Indium-111-Antimyosin Scintigraphy After Doxorubicin Therapy in Patients with Advanced Breast Cancer

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Indium-111-antimyosin (^{111}In-antimyosin) scans were performed in 20 women with advanced breast cancer after 10 cycles of chemotherapy consisting of cyclophosphamide, 5-fluorouracil and doxorubicin (total cumulative dose of doxorubicin of 500 mg/m^2). Antimyosin uptake in the myocardium was quantified by means of a heart-to-lung ratio (HLR). Antimyosin uptake in the myocardium was observed in 17/20 (85%) patients, and HLR after chemotherapy was 1.86 ± 0.25. Left ventricular ejection fraction (EF) was determined before and after chemotherapy. Patients with decreased EF (8/20, 40%) presented with more intense antimyosin uptake (HLR of 2.11 ± 0.10 versus 1.70 ± 0.16 ($p = 0.01$)). HLR values correlated with EF values after chemotherapy ($r = -0.47$, $p < 0.05$). Positive antimyosin studies after chemotherapy including doxorubicin, indicate the presence of myocardial damage in these patients. Antimyosin studies are a sensitive method to detect myocyte damage in patients after doxorubicin therapy.

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Anthracycline derivatives are effective in the treatment of advanced breast cancer, and chemotherapy, including doxorubicin hydrochloride (Adriamycin) or other anthracyclines, is widely used in the later stages of the disease. Because cardiac toxicity limits prolong administration, careful monitoring during treatment is necessary to detect toxicity and to identify patients at risk of congestive heart failure.

Detection of cardiac toxicity is based either on serial ejection fraction (EF) measurements with gated blood-pool scans (*1*) or on the performance of endomyocardial biopsy (*2*). The incidence of congestive heart failure after doxorubicin therapy is generally <20% and can be substantially reduced using guideline criteria (*3*). However, if endomyocardial biopsy is performed during doxorubicin administration, almost all patients show evidence of morphologic damage at biopsy, with the degree of damage linearly related to the dose (*4,5*).

A single estimation of left ventricular EF (LVEF) is an insensitive method to detect patients at risk of heart failure. It has been shown that a large proportion of patients with normal EF at rest are at risk of congestive heart failure by biopsy criteria (*2*). If rest/exercise EF measurements are performed, there is an increase in sensitivity accompanied by a loss of specificity (*6*). However, despite its superiority to detect doxorubicin toxicity, endomyocardial biopsy is invasive, of high cost, and not widely available.

Indium-111-antimyosin (^{111}In-antimyosin) is specific for myocyte necrosis (*7*), and has been shown to be a sensitive agent for the detection of infarct, myocarditis (*8,9*), and cardiac rejection (*10,11*). As morphologic damage in the myocytes is present in doxorubicin toxicity, this study was undertaken to assess if antimyosin scans could detect such myocardial damage after doxorubicin therapy in patients with advanced breast cancer.

PATIENTS AND METHODS

Study Patients

We studied 20 consecutive women (mean age 49 yr, range 27–68) with histologic diagnosis of breast cancer (T_{3b}-T_4 and/or metastatic disease, American Joint Committee Staging) eligible for chemotherapy including doxorubicin. Patients had estrogen receptor-negative tumors, had not responded to hormonal treatment, or presented with life-threatening disease requiring immediate chemotherapy. None of the patients had a history of hypertension, previous cardiac disease, or had received previous chemotherapy or mediastinal radiotherapy. All patients had adequate hepatic and renal function; none of them had evidence of central nervous system, mediastinal, or cardiac metastases. Informed consent was obtained from all patients.

Chemotherapy was administered in 10 cycles of cyclophosphamide (600 mg/m^2), doxorubicin (50 mg/m^2), and 5-fluorouracil (600 mg/m^2). Doxorubicin and 5-fluorouracil were administered by direct i.v. injection; cyclophosphamide was

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injected over 30 min, in a dilution of 250 cc of physiologic saline. Courses were repeated every 3 wk after hematologic control.

Congestive heart failure was defined according to the New York Heart Association criteria (Class III–IV). Clinical follow-up after chemotherapy was 4–15 mo.

Control Group

We studied eight patients with advanced breast cancer who had not received doxorubicin therapy. None of the patients had a history of hypertension, previous cardiac disease, or had received chemotherapy or mediastinal radiotherapy.

Ejection Fraction Measurements

LVEF was measured in the study patients before and after 10 cycles of chemotherapy (cumulative dose of doxorubicin: 500 mg/m^2). After in vivo red blood cell labeling with 25 mCi of technetium-99m and the patients placed in the supine position; gated blood-pool scans were acquired with a large field of view camera (Siemens Orbiter ZLC with a high resolution collimator linked to a Siemens Microdelta computer, Schaumberg, IL) in the LAO 30°–50° projection and 5°-10° caudal tilt to provide the best separation between both ventricles and atria. The cardiac cycle was separated into 30 64 × 64 frames with a minimum of 300,000 counts collected in each frame. Data were stored on magnetic disks for subsequent analysis. LVEF was measured using a semiautomatic edge detection and counts technique with a varying region of interest (ROI). Fourier phase and amplitude images were generated to help trace ROIs.

Antimyosin Studies

In the study patients, 0.5 mg of R11-D10-Fab-DTPA (Centocor Europe, Leiden, The Netherlands) labeled with 2 mCi of ^{111}In was administered by slow i.v. injection within the week of the second EF measurement. Planar scans were obtained 48 hr later using a medium-energy collimator with a 20% window centered on both peaks of ^{111}In at a preset time of 10 min. Scans were stored in 128 × 128 frames. Antimyosin scans were also performed on the patients in the control group. Repeated antimyosin scans were performed in six patients ≥4 mo after chemotherapy.

The presence of antimyosin uptake in the heart was assessed using a four-step score (*12*): 0, no uptake; 1, mild or faint uptake; 2, clear but moderate uptake; and 3, intense myocardial uptake. A quantitative method was then applied (*12*). This consisted of drawing a ROI on the heart and regions of the lungs on the anterior view of the thorax. A heart-to-lung ratio (HLR) was obtained dividing average counts per pixel in the heart by average counts per pixel in the lungs. A cutoff point of >1.58 (normal value 1.46 ± 0.4 + 3 s.d.) was used to define abnormal studies (*8,12*).

Statistical Analysis

Results are expressed as mean ± s.d. of mean with nonparametric analysis of groups using the Mann Whitney and Wilcoxon tests. Regression analysis was used to assess correlation between variables. The statistical package for social sciences (SPSS/PC) was used.

RESULTS

In the study patients, LVEF before chemotherapy was 58.4% ± 6.8% and 53.6% ± 9.9% (p = ns) after chemotherapy. (Table 1). Eight patients (40%) had a decrease in LVEF (≥5% in absolute EF units) after chemotherapy. Ejection fraction before chemotherapy in this group was 59.3% ± 6.3% and 46.7% ± 9.2% (p = 0.01) after chemotherapy (Fig. 1). In the remaining 12 patients, EF before chemotherapy was 57.7% ± 7.3%, and 58.2% ± 7.5% after chemotherapy. Ejection fraction after chemotherapy was significantly lower in the first group (46.7 ± 9.2 versus 58.2 ± 7.5, $p < 0.05$) (Fig. 1).

In the eight patients of the control group, antimyosin uptake was not visually apparent (visual score 0). HLR in this group was 1.48 ± 0.07 (p = ns with normal subjects).

In the study patients, antimyosin uptake in the myocardium was visually apparent in 17 of 20 (85%) patients (Table 1, Fig. 2). The visual score was 1 in two patients, and 2–3 in 15 patients. The HLR in antimyosin studies was 1.86 ± 0.25 (Table 1). Using a HLR of >1.58 as the cutoff point, antimyosin studies were abnormal in the same 17 of 20 (85%) patients. In the 8 patients with a decrease in EF, HLR was higher than that in the remaining 12 patients: 2.11 ± 0.10 (range 2.00–2.27) versus 1.70 ± 0.16 (range 1.40–1.93) (p = 0.01) (Fig. 1). An inverse correlation was observed between HLR and EF after chemotherapy ($r = -0.47$, $p < 0.05$). Repeated antimyosin scans in six of the patients with positive antimyosin studies after chemotherapy showed a decrease in HLR in all patients (Table 1, Fig. 3).

Congestive heart failure occurred in Patient 1 during chemotherapy and in Patient 17 one month after chemotherapy (Table 1).

DISCUSSION

Patients under anthracycline therapy need close cardiac monitoring to identify those at risk of developing heart failure, when the schedule of doses can still be modified, and to reduce mortality or severity of clinical heart failure. Patients at risk can still receive high cumulative doses if the schedule of administration is modified to avoid heart failure (*3,12, 14*).

The global incidence of congestive heart failure in patients treated with anthracyclines is <20% and presents more frequently in patients with previous risk factors, such as mediastinal radiotherapy, hypertension, or previous cardiac disease (*3,12*). However, there is considerable individual variability; at doses of > 500 mg/m^2, some patients can safely receive further treatment, while others present with heart failure at lower doses (*5,12*). Our group consisted of patients without risk factors, who were treated with conservative doses of doxorubicin. Eight of 20 patients (40%) presented with a decrease of ≥5% in EF; five had a final value of ≤50%. A similar incidence of decrease in EF after doxorubicin therapy has been noted previously (*13*).

TABLE 1
LVEF Before and After Chemotherapy, Results of Antimyosin Studies, Stage of Disease, and Response Status in All Patients

Patient no.	Stage	LVEF (%)			AM uptake		AM follow-up		AM interval months†	Response status
		Before	After	Decrease*	Visual	HLR	Visual	HLR		
1	$T_3N_2M_1$	54	30	24	2	2.10	—	—	—	Progressive disease‡
2	$T_3N_2M_1$	47	39	8	2	2.00	—	—	—	Partial remission
3	$T_1N_3M_1$	65	55	10	3	2.20	1	1.47	15	Complete remission
4	$T_3N_1M_1$	59	61	—	2	1.71	—	—	—	Complete remission
5	$T_3N_3M_1$	59	59	—	2	1.70	—	—	—	Partial remission
6	$T_1N_2M_1$	62	54	8	3	2.20	1	1.58	9	No change
7	$T_2N_2M_1$	53	51	—	2	1.93	—	—	—	No change
8	$T_2N_1M_1$	52	52	—	0	1.50	—	—	—	Partial remission
9	$T_2N_1M_1$	65	64	—	2	1.82	—	—	—	Partial remission
10	$T_2N_3M_1$	76	78	—	0	1.57	—	—	—	Progressive disease
11	$T_2N_1M_1$	62	57	5	2	2.05	1	1.63	13	Partial remission
12	$T_3N_2M_1$	57	57	—	2	1.75	—	—	—	No change
13	$T_4N_3M_1$	55	58	—	1	1.60	—	—	—	Partial remission
14	$T_2N_2M_1$	60	59	—	1	1.62	—	—	—	Partial remission
15	$T_4N_2M_1$	49	51	—	0	1.40	—	—	—	Partial remission
16	$T_3N_1M_1$	63	42	21	2	2.05	1	1.67	4	Complete remission
17	$T_3N_3M_1$	57	48	9	3	2.27	3	2.19	4	Partial remission‡
18	$T_3N_1M_1$	65	49	16	2	2.00	1	1.66	5	No change
19	$T_3N_2M_1$	50	51	—	2	1.87	—	—	—	Progressive disease
20	$T_3N_1M_1$	58	58	—	2	1.89	—	—	—	Complete remission

LVEF = left ventricular ejection fraction; AM = antimyosin scans; HLR = heart-to-lung ratio in antimyosin scans.
* Decrease ≥5 EF units.
† Interval between antimyosin scans in months.
‡ Congestive heart failure.

Four patients (Nos. 1, 3, 16, 18) presented with decrease in EF of ≥10%. Only two patients (Nos. 1 and 17) presented with clinical symptoms of congestive heart failure.

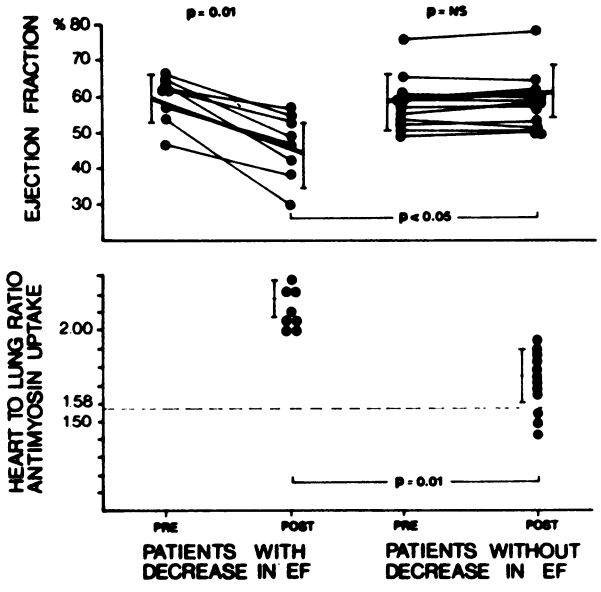

FIGURE 1
LVEF pre- and post-chemotherapy and HLR in antimyosin studies after chemotherapy. The 8 patients with decrease in EF show higher HLR than the 12 patients without decrease in EF (2.11 ± 0.10 versus 1.7 ± 0.16).

In patients with low risks of heart failure, treatment with doxorubicin, at an empirical maximal dose of <500 mg/m^2, has proven effective as a management guide (*3*). In patients at risk, serial LVEF measurements provide effective management guideline criteria (*3*). However, a noninvasive method to identify patients who may develop heart failure before they present with a decrease in EF would have clinical utility. In view of our data, antimyosin scans provide evidence of myocyte damage before EF deteriorates. This is in agreement with work reported using endomyocardial biopsy and electron microscopy of the specimens (*4,5*). At cumulative doses of 200 mg/m^2 of doxorubicin, Druck et al. (*15*), using electron microscopy of specimens after endomyocardial biopsy, found pathologic evidence of cardiotoxicity in 89% of patients. We have found antimyosin uptake in the myocardium in 85% of patients at a cumulative dose of 500 mg/m^2.

Previous work with endomyocardial biopsy indicates a linear relationship between the cumulative dose of doxorubicin and the presence of morphologic damage (*2*). This indicates the potential ability of endomyocardial biopsies to identify patients at risk of developing heart failure at intermediate doses. We have not performed antimyosin studies during treatment and the total cumulative dose at the end of chemotherapy was the same for all patients. Thus, we do not know if there is a relationship between the cumulative dose and the

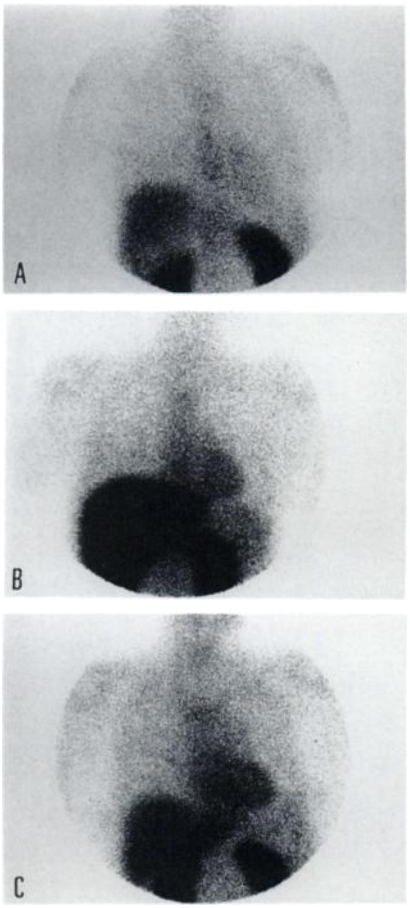

FIGURE 2
Antimyosin scans. (A) Patient 14 (visual score 1, HLR = 1.62). (B) Patient 2 (visual score 2, HLR = 2.00). (C) Patient 17 (visual score 3, HLR = 2.27).

intensity of antimyosin uptake. The calculation of a HLR provides a quantitative means to assess this relationship in future studies. We have found an inverse correlation between HLR and EF after chemotherapy, indicating a relationship between the intensity of antimyosin uptake and the functional status of these patients.

Significance of Antimyosin Uptake in These Patients

Doxorubicin is thought to cause cardiotoxicity by oxidation of membrane lipids, inhibition of oxidative phosphorylation, and interference with DNA synthesis (*16*). The histologic changes related to doxorubicin toxicity consist in the presence of degenerative myocytes and interstitial fibrosis. Morphologic changes observed with electron microscopy are distended sarcotubular systems, myofibrillar loss, and cytoplasmic vacuolization (*2,5*). Antimyosin binds to myocytes that have lost the integrity of their plasma membranes, and antimyosin studies have proven to be highly sensitive to detect myocyte damage. In myocarditis and after heart transplant, antimyosin studies can demonstrate the presence of myocyte damage when endomyocardial

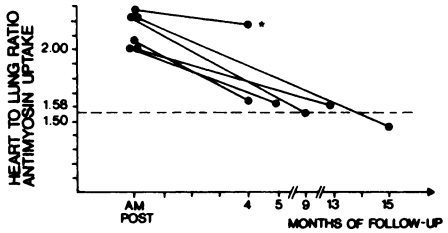

FIGURE 3
Follow-up antimyosin studies in six patients post-chemotherapy (AM POST). Patient 17 (*) presented with congestive heart failure 1 mo after chemotherapy.

biopsy and light microscopy of the specimens only reveal infiltrates or normal myocardial tissue (*8,11*).

In our study, the presence of myocardial antimyosin uptake in 17/20 (85%) patients indicates that myocyte damage has occurred in these patients. More intense antimyosin uptake in patients with decrease in EF indicates more severe myocyte damage. However, some patients (Nos. 7, 9, 19, 20) present with intense antimyosin uptake and do not show functional impairment. This could indicate that the critical amount of damage to produce functional impairment has not yet been reached. Six patients were subsequently studied at different follow-up intervals. Results showed a decrease in antimyosin uptake over time. Normal or minimal antimyosin uptake was seen after 4 mo of cessation of therapy. Interestingly, Patient 17, who presented with congestive heart failure after chemotherapy, had a positive antimyosin scan at 4 mo follow-up. A normal antimyosin scan was obtained in Patient 3; this patient had the most prolonged interval (15 mo) between antimyosin scans. Normal antimyosin studies were found in three patients after chemotherapy. We do not know whether this represents a lack of sensitivity of antimyosin studies or if these patients did not have myocyte damage after doxorubicin therapy.

Myocardial damage after doxorubicin therapy has also been studied with technetium-99m-pyrophosphate imaging. Chacko et al. (*17*) found diffuse pyrophosphate uptake in 9/15 patients with a variety of tumors after doxorubicin therapy (doses ranging between 29.1 and 550 mg/m^2). Most of their patients had prior mediastinal irradiation. In our series, none of the patients had previous mediastinal irradiation, which could have accounted for the antimyosin uptake.

Our patients received chemotherapy, including cyclophosphamide and 5-fluorouracil. 5-fluorouracil administration has been found to be associated with cardiac ischemic changes in humans. Rezkalla et al. (*18*) observed asymptomatic electrocardiographic ST changes in 68% of patients during 5-fluorouracil infusion. It is possible that simultaneous administration of these drugs could also play a role in the development of myocardial damage in patients with advanced breast cancer under doxorubicin therapy.

CONCLUSION

Our study shows that in a selected population of 20 patients treated with doxorubicin 85% present with positive antimyosin studies at a cumulative dose of 500 mg/m^2. This supports the concept that most patients under doxorubicin therapy, at moderate cumulative doses, present with myocyte damage, although only a small proportion of them to the extent necessary to deteriorate function. Patients with a decrease in EF show more intense antimyosin uptake. Antimyosin studies are a sensitive method to detect myocyte damage in patients after doxorubicin therapy.

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