The Effect of Prophylactic Antihypertensives on the Incidence of Anthracycline-Induced Cardiomyopathy in Patients with Diffuse Large B Cell Lymphoma

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Abstract

Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL). The standard of care for initial treatment of DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone on a 21-day schedule (R-CHOP21) for six cycles. Anthracyclines (or anthracycline antibiotics) are a class of drugs described as being cell-cycle non specific chemotherapy. They have been used as efficacious antineoplastic agents for many haemopoietic (Lymphomas. Leukemias) and solid cancers as in breast cancer. The heart is especially susceptible to anthracycline-induced damage, in part, owing to anthracyclines' high affinity for cardiolipin. Prophylactic use of antihypertensives to prevent anthracycline-induced cardiomyopathy has been utilized in several studies. Our study aims to assess the effect of prophylactic use of antihypertensives in prevention of doxorubicin induced cardiotoxicity.

Methods: Randomized trial of 50 adult patients with DLBCL conducted at Kasr Al-Ainy Oncology Department, ages 18-65 years DLBCL receiving doxorubicin based regimen presented at Kasr Al-Ainy Clinical Oncology Department during the period May 2013 till September 2014. They were randomly divided into 2 groups. Twenty four patients received prophylactic Enalapril and carvedilol with adjusted doses to their blood pressure.

Results: Fifty patients were enrolled between May 2013 and September 2014. At six month follow-up, cardiac reassessment of 49 patients was done (1 patients died). Troponins levels were normal, the mean ejection fraction of the anti hypertensive group was similar to the baseline ejection fraction (64.7% vs. 64.3%), however, the control group ejection fraction was significantly lower (66.56% vs. 53.92%; \( p = 0.001 \)).

Conclusion: The use of prophylactic carvedilol and enalapril can reduce the risk of the development of anthracycline induced cardiomyopathy.

Key Words: DLBCL – Anthracycline induced cardiotoxicity – Prophylactic antihypertensives.

Introduction

MANY chemotherapeutic and biologic agents have been reported to have effects on the cardiovascular system [1]. Anthracyclines are a class of drugs described as being cell-cycle non specific chemotherapy. They have been used as efficacious antineoplastic agents for many haemopoietic (Lymphomas. Leukemias) and solid cancers as in breast cancer [2].

Compared with other organs, the heart is especially susceptible to anthracycline-induced damage, in part, owing to anthracyclines' high affinity for cardiolipin. Cardiolipin is a unique mitochondrial phospholipid involved in various stages of mitochondrial membrane dynamics and the mitochondrial apoptotic process [3].

A 5% risk of cardiomyopathy is seen at 450mg/m\(^2\) for doxorubicin, 900mg/m\(^2\) for daunorubicin, 935mg/m\(^2\) for epirubicin, and 223mg/m\(^2\) for idarubicin. Cofactors for cardiotoxic risk include mediastinal irradiation, which includes the heart, older (particularly more than 70 years) or younger (less than 15 years) age, coronary artery disease, other valvular or myocardial conditions, and hypertension.

In a retrospective analysis of over 4000 patients receiving doxorubicin performed by Von Hoff and colleagues, 2.2% of the patients developed clinical signs and symptoms of congestive heart failure [4].

Doxorubicin induced cardiotoxicity is most often divided into three categories: Acute changes, early-onset chronic progressive cardiotoxicity and late acute cardiotoxicity occurs during Doxorubicin administration or immediately afterwards. It typically involves transient electrocardiographic ab-
normalities such as non-specific ST-T changes and QT prolongation. Early-onset cardiomyopathy usually occurs within one year after discontinuation of therapy. Chronic cardiotoxicity reflects a progressive injury and with increasing cumulative dose and decreased systolic performance. It is characterised by dilated (less often restrictive, mostly in children) cardiomyopathy, with subsequent development of left ventricular contractile dysfunction and congestive heart failure [8].

Left ventricular dysfunction (LVD) and the development of overt heart failure are the most common manifestations of cardiotoxicity associated with anthracyclines and according to the cardiac Review and Evaluation Committee supervising transzumab trials, LVD is characterised by:

A decrease in cardiac LVEF that was global or more severe in the septum and also, >5% decline in LVEF to <55 %with accompanying signs and symptoms of CHF, or a >10% decline in LVEF to <55% without accompanying signs or symptoms. Recent definitions include a decline in LVEF below the lower limit of normal (LLN) or to <50%. Left ventricular ejection fraction (LVEF) assessment is mandatory for basal evaluation of cardiac function prior to initiating potentially cardiotoxic therapy [6].

Echocardiography is standard procedure for basal assessment of cardiac structure and performance [7].

Multiple gated acquisition scan that uses Technetium-99m to evaluate cardiac functions and may reduce inter-observer variability, unfortunately it exposes the patient to radioactivity and provides only limited information on cardiac structure and diastolic function [8].

Cardiac troponins are highly sensitive and specific for cardiac damage. Serum levels increase within 3-4 hours from the cardiac insult and monitoring requires up to 12 hours measuring, peak at 24-48 hours, and return to baseline over 5-14 days [9].

Several preventive measures, such as combination with protective drugs are used for cardiac protection:

Carvedilol is a non selective β-adrenergic antagonist. The first human clinical trial investigating the prophylactic use of carvedilol in this clinical setting was conducted by Kalay and associates [10].

Captopril and enalapril, have been assessed as chemotherapy adjuvants to reduce oxidative stress, downregulate the activation of renin-angiotensin-aldosterone system and minimize the generation of free radicals [11].

Cardinale et al., assessed their benefits on left ventricular dysfunction in Troponin positive patients treated with enalapril. One hundred and fourteen patients were randomised to enalapril 20mg/day versus placebo. Treatment was started one month following chemotherapy and continued for one year. Only placebo patients developed reduced left ventricular functions [12].

**Patients and Methods**

This prospective randomized trial included 50 patients with a proven pathological diagnosis of DLBCL presented to Kasr Al-Ainy Clinical Oncology Department during the period from May 2013 till September 2014. The study was conducted in accordance with the International Conference on Harmonization for Good Clinical Practice guidelines and the ethical principles outlined in the Declaration of Helsinki. All patients provided written, informed consent before undergoing any study-related procedures.

Eligible patients were those with DLBCL. The age range for 18-65 years, with ECOG performance status <3 with no underlying cardiac disease. Patients were divided by simple random sample method into:

- Twenty-four patients receiving prophylactic antihypertensive drugs from the start.
- Twenty-six patients did not receive prophylactic antihypertensive (control group).

The used antihypertensive drugs were: Carvedolol with starting dose of 3.125mg and Enalapril with starting dose of 5mg/day guided by the blood pressure measurements.

The antihypertensives were started starting from day 1 of first cycle of chemotherapy and till 6 months after the end of the treatment (total of 1 year from start of chemotherapy).

Patients who were previously diagnosed as hypertensive patients were shifted on the equivalent doses of Carvedolol and Enalapril.

The following data were collected from all recruited patients:

- History of smoking, and thorough physical examination including blood pressure, node bearing areas, performance status and constitutional manifestations.
Laboratory assessment: Differential CBC, serum LDH, serum B2 macroglobulin levels, Uric acid, HBsAg & HCV antibody testing.

Cardiac assessment: Cholesterol Triglycerides, Troponins I once.

CT chest, abdomen and pelvis at the start and after 6 months from the start of chemotherapy.

Transthoracic echocardiography at the start and after 6 months at the same center.

All patients received the standard R-CHOP regimen every 3 weeks at least for 6 cycles. Response was assessed after 6 months.

Statistical methods:

All data were tabulated and statistically studied by descriptive analysis as well as survival analysis in relation to different prognostic factors.

Comparison between the two groups was done using student test for continuous data and CHI square ($\chi^2$) test for categorical data.

Survival analysis was done according to Kaplan-Meier method and compared by log-rank test for significance. Univariate analysis using cox regression module was performed to test the power of relation between the independent variables and survival Differences were considered significant if $p$-value was less than 0.05.

Results

Three patients had family history of ischemic heart diseases, serum triglycerides levels were elevated in 18 (36%) patients and 8 patients (16%) were smokers (Table 1).

The mean Ejection fraction (EF) at presentation was 66.9 ($\pm$SD 5.7). Only 1 case showed asymptomatic slight elevation of Troponin I after the first cycle only once.

During the whole treatment period patients did not develop cardiac symptoms, ECG was done to detect any cardiac insult; however all were free. No patient developed hypotension during treatment.

At six month follow-up, cardiac re-assessment of 49 patients was done (1 patients died). Troponins levels were normal, mean EF = 64.7 $\pm$ (5.8).

At the end of six months the mean ejection fraction of the anti hypertensive group was similar to the baseline ejection fraction (64.7% vs. 64.3%), however, the control group ejection fraction was significantly lower (66.56% vs. 53.92%; $p<0.001$).

**Table (1): Risk factors of cardiac disease (N=50).**

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<th>No anti hypertensives (N=26)</th>
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<td>Mean EF at presentation</td>
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Discussion

The rationale of using prophylactic antihypertensives has been utilized by Kalay et al., 2006 and Cardinale et al., 2006 [10-12].

The main aim in this study was to assess the effect of the use of prophylactic carvidolol combined with enalapril in prevention of anthracycline induced cardiotoxicity.

In this study, the clinical and laboratory characteristics of patients randomized for receiving prophylactic carvidolol and enalapril; did not show a statistically significant difference except for hypertension which is a non avoidable cause for receiving antihypertensives.

Acute cardiotoxic events were checked by ECG, troponin levels and clinical manifestations.
At the end of six months the mean ejection fraction of the anti hypertensive group was similar to the baseline ejection fraction (64.7 vs. 64.3), while, the control group ejection fraction was significantly lower (66.5 vs. 53.9; \(p=0.001\)); which were similar to the results reached by Kalay et al. In their study, Fifty patients receiving anthracyclines were randomized to either the carvedilolol group or control group. The carvedilol group was started at 12.5mg carvedilolol once daily prior to chemotherapy and continued for six months. At the end of six months the mean ejection fraction of the carvedilol group was similar to the baseline ejection fraction (70.5 vs. 69.7; \(p=0.3\), however, the control group ejection fraction was significantly lower (68.9 vs. 52.4; \(p<0.001\)) [10].

In Conclusion: The use of prophylactic carvedilolol and enalapril can reduce the risk of the development of anthracycline induced cardiomyopathy.

References

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