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Original article

Retrospective Analysis of Anthracycline-Induced Cardiotoxicity in Pediatric Cancer Patients: At Single Cancer Institute

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Abstract

Over the last fifty years, anthracyclines have remained a significant chemotherapeutic agent in treating hematological malignancies. The outlook for cancer survivors is getting better because of earlier detection and better treatment protocols. Nevertheless, the issue of anthracycline-induced cardiotoxicity is becoming concerning for medical professionals. The objective of the study was to perform a retrospective investigation into the timing of events and the manifestation of cardiotoxicity in children with cancer. We conducted a retrospective analysis of patients in the pediatric oncology department of the National Cancer Institute of Misurata, Libya, from January 2016 to June 2023. We reviewed the clinical records of 469 patients, and 123 records that received doxorubicin within a treatment protocol were included. There were 120 patients, 69 males (57.5%), and the median age at presentation was 6 years (IQR 3–11). Nearly 39.2 percent of cases (47 cases) were less than 5 years of age. The seven events (a decrease in LVEF of >10% but not a final value of <50%) were reported in children who received a doxorubicin cumulative dose between 100 and 300 mg/m^2. A statistically significant association was found between doxorubicin accumulative dose and the following study variables: left ventricular EF% difference ($\chi 2 = 87.6, p = 0.003$), primary cancer diagnosis ($\chi 2 = 45.76, p = 0.005$), and stage of disease ($\chi 2 = 58.38, p < 0.0001$). In this study, no chronic cardiotoxicity events were associated with doxorubicin administration. However, we observed early asymptomatic changes in LVEF in some patients, and we need to investigate their clinical predictors in larger cohort studies to inform cardiac safety monitoring and optimize doxorubicin dosing for pediatric malignancies in low-resource settings.

Keywords. *Doxorubicin, Cardiotoxicity, Pediatric Malignancies.*

Introduction

An estimated 400,000 children and adolescents between the ages of 0 and 19 are diagnosed with cancer globally annually [1]. The latest report of the National Cancer Registry of Libya (2020), has estimated that the age-standardized rate (between ages 0-14 years) was 114.1 per 1000000 [2]. Childhood malignancies most frequently manifest as leukemia, brain cancers, lymphomas, and solid tumors, including neuroblastoma and Wilm's tumors [2, 3]. In addition to surgery and radiotherapy, the majority of pediatric malignancies are curable with generic drugs [3]. Over the last fifty years, anthracyclines have remained a significant chemotherapeutic agent in treating hematological malignancies [4]. As the prognosis for cancer survivors improves due to earlier detection and enhanced treatment approaches, the manifestation of anthracycline-induced cardiotoxicity presents clinicians with an ever-increasing challenge [5]. The International Late Effects of Childhood Cancer Guideline Harmonization Group Cardiomyopathy guideline recommends life-long echocardiographic screening every three to five years in childhood cancer survivors treated with anthracyclines or radiotherapy involving the heart because of late-chronic cardiotoxicity [6]. The left ventricular ejection fraction (LVEF) is a recommended parameter for monitoring several cardiac conditions including cardiomyopathy, cardiac surgery, myocardial infarction, and anthracycline-induced cardiomyopathy [7, 8].

The American Society of Echocardiography defines cardiotoxicity as a 10% decrease in the left ventricular ejection fraction (LVEF) below 53% [9]. Cardiotoxicity risks associated with

anthracycline have been identified in clinical studies as cumulative anthracycline dose, infusion rates, and pre-existing heart failure [10]. Following the identification of cardiac dysfunction related to cancer therapeutics induced by anthracyclines (CTRCD), medical professionals have endeavored to reduce toxicity by adjusting chemotherapy protocols to restrict the cumulative dose of anthracycline and by closely monitoring cardiac function [9]. The anthracycline-induced cardiotoxicities are classified as acute onset after the first dose or early course of receiving the cardiotoxic drug "within 2 weeks", early-onset chronic "Within 1 year", and late-onset chronic" >1 year" [7, 9]. The objective of the study was to perform a retrospective investigation into the timing of events and the manifestation of cardiotoxicity in children with cancer.

Methods

Study design, and setting

This study is a retrospective analysis conducted in the pediatric oncology department of the National Cancer Institute of Misurata, Libya, between Jan. 2016 to June 2023, based on the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) Statement Criteria [11]. This study was approved by the Institutional Ethical Committee at the National Cancer Institute in Misurata, Libya (Ethical Approval No. 11/2024). The medical records of 469 patients were reviewed, and only 123 records of those who have doxorubicin within a treatment protocol and still following the clinic were included. Three patients were excluded because of incomplete data. The collected data includes the demographic section, primary diagnosis, protocol of treatments and doxorubicin doses, follow-up data regarding echocardiography records, and time of occurrence of values changes of cardiac function parameters (Ejection fraction EF%, fraction shortening ES %).

Statistical analysis

Frequencies and percentages were used for the descriptive statistics of the variables. For continuous variables, the mean and standard deviation (SD) or median and interquartile range (IQR) were used due to the skewness of the distribution. A chi-square test determined the association between the study variables and post-treatment events. The Spearman's rank-order correlation was run to assess the relationship between doxorubicin cumulative dose categories and systolic function difference between the initial and last follow-up. The analysis was conducted by Statistical Package for the Social Sciences (SPSS) 26 software from SPSS Inc.

Results

There were 120 patients, male accounts for 69 (57.5%), and the median age at presentation was 6 years (IQR 3-11). Nearly 39.2 percent of cases (47 cases) were less than 5 years of age. The median surface area of cases is 0.79 m^2 (IQR 0.6-1.13). The median body mass index at presentation was 15.8 (IQR 14.38- 18.1), and moderate to severe anemia was reported for 62/120 cases. The majority of cases were acute leukemia (B cell and T cell type) accounting for 64 (53.3%) of all reported cases. The median of the total doxorubicin cumulative dose was 103 mg/m^2 (IQR 68.75-127.75). The baseline characteristics of recorded patients are shown in Table 1.

The mean baseline value of LVEF was 67.07 (±SD 5.7), and the last follow-up was 67.5 (±SD 5.1). There were reported two patients who had acute doxorubicin toxicity. Both of the reported cases were acute leukemia during the induction phase of treatment. The first case was reported to have systolic dysfunction and cardiac failure (clinical/echocardiographic changes), and the second patient was reported to have asymptomatic arrhythmia (sinus bradycardia heart rate between 39-50 BPM) shortly after transfusion of doxorubicin with preserved systolic function. The first case was a lost follow-up, while the second case overcame the reported event with a modified next-dose duration of transfusion. The seven events (decrease of LVEF decline >10% but not a final value <50%) were reported in children who received a doxorubicin cumulative dose between 100-300 mg/m^2. No events were reported for those who received doxorubicin cumulative dose of less than 100 mg/m^2.

A statistically significant association was found between doxorubicin accumulative dose and the following study variables: left ventricular EF% difference ($\chi2 = 87.6$, $p = 0.003$), primary cancer diagnosis ($\chi2 = 45.76$, $p = 0.005$), the stage of disease ($\chi2 = 58.38$, $p < 0.0001$), and chemotherapy protocol intensity ($\chi2 = 21.98$, $p = 0.038$).

Preliminary analysis showed the relationship to be monotonic, as assessed by visual inspection of a scatterplot. There was a statistically significant, weak positive correlation between doxorubicin cumulative dose categories and LVEF difference between the initial and last follow-up r (0.2), $p = 0.02$.

Table 1. Baseline characteristics of study participants.

Variable	N (%)
Age in years (median, IQR)	6 (3-11)
Gender	
Male	69(57.5)
Female	51(42.5)
Mean body surface area (m2) (median, IQR)	0.79 (0.6-1.13)
BMI (kg/m^2) (median, IQR)	15.8 (14.38–18.1)
Severe underweight (<16.5)	73(60.8)
Underweight (16.5-18.5)	22(18.3)
Normal (>18.5-24.9)	21(17.5)
Overweight	3(2.5)
Obese	1(0.8)
Hemoglobin(g/dl) (mean±SD)	9.36(±2.78)
Normal level (>11)	41(34.2)
Mild(9.9-10.9)	17(14.2)
Moderate(7.0-9.8)	39(32.5)
Sever (<7.0)	23(19.2)
Type of malignancy	
Acute leukemia	64 (53.3)
Hodgkin lymphoma	24 (20)
Non-Hodgkin lymphoma	3 (2.5)
Wilm's tumor	10 (8.3)
Others*	19 (15.8)
Doxorubicin cumulative dose (mg/m2) (Median, IQR)	103 (68.75-127.75)
<100	58 (48.3)
100-200	55(45.8)
200-300	7 (5.8)
(*) Other tumors include Ewing sarcoma, Rhabdomyosarcoma, Neuroblastoma, and Retinoblastoma.	

Discussion

Doxorubicin cumulative dose has been widely reported as a limiting factor in the treatment of malignancies, with increased risk for cardiotoxicity reported cumulative dose thresholds as low as 300 mg/m2 [12]. Despite the huge development of protective measures anthracycline-induced cardiac toxicity remains a major cause of morbidity and mortality among cancer survivors [13]. In this study, no chronic doxorubicin-induced cardiotoxicity events were reported, although transient effects on cardiac function were documented. The observed result in this study could be partly explained by the low cumulative doses of doxorubicin received by participants.

The present study has illustrated that 5.8% of observed cases had an asymptomatic decline in LVEF among children who received doxorubicin-counting chemotherapy regimens in our setting, and which were not detected by the defined criteria of a decrease in LVEF by more than 10 points to the final value of <50%. The mentioned findings have been reported in previous literature [14]. In particular, LVEF recovery has been associated with lower cardiac events [15], and on the other hand, asymptomatic changes in LVEF showed a higher incidence of cardiac diseases with prolonged follow-up periods [16].

Acute doxorubicin-related arrhythmia was documented in this study and was frequently reported in the literature and most of the cases were transient without further clinical significance [17].

Doxorubicin-associated cardiotoxicity in children has been demonstrated mostly in studies predominantly done in high-income settings where patients are well-nourished and have good outcomes [18]. In the current study, about 60 % had malnutrition at baseline. Therefore, the future risk of developing doxorubicin-induced cardiotoxicity cannot be rolled out. Andolina et al. reported the possible association between nutritional status and the cardiotoxic effect of anthracycline in a long-term survival retrospective study [19].
In addition, the observed epidemiological profile of childhood malignancies in this report is similar to what has been described previously [14, 20].
Our study population had more boys than girls predominantly aged between three months and 15 years. Acute lymphoblastic leukemia was most common, followed by lymphoma (Hodgkin's more than non-Hodgkin lymphoma) and Wilm's tumor.
Further, larger studies need to be done to understand the true magnitude of these early asymptomatic changes in cardiac function and their implications for long-term treatment outcomes. This will help to inform cardiac safety monitoring and optimization of doxorubicin dosing in the treatment of pediatric malignancies in such low-resource settings.

Conclusions

There were no chronic cardiotoxicity events associated with doxorubicin administration found in this study population as defined by a decline in LVEF >10% to a final value of <50% throughout the study. However, early asymptomatic changes of LVEF were observed in some patients, and their clinical predictors need to be investigated in larger cohort studies to inform cardiac safety monitoring and optimization of doxorubicin dosing for pediatric malignancies in low-resource settings.

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