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SHORT COMMUNICATIONS

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ASSESSMENT OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY WITH ELECTROCARDIOGRAPHY

*J.M. Horacek[1, 4] *, M. Jakl[2, 4], J. Horackova[3], R. Pudil[2], L. Jebavy[1, 4], J. Maly[1]*

[1]*Department of Medicine II — Clinical Hematology*

[2]*Department of Medicine I — Cardiology*

[3]*Department of Gerontology and Metabolic Care, Faculty of Medicine, University Hospital and Charles University, Hradec Kralove 500 05, Czech Republic*

[4]*Department 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/m^2) 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.**

Cardiotoxicity is a relatively frequent and potentially serious complication of oncology treatment. Anthracyclines with their acute, chronic and late cardiotoxicity represent the greatest risk [1]. Various methods have been recommended for monitoring of cardiotoxicity in oncology [2, 3]. In our conditions, echocardiography (ECHO) and electrocardiography (ECG) are routinely used [4, 5].

ECG is among recommended diagnostic methods for detection of cardiotoxicity in oncology. It is a widely available and low-cost examination. ECG changes were registered in 11–29% patients during and shortly after anthracycline administration, but the incidence strongly depends on the frequency of monitoring. In some studies, acute ECG changes and arrhythmias were registered in up to 41% patients treated by anthracyclines [2]. The ECG changes associated with anthracyclines include non-specific changes in ST segment and T wave, sinus tachycardia, supraventricular and ventricular premature beats. These changes are usually transient and no relation to development of chronic cardiotoxicity was proven. Continuous 24-hour monitoring of ECG (Holter) may reveal arrhythmias both in early and late periods of anthracycline treatment [6]. Furthermore, QRS voltage lowering in the limb leads was reported during progression of anthracycline-induced cardiomyopathy with heart failure [7]. After anthracycline-based treatment, QTc interval prolongation and increased QTc dispersion were reported [8–10] which generally represent a risk for malignant ventricular arrhythmias and sudden cardiac death. Some prior studies suggested that QTc interval prolongation after anthracycline administration could be an early marker of left ventricular (LV) dysfunction [9]. In other studies, however, QTc prolongation was only transient and no correlation with LV dysfunction on ECHO examination was found [11].

The aim of the presented study was to monitor ECG changes during and after anthracycline treatment and to compare these changes with findings on ECHO examination.

A total of 26 patients with newly diagnosed acute leukemia were included in the study. The cohort consisted of 15 males and 11 females with the mean age of 46.2 ± 12.4 years (range: 22–61, median 49). The patients were treated with 2–6 cycles of chemotherapy (CT) containing anthracycline agents (idarubicin, daunorubicin or mitoxantrone) in combination with cytarabine. The mean total cumulative dose of anthracyclines reached 464.3 ± 117.5 mg/m^2 (range 240–

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*Correspondence: E-mail: jan.hor@post.cz

Abbreviations used: CT – chemotherapy; CTCAE – Common Terminology Criteria for Adverse Events v3.0; ECG – electrocardiography; ECHO – echocardiography; iRBBB – incomplete right bundle branch block; LAH – left anterior hemiblock; LV – left ventricular; NCI – National Cancer Institute; QTc interval – heart-rate corrected QT interval.

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/m^2), after the last CT with anthracyclines (after last CT, mean 464.3 ± 117.5 mg/m^2) 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: $QTc = QT / \sqrt{RR}$ [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.

ECHO examinations were performed on Hewlett Packard Image Point ultrasound at the same time as ECG records. Parameters of systolic and diastolic left ventricular (LV) function were assessed. Systolic LV dysfunction was defined as ejection fraction (LVEF) ⩽ 55%. Diastolic LV dysfunction was defined as E/A inversion and E-wave deceleration time above 220 ms on the transmitral Doppler curve (impaired relaxation).

Statistical analysis was performed with the "Statistica for Windows, Version 5.0" program. Analysis of variance and McNemar tests were used. Correlations were evaluated with normal and Spearman correlation tests. The values are expressed as mean ± SD, $p < 0.01$ was considered statistically significant.

ECG abnormalities in connection with anthracycline treatment are shown in Table. 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). 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)

ECG abnormalities	Before CT	After first CT	After last CT	6 months after CT
Tachycardia	4	3	0	3
Bradycardia	1	3	1	1
First degree AV block	0	1	5	2
iRBBB	1	2	3	3
LAH	0	1	2	3
Repolarization abnormalities	5	8	11	12
QTc prolongation	0 (6)	3 (8)	4 (16)	5 (15)
QRS voltage lowering	–	3	5	6

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), QRS duration below 120 ms; LAH (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.

Repolarization 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 pointes) 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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