Evaluation of early-onset cardiotoxic effects of anthracyclines used during the treatment of childhood acute lymphoblastic leukemia by speckle-tracking echocardiography

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ABSTRACT

Objective: Anthracyclines are widely used in the treatment of acute lymphoblastic leukemia (ALL). However, cardiotoxicity is the most critical side effect that requires dose limitation. It is thought to occur at first exposure, but the clinical presentation may occur years later. In this study, we aimed to determine the time of initial damage and cardiotoxicity that develops in children with ALL.

Methods: In this prospective study, 13 patients with newly diagnosed intermediate-risk precursor B cell ALL treated with the ALL-IC BFM 2009 protocol were included. Conventional echocardiography, tissue Doppler imaging (TDI), and speckle-tracking echocardiography (STE) were performed in all the patients before chemotherapy, after completing the induction phase, and at the end of the reinduction phase.

Results: The mean age of the patients was 7.8±4.6 (3.1–16.3) years. Myocardial velocity during systole (S_m) determined by TDI at the interventricular septum significantly decreased during the induction phase. Despite a decrease in STE parameters, a statistically significant reduction was determined in the global longitudinal strain rate at both left and right ventricles at the end of the induction. Nevertheless, a statistically significant increase was observed among the conventional echocardiographic findings in the left ventricular end-diastolic diameter at the end of the reinduction.

Conclusion: During the treatment of ALL, subclinical anthracycline-associated cardiotoxicity develops in the early stages of treatment. The findings detected by TDI and STE could be missed by conventional echocardiography. We recommend evaluating patients with these newly developed techniques to detect subclinical cardiotoxicity at an early stage and starting appropriate therapy on time.

Keywords: anthracycline, cardiotoxicity, speckle-tracking echocardiography, tissue Doppler imaging, acute lymphoblastic leukemia, children

Introduction

Anthracyclines are widely used antineoplastic agents in the treatment of acute lymphoblastic leukemia (ALL). However, cardiotoxicity is the most critical side effect of anthracyclines, requiring dose limitation (1-3). It can be acute, early-onset chronic progressive, or late-onset chronic progressive according to the time elapsed since chemotherapy (2). Abnormalities of the left ventricular structure and function are common in survivors of childhood leukemia years after therapy (1-4).

The evaluation of cardiac function by conventional echocardiography may help in detecting myocardial injury; however, this approach has inherent limitations in accuracy in subclinical

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cases and is not effective in the early detection of patients at risk. Tissue Doppler imaging (TDI) and speckle-tracking echocardiography (STE) are relatively new techniques that have been used to detect cardiac diseases in the early stage by overcoming some of the limiting factors associated with conventional echocardiography (5-7). STE has shown that the assessment of myocardial deformation, which determines strain (S) and strain rate (SR), has potential value for quantifying global and regional myocardial function through systole and diastole. It is believed that regional dysfunction can be detected earlier than global dysfunction (6, 8). This may be a way of diagnosing and treating early-onset cardiotoxicity in asymptomatic patients. In a previous study conducted at our center, 60 children with ALL were evaluated for anthracycline cardiotoxicity for at least 2 years after completing treatment. Subclinical cardiac dysfunction with a decrease in myocardial contraction and relaxation times with restrictive myocardial findings were detected (4). However, we did not identify at which stage of the treatment the cardiac functions began to deteriorate. In this study, we aimed to investigate the early detection of anthracycline toxicity in newly diagnosed patients with ALL.

Methods

Patient population

The study included newly diagnosed patients at intermediate risk with precursor B cell ALL between December 2015 and December 2016 at the Ankara Children's Hospital, Pediatric Hematology-Oncology Clinic. All the patients were treated with the Acute Lymphoblastic Leukemia Intercontinental Berlin Frankfurt Münster Study Group (ALL-IC BFM) 2009 treatment protocol. Patients were excluded if they had a previous cardiovascular disease, relapse therapy, and prior or additional mediastinal radiotherapy. The daunorubicin dosage was 30 mg/m²/day per course in the induction phase, and the doxorubicin dose was 30 mg/m²/day per course in the reinduction phase. Anthracycline treatment was repeated every 7 days; and in each phase, 4 doses were given for a total of 8 doses. Drugs other than anthracyclines included vincristine, asparaginase, steroids, and intrathecal methotrexate. Anthracyclines were administered through a central venous catheter in 1 hour of infusion.

The Local Ethics Committee approved the study, and all the parents provided informed consents.

Cardiac evaluation

Conventional echocardiography, TDI, and STE were performed in all the patients at diagnosis, at the end of induction and reinduction therapy by an experienced pediatric cardiologist. Conventional transthoracic echocardiographic examination (M-mode, two-dimensional, pulse wave Doppler, and continuous-wave Doppler), TDI, and STE were performed using the "iE33" ultrasound system (Philips Medical Systems, The Netherlands) using 3 and 5 MHz transducers.

Conventional echocardiography

Conventional echocardiography was performed according to the American College of Cardiology (ACC), the American Heart Association (AHA), and the American Society of Echocardiography (ASE) criteria (9-11). Left ventricular end-diastolic diameter (LVDd) and end-systolic diameter (LVDs) were measured using conventional echocardiography. The ejection fraction (EF) and fractional shortening (FS) were calculated using the previously defined formulas, based on M-mode echocardiographic measurements obtained via the parasternal long-axis view.

$$EF = [(LVDd3-LVDs3)/LVDd3] \times 100$$
$$FS = [(LVDd-LVDs)/LVDd] \times 100$$

Tissue Doppler imaging

The measurements were taken at the basal segments of the left ventricle (LV), interventricular septum (IVS), and right ventricle (RV) according to previously defined criteria (12, 13). The gates were reduced to 2–3 mm to get defined segments, filters were set to exclude high-frequency signals, the gain was minimized to obtain clear signals, and images were recorded at 100 mm/s. TDI measured myocardial velocity during systole (S_m), early (E_m) and late diastole (A_m), isovolumic contraction time (ICT), isovolumic relaxation time (IRT), and ejection time (ET).

Speckle-tracking echocardiography

Myocardial deformation parameters (S and SR) were measured using commercially available software (QLAB Advanced Quantification Software, version 6.0, TMQ, Philips Medical Systems, The Netherlands) on standard 2-dimensional grayscale LV images. The images were recorded at the apical 4-chamber view (AP4) for longitudinal strain and the parasternal short-axis view at the papillary muscle level (PML) for circumferential strain as previously described (8, 14). Two consecutive beats synchronized to continuous electrocardiography (ECG) were recorded with a frame rate set to >60 frames/s. The endocardial borders were identified manually to include the entire

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Table 1. Conventional echocardiography findings in the study population

Variables	Baseline (min-max)	Induction (min-max)	Reinduction (min-max)	*P*-value[a]	*P*-value[b]	*P*-value[c]	Adj. ind. values (%)	Adj. reind. values (%)
EF %	68.4±3.4 (62.4–73.9)	70.2±3.9 (65.1–75.3)	67.8±2.7 (62.4–71.1)	0.097▲	0.637▲	0.089▲	70.3	67.91
FS %	37.4±2.7 (32.5–41.8)	38.6±3.2 (34.2–42.7)	36.9±2.3 (32.7-40.0)	0.156▲	0.718▲	0.154▲	38.64	36.86
LVDd mm	**34.8±5.8** (27.6–47.6)	33.5±4.7 (27.5–44.5)	**35.1±4.6** (26.8–42.2)	0.085▲	**0.061**▲	0.006▲		

Values are expressed as mean ± standard deviation
[a]Baseline versus induction
[b]Baseline versus reinduction
[c]Induction versus reinduction
▲Paired samples t-test
P values showing statistical significance are presented as bold.
EF - ejection fraction, FS - fractional shortening, LVDd - left ventricular end-diastolic diameter, Adj. ind. values - adjustment induction values, Adj. reind. values - adjustment reinduction values

myocardium in all view areas. The following STE parameters were measured for LV and RV:

LVGLS: Left ventricular global longitudinal strain at AP4
LVGLSR: Left ventricular global longitudinal strain rate at AP4
LVGCS: Left ventricular global circumferential strain at PML
LVGCSR: Left ventricular global circumferential strain rate at PML
RVGLS: Right ventricular global longitudinal strain at AP4
RVGLSR: Right ventricular global longitudinal strain rate at AP4.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences for Windows (version 18.0) software (SPSS Inc., Chicago, IL, USA). The normal distribution of numerical variables was examined by the Kolmogorov-Smirnov test, and the Levene test examined homogeneity of variances. Continuous variables were presented as mean (± standard deviation) and categorical variables as frequencies and percentages. The relation between echocardiographic parameters and chemotherapy phases was further analyzed by dividing the study population into 2 groups using the Friedman test. Group 1 consisted of patients completing the induction phase, and group 2 consisted of patients completing the reinduction phase. Differences between the groups were investigated using the paired samples t-test when parametric test assumptions were provided and the Wilcoxon test when parametric test assumptions were not achieved. A p value of less than 0.05 was considered indicative of statistical significance.

Results

Clinical characteristics of the study population

A total of 23 patients were enrolled in the study. However, ten patients were excluded because they could not be examined on time during the chemotherapy phase.

The final study population consisted of 13 children with intermediate-risk ALL, who were treated with doxorubicin and daunorubicin as part of their chemotherapeutic regimen. Of the 13 patients, 9 were boys, and 4 were girls. The mean age was 7.8±4.6 (3.1–16.3) years. The cumulative doxorubicin dosage was 240 mg/m² according to the ALL-IC BFM 2009 intermediate-risk protocol. No cardiac failure developed in any patient during follow-up.

Conventional echocardiography

Among the conventional echocardiographic findings, a statistically significant increase was observed in LVDd at the end of the reinduction phase. There was no significant difference between the patient groups in terms of EF and FS. Conventional echocardiography findings are summarized in Table 1.

Tissue Doppler imaging

It was observed that S_m at IVS significantly decreased at the end of the induction phase. However, the decrease in S_m did not continue during the reinduction phase. This finding indicates a reduction in myocardial systolic activity and posits that it mainly occurs during the early courses of the induction phase. The conclusions obtained by TDI are summarized in Table 2.

Speckle-tracking echocardiography

Despite a decrease in all STE parameters, a statistically significant reduction was determined in LVGLSR and RVGLSR at the end of the induction phase. This finding is valuable, indicating that impairment in myocardial deformation owing to anthracyclines occurs, especially during the early induction phase. The findings obtained by STE are summarized in Table 3.

Discussion

The prevalence of anthracycline cardiotoxicity is increased because of improved new diagnostic methods and close follow-up periods (15-24). To detect cardiac damage, the diagnostic approach adopted was based mainly on the estimation of left ventricular ejection fraction (LVEF) or left ventricular fractional shortening (LVFS). Left ventricular systolic function (EF or FS) during and after anthracycline therapy is usually evaluated using M-mode and 2-dimensional echocardiography, that is, conventional echocardiography. EF and FS are calculated on the basis of volume calculations and dimensional changes. The sensitivity of this approach is low for the early prediction of car-

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Table 2. Tissue Doppler imaging findings in the study population

Variables	Baseline	Induction	Reinduction	P-value[a]	P-value[b]	P-value[c]	Adj. ind. values (%)	Adj. reind. values (%)
Left ventricle								
S_m (cm/s)	7±3.1	6.5±1.8	6.8±1.1	0.506[¶]	0.272[¶]	0.126[¶]	6.85	6.3
E_m (cm/s)	14.1±3.3	13.5±2.1	13.6±2	0.404[▲]	0.691[▲]	0.811[▲]	13.71	13.77
A_m (cm/s)	5.3±0.9	5.6±1.2	6.2±0.9	0.412[▲]	0.015[▲]	0.217[▲]	5.69	6.15
ET (ms)	219.2±26.8	209.5±34.4	225.3±28.8	0.156[▲]	0.798[▲]	0.389[▲]	212.4	230.03
Interventricular septum								
S_m (cm/s)	6.6±1.1	5.7±0.9	6.1±0.90	**0.014[▲]**	0.449[▲]	0.182[▲]	5.69	5.83
E_m (cm/s)	10.8±2.6	10.2±2.3	10.6±2.2	0.507[¶]	0.937[¶]	0.556[¶]	10.27	10.92
A_m (cm/s)	5.4±1.1	4.9±1	5.3±0.7	0.197[▲]	0.897[▲]	0.265[▲]	5.06	5.34
ET (ms)	224.5±17.8	214.7±19.9	225.4±17.3	0.074[▲]	0.978[▲]	0.023[▲]	215.45	226.6
Right ventricle								
S_m (cm/s)	9.8±1.3	9.7±2.1	9.3±1.7	0.770[▲]	0.528[▲]	0.868[▲]	9.8	9.2
E_m (cm/s)	14.5±2.7	14.2±3.3	14±3.1	0.774[▲]	0.656[▲]	0.959[▲]	14.37	14.11
A_m (cm/s)	7.7 ±1.6	7.5±1.8	7.9±1.7	0.600[¶]	0.563[¶]	0.286[¶]	7.68	7.8
ET (ms)	211±23.1	213.8±19.4	219.7±18.9	0.483[¶]	0.168[¶]	0.326[¶]	215.16	222.89

Values are expressed as mean ± standard deviation
[a]Baseline versus induction
[b]Baseline versus reinduction
[c]Induction versus reinduction
[▲]Paired samples t-test
[¶]Wilcoxon test
P values showing statistical significance are presented as bold.
LV - left ventricle, IVS - interventricular septum, RV - right ventricle, S_m - myocardial velocity during systole, E_m - myocardial velocity during early diastole, A_m - myocardial velocity during late diastole, ET - ejection time, Adj. ind. values - adjustment induction values, Adj. reind. values - adjustment reinduction values

Table 3. Speckle-tracking echocardiography findings in the study population

Variables	Baseline	Induction	Reinduction	P-value[a]	P-value[b]	P-value[c]	Adj. ind. values (%)	Adj. reind. values (%)
LVGLS, %	22.5±5.2	19 ±2.82	19.6±3.2	0.107[¶]	0.288[¶]	0.507[¶]	18.77	19.04
LVGLSR, s^{-1}	**0.86±0.52**	**0.42±0.2**	0.41±0.29	**0.023[¶]**	0.050[¶]	0.969[¶]	0.4	0.38
LVGCS, %	27.2±6.4	22.3±7.1	24.2±7.4	0.081[▲]	0.283[▲]	0.707[▲]	22.42	24.33
LVGCSR, s^{-1}	0.78±0.32	0.72±0.29	0.67±0.43	0.675[▲]	0.406[▲]	0.591[▲]	0.68	0.7
RVGLS, %	25.1±5.4	24.2±7.5	23.4±6.3	0.766[▲]	0.470[▲]	0.450[▲]	23.52	23.67
RVGLSR, s^{-1}	**0.56±0.23**	**0.36±0.14**	0.43±0.27	**0.040[¶]**	0.301[¶]	0.473[¶]	0.36	0.44

Values are expressed as mean ± standard deviation
[a]Baseline versus induction
[b]Baseline versus reinduction
[c]Induction versus reinduction
[▲]Paired Samples t-test
[¶]Wilcoxon test
P values showing statistical significance are presented as bold.
LVGLS - left ventricular global longitudinal strain, LVGLSR - left ventricular global longitudinal strain rate, LVGCS - left ventricular global circumferential strain, LVGCSR - left ventricular global circumferential strain rate, RVGLS - right ventricular global longitudinal strain, RVGLSR - right ventricular global longitudinal strain rate, Adj. ind. values - adjustment induction values, Adj. reind. values - adjustment reinduction values

diomyopathy. Accordingly, some studies in the literature reported no significant change in left ventricular systolic functions by conventional echocardiography (24-26). In this study, we did not detect a significant difference in LVEF or LVFS in our patients. The conventional echocardiography findings of our patients were assessed to be normal, except for LVDd. TDI can detect cardiac dysfunction earlier than conventional echocardiography. Considering that cardiac dysfunction can occur during cancer treatment, the importance of early detection of cardiac dysfunction has become invaluable (2, 4, 7, 16). A reduction in LV systolic function was found in surviving patients exposed to anthracyclines during long-term follow-up (17-20). Although

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Baysal et al. (7) did not detect any difference in diastolic function by conventional echocardiography, significantly higher values in ICT and IRT by TDI after anthracycline treatment have been noted. Kapusta et al. (20) reported a significant reduction of peak late diastolic myocardial velocities in the left side of the septum. With TDI measurements, significant global ventricular performance changes that may indicate left ventricular dysfunction in the acute and chronic periods after exposure to anthracycline were reported in other studies (8, 27, 28). Our study was conducted to evaluate early-onset cardiotoxicity, and no decrease in left ventricular systolic function was detected by conventional echocardiography in the early period. However, it was observed that S_m at IVS decreased significantly. Regarding other parameters, no impairment in systolic or diastolic myocardial functions at LV or RV was detected by TDI.

The evaluation of myocardial deformation by STE has the potential value for evaluating regional and global myocardial functions through systole and diastole. It appears that regional dysfunction can be detected earlier than global dysfunction (15). Çilsal et al. (24) showed a deterioration in the LV longitudinal strain index with STE in pediatric patients with cancer receiving anthracycline treatment. Akam-Venkata et al. (22) demonstrated that asymptomatic patients with anthracycline-treated childhood cancer with normal left ventricular fractional shortening had lower global longitudinal and circumferential strain, and left ventricular longitudinal strain was lower in the majority of the segments. Thus, they thought that anthracycline cardiotoxicity was more global than regional. In a study that included 53 pediatric patients who received a median cumulative 229 mg/m^2 anthracycline treatment, strain levels in all segments of the left ventricle, except for the basal anteroseptal segment, were lower than in the control group of healthy children (21). In another study, among 19 childhood cancer survivors exposed to anthracyclines with a mean cumulative dose of 296 mg/m^2, left ventricular peak global longitudinal strain decreased 4 months after anthracycline onset compared with baseline. A reduction in the left ventricle's peak global longitudinal strain values before the decline in left ventricular ejection fraction was detected 8 months after the chemotherapy initiation (29). In our study, we evaluated global myocardial functions by STE and found that all parameters were decreased during chemotherapy, and the decrease was statistically significant in LVGLSR and RVGLSR. In contrast to previous studies, global longitudinal changes caused by anthracycline cardiotoxicity start in the early period of anthracycline treatment, not only in the left ventricle but also in the right ventricle (15, 21, 22). Interestingly, in our study, a significant decrease in ventricular global longitudinal functions took place predominantly during the induction phase and continued after that.

Study limitations
The limitations of our study are that it included a small number of patients and the fact that all our patients were in the intermediate-risk group. A more accurate inference can be made with a higher number of patients and different risk groups.

Conclusion

Our study demonstrated that even if apparent cardiac dysfunction was not detected by conventional echocardiography in patients with ALL, myocardial dysfunction appeared in the early period and could be seen by TDI or especially by STE. It may justify the usage of cardioprotective drugs such as dexrazoxane or early treatment of anthracycline cardiotoxicity in asymptomatic patients.

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