DOI: https://doi.org/10.53350/pjmhs22164498

ORIGINAL ARTICLE

Frequency of Cardiac-Toxicity in Patient Treated with Anthracycline, An Institutional Perspective

MUHAMMAD TARIQ[1], MUHAMMAD IBRAHIM[2], SAQIB RAZA KHAN[3], SEHRISH SARWAR BALOCH[4], MEHWISH SHAHZADI[5], YASMIN ABDUL RASHID[6], MUHAMMAD JAWAD ZAHID[7], MOHAMMAD DAANYAAL KHAN[8]
[1]*Department of Oncology, Khyber Teaching Hospital, Peshawar, Pakistan*
[2]*Deaprment of Oncology, Hayatabad Medical Complex, Peshawar, Pakistan*
[3]*Deaprtment of Oncology, Aga Khan University Hospital, Karachi, Pakistan*
[4]*Deaprtment of Oncology, Aga Khan University Hospital, Karachi, Pakistan*
[5]*Deaprtment of Oncology, Aga Khan University Hospital, Karachi, Pakistan*
[6]*Deaprtment of Oncology, Aga Khan University Hospital, Karachi, Pakistan*
[7]*Rehman Medical College, Peshawar, Pakistan*
[8]*Khyber Medical College, Peshawar, Pakistan*
Corresponding author: Dr. Muhammad Tariq Email: tariq16864@gmail.com

ABSTRACT

Introduction: Cancer now affects more than one in three people in their lifetime. Cancer remains the leading cause of death in many countries. Anthracycline-based chemotherapy has played an important part in the current age of cancer treatment, with earlier diagnosis and novel medicines.

Objective: To find out the frequency of cardiac-toxicity (cardiomyopathy) in patient treated with anthracycline

Methodology: This Descriptive Study was carried out at the Oncology department of Hayatabad Medical Complex, Peshawar for duration of six months from 20 Dec, 2019 to 20 Jun, 2020. Patients attending the medical oncology department of Hayatabad Medical Complex, Peshawar were included in the study. Demographic data like age, sex was collected in the pre-designed Performa. The patients were sent for echocardiography which was done by cardiologist and ejection fraction was noted. The patients suitable for treatment on anthracycline were started with standard doses for his/her carcinoma which were for leukemia 25mg/m^2 weekly for 1 months, for lymphoma (NHL) 50mg/m^2 after every 21 days for 4.2 months, for breast carcinoma 60mg/m^2 after every 21 days for 2.8 months.

Results: As per frequencies and percentages for anthracycline induced cardiomyopathy, 31 (15.0%) patients had anthracycline induced cardiomyopathy.

Conclusion: Our research shows that although preventing chronic cardiotoxicity may be challenging, prolong infusion methods for anthracyclines offer a reduced risk, and novel liposomal formulations of doxorubicin may provide less cardiotoxicity as compared to conventional doxorubicin.

Key words: Anthracyclines; Cardiotoxicity; Treatment

INTRODUCTION

Cancer now affects more than one in three people in their lifetime. Cancer remain the leading cause of death in many countries [1, 2]. The overall 10 year rate of survival for cancer is 50% for the twenty most prevalent cancers and around 80% for melanoma, breast, uterine cancer and lymphoma [3]. It was estimated that 1684210 new cases of cancer were observed in USA in 2016 and 595690 deaths in the same year [4]. In Pakistani population approximately 406 (both male and female) new cases are diagnosed each day, out of these 23% are breast cancers and approximately 133 cancer deaths per day occur due to cancer [5].

Anthracycline-based chemotherapy has played an important part in the current age of cancer treatment, with earlier diagnosis and novel medicines [6-8]. Antibiotic overproduction methods had a major breakthrough with the development of doxorubicin [8]. Anthracycline chemotherapy has a significant role in the treatment of many types of cancer, including breast cancer (32%) [9], elderly lymphoma (57-70%) [10, 11], and childhood cancer survivors (50-60%) since its introduction [12]. World Health Organization (WHO) essential medicines list includes anthracyclines [13].

However, Anthracycline treatment is compromised by cardiomyopathy and heart failure. Cardiac complications were first reported a few years after the introduction of daunorubicin [14]. The cancer survivor is exposed to higher cardiovascular morbidity and death due to cardiotoxic adverse effects. Anthracycline-related heart dysfunction may cause significant morbidity and death among the 150 000 or more individuals in the United States who have survived childhood cancer [15]. Heart failure incidences of 1.6%, 5%, 16%, and 26% were predicted for total doxorubicin doses of 240-360, 400, 500, and 550 mg/m^2, respectively [16, 17]. With a total dosage of 400 mg/m2, age proved to be a key risk factor for doxorubicin-related heart failure, with older patients (age > 65 years) displaying a higher incidence of CHF than younger patients (age ≤65 years) [16]. The rationale of my study is to find out the frequency of anthracycline induced cardiotoxiciy in Pakistani patients as no current study have found on this subject. The result of my study can be used for the development of effective protection against anthracycline-induced cardiotoxicity which will likely to have a major impact on these patients' overall survival.

MATERIAL & METHODS

This Descriptive Study was carried out at the Oncology department of Hayatabad Medical Complex, Peshawar for duration of six months from 20 Dec, 2019 to 20 Jun, 2020. Patients attending the medical oncology department in HMC were included in the study. Study approval was given by the institutional committee for ethics and research. 207 patients being treated with anthracycline were included in our study. Informed consent was signed from all the participants. The inclusion criteria for our study includes patients having Leukemia, Breast carcinoma, Lymphoma, of stage I to IV of tumor with any grade or any durations of tumor planed for starting on anthracycline, both gender patients having age above 16 to 60 years and welling to give consent while criteria for exclusion includes patients having congestive heart failure obvious from previous record with EF less than 50%, known cardiac valvular abnormality patients like, Rheumatic Heart Disease, congenital heart anomalies etc.

Demographic data like age, sex was collected in the predesigned proforma. Duration since diagnosis of malignancy, type of malignancy before the start of anthracycline, dose of anthracycline was also noted. The patients were sent for echocardiography which was done by cardiologist and ejection fraction was noted. The patients suitable for treatment on anthracycline were started with standard doses for his/her carcinoma which are for leukemia 25mg/m^2 weekly for 1 months, for lymphoma (NHL) 50mg/m^2 after every 21 days for 4.2 months, for breast carcinoma 60mg/m^2 after every 21 days for 2.8 months. The patients were then follow up for two months and were advised to visit us in case of any symptom related to congestive heart failure (increased in breathing than his/her usual breathing, waking

up during night due to breathlessness and increase shortness of breath on exertion of normal activity). In follow up visit or in case of presentation for cardiac failure symptom, again Echocardiography was done. The decrease in the ejection fraction of less than 50% and a decrease of >10% from the baseline as per operation definition was considered to have developed cardiotoxicity. In case of any cardiotoxicity the patients were managed as per hospital protocol along with the discussion with cardiologist. Analysis and entry of data and was done by using SPSS version 23. Mean ± SD was computed for age, duration since diagnoses of malignancy, BMI, baseline Ejection Fraction and dose of anthracycline. Frequency and percentages was presented for qualitative variable like gender, type of malignancy, anthracycline induced cardiomyopathy, smoking (positive when patient take at least 3 cigarette per day) and diabetes (positive when obvious from medical record and uses medication for it).

RESULTS

This study has been conducted on 207 patients at the Department of Medical Oncology, MTI-Hayatabad Medical Complex, Peshawar. Mean and SDs for age was 41.29+12.379. Mean and SDs for duration since diagnosis of malignancy was 3.45+1.173. Mean and SDs for BMI was 25.951+1.35. Mean and SDs for baseline was 55.27+1.834. Mean and SDs for dose of anthracycline was 524.28+39.483. (Table No. 1). 141 (68.1%) patients were below fifty years of age and 66 (31.9%) patients were above fifty years of age. 125 (60.4%) patients were male while 82 (39.6%) patients were female. 26 (12.6%) patients had breast carcinoma, 90 (43.5%) patients had lymphoma and 91 (44.0%) patients had leukemia. 131 (63.3%) patients had smoking history. (Table 2) As per frequencies and percentages for anthracycline induced cardiomyopathy, 31 (15.0%) patients had anthracycline induced cardiomyopathy. (Figure 1).

Table 1: Descriptive Statistics of the participants

Parameter	N	Minimum	Maximum	Mean	Std. Deviation
Age (Years)	207	22	60	41.29	12.379
Duration since diagnosis of malignancy (Years)	207	2	6	3.45	1.173
Body Mass Index (BMI)	207	23.2	28.5	25.915	1.3514
Baseline Ejection Fraction (%)	207	52	58	55.57	1.834
Dose of Anthracycline (mg/m2)	207	500	625	524.28	39.483

Table 2: Demographic parameters of the participants

Parameter	Category	Frequency (%)
Age	< 50 Years	141 (68.1%)
	> 50 Years	66 (31.9%)
Gender	Male	125 (60.4%)
	Female	82 (39.6%)
Type of cancer	Breast Carcinoma	26 (12.6%)
	Lymphoma	90 (43.5%)
	Leukemia	91 (44%)
Smoking history	Yes	131 (63.3%)
	No	76 (36.7%)

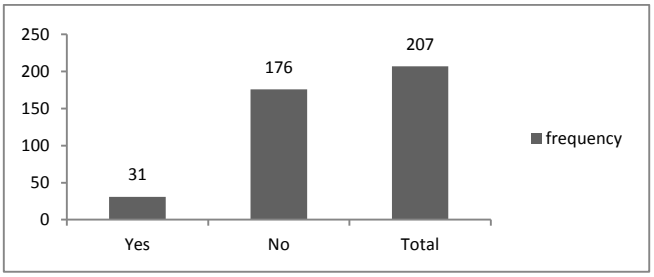

Figure 1: Frequency of Anthracycline induced Cardiomyopathy

DISCUSSION

The most important effect of anthracycline treatment is dose-dependent cardiotoxicity, which has a deleterious influence on the cardiac prognosis of cancer patients and is a major constraint on their therapeutic value [18]. When anthracycline chemotherapy is used, there is a lot of heart damage. There are three types of heart damage: acute cardiotoxicity, which normally happens right after anthracycline infusion, early-onset chronic progressive cardiotoxicity, which happens within a year of stopping chemotherapy, and late-onset chronic progressive cardiotoxicity which happens after a year of exposure [19]. Acute cardiotoxicity affects around 3 to 21 % of people, whereas late cardiotoxicity affects about 0 to 57 % of people [20]. Early diagnosis of subclinical cardiotoxicity, which is more common in patients receiving anthracycline chemotherapy, may improve patient survival rates [21].

In our study, as per frequencies and percentages for anthracycline induced cardiomyopathy, 31 (15.0%) patients had anthracycline induced cardiomyopathy. In accordance with our study, another study also reported comparable frequency of anthracycline induced cardiomyopathy [22, 23]. In comparison to our study, another study reported lower frequency of cardiomyopathy [24]. The heart failure rate in people with lymphoma who were given anthracycline and a non-anthracycline regimen was compared in another study. After 9 years of follow-up, 9.4% of people who took anthracycline had heart failure, compared to 0.8% of people who did not take anthracycline [25]. The goal of this research was to identify cardiac monitoring measures used on anthracycline-treated patients and compare them to worldwide guidelines. There is a scarcity of data on cardiac monitoring in anthracycline patients, and most research concentrate on cardiac monitoring in patients taking trastuzumab, which has been shown to be unsatisfactory [26]. Patients using anthracyclines should be continuously watched, even before they begin therapy, since early diagnosis aids in the treatment and prevention of cardiotoxicity [23].

Monitoring anthracycline-treated individuals has been shown to aid in the detection of cardiotoxicity in studies [23]. An echocardiography or MUGA scans are often used for cardiac monitoring [27]. During therapy, regular echocardiography monitoring is advised for high-risk individuals [27]. Single centre study and small sample size is the major limitation of our study. Studies based on large no of participant from multicentre are recommended.

CONCLUSION

Our research shows that although preventing chronic cardiotoxicity may be challenging, prolong infusion methods for anthracyclines offer a reduced risk, and novel liposomal formulations of doxorubicin may provide less cardiotoxicity as compared to conventional doxorubicin.

REFERENCES

1. Shin H-Y, Lee J-Y, Song J, Lee S, Lee J, Lim B, et al. Cause-of-death statistics in the Republic of Korea, 2014. Journal of the Korean Medical Association. 2016;59(3):221-32.
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115-32.
3. Coleman M, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. The Lancet. 2011;377(9760):127-38.
4. DeSantis CE, Siegel RL, Sauer AG, Miller KD, Fedewa SA, Alcaraz KI, et al. Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities. CA Cancer J Clin. 2016;66(4):290-308.
5. Sarwar MR, Saqib A. Cancer prevalence, incidence and mortality rates in Pakistan in 2012. Cogent Medicine. 2017;4(1):1288773.
6. Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med. 2002;346(9):645-52.
7. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA,

Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352(24):2487-98.
8. Rimal H, Lee S-W, Lee J-H, Oh T-J. Understanding of real alternative redox partner of Streptomyces peucetius DoxA: prediction and validation using in silico and in vitro analyses. Arch Biochem Biophys. 2015;585:64-74.
9. Giordano SH, Lin Y-L, Kuo YF, Hortobagyi GN, Goodwin JS. Decline in the use of anthracyclines for breast cancer. J Clin Oncol. 2012;30(18):2232.
10. Chihara D, Westin JR, Oki Y, Ahmed MA, Do B, Fayad LE, et al. Management strategies and outcomes for very elderly patients with diffuse large B-cell lymphoma. Cancer. 2016;122(20):3145-51.
11. Nabhan C, Byrtek M, Rai A, Dawson K, Zhou X, Link BK, et al. Disease characteristics, treatment patterns, prognosis, outcomes and lymphoma-related mortality in elderly follicular lymphoma in the United States. Br J Haematol. 2015;170(1):85-95.
12. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer. 2010;10(1):1-14.
13. Selection WECot, Medicines UoE, Organization WH. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children): World Health Organization; 2014.
14. Tan C, Tasaka H, Yu KP, Murphy ML, Karnofsky DA. Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease. Clinical evaluation with special reference to childhood leukemia. Cancer. 1967;20(3):333-53.
15. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med. 1997;126(10):827-8.
16. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2003;97(11):2869-79.
17. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol. 2007;50(15):1435-41.
18. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55(3):213-20.
19. Fradley MG, Neilan TG. Cardiovascular Outcomes in Anthracycline-Related Cardiomyopathy: When ap Value of> 0.05 Is a Good Outcome! : American College of Cardiology Foundation Washington, DC; 2017. p. 151-3.
20. Shaikh AS, Saleem AF, Mohsin SS, Alam MM, Ahmed MA. Anthracycline-induced cardiotoxicity: prospective cohort study from Pakistan. BMJ open. 2013;3(11):e003663.
21. Hu H-M, Zhang X-L, Zhang W-L, Huang D-S, Du Z-D. Detection of subclinical anthracyclines' cardiotoxicity in children with solid tumor. Chin Med J. 2018;131(12):1450-6.
22. Baech J, Hansen SM, Lund PE, Soegaard P, Brown PdN, Haaber J, et al. Cumulative anthracycline exposure and risk of cardiotoxicity; a Danish nationwide cohort study of 2440 lymphoma patients treated with or without anthracyclines. Br J Haematol. 2018;183(5):717-26.
23. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131(22):1981-8.
24. Reinbolt RE, Patel R, Pan X, Timmers CD, Pilarski R, Shapiro CL, et al. Risk factors for anthracycline-associated cardiotoxicity. Support Care Cancer. 2016;24(5):2173-80.
25. Eschenhagen T, Force T, Ewer MS, De Keulenaer GW, Suter TM, Anker SD, et al. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2011;13(1):1-10.
26. Henry ML, Niu J, Zhang N, Giordano SH, Chavez-MacGregor M. Cardiotoxicity and cardiac monitoring among chemotherapy-treated breast cancer patients. JACC Cardiovasc Imaging. 2018;11(8):1084-93.
27. Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, et al. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA Cancer J Clin. 2016;66(4):309-25.