
Detection of Doxorubicin Cardiotoxicity in Patients with Sarcomas by Indium-111-Antimyosin Monoclonal Antibody Studies

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To assess myocardial cell damage due to doxorubicin cardiotoxicity, we prospectively studied 30 patients with sarcomas who were receiving chemotherapy, including doxorubicin. Sixteen patients were treated by continuous infusion over 72 hr and 14 patients were treated by bolus injection. Antimyosin studies and left ventricular ejection fraction (LVEF) measurements were performed before chemotherapy and at intermediate and maximal cumulative doses. Myocardial antimyosin uptake was quantified by a heart-to-lung ratio (HLR). Myocardial antimyosin uptake was observed in all patients at 240–300 mg/m² when ejection fraction was still maintained. Seven patients presented with a decrease of $\geq 10\%$ in absolute ejection fraction units at 420–600 mg/m². Five of these patients had mild congestive heart failure. All patients who presented with a decrease in LVEF $\geq 10\%$ at 420–600 mg/m² had increased antimyosin uptake with HLR ≥ 1.90 at a cumulative dose of 240–300 mg/m². Patients who were treated with continuous infusion had less antimyosin uptake than those who were treated with bolus administration (mean HLR of 1.70 ± 0.09 versus HLR of 2.01 ± 0.16 at a cumulative dose of 240–300 mg/m², $p < 0.01$; HLR of 1.86 ± 0.12 versus HLR of 2.32 ± 0.34 at a cumulative dose of 420–600 mg/m², $p < 0.01$). Two of 16 patients treated by continuous infusion and 5 of 14 patients treated by bolus injection presented with a decrease in ejection fraction $\geq 10\%$. LVEF after chemotherapy in the infusion group was $56\% \pm 5\%$ and $48\% \pm 8\%$ ($p < 0.05$) in the bolus group. Antimyosin studies are helpful in the assessment of doxorubicin cardiotoxicity. Intense antimyosin uptake at intermediate cumulative doses identifies patients at risk of cardiotoxicity before ejection fraction deteriorates. Patients with sarcomas treated by continuous infusion present with less antimyosin uptake than those treated with bolus injection, indicating less severe cardiotoxicity.

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Doxorubicin is one of the most effective chemotherapeutic agents in the treatment of patients with sarcomas. It

is widely used to treat these tumors with variable doses and administration regimens. Bolus injection every 3 wk up to the classic safe cumulative dose of 450 mg/m² is the most common regimen of administration. Continuous infusion of doxorubicin over 72 hr is an alternative method, which may reduce the incidence of congestive heart failure and may permit the administration of higher cumulative doses (1,2).

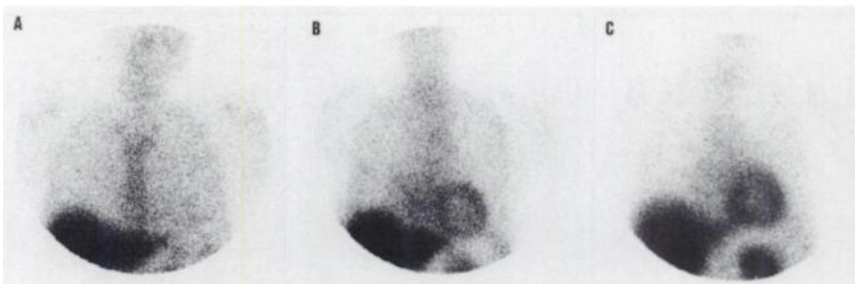
Cardiotoxicity is the most deleterious effect of this drug. Its appearance may produce irreversible and often fatal congestive heart failure, thus limiting the total cumulative dose achievable (3–5). Detection of cardiotoxicity is therefore crucial in the management of these patients and serial ejection fraction measurements have become the standard method to monitor these patients during chemotherapy. Chemotherapy is usually discontinued if there is a decrease in 10 absolute ejection fraction units to an ejection fraction of 40% or less (6). With use of this strategy, incidence and severity of heart failure can be significantly reduced. However, a more sensitive method capable to identify patients at risk of significant ejection fraction deterioration during chemotherapy could still be useful, because these patients could benefit from changes in the schedule of administration to avoid heart failure.

Indium-111-antimyosin antibody studies allow in vivo noninvasive detection of myocardial damage. Binding of this antibody to intracellular myosin takes place only when sarcolemmal disruption occurs and the cell is irreversibly damaged (7). Antimyosin studies have been shown to be sensitive in the detection of myocyte cell damage in a variety of conditions (7–10). We have recently shown that the morphologic damage in the myocytes present in doxorubicin toxicity can be detected by antimyosin scans (11), that intensity of antimyosin uptake relates to the cumulative dose of doxorubicin (12) and that antimyosin uptake precedes ejection fraction deterioration (11,12).

This study was undertaken to assess cardiotoxicity in patients with sarcomas treated with doxorubicin and to compare bolus administration with a continuous infusion technique.

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FIGURE 1. Antimyosin scans of patients with sarcomas treated with doxorubicin. (A) Normal study before chemotherapy. (B) Study obtained at 240–300 mg/m². (C) Study obtained at 420–600 mg/m². Note the increasing myocardial antimyosin uptake with the increasing cumulative dose of doxorubicin.



METHODS

Patients

We prospectively studied 30 patients with sarcomas: soft-tissue sarcoma (22 patients) and osteosarcoma (8 patients). Regimens utilizing doxorubicin were based on chemotherapeutic protocol (including dacarbazine, cyclophosphamide and vincristine) and disease status. All patients had normal baseline ejection fraction. 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. Doxorubicin was administered every 3–4 wk at a dose of 60 mg/m². Sixteen patients were treated by continuous infusion over 72 hr and 14 patients were treated by bolus injection. Antimyosin studies and left ventricular ejection fraction (LVEF) measurements were performed before chemotherapy, at intermediate cumulative doses (240–300 mg/m²) and at maximal cumulative doses (420–600 mg/m²) of doxorubicin.

Patients were examined by the study cardiologist at baseline and when the scans were performed. Symptomatic congestive heart failure was defined as mild if third heart sound gallop or rales in less than half the lung fields were present, or severe if major pulmonary edema or cardiogenic shock were present (3).

Ejection Fraction Measurements

After in vivo red blood cell labeling with 25 mCi of ^{99m}Tc and with the patients supine, 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) 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 disk 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

Antimyosin studies were performed within a week of LVEF measurements. R11-D10-Fab-DTPA (0.5 mg, Centocor Europe, Leiden, The Netherlands) labeled with 2 mCi of ¹¹¹In was administered by slow intravenous injection. Planar scans were obtained 48 hr later using a medium-energy collimator with a 20% window centered on both peaks of ¹¹¹In at a preset time of 10 min. Scans were stored in 128 × 128 frames. The presence of antimyosin uptake in the heart was assessed by applying a quantitative method (13). This consisted of drawing a ROI on the heart and lungs on the anterior view of the thorax. A heart-to-lung ratio (HLR) was obtained by 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 (9,13).

Statistical Analysis

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

RESULTS

LVEF Measurements and Antimyosin Studies

LVEF before chemotherapy was 61% ± 7%, 59% ± 6% at 240–300 mg/m² (p = ns) 52% ± 8% (p < 0.01) at 420–600 mg/m². Seven patients presented with a decrease of ≥10% in absolute ejection fraction units at 420–600 mg/m². Five of these seven patients had mild congestive heart failure. None of the patients presented with severe congestive heart failure. Antimyosin studies were normal in all patients before chemotherapy (HLR 1.39 ± 0.06). Myocardial antimyosin uptake was observed in all patients at 240–300 mg/m² (mean HLR of 1.85 ± 0.19, p < 0.01) and in all patients at 420–600 mg/m² (HLR 2.08 ± 0.33, p < 0.001) (Figs. 1–3, Table 1).

All patients who presented with a decrease in LVEF ≥ 10% at 420–600 mg/m² had increased antimyosin uptake with HLR ≥ 1.90 at a cumulative dose of 240–300 mg/m². Eight patients with HLR ≥ 1.90 at 240–300 mg/m² did not present a decrease in LVEF ≥ 10%; seven of them had a decrease in LVEF between 5% and 10% (Table 1).

Bolus Administration and Continuous Infusion

LVEF was similar in both groups at a cumulative dose of 240–300 mg/m² (59% ± 6% versus 58% ± 7%). LVEF significantly decreased in both groups at a cumulative dose of 420–600 mg/m² (Table 1, Figs. 2, 3). LVEF in the bolus group was significantly lower than that observed in the infusion group (48% ± 8% versus 56% ± 5%, p < 0.05). A decrease in LVEF ≥ 10% was observed in two patients treated by continuous infusion (one had symptoms of mild congestive heart failure) and in five patients treated by bolus injection (four had symptoms of mild congestive heart failure).

Patients treated with continuous infusion had less antimyosin uptake than those treated with bolus administration: HLR of 1.70 ± 0.09 versus HLR of 2.01 ± 0.16 at a

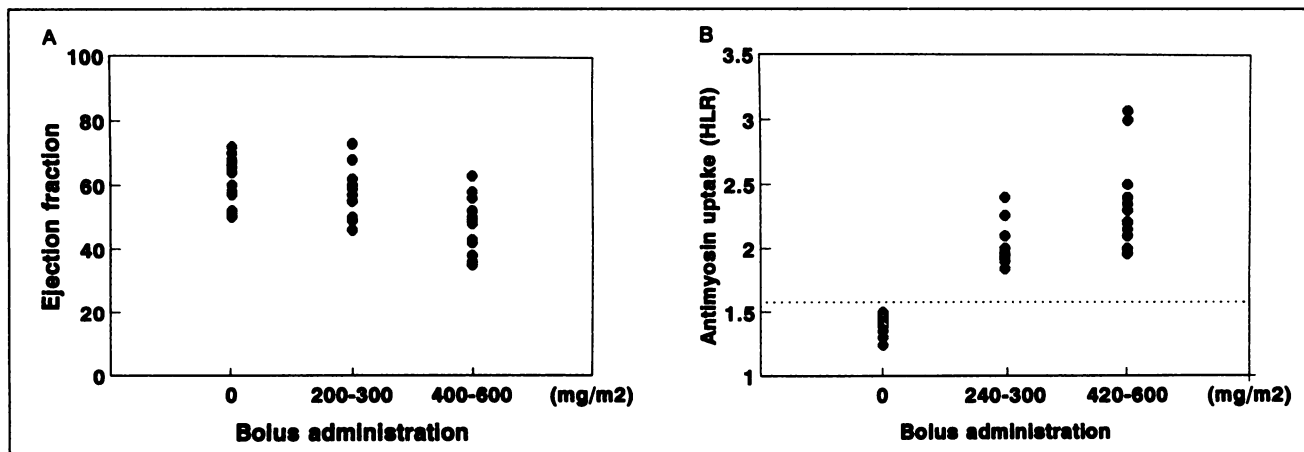


FIGURE 2. Ejection fraction measurements (A) and antimyosin uptake (B) in patients treated with a bolus injection.

cumulative dose of 240–300 mg/m², $p < 0.01$; HLR of 1.86 ± 0.12 versus HLR of 2.32 ± 0.34 at a cumulative dose of 420–600 mg/m², $p < 0.01$ (Figs. 2, 3).

The response rate observed in the group of patients treated by continuous infusion was similar to that observed in the group of patients treated by bolus injection. Of 16 patients treated by continuous infusion, a complete response was observed in one patient, a partial response was observed in four patients and one patient had stable disease after chemotherapy. Of 14 patients treated by bolus injection, a complete response was observed in one patient, a partial response was observed in three patients and two patients had stable disease after chemotherapy.

DISCUSSION

The appearance of cardiomyopathy is the most serious toxic effect of doxorubicin and is the one that limits its use for extended periods of time. Therefore, new chemotherapy regimens and alternative anthracycline derivatives are under development with the aim of rendering similar therapeutic benefit with less cardiotoxicity. Serial resting LVEF measurements provide effective management of the majority of cancer patients under doxorubicin therapy. Monitoring resting LVEF with gated blood-pool scans is

associated with low incidence and a benign course of doxorubicin-induced congestive heart failure. After reaching a total cumulative dose of 500 mg/m², however, additional treatment with doxorubicin produces a rapidly increasing incidence of clinically significant cardiomyopathy (1). This has led to the use of a fixed maximal dose of 450–550 mg/m² of doxorubicin in most chemotherapeutic protocols, although some patients may develop cardiomyopathy at lower cumulative doses. Cessation of doxorubicin administration at a fixed cumulative dose, however, has important clinical implications. In a large series of patients with a variety of cancers, Van Hoff et al. (14) showed that patients in whom chemotherapy had been stopped at a cumulative dose of 550 mg/m² could be in complete remission (19%), in partial remission (28%) or be stable (39%). Their results suggested that these remissions could have been prolonged with additional administration of doxorubicin. Patients who could tolerate higher doses could benefit from additional treatment.

Important attempts to reduce doxorubicin cardiotoxicity have been made by modifying the schedule of administration. Since doxorubicin cardiotoxicity depends on peak plasma levels (15), several continuous infusion regimens have been proposed. Initial studies suggested decreased

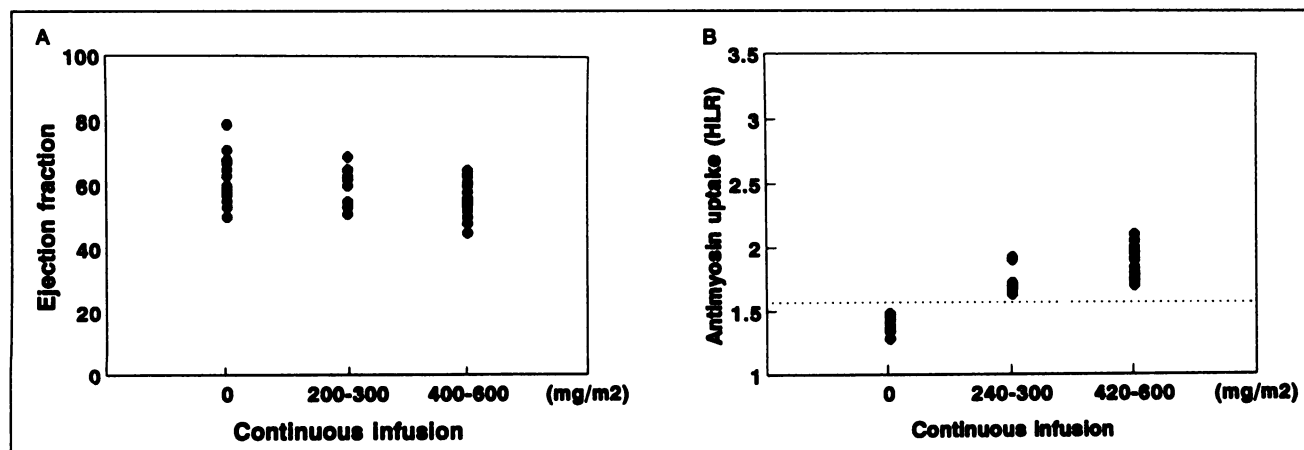


FIGURE 3. Ejection fraction measurements (A) and antimyosin uptake (B) in patients treated with continuous infusion.

TABLE 1
Results of Antimyosin Studies (HLR) and LVEF Measurements in all Patients

Before chemotherapy				At 240-300 mg/m ²				At 420-600 mg/m ²				
Bolus		Infusion		Bolus		Infusion		Bolus		Infusion		
HLR	LVEF	HLR	LVEF	HLR	LVEF	HLR	LVEF	HLR	LVEF	HLR	LVEF	
1.45	52	1.34	79	1.95	60	1.90	62	2.10	43	2.05	58	
1.40	67	1.28	53	2.00	68	1.63	55	3.07	42	1.74	53	
1.42	65	1.38	59	2.40	56	1.64	60	2.50	38	1.76	54	
1.40	51	1.42	71	1.90	50	1.65	69	2.20	48	1.70	65	
1.46	65	1.40	68	2.00	57	1.68	60	2.21	56	1.90	64	
1.50	72	1.39	60	1.92	71	1.71	63	2.35	63	1.84	63	
1.39	64	1.40	57	2.10	61	1.66	53	2.10	56	1.96	52	
1.43	66	1.38	65	1.90	60	1.70	69	1.96	58	1.75	61	
1.30	60	1.46	68	2.24	49	1.71	69	2.26	35	1.80	64	
1.40	57	1.45	58	1.90	60	1.72	53	2.10	49	2.00	55	
1.30	58	1.34	63	1.96	59	1.70	62	2.30	50	1.92	56	
1.35	68	1.48	60	2.10	55	1.67	55	3.00	36	1.80	52	
1.41	70	1.40	67	1.96	62	1.64	65	2.40	52	1.77	60	
1.24	50	1.44	50	1.84	46	1.65	54	2.00	48	1.90	48	
		1.43	58			1.64	60			1.81	60	
		1.37	55			1.92	51			2.10	45	
Mean ± s.d.	1.39 ± .07	61 ± 7	1.40 ± .05	61 ± 7	2.01 ± .16	58 ± 7	1.70 ± .09	59 ± 6	2.32 ± .34	48 ± 8	1.86 ± .12	56 ± 5

cardiotoxicity with similar antitumoral effect using constant infusion by ambulatory pump delivery systems (16), although contradictory data were subsequently reported (17,18). In a clinical study with soft-tissue sarcomas, Hamdam et al. (2) showed that continuous infusion of doxorubicin may provide the same antitumoral effect with a reduced incidence of congestive heart failure. In addition, it has to be taken into account that prolonged exposure of tumors with small growth fractions, such as soft-tissue sarcomas, to cytotoxic agents might result in more tumor cell necrosis. Our results show that continuous infusion of doxorubicin results in less intense antimyosin uptake as compared to bolus administration. This indicates more severe myocyte damage with bolus administration, although not always to the extent necessary to deteriorate function. This difference in cardiotoxicity between bolus administration and continuous infusion is better assessed with a combination of antimyosin scans and ejection fraction measurements. At intermediate cumulative doses, functional status of both groups was similar, although patients treated with a bolus injection had more increased antimyosin uptake. At maximal cumulative doses, patients treated with bolus injection presented with more severe functional impairment, resulting in an incidence of mild congestive heart failure at maximal cumulative doses which is similar to that found in other series of patients treated with doxorubicin (1,3).

Detection of those patients at risk for cardiomyopathy before ejection fraction deteriorates could be of interest, since those patients could benefit from alternative administration regimens to avoid or delay significant functional impairment. LVEF measurements seem not to be sensitive enough to detect patients at risk of significant cardiotoxicity at an early stage. This is in keeping with the concept of the need for a certain critical mass of cell damage before

functional impairment can be detected by conventional methods (4,5). Our results show that antimyosin studies can detect cell damage before LVEF deterioration is observed. At intermediate cumulative doses, a certain degree of myocardial cell damage is detected in antimyosin studies, whereas ejection fraction is still maintained. Patients with more intense antimyosin uptake at that time tend to be those with more severe functional impairment with additional doxorubicin administration, whereas patients with less intense antimyosin uptake at intermediate doses seem to be those with less functional impairment over time.

The ability of antimyosin studies to assess the time course of myocyte damage has been tested in other clinical conditions. In heart transplant rejection and myocarditis, antimyosin studies also have proven to be highly sensitive in detecting variations in active myocyte damage over time (8,19). It has been shown in these conditions that the degree of antimyosin uptake relates to the extension and severity of myocyte damage and that it can be reliably quantified in terms of HLRs (10,13). We used the same quantitative approach in our study and found that when a certain degree of myocyte damage has been reached, as shown by a certain degree of antimyosin uptake (HLR ≥ 1.90), a significant decrease in ejection fraction and symptoms of overt heart failure are more likely to occur.

It is still not clear if this early detection of cardiotoxicity may influence management strategies. Although serial resting LVEF measurements will remain the method of choice to monitor cardiotoxicity, it is possible that by using a more sensitive test, such as antimyosin scans, drug administration could be individually tailored to reduce the incidence and severity of cardiotoxicity (20). In view of our results, it seems reasonable that antimyosin studies might complement LVEF measurements in some circumstances. For example, a complementary approach could be helpful for

individual management of patients with previous risk factors or for patients who are potential candidates for future repeated doxorubicin administration. Although the prognosis for patients with advanced or metastatic soft-tissue sarcomas is still poor, this may be particularly relevant in young patients with responsive tumors who might benefit from further doxorubicin administration. Recently, it has been shown in children treated with doxorubicin for acute lymphoblastic leukemia that decreased contractility may occur several years after chemotherapy (21). An unexpectedly high incidence of late cardiac abnormalities in these children was reported in that study. It is possible that early detection of cardiotoxicity in these circumstances could prompt changes in the schedule of administration which could result in decreased cardiotoxicity over time.

We conclude that antimyosin studies are helpful in the assessment of doxorubicin cardiotoxicity. Intense antimyosin uptake (HLR ≥ 1.90) at intermediate cumulative doses identifies patients at risk of cardiotoxicity before LVEF deteriorates. Antimyosin studies provide a new quantitative method to compare different administration regimens. Patients with sarcomas treated by continuous infusion present with less antimyosin uptake than those treated with bolus injection, thus indicating less severe cardiotoxicity.

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EDITORIAL

Antimyosin Positivity in Doxorubicin Cardiotoxicity: Earlier Than the Conventional Evidence

The classical symptom of chest pain almost invariably offers an indication of acute myocardial infarction. Electrocardiographic changes

and enzyme elevation are the tell-tale accompaniments. However, the classical symptoms and diagnostic methods are not foolproof. The need for an accurate diagnostic method for the detection of ischemic necrosis led to development of antimyosin scintigraphy. The imaging procedure demonstrated high diagnostic accuracy for

the detection of an acute myocardial infarction (1-7). The high predictive values of normal and abnormal scans confirmed the clinical utility of the procedure in patients with equivocal diagnosis resulting from inadequate or uninterpretable clinical or electrocardiographic alterations (8). These studies established the lack of sarcolem-

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