The New Iraqi Journal of Medicine

Research Article
Cardiology

Early detection of mitral regurgitation in asymptomatic patients with normal left ventricular systolic function may be a predictor of cardiomyopathy after anthracycline treatment for childhood malignancy.

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Abstract

Background: Anthracycline antibiotics (doxorubicin, daunorubicin or epirubicin) rank among the most potent and clinically important anticancer drugs ever developed. However, their clinical utility is markedly hampered by a significant risk of cardiotoxicity, especially that of a chronic and delayed type[1].

Objective: To assess the incidence of new onset mitral regurgitation after treatment with anthracycline, , and to compare the prevalence of mitral regurgitation in these patients with a normal childrenof similar age.

Methods: Prospective echocardiograms study in tertiary pediatric oncology centre. Ninety one patients, aged 3 months –16 years (median 5 years), treated with anthracycline for childhood malignancy. Color flow Doppler detection of mitral regurgitation and its relation to changes in echocardiograms indices of left ventricular function (systolic and diastolic dimensions, fractional shortening); and the prevalence of mitral regurgitation in the anthracycline treated patients in comparison with normal children of similar age.

Results: Twenty patients (21.98%) developed mitral regurgitation, which was not apparent clinically, during or after anthracycline treatment, compared with only 2.4% of a normal children of similar age ($p < 0.0001$). All 20 patients had normal systolic function at the time of initial detection of mitral regurgitation, but two later developed impaired left ventricular function (after the first detection of mitral regurgitation).

Conclusion: Patients treated with anthracycline developed mitral regurgitation much more often than in the normal children. Echocardiograms detection of new mitral regurgitation may be an early predictor of anthracycline cardiomyopathy.

The N Iraqi J Med, April 2013;9(1):

Keywords:

Introduction

Cancer patients who are undergoing chemotherapy have an increased risk of developing cardiovascular complications, and the risk is even greater if there is a known history of heart disease. Among the serious clinical cardiac complications that have been reported are: arrhythmias, myocardial necrosis causing dilated cardiomyopathy, and vasoocclusion or vasospasm resulting in angina or myocardial infarction. A wide range of chemotherapy agents have been associated with cardio toxicity [2,3]. Innovative anticancer strategies have contributed to an improved survival of patients suffering from malignancies, and in some cases, have turned cancer into a chronic disease. Therefore, the early and particularly late onsets of adverse cardiovascular effects of systemic anticancer treatments are of increasing interest. Among a rapidly increasing variety of anticancer drugs, the anthracycline [4].

Echocardiograms are the most frequently used modality in the screening for cardiac disease during or after therapy. Echocardiograms are

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noninvasive and readily available. They provide means to evaluate the left ventricular ejection fraction (LVEF) along with systolic and diastolic cardiac function [5]. Many studies also use the measurement of fractional shortening (FS). In the only published guidelines for monitoring therapy during anthracycline treatment in pediatric population [6].

Mitral regurgitation in normal children and adolescents is rare [7]. My aim was to investigate the new onset of mitral regurgitation in patients with otherwise normal echocardiograms after anthracycline treatment, and to compare the prevalence of mitral regurgitation in these patients with a normal children of similar age.

Methods

in this prospective study, transthoracic echocardiograms data collected over 12 months (August 2010 –August 2011). The study was carried out at echocardiograms laboratory in Basra specialist Hospital for children. We investigate 91 patients (37 male, 54 female) following treatment with anthracycline chemotherapy for childhood malignancy. They were aged between 3 months and 16 years (median 5 years). All patients were assessed before starting chemotherapy. Patients who were on active treatment were assessed before each course of treatment . On follow up, these patients had assessments after completion of each chemotherapy regimen or earlier if there was any deterioration in their clinical status..At each visit a cross sectional, M mode, and color flow Doppler echocardiograms examinations were performed and the results analyzed by a pediatric cardiologist. The ultrasound study was performed in the left lateral position, with a single lead ECG recorded simultaneously. Sedation was not used. A Philips Sonos ultrasound imaging system (USA) was used.. The highest frequency transducer (7.5/5.5 MHz, 3.5/2.7 MHz, or 2.5/2.0 MHz) which gave adequate penetration was used. New onset mitral regurgitation was defined as a high velocity color jet detectable after mitral valve closure, occurring in a patient with a previously normal echocardiogram. Patients with mitral regurgitation secondary to established cardiomyopathy were not included in the analysis. The control group included 123 normal children and adolescent between 3 month to 16 years of age without any exclusion criteria as mentioned above and any previous history of cardiac disorder.

The data was analyzed using SPSS version 17 software.

Results

Baseline echocardiography was normal in all patients without mitral regurgitation, twenty patients (21.98%) developed recent trivial mitral regurgitation with normal other echocardiograms systolic and diastolic functions. 13 of these were female and 7 male, and they were aged between 4 months to 15 years (median 5 years). Cumulative anthracycline dosage received was calculated from chemotherapy protocols, and the maximum ranged from 150–450 mg/m^2 (median 225 mg/m^2). Tow patients—aged 7 and 15 years at time of first detection of mitral regurgitation—developed impaired left ventricular function (fractional shortening 22%, 20%, respectively), between four months and 12 months after their first course of anthracycline.

Table 1: The percentage of mitral regurgitation between patients and control.

	Mitral regurgitation		
	Positive	**Negative**	**Total**
Patients	20 (21.98%)	71 (78.02%)	91
Control	3 (2.4%)	120 (97.6%)	123
Total	23	191	214

Fisher's exact probability test:
The two-tailed P value equals 0.0001 is considered to be extremely statistically significant.

Table 2: sex distribution of the patients.

		Mitral regurgitation		
		positive	**negative**	**Total**
sex	**female**	13 (24.04%)	41 (75.93%)	54
	male	7 (18.92%)	30 (81.08%)	37
Total		20 (21.98%)	71 (78.02%)	91

Fisher's exact probability test:
The two-tailed P value equals 0.6151.
The one- tailed p value equals 0.37.
The result is considered to be not statistically significant.

Discussion

Anthracycline-induced cardiotoxicity has been categorized into acute, early-onset chronic progressive, and late-onset chronic progressive [8,9]. Acute cardiotoxicity occurs in <1% of patients immediately after infusion of the anthracycline and manifests as an acute, transient decline in myocardial contractility, which is usually reversible [10]. The early-onset chronic progressive form occurs in 1.6% to 2.1% of patients, during therapy or within the first year after treatment [10]. Late-onset chronic progressive anthracycline-induced cardiotoxicity occurs at least 1 year after completion of therapy in 1.6% to 5% of patients [9]. Early- and late-onset chronic progressive cardiotoxicity typically presents as dilated CMP in adults, which can be progressive [10]. Late-occurring cardiotoxicity may not become clinically evident until 10 to 20 years after the first dose of cancer treatment. In addition, the Childhood Cancer Survivor study demonstrated that 30 years after therapy, 73% of pediatric cancer survivors will develop at least 1 chronic physical health condition and 42% a severe, life-threatening or disabling condition, or die of a chronic condition [11]. The risk of clinical cardiotoxicity increases with a cumulative dose of anthracycline. Studies that have looked at the cumulative probability of doxorubicin-induced HF have found that it occurs in 3% to 5% with 400 mg/m^2, 7% to 26% at 550 mg/m^2, and 18% to 48% at 700 mg/m^2 [10,12]. However, in a retrospective review of 3 trials, the incidence of HF was found to be 26% with cumulative doses of 550 mg/m^2 [13]. For this reason, the maximum lifetime cumulative dose for doxorubicin is 400 to 550 mg/m^2 [10]. However, epirubicin or idarubicin appears to have less incidence of HF [14-16]. Risk factors for anthracycline toxicity include cumulative dose; intravenous bolus administration; higher single doses; history of prior irradiation; the use of other concomitant agents known to have cardiotoxic effects such as cyclophosphamide, trastuzumab, and paclitaxel; female gender; underlying cardiovascular disease; age (young and old age); and increased length of time since anthracycline completion [8,9,13].

Cancer therapy has shown terrific progress leading to important reduction of morbidity and mortality of several kinds of cancer. The therapeutic management of these patients includes combinations of drugs, radiation therapy and surgery. Many of these therapies produce adverse cardiovascular complications which may negatively affect the quality of life and the prognosis of the oncologic patients[17]. Biomarkers include B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-pro-BNP), cardiac troponin T (cTnT), and cardiac troponin I (cTnI). Mavinkurve-Groothuis wrote a review regarding biomarkers in the detection of pediatric anthracycline cardiotoxicity, it was concluded that there was a significant relation between elevated biomarkers and cardiac dysfunction [18].

Endomyocardial biopsy is the most sensitive and specific investigation available for assessment of anthracycline induced cardiotoxicity, but the invasive nature of this test limits routine use [19].

Today, the widely used non-invasive method of monitoring cardiotoxicity of cancer therapy is, however, represented by Doppler-echo ultrasound which allows to identify the main forms of cardiac involvement in cancer patient: left ventricular (systolic and diastolic) dysfunction, valve heart disease, pericarditis and pericardial effusion, carotid artery lesions. Serial Doppler echocardiographic evaluation can be helpful for early, subclinical diagnosis of cardiac involvement and to be encouraged in the oncologic patients, before, during and even late after therapy completion. This is crucial when using anthracycline, which have early but, most importantly, late, cumulative cardiac toxicity [17]. The question of whether decline in cardiac function during therapy correlates with long-term development of cardiac impairment still remains [20].

Mitral regurgitation in normal children and adolescents is rare [7]. We found mitral regurgitation in three of 123 control group (2.4%), in contrast to the 21.98% in anthracycline treated patients ($p < 0.0001$ using the χ^2 test). We found mitral regurgitation in two of 91 patients (2.17%) before the start of chemotherapy, suggesting that in children with malignant disease who have not been treated with anthracycline it is also very uncommon.

The main hypothesis for the underlying mechanism of anthracycline associated cardiotoxicity is the generation of reactive free radical species that interact and damage cellular membranes. Other possible mechanisms are the induction of apoptosis, mitochondrial DNA damage, changes in ATP production, down regulation of mRNA

expression for sarcoplasmic reticulum calcium ATPase [21].

A minor degree of papillary muscle dysfunction related to anthracycline mediated free radicals, too subtle to be detected by changes in fractional shortening, seems a reasonable explanation of the mild degrees of mitral regurgitation seen in our patients.
Tow patients—aged 7 and 15 years at time of first detection of mitral regurgitation—developed impaired left ventricular function (fractional shortening 22%, 20%, respectively) 4, and 10 months later, between four months and 12 months after their first course of anthracycline long term follow up studies will be needed to assess the implications of these findings , but our results suggest that an isolated finding of new onset mitral regurgitation may be an early predictor of anthracycline cardio toxicity.

In our study we found mitral regurgitation in 24.04% of female patients and 18.92% of males(The two-tailed P value equals 0.6151) suggest that female sex is not a risk factor for anthracycline cardio toxicity, in contrast to the study that done by Green et al. Found the correlation between female sex and development of cardio toxicity in their case control study of 2,710 treated for Wilms tumor. In this study "the risk for girls was estimated to be approximately four times that for boys with the same level of cumulative doxorubicin exposure and radiation to the lung and the left abdomen (P, .005)" [22].

References:

1. Jones RL, Swanton C, Ewer MS (2006) Anthracycline cardio toxicity. Expert Opin Drug Saf **5**: 791–809.

2. Floyd JD, Nguyen DT, Lobins RL, et al. Cardiotoxicity of cancer therapy. J Clin Oncol 2005; 23:7685.

3. Monsuez JJ, Charniot JC, Vignat N, Artigou JY. Cardiac side-effects of cancer chemotherapy. Int J Cardiol 2010; 144:3.

4. Sandra Geiger, Veronika Lange, Patricia Suhl, Volker Heinemann, Hans-Joachim Stemmler. Anticancer therapy induced cardiotoxicity: review of the literature. Int J Hematol. 2008 Jun 12;: 18548196 Cit:2.

5. R. Altena, P. J. Perik, D. J. van Veldhuisen, E. G. de Vries, and J. A. Gietema, "Cardiovascular toxicity caused by cancer treatment: strategies for early detection," The Lancet Oncology, vol. 10, no. 4, pp. 391–399, 2009.

6. E. C. van Dalen, M. van den Brug, H. N. Caron, and L. C. M. Kremer, "Anthracycline-induced cardiotoxicity: comparison of recommendations for monitoring cardiac function during therapy in paediatric oncology trials," European Journal of Cancer, vol. 42, no. 18, pp. 3199–3205, 2006.

7. Thomson JDR, Allen J, Gibbs JL(2000) Left heart valve regurgitation in normal children and adolescents. Heart **83**:185–187.

8. Grenier MA, Lipshultz SE. Epidemiology of anthracycline cardiotoxicity in children and adults Semin Oncol 1998;25:72-85.

9. Lipshultz SE, Alvarez JA, Scully RE. Anthracycline associated cardiotoxicity in survivors of childhood cancer Heart 2008;94:525-533.

10. Wouters KA, Kremer LC, Miller TL, Herman EH, Lipshultz SE. Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies Br J Haematol 2005;131:561-578.

11. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer N Engl J Med 2006;355:1572-1582.

12. Swain SM, Whaley FS, Gerber MC, et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer J Clin Oncol 1997;15:1318-1332.

13. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials Cancer 2003;97:2869-2879.

14. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence,

treatment and prevention Drug Saf 2000;22:263-302.

15. Gharib MI, Burnett AK. Chemotherapy-induced cardiotoxicity: current practice and prospects of prophylaxis Eur J Heart Fail 2002;4:235-242.

16. Vorinostat (Zolinza). Package Insert. Whitehouse Station, NJ: Merck & Co. Inc.

17. 17. Maurizio Galderisi, Francesco Marra, Roberta Esposito, Vincenzo Schiano Lomoriello, Moira Pardo, Oreste de Divitiis Cancer therapy and cardiotoxicity: The need of serial Doppler echocardiography.
Am J Vet Res. 2006 Aug ;67 (8):1319-25 16881842.

18. A. M. C. Mavinkurve-Groothuis, L. Kapusta, A. Nir, and J. Groot-Loonen, "The role of biomarkers in the early detection of anthracycline-induced cardiotoxicity in children: a review of the literature," Pediatric Hematology and Oncology, vol. 25, no. 7, pp. 655–664, 2008.

19. Mustafa M. Decreased risk of cardiotoxicity with long-term use of Doxil/Caelyx at high lifetime cumulative doses in patients with AIDS related Kaposi's sarcoma (KS). Proc Am Soc Clin Oncol 2001; **20:** abstr 2915.

20. A. Jannazzo, J. Hoffman, and M. Lutz, "Monitoring of anthracycline-induced cardiotoxicity," Annals of Pharmacotherapy, vol. 42, no. 1, pp. 99–104, 2008.

21. Jones RL, Swanton C, Ewer MS. Anthracycline cardiotoxicity. Expert Opin Drug Saf 2006;5:791-809.

22. D. M. Green, Y. A. Grigoriev, B. Nan et al., "Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group," Journal of Clinical Oncology, vol. 19, no. 7, pp. 1926–1934, 2001.