks. The median time to treatment failure (date

Table 4. Response rate according to pre-treatment performance status (ECOG) criteria

	Performance status (ECOG) (%)						
	0	1	2	3	4	Not recorded	Total
CR	2(7)	3(8)	0	0	0	1	6
PR	7(26)	13(33)	7(30)	1(25)	0	1	29
NC	7(26)	6(14)	7(30)	0	0	0	20
PD	11(41)	20(45)	9(39)	3(75)	0	1	44
Total	27(100)	42(100)	23(100)	4(100)	0	3	99

Table 5. Response rate according to site of disease

	No. of lesions	Complete response (%)	Partial response (%)	Objective response rate (%)
Primary tumour	28	3(11)	6(21)	32
Regional nodes	44	19(43)	5(11)	55
Skin metastases	68	10(15)	11(16)	31
Bone metastases	53	0(0)	17(32)	32
Lung metastases	27	0(0)	4(15)	15
Liver metastases	19	1(5)	11(58)	63
Metastatic nodes	21	5(24)	4(19)	43
Contralateral breast	8	2(25)	3(38)	63
Other	9	2(22)	5(56)	78
Total	277	42(15)	66(24)	39

of first treatment to date of progression) was >46 weeks. (The cumulative percentage still responding was 52%.)

Toxicity

Haematological toxicity. As predicted by the phase I studies, mitoxantrone was myelosuppressive, the major impact being apparent on the white cell series. Of 134 courses of treatment for which data are available, WBC nadir counts of $<0.5 \times 10^9/l$ were observed on three occasions, counts between 0.5 and $0.99 \times 10^9/l$ on five occasions, and counts between 1 and $1.99 \times 10^9/l$ on a further 30 occasions. Nadir platelet counts of $<40 \times 10^9/l$ were recorded on only six occasions and between 41 and $100 \times 10^9/l$ on another seven occasions. Persistant thrombocytopenia, however, developed in one patient, leading to cessation of treatment.

Episodes of minor-to-moderate infection associated with neutropenia were reported in 15 of the 134 patients evaluable for toxicity. Two patients developed major infections and recovered with treatment but a further two patients, aged 51 and 54 yr, died of infections while neutropenic. Both patients had extensive bone metastases. One was receiving concurrent radiotherapy to the spine, the other having received extensive radiotherapy to marrow-containing sites 4 months prior to treatment with mitoxantrone.

Petechial haemorrhages secondary to thrombocytopenia were recorded in four patients, mild bleeding occurred in one patient and major haemorrhage occurred in the 54-yr-old neutropenic patient reported above (with bone marrow infiltration and receiving concurrent radiotherapy).

Non-haematological toxicity. The incidence and severity of the non-haematological manifestations of treatment toxicity are shown in Table 5. Overall, mitoxantrone was well tolerated in comparison with other cytotoxic agents, nausea and vomiting being the most frequently reported adverse effects. However, this was usually of minor severity, with grades 2 (transient vomiting) and 3 (vomiting requiring therapy) toxicity being reported in only 9 and 2% of evaluable treatment cycles respectively. Sixty per cent of treatment courses were associated with

Table 6. Adverse effects related to mitoxantrone therapy [recorded according to WHO criteria for the assessment of acute and sub-acute treatment (toxicity)]

	No. of evaluable cycles	No. of cycles (%) WHO grade 0	1	2	3	4	5
Nausea/vomiting	709	423(60)	204(29)	64(9)	16(2)	2(0.3)	0
Diarrhoea	708	681(96)	16(2)	9(1)	2(0.3)	0	0
Oral/stomatitis	697	632(91)	44(6)	19(3)	2(0.3)	0	0
Renal	573	561(98)	12(2)	0	0	0	0
Pulmonary	704	673(96)	19(2)	6(1)	6(1)	0	0
Infection	709	669(94)	20(3)	14(2)	3(0.4)	1(0.1)	2(0.3)
Peripheral neurotoxicity	542	531(98)	10(2)	1(0.2)	0	0	0
Local	640	629(98)	10(2)	1(0.2)	0	0	0

Table 7. Cardiac events associated with mitoxantrone therapy

Drug effect	Age	Risk factor	Dose received (mg/m^2)	Abnormality	Myocardial biopsy findings	Outcome
Probable	58	None	256	VEF	hypertrophied, mildly dilated myocardium—EM: no definite degenerative change	stopped treatment
Probable	68	none	243	VEF CHF	mildly dilated, mildly hypertrophied myocardium—EM: no degenerative changes	response to digoxin/diuretics
Probable	65	chest radiotherapy	182	VEF dyspnoea	—	response to diuretics
Probable	59	mediastinal radiotherapy (6000 cGy)	174	VEF CHF	dilated, hypertrophied myocardium	response to digoxin/diuretics

VEF = ventricular ejection fraction; CHF = congestive heart failure.

neither nausea nor vomiting of any degree, and 40% of patients did not experience nausea or vomiting at any point during their treatment.

Stomatitis or frank oral ulceration were recorded in 65/697 (9%) treatment cycles but were of minor severity (WHO grade 1) on 44 of these occasions.

Alopecia was rare, with only six patients having reversible, complete alopecia (WHO grade 3). A further 12 patients had patchy alopecia, while 50 noted minimal hair loss on combing. Sixty-six patients (49%) had no detectable hair loss.

Substantial accidental extravasation of mitoxantrone was reported on one occasion. Transient blue staining of the skin was noted, but no necrosis or ulceration ensued. Minor local irritation at the infusion site was reported on 11 occasions only.

Mild transient paraesthesiae were reported following 11 courses (2%). Mitoxantrone did not adversely affect renal or hepatic function.

Cardiac function was monitored throughout treatment by clinical observation, electrocardiography and, where practical, either multiple gated angiography (MUGA) or ECHO.

Serial ECGs were followed in 60 patients over a range of 1–19 courses (mean, 6.2). No significant change was noted in 52 patients. Eight patients developed ECG changes: four patients demonstrated non-specific ST/T wave changes in the anterior chest leads after courses 1,4 and 8; one patient with a previous history of angina was noted to have sinus brachycardia after the eighth course of therapy; one patient developed ST segment depression in leads II, III and AVF after 13 courses; one developed inverted P waves in leads II, III and V4–6 after 17 cycles; and one patient was noted to show multiple ventricular ectopics after 19 courses.

Serial estimations of the ventricular ejection fraction were recorded in 34 patients by MUGA (mean, 7.9 courses; range, 2–20 courses) and in nine further patients by ECHO (mean, 7.2 courses; range, 5–10 courses). In four patients receiving cumulative doses of between 174 and 256 mg/m^2 marked falls in ventricular ejection fraction occurred, probably related to mitoxantrone therapy. All four patients were dyspnoeic, with two patients exhibiting frank congestive cardiac failure. Potential risk factors were identified in three of the four patients. All our patients responded promptly to treatment with diuretics (and digoxin in two instances).

Endomyocardial biopsies were examined in three patients and revealed essentially similar features with appearances suggesting those found in congestive cardiomyopathy. No mitochondrial vacuolation, myofibrillar drop-out or interstitial inflammatory infiltrate of significance were seen.

DISCUSSION

In this large series of previously untreated patients mitoxantrone has demonstrated substantial activity in patients with advanced breast cancer, with an objective response rate of 35% (95% confidence limit, 27–48%). Six per cent of patients achieved a complete response. The median time to treatment failure was >46 weeks. Response to therapy was not influenced by prior adjuvant chemotherapy, performance status or oestrogen receptor status. As anticipated following phase I studies, the dose-limiting toxicity was myelosuppression, but the incidence of other commonly encountered and unpleasant side-effects was impressively low. Vomiting that required treatment occurred with only 28% of treatment cycles and only 6% of patients suffered severe alopecia, compared with more than 80% of patients who are treated with cyclophosphamide or adriamycin. These factors combined to make mitoxantrone highly acceptable to patients, many of whom had preconceptions of more severe acute toxicity. Since chemotherapy for advanced breast cancer is widely recognised as being palliative rather than curative, such considerations are likely to play an increasing part in the choice of treatment.

One of the factors which led to the selection of mitoxantrone for clinical study was its reduced cardiotoxicity in beagle dogs when compared with adriamycin. Two factors which have been suggested to account for this difference are the absence of a sugar side-chain on the mitoxantrone molecule (thought to contribute to the binding of anthracyclines to the myocyte) [7] and the failure of mitoxantrone to produce the excess of free radicals observed with anthracyclines [8]. In this study clinically significant cardiotoxicity attributed to mitoxantrone was observed in four patients (3%). Endomyocardial biopsies showed a non-specific lesion simulating cardiomyopathy but without the degenerative features characteristic of anthracycline cardiomyopathy. In previous studies it has been suggested that prior treatment with adriamycin increases the risk of cardiotoxicity with mitoxantrone [9], implying the need for particular caution in any patient with prior exposure to either drug.

The objective response rate to mitoxantrone observed in this study (35%) is similar to that (38%) reported for adriamycin as a single agent in a collected series of 937 patients [10]. In previously untreated patients Hoogstraten *et al.* [11] reported a response to adriamycin of 50% for a median duration of 8 months. Ahmann *et al.* [12] and

Gottlieb *et al.* [13] found a 38 and 39% response for 7.5 and 5.0 months median duration respectively. The median time to treatment failure for mitoxantrone in this study was >46 weeks. Myelosuppression appears similar in the two drugs, while the common acute toxicities (particularly vomiting and alopecia) are considerably less frequent with mitoxantrone. Despite the preclinical studies, however, it is evident that cardiotoxicity is a potential problem with both drugs. Whilst diminished acute side-effects make mitoxantrone a significant addition to the armamentarium of drugs active in the treatment of advanced breast cancer, its potential role as a less toxic alternative to adriamycin will depend on further assessment. Chronic trials are currently in progress.

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