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Risk Factors Associated with Anthracycline Induced Cardiac Dysfunction in Pediatric Patients

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Abstract

Anthracyclines (*i.e.*, doxorubicin, daunorubicin) have significant impact on outcome in many pediatric chemotherapy protocols and therefore remain the mainstay of treatment. The objective of this study was to identify the risk factors for anthracycline induced cardiac dysfunction in pediatric patients. Multiple logistic regression model was applied to assess the risk factors for development of cardiac dysfunction. 110 pediatric oncology patients were available for final analysis. 75 (66%) children were males and mean age was 74 ± 44 months. ALL (n = 70, 64%) was the most common primary diagnosis followed by lymphoma (n = 19; 17%) and AML (n = 12, 11%). Daunorubicin alone or in combination with doxorubicin was used in (n = 94, 85%) patients and cumulative dose < 300 mg was used in (n = 95; 86%) children. 24 (22%) children received radiation therapy as per protocol and sepsis were observed in 47 (43%) cases. Post anthracycline, 15 (14%) children had cardiac dysfunction within a month; out of them 10/15 (67%) had isolated diastolic dysfunction, while 28 (25%) developed dysfunction within a year. 19 (17%) had pericardial effusion. 11 expired and out of them, 7 had significant cardiac dysfunction. Cumulative dose > 300 mg/m^2 (p < 0.001; AOR 2.3), radiation therapy (p = 0.009; AOR 3.5) and sepsis (p = 0.002; AOR 2.6) were found to be independent risk factors associated anthracycline induced cardiac dysfunction. At univariant level use of daunorubicin alone or in combination therapy (p < 0.001, OR 7) and mode of delivery (p 0.048, OR 9.7) were also found statistically significant. In conclusion anthracycline induced cardiac dysfunction is mostly related to cumulative dose > 300 mg/m^2, use of Daunorubicin alone or in combination with doxorubicin, mode of delivery, radiation therapy and sepsis. Regular long term follow-up with cardiologist is the key point for early diagnosis and therapy for a long term survival.

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Keywords

Anthracycline, Cardiac Dysfunction, Risk Factors, Pediatric Oncology

1. Introduction

The anthracycline and related compounds (doxorubicin, daunorubicin) are the backbone of current childhood chemotherapy (solid and hematological malignancies) [1]. Despite the fact that they are very potent and highly effective chemotherapeutic agents, their cardiotoxicity remains a serious concern during management [1] [2], with the incidence of cardiotoxicity ranges between 0 - 57 percent [3]. Their main adverse effects include systolic and diastolic dysfunction, cardiomyopathy, arrhythmias and pericardial effusion [1] [2] [4]. As the myocardial injury predicts the future development and severity of long term ventricular dysfunction, regular evaluation and management of early onset cardiac adverse events are important in management of children receiving anthracyclines [5].

Certain potential risk factors including age, sex, race, associated congenital or acquired heart disease, type, mode and cumulative anthracycline dosage, concomitant radiation therapy, use of other cardiotoxic or cardioprotective drugs, Down's syndrome, sepsis during management and type of malignancy have been evaluated in medical literature [1] [3] [6]-[11]. Therefore this is paramount to identify potential risk factors associated with increase cardiotoxicity so the initial damage to the heart can be prevented by adapting preventive strategies and early start of cardiac failure treatment if needed [12]-[15].

There is very little literature from the subcontinent on risk factors associated with anthracycline induced cardiotoxicity in pediatric oncology patients. The aim of this study was to identify the risk factors for cardiac dysfunction associated with anthracyclines in pediatric patients.

2. Patients and Methods

We performed a prospective cohort study during July 2010-June 2012 at the department of paediatric and child health, Aga Khan University, Hospital, Karachi, Pakistan. All pediatric oncology patients aged 0 to 16 years, who received anthracycline as a part of their chemotherapy protocol and remain in regular follow-up for at least 1 year post chemotherapy and had at least 3 echocardiographic studies within a year (at baseline, within 1 month and within a year) were included for final analysis. Children with any structural cardiac condition or cardiomyopathy were excluded. Data were collected on a structured proforma. Risk factors taken into consideration were the primary diagnosis, age, gender, type, mode of delivery and cumulative dose of anthracycline, radiation therapy, Down's syndrome and culture proven sepsis. Follow-up compliance was also recorded. Echocardiographic studies for functions (baseline, within a month and within a year post anthracycline exposure for acute and early onset chronic progressive cardiotoxicity respectively) were recorded. 190 children were enrolled in this study according to study criteria but 80 patients (42%) were further excluded due to poor or no follow-up, treatment migration, self treatment withdrawal. Thus 110 children were available for final analysis.

3. Data Collection and Analysis

Statistical analysis was performed by using SPSS software package (version 20.0, SPSS). Results were presented as mean and standard deviation for continuous variables (*i.e.*, age, height, weight, body surface area, cumulative dose, echocardiographic evaluation) and frequency and percentage for categorical variables (*i.e.*, gender, type of malignancy, and type of Anthracycline). Risk factors for anthracycline induced cardiac dysfunction were identified by comparing the patients with and without cardiac dysfunction. A *p*-value of 0.05 was considered significant at the univariate level. For the multivariate model a *p*-value cut-off of 0.01 along with high crude odds ratio were taken into account. Finally, a multiple logistic regression model was applied for all variables in such a way that the variable with the most significant *p*-value was entered first in the final model to calculate the adjusted odds ratio.

4. Echocardiographic Analysis

By using Philips IE33 ((Philips Medical Systems, Andover, MA, USA) and GE vivid 7 Pro (General Electric

Company, NYSE: GE, UK) echocardiographic machines. Real time images were obtained from standard projections. Transmitral flow velocity pattern was recorded from the apical four chamber view. M-mode was taken from parasternal long axis view. A baseline echocardiography was done in all patients as required in the management protocol. Echocardiographic assessment of systolic and diastolic left ventricular function and pericardial effusion was made. Shortening fraction (FS) and Ejection fraction (EF) calculated for systolic functions while trans-mitral flow velocities their ratio, Deceleration Time (DT) and Myocardial performance index (MPI or Tei index) [14]-[17] were evaluate for diastolic function at baseline, one month and 1 year post chemotherapy for acute and early onset chronic anthracycline cardiotoxicity.

5. Results

Of the 110 patients, 68% were males, mean age was 74 ± 44 months, and mean body surface area was 0.54 ± 0.32 m^2. Patients demographic features, risk factors and clinical profile mentioned in (**Table 1**).

Table 1. Demographic features of study population (n = 110).

Demographic features	N (%)/mean ± SD
Age	74 ± 44 months
Sex	
Males	75 (68%)
BSA	0.84 ± 0.32
Type of malignancy	
ALL	70 (64%)
AML	12 (11%)
Hodgkin + Non Hodgkin	19 (17%)
Miscellaneous (Ewing Sarcoma = 4, Wilms tumor = 5).	9 (8%)
Type of anthracycline used	
• Doxorubicin	59 (53.5%)
• Daunorubicin	16 (14.5%)
• Both	35 (32%)
Cumulative anthracycline dose	
<300 mg	95 (86%)
>300 mg	15 (14%)
Radiation therapy	24 (22%)
Down's syndrome	8 (7%)
Culture proven sepsis	47 (43%)
Gram positive bacteria	29 (61.7%)
Gram negative bacteria	8 (17%)
Gram positive and negative combine	6 (12.8%)
fungus	4 (8.5%)
Cardiac dysfunction	
• **Within a month dysfunction**	15 (14%)
Diastolic alone	10/15 (67%)
Combine systolic and diastolic	5/15 (33%)
• **Within a year dysfunction**	28 (25.4%)
Diastolic alone	12/28 (43%)
Combine systolic and diastolic	16/28 (57%)
Sign symptoms of cardiac failure	
• Within a month	4 (3.6%)
• Within a year	18 (16%)
Pericardial effusion	
• Within a month	9 (8.2%)
• Within a year	19 (17.1%)

Most of the children had primary diagnosis of Acute Lymphoblastic lymphoma (ALL) (64%) followed by Hodgkin and Non-Hodgkin lymphoma (17%). Doxorubicin alone was used in 53.5% of children and combination therapy in 32%. Anthracycline cumulative doses were <300 mg in most of children 95 (86%). Anthracycline was infused in 4 patients (3.6%) while all others received boluses. Radiation therapy was used in 24 (22%) children. None of the patient received any type of cardioprotective agents prophylactically. Eight children had trisomy 21.

Within a month echocardiography showed that fifteen (13.6%) children developed cardiac dysfunction and most of them had isolated diastolic dysfunction 10/15 (66.6%), while pericardial effusion was found in 9 patients. 28 (25%) developed cardiac dysfunction when echocardiographic study was reviewed after a year, 12/28 (43%) had isolated diastolic dysfunction and pericardial effusion was observed in 19 patients. Forty-seven (43%) children admitted due to sepsis. eleven children expired, out of them 7 had significant cardiac dysfunction.

Multiple logistic regression analysis was performed for the identification of risk factors for anthracycline induced cardiac dysfunction and crude and adjusted Odds Ratio (AOR) was calculated (**Table 2**). The analyses did not signify age, sex, type of malignancy and Down's syndrome as risk factors. Cumulative dose > 300 mg/m^2 (p < 0.001; AOR 2.3), radiation therapy (p = 0.009; AOR 3.5) and sepsis (p = 0.002; AOR 2.6) were found as independent risk factors associated anthracycline induced cardiac dysfunction in pediatric patients. At univariate level use of daunorubicin alone (p < 0.001, OR 7) and mode of delivery (p 0.048, OR 9.7) were also statistically significant.

6. Discussion

Cardiotoxic adverse effects of anthracyclines remain the major challenge for oncologist and cardiologist especially in developing countries where follow up compliance remains poor. Anthracycline associated adverse events include systolic and diastolic dysfunction, cardiomyopathy, arrhythmias and pericardial effusion. Patient can also present with asymptomatic cardiac dysfunction [1] [2] [4].

Table 2. Risk factors associated with anthracycline induced cardiac dysfunctions (n = 110).

Demographic profile (n)	No dysfunction (n = 82)	Dysfunction (n = 28)	p-value	Crude odd ratio (CI)	Adjusted OR (CI)
Age					
<5 yrs (**46**)	37 (45%)	9 (32%)	0.276	1.736 (0.703 - 4.289)	
>5yrs (**64**)	45 (55%)	19 (68%)			
Sex					
Males (75)	54 (66%)	21(75%)	0.487	1.556 (0.590 - 4.102)	
Females (35)	28 (34%)	7 (25%)			
Type of malignancy					
Hematological (**94**)	71 (87%)	23 (82%)	0.756	1.403 (0.441 - 4.463)	
Solid tumors (**16**)	11 (13%)	5 (18%)			
Daunorubicin	6 (7%)	10 (36%)	**0.001**	7.037 (2.262 - 21.895)	-
Daunorubicin + Doxorubicin	76 (93%)	18 (64%)			
*Mode of delivery					
Bolus (**106**)	81 (99%)	25(89%)	**0.048**	9.72 (0.968 - 97.647)	-
Infusion (**4**)	1(1%)	3 (11%)			
Cumulative anthracycline dose					
<300 mg (**95**)	78 (95%)	17 (61%)	**<0.001**	12.618 (3.583 - 44.43)	2.25 (0.032 - 0.522)
>300 mg (**15**)	4 (5%)	11 (39%)			
Radiation therapy (**24**)	13 (16%)	11 (39%)	**0.009**	3.434 (1.312 - 8.992)	3.46 (0.115 - 0.427)
*Down's syndrome (**8**)	5 (6%)	3 (11%)	0.331	1.848 (0.412 - 8.288)	
Sepsis (**47**)	28 (34%)	19 (68%)	**0.002**	4.071 (1.631 - 10.166)	2.58 (0.040 - 0.305)

*As the sample size was less than 5 so fisher exact test was used.

Recognition of dysfunction early, especially at the asymptomatic stage, significantly affects late outcome. In our study echocardiographic study showed 15 (13.6%) developed cardiac dysfunction within a month and most of them (66%) had isolated diastolic dysfunction. At 1 year, 28 (25%) had dysfunction and most of 16/28 (57%) had combined systolic and diastolic dysfunction. 18/110 (16%) had signs and symptoms of congestive heart failure (CHF).

Several studies have reported up to 56% subclinical echocardiographic cardiac dysfunction and incidence of clinical cardiotoxicity (CHF) ranged from 0 - 16% [7]. Study conducted by Velensek *et al*. [18] showed isolated diastolic dysfunction in 28.6% of patients.

There is no safe dose limit and anthracycline can produce cardiotoxicity at any dose. But higher the cumulative dose more will be the cardiotoxicity and this is a well-recognized association. Hence this will always be considered a significant risk factor for cardiac damage and will also remain the best predictor for long term cardiotoxicity [19]. Van Dalen *et al*. [20] in his study showed that a cumulative dose of 300 mg/m^2 or more was the only independent risk factor for anthracycline cardiotoxicity. Our study supports their findings as well as those suggested by other reports [19]-[21].

In our study AML and Ewing sarcoma had high tendency to develop cardiac dysfunction in acute and early onset phase. This was most likely due to their high anthracycline cumulative dose and primary disease. However there is no statistical significant anthracycline induced cardiotoxicity when hematological malignancies were compared with solid tumors ($p = 0.756$).

Doxorubicin and daunorubicin both are cardiotoxic. Doxorubicin, the parent drug, contributes the most to the cardiotoxicity, but for daunorubicin, the daunorubicinol metabolite contributes to about 75% of the cardiotoxicity. Conflicting data is present about anthracycline analogues and their cardiotoxicity differences [19] [22]. In our study whenever daunorubicin was used either alone or in combination with doxorubicin, the risk of cardiac dysfunction was significantly high ($p = 0.001$). Krischer *et al*. [8] in their study did not observe any difference for cardiotoxicity between doxorubicin and daunorubicin.

Godoy and associates [23] in their study showed that children younger than 4 years had a higher incidence of cardiotoxicity compared to those older than 4 years ($p < 0.01$). Other studies have suggested that females are at greater risk than males although the reason for this difference is not clear [2] [19]. In our study dysfunction was relatively common in younger children but neither age nor gender reach significance ($p = 0.28$, and $p = 0.49$ respectively) in relation to incidence of cardiac dysfunction that is comparable to other published studies [20]. Risk of cardiovascular disease increases with increasing radiation dose and time since therapy [24]. In our study 22% of patients received radiation therapy and in them risk for cardiotoxicity was high ($p = 0.009$).

Sepsis induced myocardial dysfunction is well known association; it potentiates anthracycline cardiotoxicity [19] [25]. Sepsis was a significant risk factor for cardiac dysfunction in our study ($p = 0.002$). The index of suspicion for subclinical cardiac failure should be high and ascertained by serial echocardiographic assessment particularly when high amount of fluid therapy is administered for sepsis and for tumor-lysis syndrome. This increase in preload can jeopardize cardiac function leading to frank congestive heart failure.

Increased cellular sensitivity to chemotherapy contributes to increased treatment-related morbidity and mortality for patients with DS with leukemia. Krischer *et al*. [8] found that trisomy 21 itself imparted a 3.4-fold relative risk for clinical cardiotoxicity [26]. We in our study did not find DS as a significant risk factor for cardiotoxicity ($p = 0.331$).

It is very well known that anthracycline induced cardiotoxicity is a slow progressive process that can occur even years after discontinuation of therapy [27]. Cardiac related mortality rate increases eight times and chances of developing cardiac dysfunction increases to 15 times more than the general population after 30 years of anthracycline treatment completion [28]. In our study one month's assessment showed that 14% had dysfunction which increased to 25% at 1 year after completion of therapy. At least a follow-up of six years is necessary to identify those long term survivors at risk for cardiac dysfunction, even asymptomatic patients, to prevent long term morbidity and mortality related to cardiovascular complications [29]. Unfortunately in developing countries like Pakistan we face significant morbidity and mortality due to multiple reasons like illiteracy, financial constraints and poor understanding of the need for follow-up. In our study 11 patients expired, out of them 7 had severe cardiac dysfunction.

7. Conclusion

Anthracyclines are important components of chemotherapy protocols but are associated with significant cardiac

dysfunction. Cardiotoxicity is mostly related to high anthracycline cumulative dose, use of daunorubicin isolated or in combination with doxorubicin therapy, mode of delivery of anthracycline, concomitant radiation therapy and sepsis. Pericardial effusion occurs earlier and is an early marker for cardiotoxicity. Early diagnosis and prompt treatment of cardiac dysfunction may prevent significant mortality and morbidity. Regular long term follow-up with cardiologist is the key point for long term survival.

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