Anthracycline cardiotoxicity in childhood cancer. Frequency, risk factors, and early detection
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Indium-111 antimyosin scintigraphy in the early detection of heart damage after anthracycline therapy in children

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Introduction

Despite the firmly established early and late cardiotoxic side effects of anthracyclines, these drugs are among the most widely used agents for the treatment of childhood cancer.\(^1\)\(^2\) The incidence and severity of clinical and subclinical cardiac damage after anthracycline therapy increases with increasing cumulative dose, additional radiotherapy and female sex.\(^3\) Moreover, children seem to be more susceptible than adults to the cardiotoxic effects of anthracycline therapy, although there is considerable variation in the individual susceptibility to these side effects.\(^4\)

Conventional methods, such as radionuclear angiography and echocardiography, are not suitable for investigating early cardiac damage because they are not sensitive enough; i.e., a critical number of cells may be damaged before the functional myocardial impairment is detected.\(^5\) Yet, early identification of children at risk for cardiac damage is essential because subsequent preventive measures can limit further myocardial damage. In this setting Indium-111-antimyosin (\(^{111}\)In-AM) scintigraphy may be of diagnostic use because it allows noninvasive detection of myocardial damage in vivo. The binding of this antibody to intracellular myosin takes place only when the sarcolemma is disrupted due to cell damage.\(^6\) A study of rats treated with doxorubicin showed a progressive increase in myosin uptake with increasing severity of myocardial damage. A strongly positive correlation was found between the intensity of myocardial uptake and the loss of contractile function. Immunohistochemical staining showed that In-111 AM was localized exclusively in injured myocytes.\(^7\) Studies with adult patients showed that the intensity of In-111 AM uptake was related to the cumulative dose of doxorubicin and that In-111 AM uptake preceded changes in the ejection fraction.\(^8\)^\(^9\)^\(^10\)

There have been no studies of In-111 AM uptake in children and young adults treated with anthracyclines. We performed a pilot study involving eight patients who were treated with doxorubicin to determine whether In-111 AM scintigraphy can be used to detect early cardiac damage during chemotherapy in children and in young adults.

Patients and Methods

Patients

Eight patients with a tumor eligible for doxorubicin treatment were included in the study: seven children and one young adult, with a mean age of 12 years (range 1-25 years). The patient characteristics are listed in Table 1. Additional therapy with cyclophosphamide (max dose: 8400 mg/m\(^2\)) and ifosfamide (max dose: 7800 mg/m\(^2\)) was given to patients with Ewing sarcoma and Burkitt lymphoma. One patient (no 5) was cotreated with dexrazoxane, a cardioprotective agent. The study was approved by the hospital ethics committee.
Scintigraphy

In-111 AM planar scintigraphy of the thorax in anterior-posterior projection was undertaken on one or two occasions during the course of chemotherapy, before or 3 weeks after the administration of doxorubicin. In-111 AM was prepared by adding 92 MBq (2.5mCi) 111 indium chloride to a vial containing 0.5 mg of R11-D10-Fab DTPA (Mallinkrodt Medical B.V., Petten, The Netherlands). The amount of radioactivity used depended on the patient's age: 40 MBq was used for patients younger than 10 years, 60 MBq for patients aged 10-14 years, and 80 MBq for patients older than 14 years. Scintigraphy was performed 48 hours after infusion of AM. We used a large field of view gamma camera (Diacam Siemens) equipped with a medium energy collimator and a 20 percent window set around both peaks of In-111 at a preset time of 10 minutes. Scans were stored in 128x128 frames for subsequent analysis. The scintigrams were interpreted quantitatively by an experienced nuclear physician unaware of the patient's condition and echocardiographic results. Regions of interest for heart and lungs were drawn and a heart-to-lung ratio (HLR) was calculated as the average counts per pixel in the myocardium divided by the average counts per pixel in the lungs.\(^\text{11}\) The mean value of three separate HLR evaluations was used as the HLR value of an In-111 AM scintigram.

Echocardiography

Echocardiograms were made by a pediatric cardiologist and a technician before and after 3 weeks of doxorubicin administration as a part of the treatment protocol, using 3.5 and 5 MHz transducers. All echocardiograms were recorded on videotape and fractional shortening (FS) was measured by one observer who did not know the results of the In-111 AM scintigraphy and who was unaware of the patient's condition. The FS of the left ventricle was calculated according to the formula: LVEDD-LVESD divided by LVEDD multiplied by 100, where LVEDD is left ventricular end diastolic diameter and LVESD is left ventricular end systolic diameter.

Table 1 Clinical data

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Male</th>
<th>Female</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Follow up (up to 6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td></td>
<td>1</td>
<td>Brain tumor</td>
<td>Complete remission</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td></td>
<td>4</td>
<td>Burkitt lymphoma</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td></td>
<td>16</td>
<td>Ewing sarcoma</td>
<td>Complete remission</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td></td>
<td>10</td>
<td>Ewing sarcoma</td>
<td>Complete remission</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td></td>
<td>16</td>
<td>Osteosarcoma</td>
<td>Complete remission</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td></td>
<td>14</td>
<td>Osteosarcoma</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td></td>
<td>25</td>
<td>Osteosarcoma</td>
<td>Complete remission</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td></td>
<td>10</td>
<td>Osteosarcoma</td>
<td>Progressive disease</td>
</tr>
</tbody>
</table>
Results

The scintigraphic and echocardiographic results are shown in Table 2. Three patients (patients 6, 7, 8) underwent baseline In-111 AM scintigraphy: their HLRs were 1.49, 1.5 and 1.51, respectively. Patients 1, 2, 3, and 8 underwent In-111 AM scintigraphy only once because treatment was completed (patient 1) or because of progressive disease (patients 2 and 8) or radiotherapy of the thorax (patient 3). The HLR of patient 6 increased substantially from 1.49 before doxorubicin therapy to 2.33 weeks after a cumulative dose of 150 mg/m² doxorubicin, an increase of more than 50 percent of the baseline value. The FS was normal throughout therapy. The final cumulative dose of doxorubicin was 450 mg/m². Unfortunately, 3 months after she finished chemotherapy, with her cancer in complete remission, she developed heart failure and died within a week. No autopsy was performed. The increase in the HLR between two scans in patients 4 and 7 was 0.29 in both, with a comparable time interval. The FS did not change in these patients, and neither had evidence of clinical heart failure at the time of the last follow-up (6 months after completion of cytotoxic therapy). The HLR of patient 5, who was cotreated with dexrazoxane, did not increase at all after anthracycline therapy. In none of the patients did the FS decrease by more than 10 percent compared to the baseline value or decrease to an absolute value below 30 percent. Therefore, the treatment regimen of doxorubicin was not changed. In patient 1, it was not possible to measure the baseline FS reliably, because of pericardial exudate. No echocardiographic follow-up was obtained for patients 2 and 8 because of progressive disease.

Table 2 Summary of scintigraphic and echocardiographic results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Doxorubicin</th>
<th>Antimyosin scintigraphy</th>
<th>Echocardiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cumulative dose</td>
<td>Heart-to-lung ratio</td>
<td>Fractional shortening of the left ventricle</td>
</tr>
<tr>
<td></td>
<td>(mg/m²)</td>
<td>0 mg/m²</td>
<td>120 or 150 mg/m²</td>
</tr>
<tr>
<td>1</td>
<td>160</td>
<td>1.89</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>1.97</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>1.82</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>240</td>
<td>1.59</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>450</td>
<td>1.43</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>450</td>
<td>1.49</td>
<td>2.3</td>
</tr>
<tr>
<td>7</td>
<td>450</td>
<td>1.50</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>225</td>
<td>1.51</td>
<td></td>
</tr>
</tbody>
</table>
**Discussion**

This pilot study indicates that In-111 AM can play a role in the early detection of cardiac damage due to anthracycline therapy in children and young adults. The HLR values obtained by In-111 AM scintigraphy for three patients before therapy were comparable with the normal values for adult patients. During therapy, in seven patients the measured HLR was above these normal values. In adults, myocyte damage has been detected by In-111 AM scintigraphy at intermediate cumulative doses of doxorubicin of 240-300 mg/m². In our study, we detected an early elevated HLR after cumulative doses of 120 and 150 mg/m². Patient no 6 had an HLR of 2.3 after a cumulative dose of doxorubicin of 150 mg/m². Three months after finishing the course of therapy with 450 mg/m² doxorubicin, she developed clinical heart failure and died. The left ventricular FS measured by echocardiography remained normal until the end of treatment. This case confirms the results of studies with adults: a high HLR (above 1.9) increases the risk of cardiotoxicity, defined as a decrease in ejection fraction or clinical heart failure. The HLR did not increase in the one patient who was cotreated with dexrazoxane, a cardioprotective agent. In this patient both HLR values (1.43 after 150 mg/m² and 1.36 after 225 mg/m²) were within the normal range for adults and below the three baseline values. Our results suggest that In-111 AM scintigraphy can be used to evaluate early cardiac damage associated with different treatment schedules and to assess the effectiveness of cardioprotective agents in children receiving anthracyclines. Lopez et al. described a randomized trial in which adults were treated with epirubicin with or without dexrazoxane, and cardiotoxicity was monitored by In-111 AM scintigraphy and radionuclide angiography. With In-111 AM scintigraphy they found a significant difference between the two treatment groups in an early stage of anthracycline therapy, but not when they measured the left ventricular ejection fraction by multigated radionuclide angiography.

In this study we found evidence of myocardial injury as measured by In-111 AM scintigraphy in patients with a normal FS. These results are consistent with endomyocardial biopsy findings and serum cardiac troponin concentrations measured in patients receiving anthracycline therapy. In 1983 Isner et al described histological signs of anthracycline cardiotoxicity in 52% of their patients even though these patients did not show changes in heart function. A recent publication by Herman et al demonstrated that cardiac troponin T (cTnT) concentrations were elevated in rats following doxorubicin treatment. The increased serum concentrations of cTnT occurred at a time when there was only minimal myocyte damage. Lipshultz et al found increased concentrations of cTnT in children treated with doxorubicin; the magnitude of this increase was positively correlated with echocardiographic abnormalities of the left ventricle 9 months later. In adult patients Missov et al found an increase in cardiac troponin I concentration in the absence of a
decreased left ventricular ejection fraction.\textsuperscript{17} Lipshultz et al pointed out that the ejection fraction and fractional shortening were of limited value in detecting anthracycline cardiotoxicity.\textsuperscript{18} Furthermore, functional deterioration after damage to a critical number of myocytes may be masked by several factors including reserve capacity and compensatory mechanisms. For these reasons, conventional methods like echocardiography and radionuclide angiography are unsuitable for the early detection of treatment-induced cardiac damage. The results of this pilot study suggest that In-111 AM scintigraphy can detect early myocardial damage before conventional methods detect cardiac dysfunction in children treated with anthracyclines. In future clinical trials In-111 AM scintigraphy can be used to identify patients at risk of subsequent cardiac sequelae and to measure the effect of cardioprotective agents.
References


