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Assessment of ventricular function by radionuclide angiography in patients receiving 4'-epidoxorubicin and mitoxantrone*

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Summary Serial assessment of ventricular function by means of radionuclide angiography was performed in 50 patients with malignant neoplasms who received either 4'-epidoxorubicin or mitoxantrone for longer than 3 months.

In 9 of 30 patients given 4'-epidoxorubicin, a decrease of $\geqslant 10\%$ in the left ventricular ejection fraction (LVEF) was documented at doses of 143–1200 mg/m^2. Two patients developed clinical signs of cardiotoxicity at a dose of > 1000 mg/m^2.

In 6 of 20 patients given mitoxantrone a decrease of $\geqslant 10\%$ in the LVEF occurred at doses of 26–98 mg/m^2.

Introduction

Long-term use of anthracyclines in the treatment of patients with cancer is limited by dose-related cardiotoxicity. The relationship of doxorubicin-related congestive heart failure to the total dose administered has led to general acceptance of 550 mg/m^2 body surface area as the maximum acceptable dose [20, 34]. Serial assessment of the left ventricular performance in patients treated with doxorubicin identifies patients at risk of developing heart failure and allows others to continue to receive treatment at substantially higher cumulative doses than those conventionally recommended [36].

It has been proposed that the amino sugar moiety of the anthracycline is responsible for the cardiotoxicity of the compounds. Replacement of the amino sugar group by a suitable amino- or alkylamino-substituted side chain may eliminate this toxicity [1]. 4'-Epidoxorubicin is a doxorubicin derivative obtained by modification of the natural amino sugar, daunosamine, which is replaced by the corresponding 4'-epi analog [7]. Comparative studies of doxorubicin and 4'-epidoxorubicin in experimental animals have indicated that 4'-epidoxorubicin has less marked myocardial toxicity but an equal antitumor activity. Light microscopy in rabbits and mice after the administration of 4'-epidoxorubicin and other anthracyclines showed slightly less cardiotoxic effects of 4'-epidoxorubicin. In golden hamsters, seven different anthracyclines caused similar myocardial changes recognizable on electron microscopy. Doxorubicin and 4'-epidoxorubicin were found to decrease myocardial contractility in isolated guinea pig atria by modifying the calcium turnover. 4'-Epidoxorubicin, however, produced a smaller inhibition of calcium turnover. This may be the factor responsible for the cardiotoxic effects [6, 7, 9, 32]. The effect of 4'-epidoxorubicin on the human myocardium has been studied in several phase I and II trials with different noninvasive methods. Diffuse electrocardiographic changes were documented: electrocardiographic (ECG) abnormalities had a lower incidence than was recorded in patients receiving adriamycin alone [4, 5, 27]. Systolic time intervals measured by phonocardiography and external carotid pulse indicated that 4'-epidoxorubicin is less toxic than equivalent doses of doxorubicin [33]. Equilibrium radionuclide ventriculography using ECG gating has become an accepted method for noninvasive evaluation of left ventricular function and wall motion in patients receiving potentially cardiotoxic chemotherapy [10, 17, 19, 25, 36]. Serial determination of the LVEF by radionuclide angiography was performed in patients receiving 4'-epidoxorubicin, and in a similar group of patients receiving doxorubicin for prospective comparison. The data indicate that 4'-epidoxorubicin is less cardiotoxic than doxorubicin even when used in equally myelosuppressive dosage schedules [18, 26, 38].

In 27 patients receiving 4'-epidoxorubicin 39 endomyocardial biopsies were performed. The myocardial damage was compared with that in 119 endomyocardial biopsies from patients receiving doxorubicin. Preliminary observations suggest that when equipotent doses are used 4'-epidoxorubicin is less cardiotoxic than doxorubicin, and this pattern is repeated when doxorubicin is compared with 4'-epidoxorubicin used at higher doses [29].

Dihydroxy-anthracenedione (DHAD, mitoxantrone hydrochloride, NSC 301739) is a synthetic substituted alkyloaminoanthraquinone synthesized at the American Cyanamid Laboratories [22].

The cardiotoxic effects of doxorubicin and mitoxantrone were compared in animal studies [14, 28]. In beagle dogs treated with mitoxantrone there was no change in the serum levels of cardiospecific isoenzymes and no electrocardiographic changes were recorded [14]. Sequential endomyocardial biopsies were performed. The pathologic myocardial changes were mild and did not progress with

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time or cumulative dose [28]. Only a minority of patients treated with mitoxantrone have been reported to develop acute or chronic cardiotoxicity [3, 8, 15, 16, 21, 31, 37]. Endomyocardial biopsies were evaluated in 58 patients receiving mitoxantrone treatment. Forty-four patients had received prior doxorubicin treatment. Fourteen patients had not received prior chemotherapy, and their endomyocardial biopsy scores showed only minor evidence of cardiac toxicity. In 7 of 29 patients who received previous doxorubicin a fall of 10% in their left ventricular function measured by nuclear angiography was recorded [2]. Among more than 2500 patients treated with mitoxantrone in several phase II trials sponsored by the National Cancer Institute, the overall incidence of cardiac events recorded was only 3% [11, 24].

Various invasive and noninvasive techniques have been proposed for quantification of the severity of cardiac dysfunction from anticancer drugs. The measurement of LVEF by the noninvasive radionuclide angiography method has become a reliable technique. This method evaluates the left ventricular function both qualitatively and quantitatively. The qualitative evaluation is based on visual examination of the left ventricular wall motion. The quantitative evaluation is obtained by measuring ejection function, ejection rate, filling rate, and ventricular volumes [13, 17, 19, 35, 36]. In patients who received total doses of 480–550 mg/m^2 doxorubicin a persistent subclinical impairment of the left ventricular function (measured by radionuclide cine-angiography) was reported in 56%–66% of the patients [12].

The present study investigates the LVEF in patients receiving 4-epidoxorubicin or mitoxantrone for longer than 3 months.

Materials and methods

Fifty patients with a median age of 51 years (range 18–81 years) were evaluated. Thirty patients received 4'-epidoxorubicin, while 20 patients received mitoxantrone. Of the 30 patients treated with 4'-epidoxorubicin 25 had advanced colorectal cancer and the following neoplasms were each present in 1 patient: kidney cancer, Ewing's sarcoma, malignant fibrous histiocytoma, hepatocellular carcinoma and carcinoma of unkown origin. Of the 20 mitoxantrone-treated patients 16 had advanced breast cancer, 2 had metastatic malignant melanoma, 1 had advanced non-small cell lung cancer, and a further patient had metastatic hepatocellular carcinoma.

All the patients were evaluated prior to treatment; clinical history and examination, chest X-ray, full blood count, and liver and kidney function tests were performed. All the patients had a baseline and followup electrocardiogram performed every 3–6 weeks. Radionuclide ventriculography was performed prior to the first treatment and at 3-monthly intervals.

Multigate equilibrium radionuclide angiocardiography was performed using an in vivo red blood cell technique. [^{99m}Tc] Pertechnetate 20 mCi was injected IV after a priming dose of 7.5 mg stannous pyrophosphate. Data were acquired and processed with a digital gamma camera (Elscint Apex 415). An all-purpose parallel-hole collimator was used. Imaging was performed in the 45° left anterior oblique projection with a preset program. Twenty-four frames were obtained for each cardiac cycle, allowing a minimum of 300000 counts/frame. The LVEF was automatically calculated by a computer system with a preset region of interest (ROI) program. The reproducibility, validity, and accuracy of gated cardiac blood pool imaging and statistical analysis for evaluation of observer and interstudy variances of the multigated blood pool imaging (as used in Pretoria) have been investigated and the conclusions published elsewhere [23, 30].

4'-Epidoxorubicin 90 mg/m^2 dissolved in 200 ml saline was administered IV over 20 min every 3 weeks. Mitoxantrone 9–14 mg/m^2 dissolved in 200 ml 5% dextrose in water was administered IV every 3 weeks. The doses of mitoxantrone and 4'-epidoxorubicin were modified if the nadir white blood cell and/or platelet counts were low.

Results

Thirty patients received 4'-epidoxorubicin in doses ranging from 73 mg/m^2 to 1200 mg/m^2 (median 400 mg/m^2). Nine patients showed a fall of $\geqslant$10% in their LVEF. None of these patients had had prior exposure to anthracylines. The median dose received before $\geqslant$10% reduction in LVEF was noted in these patients was 753 mg/m^2 (see Table 1).

Two patients who received 4'-epidoxorubicin (total doses 1500 mg and 2160 mg) had 39% and 49% drops, respectively, in LVEF and developed acute pulmonary edema. One of these patients died in cardiac failure. Administration of 4'-epidoxorubicin was discontinued in the other, and 3 months later a repeat test showed no further change in his LVEF. A furhter two patients collapsed at home and died: a 20-year-old man with hepatocellular carcinoma and lung metastases (treated previously with mitoxantrone, total dose 150 mg) experienced a drop of 9.2% on LVEF after receiving 125 mg 4'-epidoxorubicin; and a 53-year-old woman with colon cancer and lung metastases, who had received a total dose of 2255 mg 4'-epidoxorubicin, experienced a drop of 21% in LVEF. Neither of these patients had any known risk factors. It is probable that both died as a result of myocardial toxicity resulting from drug administration. Of the remaining 21 patients treated with 4'-epidoxorubicin, 16 had no change in LVEF and 5 had changes of less than 10% (considered to be within normal limits for our laboratory) (see Fig. 1). Only 1 patient had electrocardiographic changes (sinus tachycardia and T-wave inversion on the lateral leads).

Twenty patients received mitoxantrone in doses ranging from 21 mg/m^2 to 98 g/m^2 (median 46 mg/m^2). Six patients showed a fall of $\geqslant$10% in LVEF. The median dose administered before $\geqslant$10% reduction in LVEF was observed in the six mitoxantrone-treated patients who showed a decrease in LVEF was 51.4 mg/m^2 (see Table 1). Four of these six patients had previously received anthracycline (doxorubicin). In none of these six patients would a delayed decrease in LVEF have been expected. All six patients had normal LVEF at the start of mitoxantrone treatment and the total dose of doxorubicin previously administered was low (ranging from 85 to 242 mg/m^2).

Of the remaining 14 patients treated with mitoxantrone, 6 had no change in LVEF and 8 had changes of less than 10%, giving values considered to be within the normal range (see Fig. 2). No electrocardiographic changes were recorded in the mitoxantrone-treated patients.

Table 1. Clinical summaries of patients with a decrease in LVEF of ≥ 10%

Patient no.	Age (years)	Diagnosis	Risk factors[a]	Baseline LVEF[b]	Follow-up LVEF	4'-Epidoxorubicin dose
1	54	Rectal cancer	None	83%	74%	435 mg/m²
2	63	Colon cancer	None	72%	68% 68% 61%	143 mg/m² 190 mg/m² 260 mg/m²
3	57	Rectal cancer	None	70%	59% 58%	900 mg/m² 1000 mg/m²
4	39	Rectal cancer	None	71%	64% 59%	523 mg/m² 1046 mg/m²
5	52	Rectal cancer	None	65%	53%	750 mg/m²
6[c]	53	Colon cancer	None	80%	78% 63%	460 mg/m² 1000 mg/m²
7	62	Colon cancer	None	78%	61%	224 mg/m²
8[d]	60	Malignant fibrous histiocytoma	None	77%	47% 44%	860 mg/m² 3 months after treatment stopped
9[e]	52	Colon cancer	None	45%	48% 38% 23%	445 mg/m² 980 mg/m² 1200 mg/m²
						Mitoxantrone dose
1	71	Advanced breast cancer	Prior radiotherapy left chest	81%	70%	31.5 mg/m²
2	37	Advanced breast cancer	Prior doxorubicin 213 mg/m²	87%	74%	26 mg/m²
3	43	Advanced breast cancer	Prior radiotherapy left chest; prior doxorubicin 242 mg/m²	81%	66%	58 mg/m²
4	39	Advanced breast cancer	Mild diabetes mellitus	79%	63%	98 mg/m²
5	57	Advanced breast cancer	Prior doxorubicin 85 mg/m²	77%	60%	35 mg/m²
6	65	Advanced breast cancer	Prior doxorubicin 180 mg/m²	73%	50%	60 mg/m²

[a] Prior doxorubicin, prior radiotherapy to the left chest, diabetes mellitus, arterial hypertension, ischemic heart disease
[b] Normal LVEF in our laboratory ≥ 55%
[c] Patient collapsed at home and died, presumably of acute heart failure
[d] Patient developed acute pulmonary edema. Treatment was stopped and patient remains under observation
[e] Patient developed congestive heart failure and died

Discussion

Radionuclide angiography is of value in monitoring cardiac changes in patients receiving cardiotoxic agents.

Earlier studies comparing the cardiotoxic effects of 4'-epidoxorubicin versus adriamycin and of mitoxantrone versus adriamycin showed that the newer agents had lower cardiotoxicity. In studies carried out at the Memorial Sloan-Kettering Cancer Center to compare doxorubicin and 4'-epidoxorubicin at equi-myelosuppressive dosages, the dose of 4'-epidoxorubicin that was cardiotoxic was more than twice that of doxorubicin [18]. Endomyocardial biopsies in patients receiving 4'-epidoxorubicin have provided further confirmation that its cardiotoxicity is lower than that of doxorubicin. The biopsy scores were subjected to multivariate analysis for evaluation of drug dose, prior cardiac irradiation, and schedule [29].

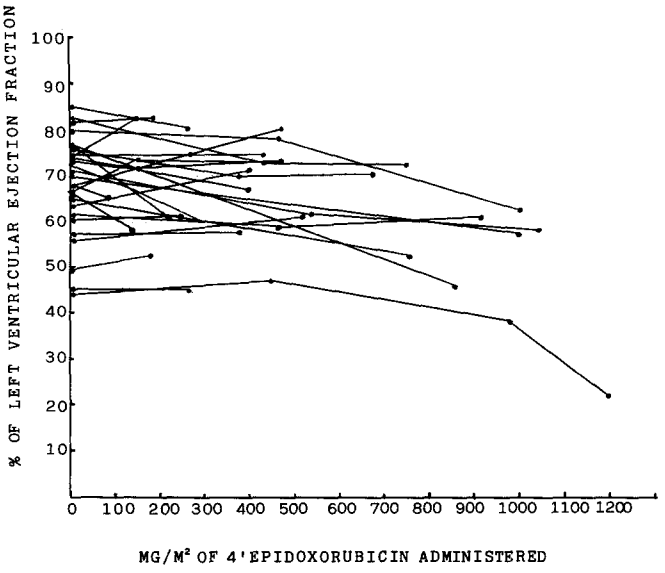

Fig. 1. Baseline and repeated radionuclide angiography in patients treated with 4'-epidoxorubicin

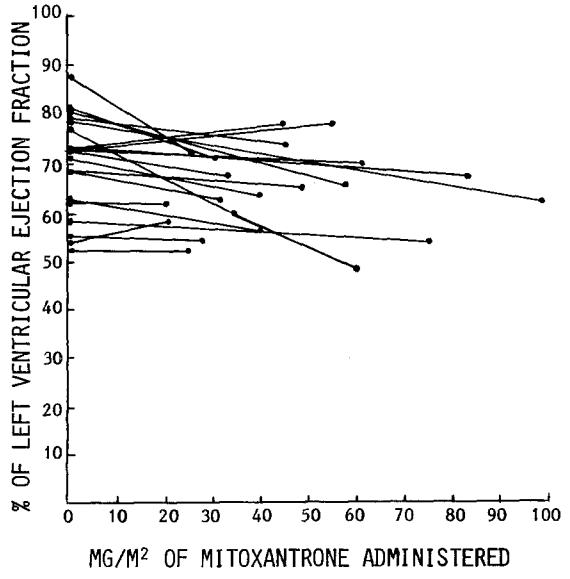

Fig. 2. Baseline and repeated radionuclide angiography in patients treated with mitoxantrone

The results of prospective studies, when analysed for the incidence of clinical congestive heart failure, changes in LVEF, and endomyocardial biopsies, showed that mitoxantrone was significantly less cardiotoxic than doxorubicin. At a comparable cumulative dose based on a mitoxantrone-to-doxorubicin dose ratio of 1:5, the mean decrease in LVEF was twice as great among doxorubicin-treated patients [24].

A decrease of $\geqslant 10\%$ in the LVEF occurred in one-third of the patients treated in our department with either 4'-epidoxorubicin or mitoxantrone. Four of the six patients treated with mitoxantrone had had previous doxorubicin treatment, and it is probable that the prior anthracycline treatment primed the myocardium, increasing its susceptibility to further insult.

In the present study the median dose administered before $\geqslant 10\%$ reduction in LVEF in patients treated with 4'-epidoxorubicin was 753 mg/m^2. The median cumulative dose administered before clinical cardiotoxicity was observed was 1030 mg/m^2. The median dose given before $\geqslant 10\%$ reduction in LVEF in patients treated with mitoxantrone was 51.4 mg/m^2. None of the mitoxantrone-treated patients developed clinical cardiotoxicity. It is therefore apparent that although there was a significant decrease in LVEF in 30% of our patients who were treated for longer than 3 months with both 4'-epidoxorubicin and mitoxantrone, there is a definite difference in the degree of this finding between those treated with 4'-epidoxorubicin and those treated with mitoxantrone. The cardiotoxicity documented with mitoxantrone occurred mainly in patients previously treated with doxorubicin, and none of the patients treated with mitoxantrone developed clinical heart disease.

Both 4'-epidoxorubicin and mitoxantrone have been introduced in to the oncologic armamentarium because they retain therapeutic activity with lower cardiac toxicity than doxorubicin. The present study confirms these findings, and furthermore, shows that mitoxantrone is probably less cardiotoxic than 4'-epidoxorubicin at a therapeutic dose range when given for longer than 3 months.

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