NT-pro-BNP and cTnT as markers for subclinical early-onset anthracycline-induced cardiotoxicity in children. A prospective study.

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Disclosures: none
NT-pro-BNP and cTnT as markers for subclinical early-onset anthracycline-induced cardiotoxicity in children. A prospective study.

Introduction

- Survival of children with childhood cancer: 75%
- Increasing number of survivors
- Growing interest in the late effects of treatment
- Cardiotoxicity is a well known side effect of anthracycline therapy
- Anthracycline-induced cardiotoxicity is an important cause of health problems
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Anthracyclines

- Effective, widely used cytotoxic drugs
- Limited by its cardiotoxic effect
- Anthracycline-induced cardiotoxicity can lead to severe heart failure

Doxorubicin

Daunorubicin
Is there a problem?

- **Early-onset cardiotoxicity:**
  - occurs during or within the first year of anthracycline treatment
  - 5% of all children
  - known risk factor for the development of late-onset cardiotoxicity

- **Late-onset cardiotoxicity:**
  - occurs after the first year of anthracycline treatment
  - 65% subclinical heart failure
  - 1-5% clinical heart failure

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Mortality

- Being a survivor of childhood cancer, the risk to die because of cardiac disease is 8 times higher than in the normal population

Biomarkers in Survivors of Childhood Cancer

- Cardiac TnT does not contribute to the early detection of late onset anthracyline-induced cardiotoxicity.

- Abnormal levels of NT-pro-BNP were detected in 13% of asymptomatic, long term survivors of childhood cancer, with a median follow up of 15 years.

- Abnormal NT-pro-BNP-levels were related to increased LVIDd in the group who received a cumulative dosage of anthracyclines of 300 mg/m² or more.

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Aim of the study

- To investigate the potential role of NT-pro-BNP and cTnT as a predictive tool for the early detection of *early-onset* anthracycline-induced cardiotoxicity.
Abnormal NT-pro-BNP Levels in Asymptomatic Long Term Survivors of Childhood Cancer Treated with Anthracyclines

Methods

- In a prospective study, we included 60 newly diagnosed patients with Acute Lymphoblastic Leukemia (ALL).

- All patients underwent a detailed echocardiographic study before, during and shortly after treatment with anthracyclines.

- Blood samples were taken to determine the levels of NT-pro-BNP and cTnT, before, during and after anthracyclines.
Methods

ALL-treatment:

- Treatment according to the DCOG ALL-10 protocol
- Risk based treatment, based on minimal residual disease
- Three groups: standard risk (SR), medium risk (MR) and high risk (HR)
Abnormal NT-pro-BNP Levels in Asymptomatic Long Term Survivors of Childhood Cancer Treated with Anthracyclines

Methods

Induction Treatment

- SR treatment
- MR treatment
- HR treatment

Stem Cell Transplantation

0 1 2 years

T=0 T=1 T=2

Cardiac evaluation
Methods

- Cumulative anthracycline dose at the different time points

<table>
<thead>
<tr>
<th>Time (T)</th>
<th>Patients</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>T=0</td>
<td>all patients:</td>
<td>0 mg/m²</td>
</tr>
<tr>
<td>T=1</td>
<td>all patients:</td>
<td>120 mg/m²</td>
</tr>
<tr>
<td>T=2</td>
<td>SR-patients:</td>
<td>120 mg/m²</td>
</tr>
<tr>
<td></td>
<td>MR-patients:</td>
<td>300 mg/m²</td>
</tr>
<tr>
<td></td>
<td>HR-patients (n=4), no SCT:</td>
<td>240 mg/m² + 18 mg/m² idarubicin + 52.5 mg/m² mitoxantrone</td>
</tr>
<tr>
<td></td>
<td>HR-patient (n=1), SCT:</td>
<td>120 mg/m²</td>
</tr>
<tr>
<td></td>
<td>HR-patient (n=1), SCT:</td>
<td>120 mg/m² + 18 mg/m² idarubicin + 26.25 mg/m² mitoxantrone</td>
</tr>
</tbody>
</table>
### Study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (N)</td>
<td>60</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>62%</td>
</tr>
<tr>
<td>Age at diagnosis, (yr), median (range)</td>
<td>6 (2.2-15.4)</td>
</tr>
<tr>
<td>Hb* level at diagnosis, (mmol/l), median (range)</td>
<td>5.5 (2.2-9.5)</td>
</tr>
<tr>
<td>TLC† at diagnosis, (*10^9/l), median (range)</td>
<td>10.4 (0.7-348)</td>
</tr>
<tr>
<td>Hyperhydration at T=0, (%)</td>
<td>95%</td>
</tr>
</tbody>
</table>

#### Risk stratification

- SR (N) 20
- MR (N) 30
- HR (N) 10

*Hemoglobin, †Total Leucocyte Count
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**Results (1)**

<table>
<thead>
<tr>
<th></th>
<th>T=0</th>
<th>T=1</th>
<th>T=2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (N)</td>
<td>60</td>
<td>60</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Number of biomarker samples (N)</td>
<td>46</td>
<td>45</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Abnormal cTnT (%) [N]</td>
<td>0 [0]</td>
<td>11 [5]</td>
<td>2.5 [1]</td>
<td>0.2*</td>
</tr>
<tr>
<td>cTnT (ng/ml), median (range)</td>
<td>0.01 (-)</td>
<td>0.01 (0.01-0.04)</td>
<td>0.01 (0.01-0.02)</td>
<td>0.08†</td>
</tr>
<tr>
<td>NT-pro-BNP (pmol/l), median (range)</td>
<td>13 (2-185)</td>
<td>10 (1-45)</td>
<td>11 (1-68)</td>
<td>0.5†</td>
</tr>
</tbody>
</table>

*McNemar test based on 37 paired available observations at T=1 and T=2,
† Wilcoxon signed ranks test on 37 paired available observations at T=1 and T=2
Results (2)

- Abnormal cTnT levels were documented in 11% of the patients at t=1 and normalized in all patients at t=2. In one patient cTnT became abnormal only at t=2.

- NT-pro-BNP levels increased in 58% of the patients throughout treatment.
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## Results (3)

<table>
<thead>
<tr>
<th></th>
<th>T=0</th>
<th>T=1</th>
<th>T=2</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (N)</td>
<td>60</td>
<td>60</td>
<td>49</td>
<td>overall</td>
</tr>
<tr>
<td>FS (%), mean (±SD)</td>
<td>40 ± 5</td>
<td>36 ± 3</td>
<td>35 ± 3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVIDd/BSA (cm/m²), mean (±SD)</td>
<td>4.0 ± 0.8</td>
<td>4.2 ± 0.9</td>
<td>4.0 ± 0.9</td>
<td>0.05</td>
</tr>
<tr>
<td>LVPWd/BSA (cm/m²), mean (±SD)</td>
<td>0.62 ± 0.18</td>
<td>0.59 ± 0.16</td>
<td>0.55 ± 0.16</td>
<td>0.006</td>
</tr>
<tr>
<td>IVSd/BSA (cm/m²), mean (±SD)</td>
<td>0.54 ± 0.15</td>
<td>0.54 ± 0.15</td>
<td>0.49 ± 0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>IVRT (msec)</td>
<td>72 ± 12</td>
<td>67 ± 9</td>
<td>71 ± 10</td>
<td>0.01</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.8 ± 0.6</td>
<td>1.8 ± 0.5</td>
<td>1.8 ± 0.6</td>
<td>0.83</td>
</tr>
<tr>
<td>E/E’ ratio</td>
<td>10.1 ± 4.8</td>
<td>12.4 ± 3.9</td>
<td>11.6 ± 5.7</td>
<td>0.11</td>
</tr>
<tr>
<td>LVM/BSA (g/m²), mean (range)</td>
<td>53.6 ± 14.5</td>
<td>56.9 ± 9.5</td>
<td>52.8 ± 15.0</td>
<td>0.07 (T=1 to T=2)</td>
</tr>
</tbody>
</table>
Results (4)

- FS en LVPWd/BSA decreased significantly during treatment

- No significant relation was found between biomarkers and echocardiographic parameters.
Conclusions (1)

- cTnT and NT-pro-BNP were frequently abnormal in children during treatment with anthracyclines.

- While cTnT levels normalized after one year of treatment, NT-pro-BNP levels increased during treatment in most of the patients.

- FS and LVPWd/BSA decreased significantly during moderate dose cumulative anthracyclines.

- Both biomarkers are important in the detection of subclinical *early-onset* anthracycline-induced cardiotoxicity.
Conclusions (2)

- Long term follow-up of those patients who had abnormal cTnT and NT-pro-BNP levels during or shortly after treatment will also learn us whether these biomarkers can be used as a predictor of *late-onset* anthracycline-induced cardiotoxicity.
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