ASSESSMENT OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY WITH ELECTROCARDIOGRAPHY

J.M. Horacek¹, 4, *, M. Jakl², 4, J. Horackova⁴, R. Pudil², L. Jebavy³, 4, J. Maly¹

¹Department of Medicine II — Clinical Hematology
²Department of Medicine I — Cardiology
³Department of Gerontology and Metabolic Care, Faculty of Medicine, University Hospital and Charles University, Hradec Kralove 500 05, Czech Republic
⁴Department of Internal Medicine, Faculty of Military Health Sciences, University of Defence, Hradec Kralove 500 01, Czech Republic

Aim: Monitoring of anthracycline-induced cardiotoxicity with electrocardiography (ECG) and comparing ECG changes with findings on echocardiography (ECHO). Methods: A total of 26 adult acute leukemia patients (mean age 46.2 ± 12.4 years, 15 males) treated with 2–6 cycles of anthracycline-based chemotherapy (CT) were studied. Cardiac evaluation was performed at the baseline (before CT), after first CT, after last CT (cumulative anthracycline dose 464.3 ± 117.5 mg/m²) and circa 6 months after CT. Time ECG parameters, QRS voltage, presence of repolarization changes, arrhythmias and other abnormalities were evaluated. Results: During treatment and follow-up, we found a statistical significant QTc interval prolongation — 414.7 ± 16.0 ms (before CT), 419.6 ± 21.6 ms (after first CT), 428.0 ± 16.2 ms (after last CT) and 430.1 ± 18.4 ms (6 months after CT). Significant QTc interval prolongation (> 450 ms) occurred in 3 patients after first CT, in 4 patients after last CT and in 5 patients within 6 months after CT. Significant total QRS voltage lowering in the limb leads (> 1.0 mV versus before CT) occurred in 3 patients after first CT, in 5 patients after last CT and in 6 patients within 6 months after CT. We found a statistically significant correlation between decreased QRS voltage, QTc interval prolongation and left ventricular (LV) dysfunction on ECHO. Repolarization changes associated with oncology treatment were present in 9 patients within 6 months after CT. Conclusion: Anthracycline treatment is associated with changes in electrical activity of the myocardium. Prolonged QTc interval represents a risk for development of malignant ventricular arrhythmias. Decreased QRS voltage and prolonged QTc interval after anthracycline treatment could correlate with LV dysfunction on ECHO. Further studies will be needed to prove whether these ECG changes could serve as an accessible and non-invasive screening method indicating LV dysfunction after anthracycline treatment.

Key Words: cardiotoxicity, anthracyclines, electrocardiography, QTc interval, QRS voltage.
715, median 429). Myeloablative preparative regimen followed by hematopoietic cell transplantation was subsequently administered in 16 patients. The study was approved by the local ethical committee and all patients gave a written consent before they were included in the study.

In all patients, resting 12-lead ECG records with a paper speed of 50 mm/s were performed at the baseline (before CT), after the first CT with anthracyclines (after first CT, mean cumulative anthracycline dose 136.3 ± 28.3 mg/m²), after the last CT with anthracyclines (after last CT, mean 464.3 ± 117.5 mg/m²) and circa 6 months after completion of the treatment (6 months after CT). Evaluated ECG parameters were as follows: time parameters (heart rate, RR interval, PQ interval, QRS duration, QT interval), voltage parameters (total QRS voltage in the limb leads) and presence of repolarization changes, arrhythmias or other abnormalities. The ECG measurements were performed manually by 2 independent physicians who were blinded to clinical data. A total of 104 ECG records were evaluated.

To obtain heart-rate corrected values for QT interval (QTc interval), we used the Bazett’s formula: QTc = QT / √RR [12]. The upper limits of normal for QTc interval duration using the Bazett’s formula were suggested 420 ms for males and 430 ms for females. According to the latest guidelines of the National Cancer Institute (NCI) — Common Terminology Criteria for Adverse Events v3.0 (CTCAE), QTc interval prolongation above 450 ms in connection with oncology treatment is regarded as cardiac adverse event [13]. In our study, the QTc interval above 450 ms was considered significantly prolonged and representing a risk factor for development of ventricular arrhythmias. Decreases in the total QRS voltage in the limb leads (measured in leads I, II, III, aVR, aVL, aVF) by > 1.0 mV versus baseline values were considered significant.

ECG abnormalities in connection with anthracycline treatment are shown in Table. During treatment and follow-up, we found a statistically significant QTc interval prolongation — 414.7 ± 16.0 ms (before CT), 419.6 ± 21.6 ms (after first CT), 428.0 ± 16.2 ms (after last CT) and 430.1 ± 18.4 ms (6 months after CT). After last CT and 6 months after CT, QTc interval prolonged significantly in comparison with the baseline value (p < 0.01). After first CT, no patient had QTc interval prolongation above 450 ms. After first CT, QTc interval prolonged above 450 ms in 3 (11.5%) patients, after last CT in 4 (15.4%) patients, and 6 months after CT in 5 (19.2%) patients.

Table. Occurrence of ECG abnormalities in connection with anthracycline chemotherapy for acute leukemia (n = 26)

<table>
<thead>
<tr>
<th>ECG abnormalities</th>
<th>Before CT</th>
<th>After first CT</th>
<th>After last CT</th>
<th>6 months after CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>First degree AV block</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>IRBBB</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>LAM</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Repolarization abnormalities</td>
<td>5</td>
<td>8</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>0 (6)</td>
<td>3 (8)</td>
<td>4 (16)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>QRS voltage lowering</td>
<td>–</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Notes: tachycardia — heart rate above 100/min; bradycardia — heart rate below 60/min; first degree AV block — PQ interval above 200 ms; IRBBB (incomplete right bundle branch block) — RSR' pattern in V1 (V2), QT duration below 120 ms; LAD (left anterior hemiblock) — left axis deviation, heart axis below –30°; nonspecific repolarization abnormalities — changes in ST segment and T wave in 2 and more leads; QTc prolongation — QTc interval above 450 ms regardless gender (above 420 ms in males, above 430 ms in females); QRS voltage lowering — decrease in the total QRS voltage in the limb leads > 1.0 mV vs baseline values.

The total QRS voltage in the limb leads changed from baseline 4.58 ± 1.31 mV (before CT) to 4.57 ± 1.55 mV (after first CT), 4.42 ± 1.15mV (after last CT) and 4.22 ± 1.06 mV (6 months after CT). In comparison with the baseline values, QRS voltage decreased significantly in 3 (11.5%) patients after first CT, in 5 (19.2%) patients after last CT and in 6 (23.1%) patients within 6 months after CT.

Re polarization abnormalities associated with oncology treatment (de novo changes or distinct progression of the baseline changes) were found in 9 (34.6%) patients within 6 months after CT.

On ECHO examination, we found systolic LV dysfunction in 1 (3.8%) patients after first CT, in 3 (11.5%) patients after last CT and in 5 (19.2%) patients within 6 months after CT. Diastolic LV dysfunction on ECHO was detected in 5 (19.2%) patients after first CT, in 6 (23.1%) patients after last CT and in 12 (46.2%) patients within 6 months after CT.

We found significant correlations between QRS voltage lowering and LV dysfunction on ECHO (r = 0.660, p < 0.001 for systolic LV dysfunction; r = 0.592, p < 0.01 for diastolic LV dysfunction). Correlations between prolonged QTc interval and LV dysfunction on ECHO also reached statistical significance (r = 0.246, p < 0.01 for systolic LV dysfunction; r = 0.257, p < 0.01 for diastolic LV dysfunction).

Our results show that anthracycline-based treatment for acute leukemia causes changes in electrical activity of the myocardium, both during the treatment (acute cardiotoxicity) and during the follow-up (chronic cardiotoxicity). QTc interval prolongation above 450 ms, in our cohort in 5 (19.2%) patients within 6 months after CT, represents a risk factor for development of malignant ventricular arrhythmias (torsade de points) and sudden cardiac death. In these patients, regular monitoring of QTc interval is necessary, complemented with searching for electrolyte disorders (especially hypokalemia and hypomagnesemia, e. g. in case of vomiting or diarrhea) with potential
correction, and rational prescription of QTc interval prolonging drugs (many antiarrhythmics, tricyclic antidepressants, antipsychotics, some antibiotics and antifungal drugs etc.) [14, 15]. In our cohort, malignant ventricular arrhythmias did not occur during the follow-up in any of the patients with significantly prolonged QTc interval.

In our study, decreased total QRS voltage in the limb leads and prolonged QTc interval on ECG correlated with systolic and diastolic LV dysfunction on ECHO. Further studies on a larger number of patients will be needed to prove whether these ECG changes could serve as an accessible and non-invasive screening method indicating LV dysfunction after anthracycline treatment.

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