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Cardiotoxicity of Mitozantrone Assessed by Stress and Resting Nuclear Ventriculography

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Abstract—*Fourteen patients with advanced breast cancer were treated with a combination of vincristine, mitozantrone and prednisolone. Before, during and after cessation of treatment radionuclide assessment of ventricular performance was obtained at rest, in response to cold pressor-induced stress and on recovery from stress.*

Six of 14 patients (46%) developed abnormalities of left ventricular ejection fraction (LVEF). One patient developed clinical signs of cardiac failure.

Mitozantrone is an active agent in the treatment of advanced breast cancer but it can produce cardiotoxicity. In this particular middle-aged population, changes in LVEF occurred over a wide range of cumulative doses. Further investigation is required to determine the nature and prognosis of this iatrogenic toxicity.

INTRODUCTION

MITOZANTRONE is a synthetic amino-anthraquinone developed in a search for a new subclass of agents, retaining the anticancer activity of the anthracyclines but without the cardiotoxicity which characterizes the first generation drugs such as doxorubicin (Adriamycin).

In animal studies mitozantrone has a spectrum of antitumour activity similar to doxorubicin [1]. In phase II studies mitozantrone has been shown to have significant single agent activity in patients with advanced breast cancer [2–4] and haematological malignancies [5–7]. More recently it has been incorporated into combination chemotherapy [8–11].

In animal toxicity studies, mitozantrone caused marrow, gastrointestinal and lymphoid damage. Cardiotoxicity was not observed within the therapeutic range of animal doses. However reduced left ventricular function, decreased diastolic pressure and cardiac output occurred when higher doses were administered to beagle dogs [12].

Since the drug was first used clinically, there have been several reports of patients devloping congestive cardiac failure (CCF) following mitozantrone although most have had pre-existing heart disease and/or mediastinal irradiation [4, 13–15]. There are fewer data on the incidence of cardiac damage in patients not previously exposed to doxorubicin or possessing other risk factors [13, 16, 17].

PATIENTS AND METHODS

We have recently completed a randomized comparison of 3-weekly cycles of vincristine 1.4 mg/m^2 (maximum 2 mg) with doxorubicin 50 mg/m^2 i.v. on day 1 with oral prednisolone 40 mg daily × 5 days (VAP) against vincristine 1.4 mg/m^2 (maximum 2 mg), mitozantrone 14 mg/m^2 i.v. on day 1 and oral prednisolone 40 mg daily × 5 days (VMP) in patients with advanced breast cancer. Full details of this study appear elsewhere [18]. Patients were excluded from the study if there was a past or present history of cardiac disease. Initial LVEF abnormalities however did not by themselves exclude patients from entry into the study. Cardiac function was monitored throughout by clinical observation and nuclear ventriculography (both at rest and under conditions of cold pressor-induced stress) [19].

We adopted standardized criteria for measuring stress response. In our laboratory the normal resting LVEF is 40% or greater, there is a rise of ≥5% with stress, and the LVEF returns to resting value on recovery. An abnormal stress test is defined by a fall below resting in excess of 5%. The reproducibility of the measurement in our institution is ±3%. The mean age of the total study population was 53.3 years (range 31–80); mean age of patients developing abnormalities on serial ventriculogra-

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Table 1. Patient characteristics

Patient XRT	Age	Medical history	Previous adjuvant regional (4000–5000 Rad T.A.D.)
1*	62	Psoriasis	L. breast
2*	57	Nil	L. breast
3	62	Duodenal ulcer	L. breast
4	52	Duodenal ulcer	No
5	60	Nil	L. breast
6*	40	Nil	R. breast
7	48	Nil	R. breast
8	69	Nil	No
9*	35	Nil	R. breast
10*	54	Hypertensive for 7 years	L. breast
11	52	Nil	L. breast
12	48	Nil	No
13*	61	Chronic obstructive airways disease	L. breast
14	55	Nil	No

*Patients with initially normal LVEF who subsequently became abnormal.

Table 2. Serial LVEF measurements

Patient No.	Date	Resting ejection fraction %	Stress ejection fraction %	Recovery ejection fraction %	Cumulative dose mitozantrone mg/m²
1	16/3/84	55	59	58	14
	30/7/84	54	48	53	98
	2/11/84	32	ND	ND	126
2	17/5/84	49	43	45	14
	27/7/84	48	41	50	56
	21/9/84	38	ND	ND	83
6	5/9/84	55	50	49	0
	20/2/85	46	33	40	76
9	16/4/85	70	63	62	14
	3/9/85	60	58	70	69
	5/11/85	60	45	48	76
10	31/5/85	44	44	53	0
	16/7/85	46	39	42	27
13	30/8/85	49	54	55	0
	30/10/85	54	48	55	25

ND = not done.

phy was 51.5 years (range 35–62). The mean total dose of administered mitozantrone was 77 mg/m². Fourteen patients had serial ventriculography on the VMP arm of the study. Individual patient characteristics are shown in Table 1. Age is quoted at entry to the study.

RESULTS

Of the 14 patients who had serial examinations, six were found to be abnormal at cessation of therapy having been normal at entry to the study. The results of serial LVEF estimations are shown in Table 2. The numbering of patients corresponds to Table 1.

In patients 1 and 2 the resting LVEF had fallen to a level considered too low to risk stress testing.

Five patients had abnormal stress LVEF and one abnormal resting LVEF at entry to this study; of these three showed no deterioration, one became worse and two improved by the end of treatment (Table 3).

In keeping with the known potential of doxorubicin to cause cardiac damage, we saw LVEF changes in six patients on the VAP arm of the study.

One of two patients who received 126 mg/m² total dose of mitozantrone developed clinical evidence of cardiac failure (patient No. 1).

Table 3. Serial LVEF in patients with initially abnormal studies

Patient No.	Date	Resting ejection fraction %	Stress ejection fraction %	Recovery ejection fraction %	Cumulative dose mitozantrone mg/m²
3	7/8/84	24	ND	ND	28
	5/11/84	37	59	56	63
4	29/8/84	51	38	44	14
	8/1/85	52	49	48	85
5	8/10/84	52	37	48	28
	15/1/85	53	47	49	70
8	3/12/84	71	50	74	36
	1/3/85	59	55	58	84
	3/4/85	68	52	66	98
11	17/7/85	55	46	54	0
	12/11/85	52	36	55	77
12	30/7/85	69	50	64	14
	24/9/85	42	44	52	112
	19/11/85	52	44	49	126

ND = not done.

DISCUSSION

Our study was conducted in a middle aged population of women from the central region of Scotland. In this area the prevalence of ischaemic heart disease is amongst the highest in the world. It is therefore not surprising that we have found several patients in this group with impaired ventricular function before chemotherapy.

Nevertheless, six of 14 patients (46%) developed abnormalities of LVEF temporally related to the administration of mitozantrone. In three of these (patient Nos 9, 10, 13), even though there was a fall on stress, the stressed values remained within (or minimally below) normal limits. In these cases although the myocardial reserves were substantially reduced, nevertheless they remained at a level unlikely to produce clinical symptoms.

We decided at the start of this trial to study patients regardless of initial LVEF if there was no clinical evidence of cardiac dysfunction. Only one of our patients developed clinical evidence of congestive cardiac failure. None of the patients with initially abnormal LVEF developed any overt cardiac dysfunction, despite a worsening LVEF in one out of six such cases.

Other groups have reported mitozantrone-associated cardiomyopathy, but in most cases the patient population was not a 'clean' one in terms of other risk factors, notably prior anthracycline chemotherapy [14, 15, 20, 21]. Our population displayed a variety of well known risk factors for anthracycline cardiomyopathy but it is our contention that in clinical practice our group of middle aged women is typical of women receiving chemotherapy for advanced breast cancer. Prediction of cardiac damage due to anthracenedione is difficult [22, 23]. Radionuclide imaging techniques are the most commonly used non-invasive method. However, Ewer *et al.* [24] demonstrated a poor correlation between morphological changes and cardiac biopsy and ejection fraction obtained by computer-assisted multigated cardiac blood pool imaging techniques in patients receiving doxorubicin. Our own technique does not seem to be predictive for subsequent clinical cardiac dysfunction, presumably because the technique is in some respects too sensitive. It is however probable that histopathological changes are a late event, indicating irreversible damage. Only one patient of six with initial abnormal LVEF showed any progressive deterioration with mitozantrone, whereas six of eight patients with initially normal LVEF developed abnormalities using our well established criteria [19]. However, it may be significant that the most striking stress LVEF fall in the initially abnormal group was seen in the one patient (11) who had an assessment pretreatment as well as after mitozantrone exposure.

Various authors have suggested caution at cumulative doses of mitozantrone in excess of 100–200 mg/m² [13, 20, 23]. Our study indicates a risk of subclinical cardiotoxicity at much lower doses, and highlights the difficulties in predicting which individuals are at risk in this middle aged population. Our findings however suggest that stress testing may be too sensitive, and that repeated measurements of the resting LVEF may combine simplicity, patient acceptability and an adequate level of clinical sensitivity.

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