Anthracycline cardiotoxicity in childhood cancer. Frequency, risk factors, and early detection
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A longitudinal echocardiographic study in children treated with anthracyclines

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Introduction

Despite their dose-dependent cardiotoxic effects, anthracyclines continue to be prescribed because they are among the most effective agents against childhood cancers.\textsuperscript{1} The frequency of cardiotoxicity after anthracycline therapy varies, depending on the selection of the study population, follow-up time, and the definition of cardiotoxicity. The estimated risk of anthracycline-induced clinical heart failure, 15 years after the start of anthracycline chemotherapy, was found to be 5\% in a study of 607 children treated with a mean cumulative dose of 301 mg/m\textsuperscript{2} anthracycline.\textsuperscript{2} None of the patients treated with a dose less than 200 mg/m\textsuperscript{2} developed clinical heart failure during the study period. Echocardiographic abnormalities have been found in 57\% of the survivors of leukaemia who had received 228-550 mg/m\textsuperscript{2} of doxorubicin.\textsuperscript{3} It is important to know which patients may be at increased risk for developing cardiotoxicity after anthracycline therapy because possible preventive measures can be taken. There is considerable variation among patients in their tolerance of anthracyclines. A higher cumulative dose and higher dose intensity, younger age at diagnosis, female sex, and radiation therapy to the heart region have been reported to be risk factors for development of cardiotoxicity.\textsuperscript{4} It is also suggested that impaired ventricular function at the end of treatment or early thereafter may predict adverse cardiac outcome.\textsuperscript{3,5} The current recommendations for cardiac evaluation after anthracycline therapy state that patients with an abnormal left ventricular shortening fraction in the first year after therapy should be evaluated more frequently than others.\textsuperscript{6} However, there is no evidence to support this recommendation, and it is unknown whether this increased monitoring leads to better outcomes.

We examined determinants for the LVSF during follow-up in a cohort of children with cancer who had been treated with anthracycline therapy, and assessed the prognostic value of an echocardiographic measurement at the end of therapy in the prediction of subclinical cardiotoxicity.

Patients and methods

Patients
All children with cancer who were treated with a cumulative dose of more than 200 mg/m\textsuperscript{2} of anthracycline between 1985 and 1996 in the Academic Medical Centre formed the initial cohort of this study. Patients were excluded if they developed clinical heart failure during anthracycline therapy, or if no echocardiographic measurement was made within one month of the end of treatment. Screening for echocardiographic abnormalities after anthracycline therapy was performed at our follow-up clinic for childhood cancer.
Echocardiographic evaluation
Left ventricular systolic function at the end of anthracycline therapy and during follow-up were assessed by means of standard M mode echocardiography. Paediatric cardiologists assessed and analysed the left ventricular shortening fraction (LVSF), using the formula: LVSF (%) = ((LVDD - LVDS) / LVDD) * 100%, where LVDD is the left ventricular diastolic diameter and LVDS is the left ventricular systolic diameter. Echocardiography was performed with a concurrent ECG and the LVDD was measured at the start of the QRS complex. A LVSF ≤ 28% was considered as abnormal.5,7

Statistical evaluation
We compared base-line characteristics between our study population and excluded patients to assess the potential for selection bias. Baseline characteristics were compared by Student t tests and χ² tests. Determinants of the LVSF at follow-up were examined using linear regression models. In a first step, the following determinants were assessed in a univariate and multivariable way, cumulative dose of anthracycline > 450 mg/m², age at diagnosis, radiation therapy to the heart region, and female sex. In the next step, the LVSF at the end of therapy was added to the model and changes in regression coefficients were analysed. If the end of therapy measurement could be used as a proxy for the follow-up echo, previous identified risk factors would loose their prognostic value. To adjust for the potential effect of longer follow-up in patients considered at an increased risk for cardiac abnormalities, the time interval between the end-of-treatment and follow-up measurement was included in all models. In a final step, we assessed the value of LVSF at the end of treatment as a screening test for subclinical cardiac abnormalities (defined as LVSF at follow-up <= 28%) by describing the characteristics (accuracy) at different cut-off values.

Results
Patients
Between 1985 and 1996, 291 children were treated with a cumulative dose of more than 200 mg/m² of anthracyclines. Nine of the 291 children developed clinical heart failure either during the treatment or within one month after the end of treatment. These 9 patients have been described in an earlier study; and were excluded for this study.2 A sample of 181 patients (62%) underwent an ‘end-of-treatment’ echocardiography within one month after the end of treatment. (Figure 1) There were no significant differences in the cumulative dose of anthracyclines, age at diagnosis, sex or received radiation therapy to the heart region between the patients who did and who did not undergo an echocardiography at the end of treatment. Of the 181 patients with an ‘end-of-treatment’ echocardiography 41 patients died before follow-up echocardiography.
A dose: median (range) of cumulative anthracycline dose in mg/m²
Age: median (range) age at diagnosis in years
SF: left ventricular shortening fraction in %

**Figure 1** Formation of the study cohort
Table 1 Clinical characteristics of the study group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Female n=51</th>
<th>Male n=62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 years</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2-10 years</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Cumulative dose of anthracycline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-450 mg/m</td>
<td>44</td>
<td>55</td>
</tr>
<tr>
<td>&gt;450 mg/m</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Irradiation involving the heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>No</td>
<td>38</td>
<td>56</td>
</tr>
</tbody>
</table>

None of these patients died from cardiac failure. Twenty-seven patients (15%) had no follow-up echocardiography because they had left the country or were otherwise lost to follow-up. The study group therefore consisted of 113 patients. We found no significant differences in either the sex distribution, the cumulative dose of anthracyclines, the proportion of patients receiving radiation therapy to the heart region, or in the median value of the LVSF at the 'end-of-treatment' echocardiography, between our study group and patients lost to follow-up. There was only a mean difference in age of 2.2 years with our study group. Characteristics of the 113 patients are shown in Table 1.

Echocardiographic results
In 94 of the 113 patients, an LVSF was performed before the start of treatment. There was no association between age at diagnosis and the pre-treatment LVSF. The mean (SD) LVSF before the start of therapy was 38.4% (4.1) for 94 patients. None of the patients had an abnormal LVSF before start of therapy. For the whole study group the mean (SD) LVSF within one month after the end of treatment was 35.4%(4.1). Four patients (3.5%) had an abnormal LVSF within one month after the end of treatment. The mean (SD) interval from the end of anthracycline therapy to echocardiographic follow-up evaluation was 4.6 (3.5) years (range, 0.2-13 years). The mean (SD) LVSF at follow-up after anthracycline therapy was 34.3% (4.7). The echocardiographic data are shown in Figure 2. Sixteen patients (14.2%) had an abnormal LVSF at follow-up. For these 16 patients the mean LVSF (SD) within one month after the end of treatment had been 32.3 (2.6)%. A scatter plot of the values of the LVSF at the end of treatment against the LVSF at follow-up is presented in Figure 3.
Subclinical cardiotoxicity 2.2

Figure 2 Echocardiographic results before, at the end of, and after anthracycline treatment

Figure 3 LVSF at the end of therapy related to the LVSF at follow-up
Table 2 Relationship between risk factors and the LVSF at follow-up in multivariate linear regression

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Multivariate excluding the LVSF end therapy</th>
<th>Multivariate including the LVSF end therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>LVSF end therapy %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A dose &gt; 450 mg/m²</td>
<td>-3.34</td>
<td>-5.88 to -0.80</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>-0.21</td>
<td>-0.39 to -0.03</td>
</tr>
<tr>
<td>RT</td>
<td>0.08</td>
<td>-2.21 to 2.37</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.69</td>
<td>-1.03 to 2.41</td>
</tr>
</tbody>
</table>

LVSF: left ventricular shortening fraction, A dose: anthracycline dose, 95% CI: 95% confidence interval, RT: radiation therapy to the heart region.

Multivariate model is adjusted for follow-up time.

Table 3 The accuracy of the end-of-treatment LVSF in the prediction of subclinical cardiotoxicity in a cohort of 113 children who had been treated with anthracycline

<table>
<thead>
<tr>
<th>Cut off value of end-of-treatment LVSF</th>
<th>No of patients ≤ cut off value</th>
<th>No of patients &gt; cut off value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Cardiotoxicity¹</td>
</tr>
<tr>
<td>LVSF of 30%</td>
<td>12</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>LVSF of 32%</td>
<td>25</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>LVSF of 34%</td>
<td>47</td>
<td>13 (28%)</td>
</tr>
<tr>
<td>LVSF of 36%</td>
<td>75</td>
<td>15 (21%)</td>
</tr>
<tr>
<td>LVSF of 38%</td>
<td>91</td>
<td>16 (16%)</td>
</tr>
</tbody>
</table>

¹cardiotoxicity defined as a LVSF at follow-up ≤ 28%

Determinants of LVSF at follow-up
The results of the multivariate analysis of determinants of LVSF at follow-up are presented in Table 2. The first model, excluding the LVSF at the end of treatment, showed that a cumulative dose above 450 mg/m² and a higher age at diagnosis were associated with lower values of LVSF at follow-up. Female sex and radiation therapy to the heart region had no impact on the LVSF value at follow-up. When the LVSF value at the end of treatment was entered to the model, LVSF at follow-up had a highly significant relationship with the end-of-treatment LVSF. Furthermore, the association between a higher dose of anthracycline and a higher age at diagnosis with lower values of LVSF became significantly weaker. No meaningful changes were found in the magnitude of the β of the LVSF at the end of treatment if the follow-up time was dropped from the model (data not shown).
Value of end-of-treatment LVSF measurement in the prediction of subclinical cardiotoxicity

The accuracy of the end-of-treatment LVSF measurement in the prediction of subclinical cardiotoxicity using various cut-off values is given in table 3. None of our patients with LVSF above 38% developed subclinical cardiac abnormalities during follow-up.

Discussion

In the present study of survivors of childhood cancer who ever treated with more than 200 mg/m$^2$ of anthracycline there was an association between the LVSF at the end of treatment and the LVSF at follow-up. This association remained after adjustment for other possible risk factors. These results confirm two earlier studies which investigated the relationship between echocardiography at the end of therapy and subsequent cardiac abnormalities.$^{3,5}$ They suggested a relationship between an abnormal LVSF at the end of treatment and the presence of later abnormal echocardiographic measurements. However, the value of these findings is limited by either the selection of a non-random subgroup of children, a lower number of patients, and by the absence of consideration of other risk factors.

The authors know of no published data of prospective or retrospective longitudinal systolic function measurements in children treated with anthracyclines until subsequent follow-up. The high percentage of abnormal function at follow-up in our study, defined as a LVSF ≤ 28% is in accordance with the earlier reported frequency of abnormal systolic function.$^{7,8}$ However, comparison of so called subclinical cardiotoxicity between different studies is difficult, because studies use different definitions of subclinical cardiotoxicity and many variables across the studies vary.

First an analysis was made of the relationship of risk factors with the LVSF at follow-up, excluding the LVSF at the end of treatment. A cumulative dose of more than 450 mg/m$^2$ and an older age at diagnosis were risk factors for a lower LVSF at follow-up. Reports on the influence of age at diagnosis on subsequent abnormal echocardiographic measurements are not consistent. Lipshultz et al reported a lower age at diagnosis and Sorensen et al a higher age at diagnosis as a risk factor for later subclinical cardiotoxicity.$^{9,10}$

One limitation of the present study is that it was a retrospective cohort study of patients who were treated with anthracyclines and underwent echocardiographic measurement at the end of their treatment. Possible patients with a higher risk of cardiac abnormalities were selected, because only 62% of the patients underwent echocardiography within 1 month after the end of treatment. However, with regard to the known risk factors of subclinical cardiotoxicity, this study group seems to be more like a "random" sample of the patients treated with a cumulative dose ≥ 200 mg/m$^2$ anthracyclines. Although measurement of the SF has limitations in the reproducibility.
and accuracy of assessing cardiac damage, in children the measurement of the SF is the clinical standard in most centres.

The results of this study can be of importance for the future follow-up of patients who have been treated with anthracyclines. The results suggest that patients with a lower LVSF at the end of treatment should be evaluated more frequently than patients with a higher LVSF. However, the predictive value of the cardiac function at the end of treatment for an abnormal cardiac function at later follow-up needs to be evaluated in a prospective study of a cohort of children treated with anthracyclines at fixed time points after the end of treatment. Long-term follow-up studies are necessary to relate abnormal echocardiographic measurements to subsequent clinical heart failure in patients treated with anthracyclines.

References


