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Incidence of cardiotoxicity in treated cases of pediatric Hodgkin lymphoma

Abstract

Background: With the advent of modern chemo-radiotherapy, more patients of Hodgkin Lymphoma (HL) have increased 5year survival rate. The therapy related cardiac diseases have become the established cause of non-cancer related morbidity and mortality.

Materials and methods: This is a retrospective study of 58 patients with HL up to 18years of age treated in Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore, Pakistan, during 2013. Baseline cardiac status was determined by echocardiography with ejection fraction (EF) as the main determinant. After treatment post treatment EF was determined. Comparison was made between pretreatment and post treatment EF according to age, sex, weight, stage of disease, presence/absence of mediastinal mass, chemotherapy protocol and whether radiotherapy (XRT) was given or not. Data was analyzed using SPSS 13. P value <0.05 was taken as significant.

Results: Out of 58 patients 10 were female (17.2%) and 48 were male (82.8%). Mean age and weight were 9.07 years & 27.68kg respectively. Patient with stage I was 1(1.7%), stage II patients were 21(36.2%), stage III were 26(44.8%) & stage IV were 10(17.2%). Out of 58 patients 5 had nodular predominance HL (8.6%) & the remaining classical HL (91.2%).In classical HL category, 30 patients had nodular sclerosis (NS) (51.6%), 10 patients had mixed cellularity (MC) (17.2%), 10 patients had lymphocyte rich HL (17.2%) & only 3 patients had lymphocyte depleted HL (5.2%). Patients were also screened for EBV status only 7patients had positive result (12%), while remainder was negative (87.7%). Mediastinal widening was present in 31patients (53.4%), absent in 25 patients (43.1%). 1 patient received COPP (Cyclophosphamide, Vincristine, Prednisolone, Procarbazine) 1.7%, 19 received OEPA (Vincristine, Etoposide, Prednisolone, Adriamycin) 32.8%, 1 patient received OEPA/ABVD (Adriamycin, Bleomyocin, Vincristine, Doxorubicin) 1.7%, 36 received OEPA/COPP (62.1%) and 1 patient received OEPA/COPP/EPIC (Etoposide, Prednisolone, Ifosfamide, Cisplatin) 1.7%. Radiotherapy (XRT) was given to 26 patients (44.8%) only. Mean EF before treatment was 67.38% with SD±6.746% and after treatment was 65.62% with SD±4.701%. The difference between the two values was not statistically significant (P>0.05).

Conclusion: In this study the difference between pre-treatment and post treatment groups was not significant statistically and needs to be confirmed with large scale studies.

Keywords: cardiotoxicity, chemotherapy, anthracyclines, lymphoma, pediatric

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Abbreviations: HL, hodgkin lymphoma; EF, ejection fraction; XRT, radiotherapy; MC, mixed cellularity; ABVD, adriamycin, bleomyocin, vincristine, doxorubicin; EPIC, etoposide, prednisolone, ifosfamide, cisplatin; SD, standard deviation; NS, nodular sclerosis; COPP, cyclophosphamide, vincristine, prednisolone, procarbazine

Introduction

Increased survival of paediatric patients with malignancies has led to the emphasis on the side effects of chemotherapy and impact on survival in later life.[1] Hodgkin's lymphoma patients survival has increased markedly over the last few decades as a result of recent advancements in chemo-radiotherapy.[2] Late side effects of therapy may present in 2 of every 3 treated cases. After initial diagnosis, the patients with cancer and its treatment, about 1/3 of patients can develop profound morbidity after two to three decades of cancer treatment.[3]

The incidences of second primary malignancies, infections and cardiotoxicity have increased with improved prognosis of paediatric Hodgkin's lymphoma.[4–6] Post chemo/radiotherapy cardiotoxicity is one of the leading complications.[7] In paediatric cancer patient's death due to cardiac complications is ten times more than children of similar age group.[8] In children heart and lung disorders are one of the three main causes of death.[8] The recurrence of primary disease and secondary malignancies are the two most common causes among childhood cancer survivors.[9] Cardiac dysfunction may present as myocardial dysfunction, myocarditis, congestive cardiac failure, arrhythmias, valvular dysfunction and accelerated risk of myocardial dysfunction in later life. Though each chemotherapeutic agent has unique cardiac effects yet radiotherapy also has additive effects in increasing morbidity.[10] Majority of cardiac adverse effects are due to anthracycline based chemotherapy, mediastinal and neck radiation. Cardiotoxicity has also been documented with various other chemotherapeutic agents like platinum based compounds, carmustine,

busulfan, mechlorethamine, mitomycin, paclitaxel, etoposide, teniposide, cystosine arabinoside, antimetabolites, cyclophosphamide and ifosfamide.[11] Though mortality due to cardiac disease after mediastinal radiotherapy has increased yet cardiotoxicity due to anthracyclines has also been noticed in various studies.[10,12]

Previously no study has been done in our setup to see the incidence of cardiotoxicity in treated cases of paediatric Hodgkin lymphoma. After treatment patients with Hodgkin Lymphoma experience increased risk of various cardiovascular diseases for a prolonged period as cardiac dysfunction is a prominent cause of disability in later life. Late cardiotoxicity is caused by thoracic radiation and anthracyclines. As survival rates of patients treated for Hodgkin Lymphoma continue to improve, management and prevention of treatment related adverse effects have gained importance. Clinicians treating paediatric patients of Hodgkin Lymphoma who have received chemo/radiotherapy should advise them about future risk factors such as increased blood pressure, dyslipidemia, and lifestyle modifications such as exercise, weight reduction and avoidance of smoking. This study highlights the effect of chemo-radiotherapy in survivors of childhood Hodgkin lymphoma cases.

Patients and methods

This is a retrospective study done at Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore, Pakistan as data was retrieved from January 2013 to December 2013. Fifty eight patients up to the age of 18 years fulfilling the criteria were included in this study, both from indoor and outdoor settings. Baseline cardiac status was determined by echocardiography with ejection fraction (EF) as the main determinant. Patients were given treatment in the form of chemotherapy as well as radiotherapy according to Euronet protocol for paediatric Hodgkin lymphoma. The main chemotherapeutic agents used were anthracycline, bleomycin, cyclophosphamide, prednisolone and cisplatin. After treatment in the form of chemo-radiation depending upon stage of disease, post treatment EF was determined. These patients were followed up to 2years after treatment. Comparison was made between pretreatment and post treatment EF according to age, sex, weight, stage of disease, presence/absence of mediastinal mass, chemotherapy protocol and whether radiotherapy (XRT) was given or not. Data was analyzed using SPSS version 13. P value<0.05 was taken as significant.

Results

Out of fifty eight patients 10 were female (17.2%) and 48 were male (82.8%). The age range was from 3 years to 17years. Mean age was 9.07years with standard deviation SD±4.086years. The weight range was from minimum of 11kg to maximum of 56kg. Mean weight was 27.68kg with SD±12.011kg. For all patients staging was done on the basis of CT/PET, bone scan and bone marrow aspirate, along with radiotherapy, chemotherapy was given according to standard protocol followed in hospital. Only one patient was having stage IA (1.7%), 20 patients were having stage II A(34.5%), 1 patient II B E (1.7%), 11 patients had III A (19.0%), one patient had III AS (1.7%), 14 patients having III B (24.1%), 2 patients IVA (3.4%) and 8 patients had IVB (13.8%) as shown in Table 1. Out of 58 patients 5 had nodular predominance HL (8.6%) & the remaining classical HL (91.2%). In classical HL category, 30 patients had nodular sclerosis (NS) (51.6%), 10 patients had mixed cellularity (MC) (17.2%), 10 patients had lymphocyte rich HL (17.2%) & only 3 patients had lymphocyte depleted HL (5.2%). Patients were also screened for EBV status, only 7 patients had positive result (12%), while remainder was negative (87.7%). Mediastinal widening was present in 31 patients (53.4%), absent in 25 patients (43.1%). Patients were given standard protocol chemotherapy as one patient received COPP (Cyclophosphamide, Vincristine, Prednisolone, Procarbazine) (1.7%), 19patients received OEPA (Vincristine, Etoposide, Prednisolone, Adriamycin) (32.8%), one patient received OEPA/ABVD (Adriamycin, Bleomyocin, Vincristine, Doxorubicin) (1.7%), 36patients got OEPA/COPP (62.1%) and one patient received OEPA/COPP/EPIC (Etoposide, Prednisolone, Ifosfamide, Cisplatin) (1.7%) as shown in Table 2. Radiotherapy (XRT) was given to 26 patients (44.8%) only as 32patients got no radiotherapy. Ejection fraction (EF) before chemotherapy in overall patients range in between 30% and 81% and after chemotherapy ranged in between 58% and 79%. Mean EF before treatment was 67.38% with SD±6.746% and after treatment was 65.62% with SD±4.701% as shown in Table 3. The difference between the two values was not statistically significant (P> 0.05). In female patients the minimum EF was 62% and maximum was 81% before chemotherapy with mean EF of 69.20% with SD±5.432. And after chemotherapy the EF fraction range was in between 58% and 78% with mean of 66.90 with SD±5.971 as shown in Table 4. In male patients before chemotherapy the EF range was in between 30% and 75% having mean EF of 67% with SD±6.977. The EF ranged from minimum of 59% to maximum of 79% after chemotherapy with mean EF of 65.35% with SD±4.422 as shown in Table 5. EF in different stages of HD before and after chemotherapy in shown in Table 6. The patients who got radiation therapy, minimum EF before XRT was 30% and maximum EF was 81%, having mean of 66.23% with SD±9.026. After radiotherapy minimum EF was 58% and maximum was 72% having mean of 64.42% with SD of ±.291 as shown in Table 7.

Table 1 Stage on BL CT/PET

Stage	Frequency	Percent
IA	1	1.7
IIA	20	34.5
IIBE	1	1.7
IIIA	11	19
IIIAS	1	1.7
IIIB	14	24.1
IVA	2	3.4
IVB	8	13.8
Total	58	100

Table 2 Chemotherapy protocol

Protocol	Frequency	Percent
COPP	1	1.7
OEPA	19	32.8
OEPA/ABVD	1	1.7
OEPA/COPP	36	62.1
OEPA/COPP/EPIC	1	1.7
Total	58	100

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Table 3 Echo EF% before and after Chemotherapy

Total patients	Echo EF% before chemotherapy	Echo EF% after chemotherapy
N	58	58
Minimum	30	58
Maximum	81	79
Standard Deviation	6.746	4.701
Mean	67.38	65.62

Table 4 Echo EF% in female patients before and after chemotherapy

Female patients	Echo EF% before chemotherapy	Echo EF% after chemotherapy
N	10	10
Minimum	62	58
Maximum	81	78
Standard Deviation	5.432	5.971
Mean	69.2	66.9

Many cancers are treatable like TB, hypertension and nephrotic syndrome in children but require proper management and treatment.[13] The aim should be not only to treat the primary disease but also to improve quality of future life in cancer patients. Paediatric cancer patients are at a great risk of suffering from cardiac problems as a result of toxicity of both chemotherapy and radiotherapy. They also are at risk of suffering from either secondary malignancy or recurrence of primary disease.[14] Current therapeutic modalities for paediatric Hodgkin lymphoma include chemotherapy, radiotherapy alone or sometimes in combination. In addition to their beneficial effects these treatment regimens also pose some serious, devastating cardiac side effects. So it is very important to understand their benefits and adverse effects when formulating treatment regimens for Hodgkin lymphoma in paediatric population.[10]

Table 5 Echo EF% in male patients before and after chemotherapy

Male patients	Echo EF% before chemotherapy	Echo EF% after chemotherapy
N	48	48
Minimum	30	59
Maximum	75	79
Standard Deviation	6.977	4.422
Mean	67	65.35

Each chemotherapeutic agent bears some important and vivid cardiac side effects. Radiation therapy also increases the chances of cardiotoxicity in these patients. As cancer patients are already critically ill, so both condition and treatment may go side by side in causing cardiotoxicity and potentiating adverse effects of one and the other.[10] In both symptomatic and asymptomatic patients, cardiac adverse effects can be detected. Both biochemical and histological markers can detect toxicity in asymptomatic patients. For example toxicity due to anthracycline may be detected in cardiac biopsy specimens but laboratory parameters like Troponin T and I may remain normal or near normal. In 1981 WHO published scoring system to classify drug side effects but it does not consider biochemical markers that show cardiotoxicity (Table 8). [13]

Table 6 Echo EF% in different stages of Hodgkin Lymphoma

		Stage on BL CT/PET							
		IA	IIA	IIBE	IIIA	IIIAS	IIIB	IVA	IVB
Echo EF% before chemo	N	1	20	1	11	1	14	2	8
	Minimum	68	63	81	58	73	30	55	62
	Maximum	68	75	81	75	73	73	72	69
	Mean	68	69	81	67.18	73	65.71	63.5	65
	Standard Deviation	..	3.449	..	5.363	..	10.781	12.021	2.39
Echo EF% after chemo	N	1	20	1	11	1	14	2	8
	Minimum	69	58	71	60	65	59	61	60
	Maximum	69	79	71	70	65	72	63	78
	Mean	69	67.4	71	64.36	65	64.07	62	65.5
	Standard Deviation	..	4.978	..	3.139	..	4.393	1.414	6.047

Table 7 Echo EF% in patient given Radiation Therapy

Radiation therapy		Echo EF% before chemo	Echo EF% after chemo
Not Given	N	32	32
	Minimum	58	60
	Maximum	75	79
	Mean	68.31	66.59
	Standard Deviation	3.995	4.858

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Table Continued.....

Radiation therapy		Echo EF% before chemo	Echo EF% after chemo
	N	26	26
	Minimum	30	58
Given	Maximum	81	72
	Mean	66.23	64.42
	Standard Deviation	9.026	4.219

Table 8 Histological subtypes

Histological subtype	Frequency	Percent
Nodular lymphocyte Predominance	5	8.60%
Classical	53	91.20%
Nodular Sclerosis	30	51.60%
Mixed cellularity	10	17.20%
Lymphocyte rich	10	17.20%
Lymphocyte depleted	3	5.20%

Discussion

Nonspecific ST-segment and T-wave abnormalities are manifestations of acute cardiotoxicity, but cardiac adverse effects due to anthracyclines in later life is dose dependent. Cardiotoxicity can be due to increased dose and pathogenesis is presumed to be due to free radical induced cardiac damage.[15] The patients who are given doxorubicin in dose range of 550mg/m^2 are at risk of suffering from cardiomyopathy. However studies done recently have depicted that even lower cumulative doses can cause similar cardiomyopathy.[16] Nowadays most cancers are treated with radiotherapy and radiation to chest cage can damage heart and surrounding major structures.[17] Using radiotherapy alone or in combination with chemotherapy can increase the risk of cardiotoxicity.[18] In patients who have underlying heart diseases like rheumatic and valvular heart diseases are more prone and the earliest warning sign is endothelial cell damage.[19]

Out of fifty eight patients 10 were female (17.2%) and 48 were male (82.8%). The age range was from 3years to 17years. Mean age was 9.07years with standard deviation SD±4.086years. In one study by Mulrooney et al.[20] among the 14 358 survivors of cancer patients 53.7% were male and 46.3% were females while in our study only 17.2% patients were females. Median age at diagnosis was 6.0years (range 0-20years), with 40% of participants under 5years of age at diagnosis. The weight range was from minimum of 11kg to maximum of 56kg. Mean weight was 27.68kg with SD±12.011kg.

In another study by Hull et al.[21] 60% were male and 40% were female. In his study Ann Arbor stages, 24% patients were stage I, while in our study patients with stage I Hodgkin lymphoma were just 1.7%. Patients with stage II Hodgkin lymphoma were 44%, while in our study stage II patients were 36.2%. Stage III Hodgkin lymphoma patients were 25%, while in our study patients with HD stage III were 24.1% which is almost equivalent. 7% patients were in stage IV, while in our study patients with stage IV Hodgkin lymphoma were 17.2%. In our study 44.8% patients got chemotherapy and radiotherapy, while 55.2% patients got only chemotherapy, while in study by Hull et al.[21] 62% patients received chemotherapy and radiotherapy, while 38% patients received only radiotherapy.

Ejection fraction (EF) before chemotherapy in overall patients range in between 30% and 81% and after chemotherapy ranged in between 58% and 79%. Mean EF before treatment was 67.38% with SD±6.746% and after treatment was 65.62% with SD±4.701% as shown in Table 3. In one study done by Myrehaug et al.[22] showed that cardiotoxicity was more among the patients treated with chemotherapy along with radiotherapy. In another study done by Lipshultz et al.[23] showed that females treated with chemotherapy have higher risk of late cardiotoxicity.

Conclusion

The incidence of cardiotoxicity in treated cases of HD depends to a large extent on gender, weight, presence or absence of mediastinal mass, type and dosage of chemotherapy and whether XRT was given or not as mentioned in literature and previous data. The childhood cancer survivor patients are prone to develop hypertension, increased risk of coronary artery disease, heart failure, valvular diseases and arrhythmias. As this study was conducted on small scale, the difference between pre-treatment and post treatment groups was not significant statistically and needs to be confirmed with large scale studies.

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Conflict of interest

The author declares no conflict of interest.

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