Anthracycline cardiotoxicity in childhood cancer. Frequency, risk factors, and early detection
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Troponin T in the first 24 hours after administration of chemotherapy and the detection of myocardial damage in children

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Introduction

Early identification of patients at risk for cardiac damage after cardiotoxic therapy is important, especially in children. Children have a long life expectancy after surviving childhood cancer and they seem to be more susceptible to the cardiotoxic effects of anthracycline therapy than adults.\(^1\) In a recent study we showed that 1 out of 20 children treated with anthracyclines develops anthracycline induced clinical heart failure within 15 years after the start of treatment.\(^2\) The possibility of early detection of cardiac damage during chemotherapy might have important clinical implications because subsequent preventive measures can limit further myocardial damage. Yet, no parameter during chemotherapy exists to predict which patients will develop cardiac dysfunction or heart failure. Cardiac troponin T (cTnT), a part of the tropomyosin complex associated with the thin-filament of the myocardium, has been shown to be a very sensitive and specific marker for myocardial injury of various aetiologies.\(^3\) Recently, cTnT has been suggested to also be an early marker of anthracycline-induced myocardial damage.\(^5\)\(^9\) In animal studies, levels of cTnT increased after administration of anthracyclines, and the degree of increase was associated with the cumulative dose and histologic cardiomyopathy scores.\(^5\) Lipshultz et al. found elevated cTnT levels (>0.03 ng/mL) in a group of 15 children treated with anthracyclines and a positive correlation between cTnT levels and subsequent echocardiographic abnormalities.\(^6\) In another study, a minor increase was found in cardiac troponin T levels (>0.01 ng/mL) in 29% of the children treated with doxorubicin.\(^9\) One of the questions arising from these observations was whether testing for cTnT can detect myocardial damage within 24 hours after administration of chemotherapy. Early changes within 24 hours were seen in the myocardial nuclei in myocardial biopsy of patients treated with anthracyclines and in rats, biochemical changes caused by oxygen free radical related mechanisms occurred around 2 hours after the administration of anthracyclines.\(^10\)\(^11\) cTnT is detected in human serum within 24 hours after myocardial injury in the setting of the acute coronary syndromes.\(^12\) We prospectively investigated whether cTnT levels can be detected in the first 24 hours after drug administration in children treated with cardiotoxic chemotherapy and whether cTnT elevations predict echocardiographic myocardial dysfunction.

Methods

Patients
Between December 1998 and May 2000, we prospectively included children treated for various kinds of malignancies with cardiotoxic chemotherapy. The hospital ethics committee approved the study protocol. All parents, and patients older than 12 years, provided written informed consent.
Cardiac Troponin T
Heparin-plasma samples were collected prior to, 4-6 hours after and 24 hours after administration of chemotherapy. The samples were centrifuged immediately and were stored at -20°C until further analyses. Troponin T was measured using the third-generation Elecsys Troponin T STAT immunoassay, (Roche Diagnostics Mannheim, Germany), standardised with human recombinant cTnT. An abnormal level was defined as a cTnT >0.010 ng/mL. The technician who performed the assay was blinded to both clinical and echocardiographic results.

Echocardiography
Two-dimensional transthoracic echocardiography was performed in all patients treated with cardiotoxic chemotherapy before, during and after the last cycle of chemotherapy. Echocardiography was performed by one experienced echocardiographic technician who was unaware of the cumulative dose of chemotherapy and of the cTnT levels. Left ventricular shortening fraction (SF) was measured with M-mode 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. The mean of three measurements for each patient was considered the SF value.

LV dysfunction
In this study we defined left ventricular dysfunction (LV dysfunction) as either a SF below 30% or a decline of more than 15% from the baseline SF. In a paediatric study Sandor et al. determined the reproducibility of serial measurements of the SF in children, and found maximum variability of the SF of 15% Anthracycline induced clinical heart failure was defined as heart failure not due to other factors than anthracyclines.

Data analysis
Mean differences in continuous variables were compared by the student t test. Sensitivity and specificity of a cTnT ng/mL for LV dysfunction were calculated. The predictive values of elevated and non-elevated cTnT levels for LV dysfunction were calculated.

Results
Patients
Thirty-eight patients, 16 with a solid tumour and 22 patients with leukaemia or lymphoma were included at different stages of their treatment. They were treated with cardiotoxic chemotherapy, i.e. doxorubicin (20 patients), daunorubicin (4 patients), epirubicin (9 patients), or mitoxantrone (5 patients). The characteristics of the patients are shown in Table 1.
Table 1 Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (year)</td>
<td>9.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Mean cumulative dose at sampling (mg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline</td>
<td>172</td>
<td>112.3</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>67.5</td>
<td>26.4</td>
</tr>
<tr>
<td>Mean SF (%)</td>
<td>40.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Start of treatment</td>
<td>36.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Mean cumulative dose end of treatment (mg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline</td>
<td>255</td>
<td>118.9</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>106</td>
<td>13.7</td>
</tr>
</tbody>
</table>

SF, shortening fraction

Cardiac Troponin T
A total of 163 blood samples were collected during 58 treatment cycles from 38 patients for cTnT measurements. Elevated levels of cTnT (0.018 - 0.040 ng/mL) were detected in 6 (4%) samples of 3 (8%) patients.

Echocardiography
In 6 patients (16%) no echocardiogram at the end of treatment was performed because they did not finish their treatment (2 patients) or left the country (2 patients) or because it was impossible to obtain a good echo window (2 patients). None of these 6 patients had abnormal cTnT levels, nor had they signs or symptoms of clinical heart failure. The SF at the end of treatment was significantly different from the SF at the start of treatment (mean difference: 4.1%, SE: 0.8). Seven patients developed LV dysfunction. One of these 7 patients had clinical heart failure.

Relation between cTnT and LV dysfunction
Table 2 shows the relation between cTnT levels and SF in patients with LV dysfunction or patients with elevated cTnT levels. One of the 7 patients with LV dysfunction had an elevated cTnT level (patient 1) and developed anthracycline-induced clinical heart failure 6 months later. Six patients with LV dysfunction showed no elevated levels of cTnT during treatment. In patient 2, 4 and 6 elevation was neither seen around a next cycle of chemotherapy four weeks later.
Two of 3 patients with elevated cTnT levels did not develop LV dysfunction (patients 8 and 9). Patient 8 died 2 months after the end of treatment because of tumour progression. Patient 9 did not develop signs of cardiotoxicity until a cumulative dose of 300 mg/m² seven months after blood sampling.
Table 2 Patients with Left Ventricular Dysfunction or elevated cTnT Levels

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Chemotherapy</th>
<th>Total Dose (mg/m²)</th>
<th>Dose (mg/m²)</th>
<th>cTnT (ng/mL) Before therapy</th>
<th>SF Before therapy</th>
<th>SF End therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Daunorubicin</td>
<td>300</td>
<td>150</td>
<td>0.025</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>Daunorubicin</td>
<td>300</td>
<td>250</td>
<td>0</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>Doxorubicin</td>
<td>125</td>
<td>100/125</td>
<td>0/0</td>
<td>0/0</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Mitoxantrone</td>
<td>120</td>
<td>84/96</td>
<td>0/0</td>
<td>0/0</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Mitoxantrone</td>
<td>96</td>
<td>60/72</td>
<td>0/0</td>
<td>0/0</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>Mitoxantrone</td>
<td>96</td>
<td>96</td>
<td>0</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>Mitoxantrone</td>
<td>120</td>
<td>72</td>
<td>0</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>Epirubicin</td>
<td>450</td>
<td>450</td>
<td>0.019</td>
<td>0.040</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>Doxorubicin</td>
<td>300</td>
<td>90</td>
<td>0.019</td>
<td>0.018</td>
<td>44</td>
</tr>
</tbody>
</table>

cTnT, cardiac troponin T; SF, shortening fraction

The sensitivity of the cTnT test for LV dysfunction was 14% (95% CI: 0%-40%) and the specificity was 94% (95% CI: 85%-100%). The predictive value of an elevated troponin T level for LV dysfunction was 33% (95% CI: 0%-87%). The predictive value of a non-elevated cTnT level (≤ 0.01 ng/mL) for a normal LV function was 83% (95% CI: 70%-95%).

Discussion

Although the results of cTnT levels to detect early myocardial damage after anthracycline therapy are encouraging, so far there are no published data available on the time lapse between the administration of cardiotoxic therapy and occurrence of detectable levels of troponin in children. The present study shows that cTnT, measured in the first 24 hours after administration of cardiotoxic chemotherapy, can not identify patients who are at increased risk for developing LV dysfunction. One possible explanation could be that sampling within 24 hours after the administration of chemotherapy is too early to detect myocardial damage. It is unclear if the mechanisms of cardiotoxicity result in myocyte necrosis which can be detected by cTnT elevations in the first 24 hours after administration of anthracyclines. In adults conflicting data exist about the relationship between the time lapse between the administration of chemotherapy and occurrence of detectable levels of troponin. Auner et al. reported a rise in the cTnT up to 2 weeks after the administration of chemotherapy. The low predictive value of cTnT in the present study seems to conflict with the results of Lipshultz et al. However, besides the possibility that sampling within 24 hours is too early, it is not likely that differences in study groups or differences in cut-off levels of cTnT.
could explain this discrepancy. On the contrary, the cumulative dose received by patients was higher in our study than in the study by Lipshultz et al., and the third-generation cTnT assay that we used is the most sensitive and specific assay currently available.\textsuperscript{8,9,13}

We used a low detection threshold of 0.010 ng/mL while Lipshultz et al. considered a level above 0.03 ng/mL as evidence of damage to the myocytes.\textsuperscript{8}

A limitation of the present study is that we may have investigated the diagnostic value of cTnT in too few patients treated with cardiotoxic chemotherapy. The few samples with elevated levels and the inability to demonstrate a predictive value could be based on coincidence in this study. However, 7 patients developed LV dysfunction but only one of these patients had an elevated cTnT level. Another limitation may lie in the definition of cardiac damage we used. All echocardiographic parameters may eventually turn out to be surrogate markers for the outcome of cardiac damage after chemotherapy with clinical signs and symptoms. In studies which investigate the relation between predictive markers and cardiac damage, clinical heart failure should be the only definitive endpoint. In our study one patient developed clinical heart failure and this patient showed an elevated cTnT level 6 months before heart failure became manifest. cTnT elevation was measured before the administration of daunorubicin. However, 24 hours after this administration no elevation was measured.

Our data show that sampling of cTnT, within 24 hours after the administration of chemotherapy, seems to be too early to identify patients who are at increased risk for developing LV dysfunction. In our opinion serial cTnT levels over a longer period of time after administration of chemotherapy have to be further studied before cTnT can be recommended as a diagnostic tool of cardiac injury after chemotherapy.

Acknowledgements

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References


