Cardiotoxicity evaluation in pediatric patients with acute lymphoblastic leukemia – results of prospective study

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Abstract

Aim: The chemotherapy protocol for acute lymphoblastic leukemia (ALL) uses low doses of anthracyclines (AC), generally associated with subclinical cardiotoxicity. The aim of our study was to evaluate the serum biomarkers and echocardiography parameters in children with ALL treated with AC in order to determine the most useful element for early detection of cardiotoxicity. **Material and methods**: In this prospective study, troponin I (TnI) and heart-type fatty acid binding protein (HFABP) were assessed five times during the first year after the onset of ALL. Serial Tissue Doppler Imaging and conventional cardiac echography were performed by two pediatric cardiologists (intraclass correlation coefficient over 0.85 for all measurements) in three periods during the study protocol. **Results**: We evaluated 48 children with ALL. TnI increased during therapy, without returning to baseline values one year after diagnosis. HFABP did not show significant changes during the study protocol. Left ventricle outflow tract time-velocity integral and peak systolic septal mitral annulus velocity decreased during chemotherapy and returned to baseline levels at one year after diagnosis, while peak systolic tricuspid annulus velocity and excursion, maintained a descending tendency. Early filling transmitral flow velocity and E/A ratio were also transiently influenced by chemotherapy. **Conclusions**: The study showed signs of transient cardiotoxicity in the left ventricle and diastolic parameters after chemotherapy, compared to right ventricle parameters which maintained low values even one year after diagnosis. TnI proved to be directly proportional to chemotherapy doses but HFABP was not useful in this setting.

Keywords: acute lymphoblastic leukemia; cardiotoxicity; biomarkers; Tissue Doppler Imaging

Introduction

Acute leukemia represents 25-30% of all pediatric neoplasms and acute lymphoblastic leukemia (ALL) comprises 80% of cases [1]. At present, the overall survival rates of ALL patients are between 80-90% [2], being the most successful story of modern multi-agent chemotherapy [3].

The harmful effect of chemotherapy on the heart muscle is well known, the most impugned being the anthracyclines (AC) class [4], which triggers the prototype for type I chemotherapy-induced cardiotoxicity (CIC), characterized by dose-dependent irreversible myocardial cell death [5]. Three types of CIC were described: acute (one week after AC administration, in less than 1% of patients), early-onset (during the first year after diagnosis, in approximately 2% of patients) and late-onset (one year after diagnosis) [6].

The gold standard for CIC diagnosis is serial ultrasound [7], transthoracic echocardiography being the recommended method [8]. Due to frequent asymptomatic cardiotoxicity, more sensitive methods of diagnosis are required [9] and Tissue Doppler Imaging (TDI) provides a promising technique for evaluating cancer patients [10]. Cardiac biomarkers may represent an operator-independent alternative for CIC detection, but an optimal schedule of biomarker assessments remains unclear [11]. Alongside cardiac troponins and natriuretic peptides, novel biomarkers emerge, such as high-sensitivity C-reactive protein and fatty acid binding protein [12]. Clear recommendations remain to be established.

The aim of our study was to assess the early-onset CIC after low-dose doxorubicin-based treatment in children diagnosed with ALL, in a single pediatric hematology-oncology center, by monitoring the changes of troponin I (TnI) and heart-type binding protein (HFABP) levels and the parameters of conventional and TDI echocardiography over a period of one year after diagnosis.

Material and methods

Patients

A prospective non-randomized observational study was conducted between February 2015 and November 2017 in the Department of Pediatric Hematology and Oncology. All legal guardians signed an informed consent form. The study and the informed consent form were preapproved by the local Ethics Committee. Patients 1 to 18 years of age, newly diagnosed with ALL and treated according to BFM ALL IC 2009 protocol [13], plus minimal residual disease monitoring on days 15, 33 and 78, were enrolled. Based on risk stratification imposed by BFM ALL IC 2009 protocol [13] the patients received 8-10 doses of 30 mg/m^2 AC, adapted to the neutrophil count. The first dose of AC was given on day 8 and the last one at 9 months after diagnosis. The discontinuation criteria from the study were death of any cause, recurrence of the disease, emigration (at any moment during the monitoring period).

Cardiac biomarkers

Second generation TnI was assayed on Tosoh Bioscience, AIA-1800 (Immunoassay), normal range 0-0.05 pg/dl, sensitivity 0.01 pg/dl. HFABP was analyzed on calibrated ELISA plate reader using the human HFABP kit (Hycult biotech), normal range 0-1.6 ng/ml, sensitivity 0.102 ng/ml. Five blood samples were obtained: at diagnosis (TnI1, HFABP1), one hour after the first AC dose (TnI2, HFABP2), before the last AC dose (TnI3, HFABP3), one hour after the last AC dose (TnI4, HFABP4) and one year after diagnosis (TnI5, HFABP5).

Echocardiographic evaluation

Echocardiographic evaluation, including TDI, was performed at 3 different times: at diagnosis, after all AC doses and one year after diagnosis. The scans were performed and analyzed online on a Vivid E95 (GE Vingmed Imaging, Horten, Norway) by two pediatric cardiologists with more than 10 years of experience in pediatric echocardiography, blinded to patients' status. In order to determine intra/inter variability, 10 echocardiographic examinations were selected and reevaluated. An intraclass correlation factor over 0.85 for all measurements was obtained. The following measurements were performed: left ventricle ejection fraction (LVEF) with the M mode Teichholz method, LV outflow tract time-velocity integral (TVI), tricuspid annular plane systolic excursion (TAPSE), peak systolic septal mitral annulus velocity (SS), peak systolic lateral mitral annulus velocity (SL) and right ventricle (RV)-peak systolic tricuspid annulus velocity (RVS), early filling transmitral flow velocity (E), late filling transmitral flow velocity (A), E-wave deceleration time (EDT), isovolumic relaxation time (IVRT), E/A. All acquisitions and measurements were performed in concordance with current recommendations [14].

Statistical analysis

The statistical analysis was performed using IMB Statistical Package for Social Sciences, SPSS 25. For bivariate analysis Mann-Whitney U and Kruskall Wallis tests were used and the results were reported as median and interquartile range (IQR). A p value of <0.05 was considered statistically significant, unless otherwise stated. For the evaluation of biomarkers and ultrasound parameters Friedman's test was used, with post-hoc analysis by Wilcoxon Signed Rank, applying Bonferroni correction. The representation was done using parallel graphics.

Results

During the enrolment period, 70 children were diagnosed with ALL. After applying the discontinuation criteria, 48 patients finalized the study protocol. The demographic and hematologic data of these patients are detailed in Table I.

The serum levels of the two cardiac biomarkers are presented in Table II. After applying Boferroni correction, p<0.005 was considered significant for serum biomarkers analysis. No significant changes in HFABP values were found during the study protocol (p=0.37). As shown in figure 1, TnI increased after therapy compared to baseline (p<0.001). TnI5 levels decreased compared to TnI4 (no statistical significance, p=0.118), but remained higher than baseline values. There were no correlations

Table I. Demographic and hematologic data of patients

		Number of patients (%)
Gender male: female		29:19 (60.4:39.6)
Age groups	1-5 years	24 (50)
	6-10 years	11 (22.9)
	> 10 years	13 (27.1)
Leucocyte count at diagnosis	< 10×10^9/L	22 (45.8)
	10-20$\times 10^9$/L	11 (22.9)
	20-50$\times 10^9$/L	5 (10.4)
	>50$\times 10^9$/L	10 (20.9)
Morphology	L1	44 (91.7)
	L2	4 (8.3)
Immunophenotype	B-cell	39 (81.3)
	T-cell	9 (18.7)
Cytogenetics	abnormalities	12 (25)
	no metaphases	20 (41.7)
	normal karyotype	16 (33.3)
Molecular biology*	negative	32 (66.7)
	TEL-AML1	10 (20.8)
	E2A-PBX1	4 (8.3)
	BCR-ABL1	2 (4.2)
Prednisone response**	good	43 (90.6)
	poor	5 (9.4)
Risk groups	standard risk	19 (39.6)
	intermediate risk	21 (43.8)
	high risk	8 (16.6)
Cumulative dose of AC	< 200 mg/m^2	7 (14.6)
	200-240 mg/m^2	25 (52.1)
	≥240 mg/m^2	16 (33.3)

* fusion genes analyzed: TEL-AML1, SIL-TAL1, E2A-PBX1, MLL-AF4, BCR-ABL1

** prednisone good response: <1 blast x 10^9/L on day 8; prednisone poor response: >1 blast x 10^9/L on day 8

Table II. The serum levels of troponin I (TnI) and heart-type binding protein (HFABP)

	TnI (pg/dl)	HFABP (ng/ml)
T1, before the first AC dose	0.01 (0.01,0.01)	1.9 (1.71,2.18)
T2, one hour after the first dose	0.01 (0.01,0.01)	1.91 (1.75,2.27)
T3, before the last AC dose	0.015 (0.01,0.02)	1.85 (1.62,1.98)
T4, one hour after the last dose	0.02 (0.01,0.03)	1.75 (1.6,1.97)
T5, one year after diagnosis	0.01 (0.01,0.02)	1.69 (1.56,1.75)

The results are expressed as median value (interquartile range).

Tnl3-Tnl1: p=0.003
Tnl4-Tnl1: p<0.001
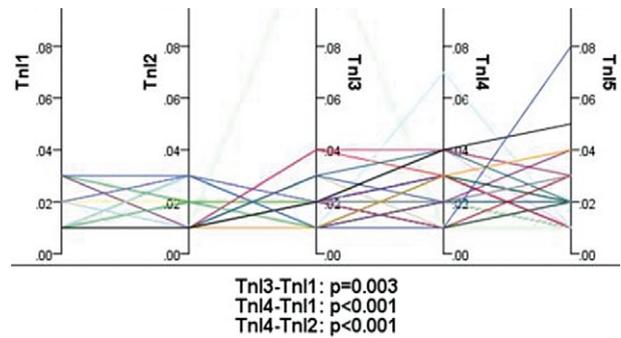Tnl4-Tnl2: p<0.001

Fig 1. Parallel coordinates plot, showing the variability of TnI among all 48 patients at five timepoints; TnI1 = before the first AC dose; TnI2 = one hour after the first AC dose; TnI3 = before the last AC dose; TnI4 = one hour after the last AC dose; TnI5 = one year after diagnosis.

between the two biomarkers at the end of treatment and cumulative dose of AC (p=0.715, respectively p=0.876).

Serial echocardiographic evaluations were performed on 46 patients; in two children, due to technical difficulties, the results were not considered for analysis (Table III).

Applying Boferroni correction, p<0.017 was considered statistically relevant for echocardiographic evaluations. TVI and E decreased during therapy (p<0.001) and returned to pre-treatment values at one year after diagnosis (p<0.001). SS decreased at the end of therapy (p=0.008) and slightly increased one year after diagnosis, with no statistical significance. E/A decreased after all AC doses (p=0.014) and increased one year after diagnosis (p=0.026, marginal).

TAPSE decreased after treatment (p<0.001) and maintained a lower value than baseline one year after diagnosis (p=0.002); RVS also decreased (p=0.006) and remained so one year after diagnosis (p=0.001).

No significant correlations between hematological tests, including morphological, cytogenetic or molecular subtypes, the two biomarkers and echocardiographic findings could be established (all p>0.05).

Discussion

Troponin is considered to be the best suited cardiac biomarker for detecting CIC, cellular damage and apoptosis [15,16], but also for subclinical cardiac dysfunction [17]. TnI is more feasible than the other cardiac troponins for early CIC diagnosis due to its kinetic curve [18], but the exact dynamic of troponin release into bloodstream is not well known [5,12,19]. Although several papers have been published regarding CIC evaluation by troponin measurements, there are only a few studies on this subject in pediatric ALL setting [20-29].

Table III. The echocardiographic parameters of the study group (46 patients)

	At diagnosis	After all AC doses	1 year after diagnosis	p
LVEF, %	63 (60.5,65)	64.5 (60,67)	62 (60,65)	0.833
TVI, cm	19.1 (11.22,21.77)	15.75 (14.57,18.6)	19.6 (16.37,24.52)	**<0.001**
TAPSE, cm	2.1 (1.9,2.3)	1.8 (1.6,1.9)	1.9 (1.7,2.1)	**<0.001**
SS, cm/s	7.7 (6.8,8.6)	6.9 (6,7.5)	7 (6,8)	0.07
SL, cm/s	8.7 (7.9,10.3)	8.7 (7,10)	8 (6.6,10)	0.488
RVS, cm/s	14.4 (12,15)	12 (10.8,13.5)	12 (10.4,13.1)	**0.002**
IVRT, ms	50 (41,63.5)	44 (38,61)	57 (43,69)	0.173
E, m/s	0.9 (0.8,1)	0.8 (0.7,0.9)	0.9 (0.9,1.1)	**0.001**
A, m/s	0.6 (0.5,0.7)	0.6 (0.5,0.7)	0.7 (0.5,0.8)	0.936
E/A	1.5 (1.2,1.9)	1.4 (1.2,1.6)	1.4 (1.2,1.9)	**0.031**
EDT, ms	121 (97.8,149.2)	115 (100.8,136)	129 (106,169)	0.05

The results are expressed as median value (interquartile range). A = late filling transmitral flow velocity; E = early filling transmitral flow velocity; EDT = E-wave deceleration time; risk; IVRT = isovolumic relaxation time; LVEF = left ventricle ejection fraction; RVS = peak systolic tricuspid annulus velocity; SL = peak systolic lateral mitral annulus velocity; SS = peak systolic septal mitral annulus velocity; TAPSE = tricuspid annular plane systolic excursion; TVI = left ventricle outflow tract time-velocity integral

Different groups monitored large cohorts of children with ALL and concluded that TnI was predictable for myocardial injury [20-22]. There is evidence that TnI level is correlated with AC treatment in a dose-dependent manner [23-24] and the increase occurs 2-4 weeks after administration [25] but there are studies in which no changes in the troponin values during AC treatment were found [26-29]. In our study, in children with ALL receiving low CD of AC, TnI increased in direct proportion with the number of doses (p<0.001), only one hour after the administration. One year after ALL onset, TnI had the tendency to decrease, remaining higher compared with the baseline value, suggesting that subclinical lesions could be reversible in these patients.

There are no published data about HFABP levels in pediatric ALL patients and data provided by adult cohorts and mice studies are contradictory: two studies found increased levels after AC-based treatment [30-31], while two showed no relevant changes [32-33]. We found no statistically significant variation in HFABP levels in children but, knowing that this biomarker decreases slowly as the cumulative dose of AC increases due to the HFABP gene suppression [34], a longer period of monitoring would be useful.

No significant changes in LVEF could be established in our study group, the parameter appearing to be insufficiently sensitive in detecting early signs of cardiac dysfunction after low-dose AC treatment, as previously mentioned [5,35-38].

Both in adults and children, TVI monitoring is recommended in several pathologies [39]. In a reference paper, normal values for TVI are proposed [40]. In our study TVI baseline values were within normal range and after AC-based therapy the values decreased (p<0.001), suggesting that TVI is a sensitive and independent predictor for CIC, as Schmitt et al previous founded [41]. Our patients were evaluated also at one year after diagnosis, TVI returning to normal (p<0.001), showing a rapid, but transient global dysfunction.

The normal values for SS were established in measurements realized in an offline mode [42]. Our measurements (at baseline and one year after diagnosis) were performed in an online mode but we obtained similar results. We suggest that the decrease of the SS at the end of treatment (p=0.008), represents transient contractility dysfunction as the values obtained after 1 year after diagnosis return to normal, quite similar with previous published studies [36,43,44].

Regarding SL, our results were similar to reported normal values [10,42]. Conversely, some studies observed significant changes in SL after AC treatment [36]. The difference between SS and SL dynamics in our patients could suggest a higher sensitivity for contractile dysfunction at the interventricular septum level.

We evaluated the RV based on TAPSE, useful for global and longitudinal function, and RVS, which assesses longitudinal and contractile function. We found a decrease in both parameters at the end of therapy (p<0.001, p=0.006), similar to other published data [44-47]. However, another study did not describe any changes in TAPSE or RVS [48]. The decrease in RV parameters was maintained even one year after diagnosis, compared to LV parameters which returned to baseline levels. The distinct way of reacting to injury could be due to a different pattern of dysfunction regarding the two ventricles [44,49-50].

At present, diastolic dysfunction in children is not clarified; more to the point, the necessary parameters for its evaluation are not established [51]. Even though it is well known that hydric balance influences diastolic measurements, it is virtually impossible to adjust the evaluation protocol in ALL pediatric setting [52]. In our group, IVRT and A wave did not change during AC treatment, in opposition to other studies [53-55]. E and E/A ratio decreased during therapy (p<0.001, p=0.014), suggesting a dysfunction in LV filling, similar results being encountered in different papers [54-55]. One year after diagnosis, E and E/A ratio returned to baseline values. Conclusions regarding diastolic changes in this cohort cannot be drawn, probably due to the unreliable method of evaluation, considering the volemic status of the pediatric patients undergoing chemotherapy.

Limitations

The Teichholz method was used in order to obtain images in a shorter amount of time; the patients were immunocompromised and the majority under the age of 5, therefore, not very cooperant. The Speckle tracking technique was not used for the same reasons. The echocardiographic protocol was focused on systolic ventricular function; only a few of the diastolic parameters were measured. The variation in parameters due to age was limited by mainly comparing the same patient at different time points.

Conclusions

The TnI levels decreased proportionally with anthracycline administration. Left ventricle and diastolic parameters (TVI, SS, E, E/A) decreased during therapy and returned to pre-treatment values one year after diagnosis. Right ventricle parameters (TAPSE, RVS) remained at lower values one year after diagnosis. HFABP, LVEF, SL, IVRT and A wave were not influenced during protocol. Further studies are required to establish a protocol for early diagnosis and monitoring of CIC in children with ALL in order to minimize acute and chronic cardiac side effects in cancer survivors.

Conflict of interest: none

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