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Original Research Article

Assessment of left ventricular function in pediatric oncology by two different methods of echocardiography: a short-term outcome

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ABSTRACT

Background: Chemotherapy-induced myocardial dysfunction (CIMD) is a documented actuate of heightened morbidity and mortality. The gold standard for the surveillance of CIMD is the serial echocardiogram. Two-dimensional speckle echocardiography i.e. global longitudinal strain (GLS) is affirmative diagnostic tool than conventional echocardiography.
Methods: We retrospectively reviewed the data of children (age between 6 months to 18 years) who received cardio-toxic chemotherapeutic agents and underwent echocardiography assessment with conventional and GLS imaging at-least 2 times between January 2020 to January 2021 in The Indus Hospital, Karachi at start, 3rd months and 6th months of treatment.
Results: We enrolled 122 patients in our study. The mean age was 8.19±4.43. 82 (67.2%) children got the 2 echocardiographic evaluations while 40 (32.8%) children completed three. Of 82 subjects, 17 (22.6%) had a significant reduction in early myocardial deformation indices as measured by two-dimensional (2D) STE using GLS at the end of 3 months of chemotherapy. Before the start of therapy, mean values of ejection fraction (EF), fractional shortening (FS) and GLS were 68.6±10.44, 38.8±7.44, and -20.7±4.19 respectively. At 3rd month and 6th month follow up, EF decreased 65.80±9.00 and 62.06±10.62 (p value 0.000) respectively while the values for GLS decreased significantly as -18.4±3.86, -16.68±3.63 (p value 0.02) respectively.
Conclusions: GLS is an effective, and non-invasive cardiac imaging modality than a conventional echocardiography in assessment of left ventricular (LV) dysfunction in non-symptomatic as well as in symptomatic children with cancers.

Keywords: Pediatric cancer, Hematological malignancies, Echocardiography, Strain imaging, GLS, Heart failure

INTRODUCTION

Malignancies in children are upsurging but fortunately in last decade, the outcome has improved due to comprehensive and multi-disciplinary care.[1,2] Cardiovascular complications are the second most significant contributor to morbidity and mortality in children with cancer.[3] Anthracycline is most commonly used in the treatment of leukemia and sarcoma in children. Cancer therapy-related cardiac dysfunction (CTRCD) due to anthracyclcine has been extensively described in the literature.[4,5] The exact mechanism of anthracyclcine-induced cardiotoxicity is unclear and it is most likely to be multifactorial. Anthracycylcine-related cardiac toxicity is related to the formation of reactive oxygen species. Chemotherapy-induced myocardial dysfunction (CIMD) is a documented trigger of increased morbidity and mortality. Anthracyclcine can cause acute (less than a week), early-onset (within one year), and late (>1 year) cardiac toxicity after the onset of therapy.[6,7] Vigilant surveillance is essential to detect early cardiac dysfunction and treat according to the guideline-based therapy to prevent worsening of late-onset cardiotoxicity.[8,9] The gold standard for the surveillance of chemotherapy-induced cardiac dysfunction is the serial echocardiogram being the recommended method.

Children with malignancies are prone to have myocardial dysfunction due to many other factors, including sepsis, neurogenic trauma, malnutrition, poison, myocarditis, infections, storage disorders, and medications.[10]

Echocardiography is a well-established tool for the assessment of cardiac functions, hemodynamic monitoring, and early diagnosis of various heart conditions. Conventional echocardiography with M-mode and 2D imaging is being performed for this purpose as a diagnostic tool for measurement of ejection fraction (EF), fractional shortening (FS) that has proved ineffective with many limitations.[11] Recently, two-dimensional speckle echocardiography i.e. global longitudinal strain (GLS) is a more favorable diagnostic tool. This novel, non-invasive modality assesses myocardial deformation by measuring strain values, which measure the size of myocardial fibers relative to their original size.[12-14] Most of the reports on this novel imaging on pediatric oncology patients were published from developed countries.[15,16] There are limited data available from low-middle income countries (LMIC).[17]

The objective of this study is to compare the GLS with conventional EF and FS for assessment of cardiac function over a short period in children with newly diagnosed cancer from a large pediatric-oncology center of Pakistan.

METHODS

Study population

We retrospectively reviewed the data of children (age between 6 months to 18 years) who received cardiac-toxic chemotherapeutic agents as a part of the treatment of their oncological diagnosis and underwent echocardiography for the assessment of cardiac function in a large comprehensive pediatric-oncology center from January 2020 to January 2021 in The Indus Hospital, Karachi. Sample size was calculated by World Health Organization (WHO) sample size calculator with using 95% confidence level (beta error), 10% detection rate in the population and alpha 0.05, and it came out 120. All children who were recently diagnosed with cancer and plan to start the therapy were included. Children with leukemia, lymphoma or solid tumors were enrolled in this study. The patients who have rheumatic, hypertensive, ischemic, or congenital heart disease, or having arrhythmias were excluded from the study. The study was conducted after approval from the ethical committee (IRD_IRB_2020_09_04).

Study protocol

Echocardiography was performed by a trained echocardiographic technician in the pediatric cardiology department. Transthoracic echocardiography was performed on patients in the left lateral decubitus position using a GE VIVID S60 ultrasound system equipped with a phased-array transducer (3Sc and 6S). The echocardiography was performed three times: pre-treatment, 3-month, and 6-months after initiation of treatment. We included the children who have completed three months of therapy and have undergone at least two times echocardiographic examinations in this duration.

Some tests were performed in between that were also added in data with relation to patient cardiovascular status and heart failure. The GLS was defined as a reduction in LS according to age-specific partition values. Heart failure was diagnosed and categorized by modified Ross classification.[8]

Echocardiography

Data were acquired from parasternal long-and short-axis views and the three standard apical views. For each view, cine loops were obtained by recording 3 consecutive heart cycles. Grayscale recordings were optimized for LV evaluation at a frame rate of 50–80 frames per second. All echocardiograms were stored digitally and analyzed with offline software on the echo-pack workstation. Standard echocardiographic parameters such as LV end-diastolic (EDV) and end-systolic (ESV) volume, left atrium diameter (lads) were analyzed according to the principles. Left ventricular ejection fraction (LVEF) was measured by Simpson's biplane method.

Analysis of GLS

LV longitudinal function was assessed by the semiautomatic algorithm (automated function imaging, GE). Briefly, three myocardial markers were placed in an end-diastolic frame in the apical 4-, 2- and 3-chamber views, respectively. The software automatically tracked the contour of the myocardium throughout the heart cycle to cover the entire thickness of the left ventricle (LV) wall. Adequate tracking could be verified in real-time and corrected by adjusting the region of interest or by manually correcting the contour to ensure optimal tracking. The value of peak GLS derived by 2D STE was analyzed from three apical views and calculated in the 17 segments (6 basal, 6 mid, 4 apical, and the apex) concerning the strain magnitude at aortic valve closure. In the present study, the higher absolute value of peak GLS (more negative) is assumed to be as better, and the value closer to zero is described as worse.[18,19] Abnormal LV systolic function was defined as LVEF $<55\%$ or FS $<27\%$. Abnormal LV systolic function was defined as GLS $<18\%$ for the study purpose.[20]

Continuous variables are expressed as mean (SD) or as percentages. Correlation between strain measurements and LVEF, FS were assessed with Pearson's correlation coefficient (r) while controlling the confounder as use of doxorubicin. P values <0.05 were considered statistically significant. Data were analyzed using standard statistical software (SPSS version 23.0; SPSS, Inc, Chicago, IL). The patient's confidentiality was strictly maintained by keeping data on a password-protected computer.

RESULTS

We enrolled 122 patients in our study. The mean age was 8.19±4.43. The male to female ratio was 80 (65.6%) and 42 (34.4%). Mean weight and height were 21.08±11.02 kilogram and 114±24.45 centimeters respectively. There were 41 (33.6%) leukemic, 27 (22.1%) lymphoma, and 54 (44.3%) children with solid tumors. Among all children, 68 (55.7%) children received doxorubicin (Figure 1).

Among these cases, 82 (67.2%) children got the 2 echocardiographic studies, while 40 (32.8%) children completed three cardiac echocardiographic evaluation i.e. [baseline (0-month), 3-month and 6-month]. Among these 122 children, 16 (13.1%) children developed symptomatic heart failure, required pediatric intensive care unit admission, and underwent cardiac evaluation. Echocardiography was performed for symptomatic heart failure (Table 1).

Of 82 subjects, 17 (22.6%) had a significant reduction in early myocardial deformation indices as measured by two‑dimensional (2D) STE using GLS at the end of 3 months of chemotherapy. Of 17 subjects who had a significant reduction in GLS at the end of 3 months of cancer chemotherapy, 11 subjects (64.7%) had received anthracycline-based chemotherapy. Before the start of therapy, mean values of EF, FS and GLS were 68.6±10.44, 38.8±7.44, -20.7±4.19 respectively. At 3rd month and 6th month follow up, EF decreased 65.80±9.00 and 62.06±10.62 (p value 0.000) respectively while the values for GLS decreased significantly as -18.4±3.86, -16.68±3.63 (p value 0.02) respectively (Table 2).

In our cohort, 16 patients 13% presented with heart failure, and among them, 09 patients have received the doxycycline. There was a significant difference in values among the children who presented with heart failure during the treatment. In these cases, echocardiography showed the EF and GLS values of 49.43±8.05 and -10.68±2.27 (p value of 0.001) respectively.

Table 1: Demographic variables.

Variables	N=122
Age (years)	8.19±4.43
Weight (kg)	21.08±11.02
Height (cm)	114±24.45
Gender (%)	
Male	80 (65.6)
Female	42 (34.4)
Oncology groups (%)	
Leukemia	41 (33.6)
Lymphoma	27 (22.1)
Solid tumors	54 (44.3)
Doxorubicin treatment (%)	
Yes	68 (55.7)
No	54 (44.3)
Patients with heart failure (%)	16 (13.1)
Heart failure patients who received doxorubicin (%)	09 (13.23)

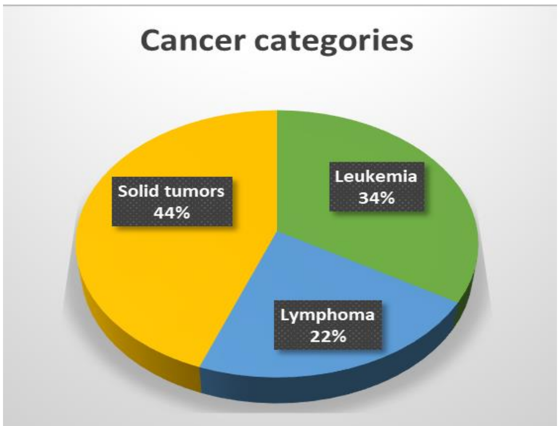

Figure 1: Cancer categories.

Table 2: Mean echocardiographic values at start, 3 months, and 6 months of therapy and in heart failure.

Parameters	Ejection fraction (EF)	Fractional shortening (FS)	Global longitudinal strain (GLS)	P value
Baseline at start (n=122)	68.6±10.44	38.8±7.44	20.7±4.19	0.001
At 3rd months (n=82)	65.80±9.00	36.42±6.32	18.4±3.86	0.000
At 6 months (n=40)	62.06±10.62	33.4±7.23	16.68±3.63	0.02
Heart failure patients (n=16)	49.43±8.05	31.08±4.12	10.68±2.27	0.001

DISCUSSION

Our observation reassured that GLS is a better cardiac imaging modality than a conventional echocardiographic assessment to assess the LVS function and is useful to predict early cardiac dysfunction in children with cancers from LMICs like many other reports from developed countries.[4,16,21,22] Few recent reports from LMIC on assessment of cardiac function in children with cancer also confirmed the above findings.[17,23] It is a highly sensitive and accurate index to detect subclinical myocardial dysfunction objectively.[24] Current imaging guidelines recommended the use of strain imaging as an echocardiographic assessment in oncology patients.[25]

Cardiac toxicity can be a considerable complication both during and after cancer therapy and contributes to significant morbidity and mortality in patients treated for cancer.[8] Cardiovascular complications are the leading cause of death among children with cancer.[3] Many studies focusing are on the long-term cardiotoxicity of childhood cancer survivors.[9,26] However, few pediatric-oncological publications report early cardiac dysfunction in children with malignancies.[17,23]

Congestive heart failure was the most common cardiac complication among children with cancers. The primary purpose of introducing this imaging modality in our echo lab this clinic is to facilitate early detection of CTRCD by performing serial echocardiographic assessments to optimize the management and by instituting prompt heart-failure guideline therapies to prevent overt heart failure. It is a cost-effective strategy. The clinical application of strain imaging in cardiac assessment is widespread and is a powerful tool in the management of various cardiac diseases.

The mean age of patients in our cohort is like other recently published reports.[5,17,21] Most of these pediatric reports have focused solely on acute leukemia especially ALL.[5,10,23] However, our cohort includes children with solid tumors who received the anthracycylcine group of medicine. We have observed 20% of our cohort developed a decline in GLS with preserved normal EF. Pardeep et al have described similar results (22.6%) in their cohort.[17]

The left ventricular systolic dysfunction in children with cancers has been described in several studies like our report.[15] Several risk factors contribute to left ventricular systolic dysfunction in children with cancers. The increased thickness of the posterior wall left ventricle is secondary to wall edema of myocardial cell injury induced by chemotherapy.

Another possible explanation is an increase in systemic vascular resistance and arterial wall stiffness following chemotherapy. Anemia can cause relative myocardial hypoxemia and increased heart rate due to sympathetic stimulation. Left ventricular volume overload secondary to hyperhydration can also depress myocardial dysfunction. Sepsis-induced myocardial dysfunction is another possible mechanism too.[21]

Limitations

The main limitation of our study is: retrospective, single-center, and short-period.

CONCLUSION

GLS is an effective, and non-invasive cardiac imaging modality than a conventional echocardiography in assessment of LV dysfunction in non-symptomatic as well as in symptomatic children with cancers.

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