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Mitoxantrone in Advanced Breast Cancer—a Phase II Study with Special Attention to Cardiotoxicity

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Abstract—*Thirty-four patients with advanced breast cancer, who had not received previous chemotherapy for metastatic disease, were treated with mitoxantrone* 14 mg/m^2 *i.v. every* 21 days. *Eleven of* 33 *evaluable patients* (33%) *achieved a partial response; there were no complete responders. Before commencing mitoxantrone, and* 3*-monthly thereafter, radionuclide assessment of ventricular performance was obtained at rest and in response to stress. Ten patients showed a deterioration in ejection fraction, two of whom developed congestive cardiac failure. Dose-limiting toxicity was myelosuppression. Nausea and vomiting were generally mild and transient. Alopecia was minimal in most patients. Mitoxantrone is an active, well-tolerated new drug in the treatment of advanced breast cancer, but cardiotoxicity may occur in a proportion of patients. Further investigation is required to determine the precise nature, incidence and prognosis of cardiotoxicity encountered with mitoxantrone.*

INTRODUCTION

CYTOTOXIC drug therapy is of value in the management of advanced breast cancer. However, many of the effective agents have unpleasant and sometimes life-threatening side-effects. Mitoxantrone is one of a number of relatively new anthracenedione derivatives currently being investigated in the search for a drug with the activity of doxorubicin but with less associated toxicity.

Animal studies have shown mitoxantrone to have significant antitumour activity [1,2] and, like doxorubicin, it binds to DNA to inhibit nucleic acid synthesis [3]. A phase I study showed that marrow suppression was the dose-limiting toxicity [4] and a response rate of 28% in 39 patients with advanced breast cancer was reported in a phase II trial [5]. Animal studies have suggested that cardiotoxicity is less frequent in comparison to anthracycline derivatives [6].

In this paper we report a phase II study in patients with breast cancer in which mitoxantrone has been used as the first chemotherapy for advanced disease. Because of the known dose-related cardiotoxicity seen with anthracycline derivatives, serial evaluation of ventricular function using radionuclide estimation of ejection fraction both at rest and in response to stress was performed.

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MATERIALS AND METHODS

Thirty-four women with advanced breast cancer aged between 25 and 81 yr (mean, 57 yr) were studied. All had evaluable progressive disease after previous endocrine therapy. Five patients had received previous adjuvant chemotherapy, which in two patients included doxorubicin [7]. None of the patients had received chemotherapy for metastatic disease. Twenty-nine patients had prior radiotherapy to the primary site and/or metastases. Three of these had prior mediastinal irradiation during adjuvant treatment of the internal mammary chain and one patient had mediastinal irradiation for metastatic disease. Patients with brain metastases and jaundice (bilirubin >23 mmol/l) were excluded. The WHO performance status [8] was grade 0 in five patients, 1 in 10, 2 in 16 and 3 in the remaining three. Patients with known ischaemic heart disease, cardiac failure or a pretreatment ejection fraction of less than 50% were excluded. Patients with bundle branch block or haemo-

dynamically insignificant heart murmurs were not excluded.

Baseline investigations included a haematological and biochemical screen, radionuclide bone scan ([^{99m}Tc]-methylene diphosphonate) with radiographs of abnormal areas, chest radiograph and electrocardiogram. Radionuclide liver scan (^{99m}Tc-colloid) was performed in patients with hepatomegaly or raised levels of liver enzymes. Before entering the study patients had a total white cell count of $>4000/mm^3$ and a platelet count of $>100,000/mm^3$.

Thirty-one patients were studied using radionuclide angiocardiography, but this was omitted in three others because of age and/or debility. The gated equilibrium blood pool method was used. For this 750 MBg of ^{99m}Tc-labelled autologous red blood cells were injected and, after a few minutes to allow for equilibrium, the cardiac blood pools were imaged with an ECG gate-synchronised gamma camera interfaced to a dedicated minicomputer. An anterior view followed by a left anterior oblique 45° view was obtained. The left anterior oblique view was then repeated during (a) cold pressor stress (hand and wrist in iced water), (b) isometric hand grip (a sphygmanomometer cuff rolled up and 2/3 maximum pressure maintained) and (c) repeat rest. Acquisition times were 5 min or less and haemodynamic parameters returned to baseline between each acquisition. The ejection fraction was calculated from the volume change in the left ventricle using standard methods and the images were viewed simultaneously on a TV monitor in 'cine' mode. These two adynamic forms of stress were selected because of the difficulty of exercising patients with advanced cancer. Radionuclide angiocardiograms and electrocardiograms were performed before commencing therapy and after every fourth course of treatment.

Mitoxantrone was given at a dose of 14 mg/m^2 as an i.v. infusion in 100 ml 5% dextrose every 21 days. Dosage modification in the presence of bone marrow suppression is detailed in Table 1. With grade 2 toxicity treatment was omitted until grade 1 was reached, when therapy was resumed with 50% dosage. In the absence of both response and treatment toxicity the dose was raised by 2 mg/m^2 every 2 courses.

Table 1

Grade of toxicity	Total WBC	Platelet count	Drug dosage (%)
0	≥4000	≥120,000	100
1	2000–4000	70,000–120,000	50
2	≤2000	≤70,000	0

Before each course a full physical examination was performed. Superficial and palpable lesions were measured in two perpendicular axes and photographed when visible. Skeletal and visceral disease was evaluated by appropriate radiographs and scans every four courses. Details of toxicity were recorded following each course and graded according to the WHO classification [8]. Treatment was continued for a minimum of 12 courses or until the development of progressive disease. Patients received between one and 17 courses, with a median cumulative dose of 54 mg/m^2 (range, 10–192 mg/m^2). Objective response was assessed using the system recommended by the UICC [9] and confirmed by external review.

RESULTS

Thirty-three of the 34 patients entered into this study were evaluable for response. One patient who achieved a partial response was deemed non-evaluable because of insufficient time (3 days) between stopping norethisterone acetate and commencing mitoxantrone, thereby raising the possibility of a withdrawal response. This patient has been included in the analysis of toxicity.

No patient achieved a complete response. Partial response was achieved in 11 of the 33 patients (33%). Four patients (12%) showed no change in their disease after 3 months or at the time treatment was stopped. There was only one early death, due to septicaemia, and this patient is included in the 18 (55%) who had progressive disease (Table 2). None of the five patients who received prior adjuvant chemotherapy responded to mitoxantrone.

Responses were seen in all sites of disease (Table 3). The median duration of response was 30 weeks (range, 12–59 weeks) and the overall median duration of survival 38 weeks (range, 1–103 weeks).

Toxicity

Marrow suppression was the most frequent dose-limiting toxicity. Twenty-five patients developed marrow suppression at some time during treatment and nearly half the prescribed courses were modified because of marrow suppression (Table 4). Seventeen (50%) of the patients received less than 75% of the projected

Table 2. *Objective responses*

Response	No. of patients (%) (n = 34)
Complete response	0
Partial response	11 33%
No change	4 12%
Progressive disease	18 55%
Non-evaluable	1

dose because of marrow suppression. Septicaemia occurred in three patients and proved fatal in two. Two of these episodes occurred after the first course, the third patient developing pneumonia and septicaemia after the 16th course of treatment.

Nausea and/or vomiting was experienced at some time during treatment by 21 (62%) patients. Eleven patients developed mild nausea (WHO grade I) and ten patients had transient vomiting (WHO grade II). However, only one patient developed vomiting which required therapy (WHO grade III) other than the prophylactic, 'as required' anti-emetics prescribed to all patients. Minimal alopecia was noted by 17 (50%) of the patients but significant hair loss was uncommon and only two patients felt it necessary to wear a wig. Mild stomatitis occurred in three patients.

Table 3. Response according to site

Site	Response rate†
Skin	3/16
Breast	3/13
Lymphatic	4/12
Bone	5/20
Lung	3/11
Liver	2/6
Other (pleura and endometrium)	3/4

*Numerator = No. of patients with response at site stated; denominator = No. of patients with involvement of stated site at start of treatment.

Table 4. Marrow suppression secondary to mitoxantrone

Toxicity	No. of patients* (%) ($n = 34$)	No. of courses† (%) ($n = 220$)
Grade 1		
WBC <4000	25 (73%)	102 (46%)
Platelets <120,000	4 (12%)	5 (2.5%)
Grade 2		
WBC <2000	3 (9%)	4 (2%)
Platelets <70,000	3 (9%)	3 (1.4%)
Septicaemia	3 (2 fatal)	

*Experiencing a stated toxicity on one or more occasions.
†Associated with stated toxicity.

Twenty-three of 31 patients who had baseline ejection fraction measurement had subsequent measurements during or after treatment. Ten patients showed a 15% or greater deterioration in ejection fraction at rest and/or following stress. Eight of these were responders. Two developed cardiac failure during treatment on mitoxantrone (Table 5). Six patients had pretreatment abnormalities on electrocardiograph which were unchanged throughout treatment. These included non-specific T wave changes (four patients), left bundle branch block (one patient) and ventricular extrasystoles (one patient). Only one patient developed an abnormal electrocardiogram during treatment and this coincided with an episode of myocardial ischaemia during anaesthesia (discussed below).

One patient (DJ) who developed cardiac failure had a clear 20% deterioration in ejection fraction following stress, before showing deterioration in the resting value. Mitoxantrone was stopped when her symptoms were minimal and her resting ejection fraction was 37% (baseline 87%). Despite conventional diuretic therapy she developed severe cardiac failure with orthopnoea, paroxysmal nocturnal dyspnoea and postural hypotension. Two months after stopping mitoxantrone, the ejection fraction had deteriorated to 22%. Over

Table 5. Significant (>15%) deterioration at rest and/or following stress

Patient	Mitox dosage	Δ Resting EF*	Δ Stress EF†	Clinical features
DJ	192	-57	-47	severe LVF,‡ orthopnoea. Slow recovery
MC	143	-3	-29	asymptomatic
MF	122	-8	-23	asymptomatic
MB	109	-18	-20	dyspnoea attributed to lymphangitis
AM	96	-30	-29	asymptomatic. No follow-up
IR	85	-3	-25	asymptomatic
RG	82	-52	-46	mild LVF. Spontaneous recovery
PP	62	-60	-	dyspnoea attributed to lymphangitis and micro-emboli throughout pulmonary vasculature seen at post mortem
MP	34	-12	-21	dyspnoea attributed to lymphangitis
EB	25	-34	-32	ischaemic episode during anaesthetic

*% change in resting ejection fraction at time of stopping mitoxantrone compared with pretreatment value.
†% change in ejection fraction following stress intervention at time of stopping mitoxantrone compared with pretreatment value.
‡LVF = left ventricular failure.

the next 2 months her clinical condition improved, with an increase in exercise tolerance accompanied by some recovery of ejection fraction to 40%. No predisposing factors could be identified and she showed no electrocardiographic changes. Her breast cancer was in partial remission throughout this period and did not appear to be contributing to her symptoms. Her disease subsequently relapsed and she resumed chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil, which she tolerated well. However, she died suddenly following a stroke. A post mortem was not performed.

A second patient (RG) also developed cardiac failure with an ejection fraction of 34%. This was controlled by diuretics and after stopping mitoxantrone the ejection fraction improved over the next 3 months to 56%. This patient had some pre-existing non-specific changes on electrocardiograph and the initial deterioration in ventricular contraction appeared to be segmental, consistent with ischaemic heart disease. However, the subsequent development of global impairment of ventricular contraction with further courses of mitoxantrone followed by a spontaneous improvement suggested that drug-induced cardiotoxicity may be responsible.

In three of the other eight patients who showed changes in the ejection fraction, deterioration was attributed to progressive pulmonary and mediastinal infiltration. One of these patients has since died and post mortem revealed multiple microthrombi containing tumour throughout the pulmonary vasculature, in addition to pulmonary nodules and lymphatic infiltration. Examination of the cardiac muscle by light and electron microscopy showed non-specific changes consistent with pulmonary hypertension. This patient had had previous mediastinal irradiation for metastatic disease. Another patient had ischaemic changes on the electrocardiograph at the time of a prosthetic hip replacement. A further patient had no cardiac symptoms and died in another hospital following septicaemia. Three patients have shown a deterioration in ejection fraction following stress but no changes at rest. All of these are asymptomatic and continue off mitoxantrone. None of the five patients who received previous adjuvant chemotherapy showed a deterioration in ejection fraction.

DISCUSSION

The results of this study confirm that mitoxantrone can induce regressions in advanced carcinoma of the breast. The observed response rate of 33% compares favourably with response rates for several other single agents [10], but is perhaps less active than doxorubicin [11]. Marrow suppression was the dose-limiting toxicity for mitoxantrone, particularly in patients with extensive bony disease or previous extensive radiotherapy, but gastric intolerance and alopecia were relatively mild and certainly less than with doxorubicin.

Cardiotoxicity is a well-recognised effect of anthracycline administration [12]. Acute cardiotoxicity in the form of dysrhythmias and electrocardiographic changes which may occur with doxorubicin was not seen in this study, but continuous electrocardiographic monitoring during and after administration of mitoxantrone was not performed. This study aimed to predict and identify the development of any cumulative dose-related cardiomyopathy following mitoxantrone, as seen with doxorubicin. The steep rise in the incidence of cardiomyopathy with cumulative doses of doxorubicin in excess of 500 mg/m^2 [13] restricts the use of this agent despite various attempts to increase this threshold by modifying the method of administration [14]. An alternative anthracycline-like drug such as mitoxantrone would have an advantage if cardiomyopathy was less common or occurred at a greater equivalent therapeutic dose.

Prediction of anthracycline-induced cardiomyopathy has proved to be difficult. A decrease in electrocardiographic limb-lead QRS voltage [15] or prolongation of the systolic time interval [16] may correlate with the development of cardiomyopathy but are indirect estimates of ventricular performance. Echocardiography, although widely available, is operator-dependent and technically difficult, as well as making certain assumptions of ventricular geometry. Because of these difficulties, this study used radionuclide angiocardiography to assess ventricular function. The measurement of ejection fraction by the first pass and blood pool techniques have been shown to correlate well with contrast angiography [17]. The blood pool technique used in this study has the advantage that repeated imaging for several hours is possible and allows monitoring of ventricular function in response to stress or exercise. In addition, the gated time frames can be summed from multiple contractions and displayed in 'cine' format. Using this technique, it has been suggested that a decline in ejection fraction of >15% may predict the development of cardiac failure [18].

The two patients who developed cardiac failure did show a deterioration of more than 15% before developing cardiac failure and consequently stopped mitoxantrone. Deterioration of ejection fraction with exercise has been shown to precede resting changes in ischaemic heart disease [19] and is more pronounced than resting changes after mediastinal irradiation [20]. One patient in

our study showed a deterioration following stress before changes at rest occurred.

Cardiac failure has been described in patients receiving mitoxanthrone, but all of these had received doxorubicin [21]. The two cases in this study occurring after cumulative doses of 82 and 192 mg/m^2 respectively do appear to be related to the chemotherapy. Both of these cases showed signs of spontaneous recovery. Only one patient in this series who received more than 80 mg/m^2 does not appear in Table 5. Our experience suggests that mitoxantrone should be used with caution above this dose with regular monitoring of the ejection fraction. As comparable studies have not been performed at a similar stage in the evaluation of older drugs, it is not possible to discern with accuracy the relative cardiotoxic potential of mitoxantrone in comparison with other drugs. Further investigation is required to determine whether there is a safe maximum cumulative dose which can be administered, as has been determined for doxorubicin, and whether the same risk factors apply.

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