Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Cardiology

One-Year Study of Clinical Cardiotoxicity Follows Anthracyclin Treatment in Childhood Malignancy at Benghazi Children Hospital

D. Najat Elrugige[1*], Dr. Muna Mustafa Ali[2], Dr Mohamed Masoud Alferjani[3]

[1]Consultant Cardiologist Pediatric Lecturer at Benghazi University
[2]Consultant Pediatric Benghazi University
[3]Consultant Neonatology and Genetics, Associated Professor Pediatric Department Benghazi University

DOI: 10.36347/sjams.2023.v11i09.012 | **Received:** 01.08.2023 | **Accepted:** 05.09.2023 | **Published:** 15.09.2023

***Corresponding author:** D. Najat Elrugige
Consultant Cardiologist Pediatric Lecturer at Benghazi University

Abstract **Original Research Article**

Background: Treatment of pediatric malignancy has greatly improved and survival according to SEER data, mortality rate declined by 40 percent between 1975 and 1995. This declined in mortality has accompanied by increase in the recognition of long term side effect from treatment of childhood cancer, one of major complication is cardiac, during or after administration of anthracyclin patient can develop acute cardiac toxicity. ***Aim:*** To determine the incidence of clinical cardiotoxicity from anthracycline chemotherapy in children with cancer and to identify risk factors. ***Material and Method:*** One-year study (2021) to children with cancer were received anthracycline as part of chemotherapy at Children Hospital Benghazi. ***Results:*** During the study period one year (Jan.2021- Dec. 2021) 51 cases received anthracyclin as part of chemotherapy were evaluated with echocardiography there is male predominance represented 62.7% & females37.3%, M: F 1.6:1, Age range from 5 months to 14 years, the commonest age group 1-5 years around 25cases represented 49%, Most cases evaluated in our study diagnosed with Acute Lymphoblastic Leukemia (ALL) 24 cases represented 47.1%, 9 cases with Acute Myeloid Leukemia (AML) 17%, Lymphoma 7 cases represented 13,7%, wilm's tumor 5 cases 9.8%, neuroblastoma 3 cases 5.8%, Each of Retinoblastoma, adrenocortical carcinoma and hepatoblastoma 1 case (2%), 34 cases were evaluated still on treatment 66.7%, 17 cases 33.3% were finished treatment on follow up 29 cases were received treatment for less than or equal to one year represented to 56.9%, while 22 cases 43.1% >1year, We were divided the patient according to type of anthracyclin (Adriamycin or douanomycin) results show those received Adriamycin only 39.2%, cases were received douanomycin 7.8%, while cases received both of them 53%, 35.9 % of cases received total doses between 201-250 mg\ S.A of anthracyclin, 25 cases 32.1% were received less than 100 mg\S. A, Echocardiography finding were normal in 47 cases represented 92.2%, Acute dilated cardiomyopathy (DCM) noted in 1.9%, was improved with treatment reversible, 3 cases with chronic dilated cardiomyopathy represented 5.9%, these 3 cases need treatment and follow up cardiac clinic for long life, 2 cases with trisomy 21 represented 4%, received anthracyclin chemotherapy without complication, 2 cases have congenital heart disease (4%) one has patent ductus arteriosus (PDA), 2nd ventricular septal defect (VSD), Both of them received anthracyclin chemotherapy without complication, When we compare cases that develop cardiac complications with age 1 case below one year, 2 cases between 6 – 10 years, 1 case more than 10 years of age, 4 cases with cardiac complication 3 cases were males, 1 case was female, 4 cases with cardiac complication 3 were males,1female. When compare result of Echo with type of drugs if child was received Adriamycin, duanomycin or both of them, with duanomycin only 1 had cardiac toxicity, with adriamycin 1 had cardiac toxicity, 27 patients were received both types of anthracyclin 2 patients get cardiac complications 7.8%. ***Conclusion:*** Our study proven anthracyclin is cardio toxic drugs especially in young age group, no mortality in our study, but anthracyclin causing morbidity, No differences between males and females.

Keywords: pediatric malignancy, Acute Myeloid Leukemia (AML), patent ductus arteriosus (PDA), anthracyclin chemotherapy, Echocardiography.

INTRODUCTION

Treatment of pediatric malignancy has greatly improved and survival according to SEER data, mortality rate declined by 40 percent between 1975 and 1995 [1]. This declined in mortality has accompanied by increase in the recognition of long term side effect from treatment of childhood cancer [2]. The child was surviving was found to increase chronic health care condition included

respiratory function, cardiovascular disease, infertility, cognitive delay and renal failure [3].

Anthracyclin are class of chemotherapeutics agents that are most frequently linked cardiac dysfunction in children. [4]. The class of anthracyclin agents was produced in 195 s, with isolation of daunomycin from strain of Streptomyces paucities fungi [5]. Hydrophilic derivative of daunomycin named Adriamycin (doxorubicin) [6]. During or after administration of anthracyclin patient can develop acute cardiac toxicity [7].

Doxorubicin is an effective and essential anticancer agent that is an indispensable treatment component for majority of childhood cancer, most patient develop cardiomyopathy leading to congestive heart failure currently the heart failure developed in these patient is irreversible [8]. Cardiovascular toxicity rather than heart failure is arrhythmia, vascular dysfunction and atherosclerosis [9]. The most frequently doxorubicin related cardiac toxicity is dose related myocardial dysfunction [10].

AIM OF STUDY

To determine the incidence 0f clinical cardiotoxicity from anthracycline chemotherapy in children with cancer and to identify risk factors.

METHODS AND MATERIALS

One-year study from (January to December 2021) to children with cancer were received anthracycline as part of chemotherapy at cardiac unit of Benghazi Children's Hospital, Libya. 51 cases were visited cardiac unit for evaluation by Echocardiography, data were collected from patients' files, data included age, sex, diagnosis, duration of treatment with chemotherapy, type of anthracycline Adriamycin, Douanomycin one or both of them, total doses of anthracycline, Echocardiography findings, if patient still on chemotherapy or finished.

RESULTS

During the study period 0ne year (Jan.2021-Dec. 2021) 51 cases received anthracyclin as part of chemotherapy were evaluated with echocardiography there is male predominance 32 cases represented 37% while 19cases were females 37.3% of total cases M: F 1.6:1. Table 1. Age range from 5 months to 14 years, the commonest age group 1-5 years around 25cases represented to 49%, below 1 year 1case represented 2%, from 6-10 years 18 cases 35.3%, while more than 10 years 7 cases represented 13,7%. Table 2 Most cases evaluated in our study diagnosed with Acute Lymphoblastic Leukemia (ALL) 24 cases represented 47.1%, 9 cases with Acute Myeloid Leukemia (AML) 17%, Lymphoma 7 cases represented 13,7%, wilm's tumor 5 cases 9.8%, neuroblastoma 3 cases 5.8%. Each of Retinoblastoma, adrenocortical carcinoma and hepatoblastoma 1 case for each diagnosis represented 2% each one. Table3 34 cases were evaluated still on treatment 66.7%, 17 cases 33.3% were finished treatment on follow up. table 4 29 cases were received treatment for less than or equal to one year represented to 56.9%, while 22 cases 43.1%. table5 We were divided the patient according to type of anthracyclin (Adriamycin or douanomycin) results show 20 cases were received Adriamycin only represented 39.2%, 4 cases were received douanomycin 7.8%, while 27 cases received both of them 53% of total cases. table 6 35.9 % of cases received total doses between 201-250 mg\ S.A of anthracyclin, 25 cases 32.1% were received less than 100 mg\S. A, 251-300 mg\ S.A noted in 4 cases represented 5.1%, 10 cases represented 12.8% doses range from 100-150 mg\ S.A , while 151-200 mg\S.A noted in 11cases represented 14.1% .table 7 Echocardiography finding were normal in 47 cases represented 92.2%, Acute dilated cardiomyopathy (DCM) noted in 1 case 1.9%, was improved with treatment reversible, 3 cases with chronic dilated cardiomyopathy represented 5.9%, these 3 cases need treatment and follow up cardiac clinic for long life. Table 8 2 cases with trisomy 21 represented 4%, received anthracyclin chemotherapy without complication. 2 cases have congenital heart disease (4%) one has patent ductus arteriosus ventricular septal defect (VSD), and (PDA) ,2 Both of them received anthracyclin chemotherapy without complication. When we compare cases that develop cardiac complications with age 1 case below one year, 2 cases between 6 – 10 years ,1 case more than 10 years of age. Table 9 4 cases with cardiac complication 3 cases were males, 1 case was female. Table 10 When analyzed the data we observe the 3 cases from 4 cases develop cardiotoxicity received chemotherapy >1 year, while 1 case

< 1 year. 29 cases were received chemotherapy1year. Table 11 When compare the results 17 cases were finished treatment with chemotherapy 3 cases (17.6%) develop cardiac toxicity ,34 cases still on treatment with chemotherapy 1 of them (2.9%) developed reversible cardiotoxicity. Table 12 When compare result of Echo with type of drugs if child was received adriamycin, duanomycin or both of them 4 patients were received duanomycin 1only 1 had cardiac toxicity 25%, while 3 patients had normal heart 75%, 20 patients were received adriamycin 1 of them had cardiac toxicity 5%,19 patient have normal heart 95%, 27 patients were received both types of anthracyclin 25 patients have normal heart92.2% ,2 patients get cardiac complications 7.8%.

Table 1: Distribution of patients according to sex

Sex	No.	%
Male	32	62.7
Female	19	37.3
Total	51	100

Table 2: Distribution of patients according to age

Age /year	No.	%
< 1	1	2
1 -5	25	49
6- 10	18	35.3
>10	7	13.7
Total	51	100

Mean age = 5.99yeas. Std. Deviation =3.6 years. Median=5 years. Mode =3 Minimum age= 5 months. Maximum = 14 years.

Table 3: Distribution of patients according to diagnosis

Diagnosis	No.	%
Acute lymphoid leukemia	24	47.1
Acute myeloid leukemia	9	17.6
Lymphoma	7	13.7
Wilm's tumor	5	9.8
Neuroblastoma	3	5.8
Adrenocortical carcinoma	1	2
Retinoblastoma	1	2
Hepatoblstoma	1	2
Total	51	100

Table 4: Distribution of patients according to treatment status

Treatment status	No.	%
Finished treatment	17	33.3
Still on treatment	34	66.7
Total	51	100

Table 5: Distribution of patients according to duration of treatment

Duration of treatment/year	No.	%
≤ 1	29	56.9
< 1	22	43.1
Total	51	100

Table 6: Distribution of patients according to type of drugs

Type of drugs	No.	%
Daunomycin	4	7.8
Adriamycin	20	39.2
Both	27	53
Total	51	100

Table 7: Distribution of patients according to dose of drugs

Dose of drugs	No.	%
<100	25	32.1
100 -150	10	12.8
151 -200	11	14.1
201 -250	28	35.9
251 -300	4	5.1
Total	78	100

Table 8: Distribution of patients according to Echo finding

Echo finding	No.	%
Normal	47	92.2
Acute cases	1	1.9
Chronic cases	3	5.9
Total	51	100

Table 9: Distribution of patients according to Echo finding and age

Age /year	Echo finding			
	Normal heart		Abnormal heart	
	No.	%	No.	%
< 1	0	0	1	100
1 -5	25	100	0	0
6- 10	16	88	2	12
>10	6	84	1	16
Total	47	92.2	4	7.8

X^2=14.546 df= 3; p=0.002 (Significant)

Table 10: Distribution of patients according to Echo finding and sex

Sex	Echo finding			
	Normal heart		Abnormal heart	
	No.	%	No.	%
Male	29	90.6	3	9.4
Female	18	94.7	1	5.3
Total	47	92.2	4	7.8

X^2=0.279 df=1 p=0.597(Not Significant)

Table 11: Distribution of patients according to Echo finding and

Duration of treatment	Echo finding			
	Normal heart		Abnormal heart	
	No.	%	No.	%
≤ 1	28	96.6	1	3.4
> 1	19	86.4	3	13.6
Total	47	88.2	4	11.8

X^2=1.796 df=1; p=0.180 (Not Significant)

Table 12: Distribution of patients according to Echo finding and treatment status

Treatment status	Echo finding			
	Normal heart		Abnormal heart	
	No.	%	No.	%
Finished treatment	14	82.4	3	17.6
On treatment	33	97.1	1	2.9
Total	47	92.2	4	7.8

X^2=3.391df= 1; p=0.066 (Not Significant)

Table13: Distribution of patients according to Echo finding and type of drugs

Type of drugs	Echo finding			
	Normal heart		Abnormal heart	
	No.	%	No.	%
Daunomycin	3	75	1	25
Adriamycin	19	95	1	5
Both	25	92.6	2	7.4
Total	47	92.2	4	7.8

X^2=1. 86df=2; p=0.395 (Not Significant)

DISCUSSION

In our study the males are more common 62.7%, and median age is 5.99 years, in study at Pakistan males represented 68% with median age is 74 months (6years) [17], almost same result. Males &females have same risk for cardiac toxicity after anthracyclin treatment as our study showed.

At another study done on 589 patients proven that male sex associated with increased risk of cardiotoxicity [12]. Another study done by Steven E Lipchitz, etal, showed female sex associated with increased risk of cardiotoxicity [13].

Younger age group is risk factor for developing cardiac toxicity after anthracyclin treatment as our study showed, same result noted in study done by Vivan I Franco, etal, younger age group is significant risk factor [13], while at another place KK Woman's &children's Hospital study showed age not risk factor [14].

Our results show most common malignancy is acute leukemia 64%, acute lymphoblastic leukemia represented 47.1%, it is most common malignancy in children, in study done by Abdal Saltan, etal, show acute lymphoblastic leukemia is the commonest malignancy 70% of total patients in study [17].

Our study showed if used the combination of anthracyclin (Adriamycin &douanomycin) or one of them no significant difference, risk of cardiotoxicity is the same, conversely in study done at Pakistan by Abdal Saltan,etal, showed the combination of Adriamycin and douanomycin carried high risk of cardiotoxicity [17].

No mortality in our study, while study done at Singapore there were 3 patient die from End stage heart failure 9.4%. This difference in results can be explained by difference in duration of each study.

In our study result showed trisomy 21 is not a risk of cardiotoxicity either have normal heart or congenital heart disease before starting treatment, While in study done by Vivan I Franco,etal, showed trisomy 21 and preexisting cardiovascular disease have higher risk of cardiotoxicity after anthracyclin treatment [13].

Duration of treatment with anthracyclin not associated with risk for cardiotoxicity as result of our study. Higher accumulative doses of anthracyclin associated with higher risk of cardiotoxicity as result of two studies first in childhood cancer center [15], and retrospective study done in Dr.Soe tomo General Hospital [16]. While in our study higher doses of anthracyclin not associated with risk of cardiotoxicity.

CONCLUSION

Our study proven anthracyclin is cardio toxic drugs especially in young age group, no mortality in our study, but anthracyclin causing morbidity. No differences between males and females. We need more and more prospective studies to detect risk factors and decrease morbidity for child who cure from malignancy. For any child diagnosed with malignancy should have base line Echo and to be repeated every 3 months in case of normal heart, if have any cardiac lesion repeated according to cardiologist. Most important point follow up any child cure from malignancy and finished chemotherapy every 3 to 6 months with Echo for 3 to 5 years.

REFERENCES

1. Childhood cancer mortality http://seer.cacer.gov / publications/childhood/mortiality.PFP
2. Robison, L. L. (2005). The Childhood Cancer Survivor Study: a resource for research of long-term outcomes among adult survivors of childhood cancer. *Minnesota Medicine*, *88*(4), 45-49. [pub Med] [Google Scholar].
3. Oeffinger, K. C., Mertens, A. C., Sklar, C. A., Kawashima, T., Hudson, M. M., Meadows, A. T., ... & Robison, L. L. (2006). Chronic health conditions in adult survivors of childhood cancer. *New England journal of medicine*, *355*(15), 1572-1582. [pub Med] [Google Scholar].
4. Galderisi, M., Marra, F., Esposito, R., Lomoriello, V. S., Pardo, M., & de Divitiis, O. (2007). Cancer therapy and cardiotoxicity: the need of serial Doppler echocardiography. *Cardiovascular ultrasound*, *5*(1), 1-14. [PubMed][Google Scholar].
5. Tan, C., Tasaka, H., Yu, K. P., Murphy, M. L., & Karnofsky, D. A. (1967). Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease. Clinical evaluation with special reference to childhood leukemia. *Cancer*, *20*(3), 333-353. [PubMed][Google Scholar].
6. Di Marco, A. (1969). Adriamycin (NSC-123,127): a new antibiotic with antitumor activity. *Cancer Chemoth. Rep.(Part 1)*, *53*, 33-37. [Pub Med] [Google Scholar]
7. Dazzi, H., Kaufmann, K., & Follath, F. (2001). Anthracycline-induced acute cardiotoxicity in adults treated for leukaemia: Analysis of the clinico-pathological aspects of documented acute anthracycline-induced cardiotoxicity in patients treated for acute leukaemia at the University Hospital of Zurich, Switzerland, between 1990 and 1996. *Annals of oncology*, *12*(7), 963-966. doi:10.1023/a:1011196910325.
8. Chatterjee, K., Zhang, J., Honbo, N., & Karliner, J. S. (2010). Doxorubicin cardiomyopathy. *Cardiology*, *115*(2), 155-162. [PMC free article] [pub Med].
9. Susan, D., Loannis, M., Harsh, P., Brandy, P.,

Avirup, Guha. (2021). Essential of cancer survivorship ,177-193.

10. Mohmed, K. A., Michael, S.E., *et al.,* (1992). Late doxorubicin associated cardiotoxicity in children with cancer 74(1),182-188.
11. Retrospective cohort study from Jun.2015 to Dec. 2018.Jiawei Xu, Xia Wan, Xia Uyan Wu, fen Z hozr. Department of Pediatric, Union Hospital Tongjie Medical Collage, Hua Zhory of Science and Technology Wuhan, China.
12. Layja, D., Jennifer, R., *et al.,* (2019). Electrocardiogram for cardiomyopathy risk stratification in children with anthracyclin exposure. Cardio oncology 5, Article number, 10.
13. Vivan, I. F., Steven, E. l. (2015). cardiac complications in childhood cancer survivors treated with anthracyclin. Cardiol Young. 25 supp/2, 107 – 16.doi:10.2017/S 104755-1115000906.
14. cardiotoxicity after anthracyclin chemotherapy for childhood cancer in multiethnic Asian population. (Varen Zhi, Zherg Tan, Nicple Min Chan, *et al.,*). Front Pediatric.03 February 2021/https://doi.org/103389/F ped.2021.639603.
15. Harake, D., Franco, V. I., Henkel, J. M., Miller, T. L., & Lipshultz, S. E. (2012). Cardiotoxicity in childhood cancer survivors: strategies for prevention and management. *Future cardiology*, *8*(4), 647-670.
16. Asian Pac J cancer prev., 22(5), 1407-1412.
17. Shaikh, A. S., Saleem, A. F., Mohsin, S. S., Alam, M. M., & Ahmed, M. A. (2013). Anthracycline-induced cardiotoxicity: prospective cohort study from Pakistan. *BMJ open*, *3*(11), e003663.