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The Role of Metoprolol and Enalapril in the Prevention of Doxorubicin-induced Cardiotoxicity in Lymphoma Patients

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Abstract. *Background/Aim: Anthracyclines, such as doxorubicin, though widely used in anticancer therapy, they are associated with cardiotoxic side-effects. The aim of this trial was to investigate long-term follow-up cardiotoxicity findings in patients treated with doxorubicin and concomitant metoprolol or enalapril 10 years earlier. Patients and Methods: Overall, 147 patients were randomized into the treatment arms. A total of 125 patients treated with doxorubicin without evidence of heart disease at the start of chemotherapy were analyzed. They were followed-up for up to 10 years after treatment start. Results and Conclusion: A total of 47 patients completed the follow-up and 21 patients died, none due to cardiotoxicity events. Clinical signs of heart failure were not seen in any patients and no statistically significant differences between baseline and 10-year findings were seen for echocardiographic variables. No evidence of long-term cardiotoxicity was seen and nor metoprolol or enalapril offered an additional benefit.*

Anthracyclines, such as doxorubicin, are cytotoxic agents widely used as chemotherapy (CT) for many cancers. In fact, doxorubicin is included in the World Health Organization's Model list of essential medicines, which lists the most efficacious, safe and cost-effective medicines for priority conditions (1-4). Unfortunately, anthracyclines are associated with cardiotoxic side-effects that may result in congestive heart failure (CHF) (3, 5-8). The cumulative dose of anthracyclines is considered as a basic determinant for the development of CHF (2, 9). Known risk factors for cardiovascular disease, such as hypertension, aging, and diabetes also contribute to the development of CHF (10). Anthracycline-induced cardiotoxicity may occur in the first year after the completion of CT (early-onset cardiotoxicity) or many years later (late-onset cardiotoxicity) (2, 11). Oxidant stress induced by anthracyclines leads to left ventricular (LV) dysfunction and CHF, and therefore, efforts targeting this mechanism of cardiotoxicity have been suggested to prevent the development of CHF (2, 3). Primary prevention with cardioprotective agents such as the beta-blocker metoprolol (12, 13) or the angiotensin converting enzyme inhibitor enalapril (13-15) have been proposed, but when assessed in clinical trials did not achieve cardioprotective results that would establish them as routine prophylactic agents (3, 13, 15, 16). These studies, however, often had small sample sizes, and long-term follow-up data are lacking (1, 16).

Under this perspective, the present trial aimed to investigate long-term cardiotoxicity of doxorubicin with and without the co-administration of a cardioprotective agent, in terms of development of CHF and change in baseline echocardiographic measurements. Herein, we report on the long-term follow-up cardiotoxicity findings in patients with Hodgkin or non-Hodgkin lymphoma (HL, or NHL), without heart problems, who had received CT with doxorubicin and concomitant administration of metoprolol or enalapril 10 years earlier.

Patients and Methods

This was an open-label study, prospective randomized trial. Patients with HL or NHL were prospectively followed-up for cardiotoxicities up to 10 years after doxorubicin therapy. Patients were block randomized according to their sex, age, and type of lymphoma in 1:1:1 into three parallel groups: a metoprolol group, an enalapril

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Table I. *Eligibility criteria*.

Inclusion criteria	Exclusion criteria
Age > 18 years	History of heart failure, cardiomyopathy, coronary artery disease, atrial fibrillation, arrhythmias needing medication, bundle-branch block, moderate or severe valvular disease
Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 (20)	Abnormal 12-lead ECG, or segmental or global wall motion abnormality at 2-dimensional echocardiography
Serum bilirubin <2.0 mg/dl	Prior CT with any anthracycline derivative
Serum creatinine <2.0 mg/dl	Chest irradiation therapy between the first dose and up to 3 weeks after the last dose of anthracycline
Normal sinus rhythm	Contraindication or intolerance to ACE inhibitors or beta-blockers
LV ejection fraction (LVEF) >50%	Thyroid disorders
Fraction shortening (FS) >25% before CT	Uncontrolled hypertension
	Systolic blood pressure <90 mmHg
	Heart rate <55/min
	Ongoing therapy with an ACE inhibitor or beta-blocker

group, and a control group. Cardiotoxicity was assessed in three periods (Figure 1): a) in the first 12 months after starting treatment (early cardiotoxicity), b) from the 13th to the 36th month after the start of treatment (late cardiotoxicity), and c) up to 10 years after the start of treatment (long-term cardiotoxicity). We have already published the results for early and late cardiotoxicity collected from April 2003 to June 2006 (13). Here we report our study's second-phase long-term findings collected between July 2006 to June 2017.

The study was conducted at Third Department of Internal Medicine, Medical School University of Athens Sotiria Hospital, the Cardiological Department of Gennimatas General Hospital of Athens and the Cardiological Department of Metropolitan Hospital Faliron. It was approved by the local ethics committees and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

Objectives. The primary objective was the occurrence of doxorubicin-induced clinical or subclinical long-term cardiotoxicity in lymphoma patients after concomitant prophylactic therapy with metoprolol or enalapril, or no concomitant treatment during chemotherapy.

Participants. Patients with a diagnosis of HL or NHL scheduled for doxorubicin-based CT were enrolled consecutively between April 2003 and April 2005. All participants of the first randomized phase who achieved long-term follow-up were included. Eligible patients (Table I) had completed their CT cycles and were not receiving any beta-blockers or ACE inhibitors during follow-up, other than the respective treatment to which they were randomized to receive. Patients were withdrawn from the study if any of the exclusion criteria occurred. All patients provided written informed consent at the initiation of the study.

Interventions. The CT regimen consisted of six to eight cycles of the 'ABVD schema' for HL: doxorubicin (25 mg/m^2), bleomycin (10 mg/m^2), vinblastin (6 mg/m^2), and decarbazine (375 mg/m^2) intravenously on day 1 and day 15 every four weeks. The NHL patients received six to eight cycles of the 'R-CHOP schema': rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and vincristine (1.4 mg/m^2) intravenously on day 1 and prednisolone (100 mg/m^2) orally on days 1-5 every three weeks.

The concomitant treatment started at week 1 with 25 mg metoprolol twice daily or 2.5 mg enalapril twice daily and was titrated weekly up to daily target doses of 100 mg metoprolol and 20 mg enalapril after three weeks. The previous dose could be maintained for a further week before increasing the dose. The highest dose tolerated during the titration period was used for the whole period. If persistent hypotension or bradycardia developed, the dose was reduced to the next level down.

Assessments and outcomes. Patients were assessed before the start of CT (baseline), after the third, sixth, and eight CT cycle, three months after the completion of CT, and then every six months thereafter up to the 10th year after the start of CT.

Assessments included history and physical examination to assess for heart failure, electrocardiography (ECG), chest X-ray, comprehensive, transthoracic, two-dimensional, pulsed and Doppler color-flow echocardiography, systemic blood pressure (average of three measurements). Echocardiographic evaluations were conducted by blinded examiners.

Clinical cardiotoxicity was defined as the presence of CHF. The definition of CHF included two or more of the following: cardiomegaly at chest X-ray, basilar rales, S3 gallop, or either paroxysmal nocturnal dyspnea, orthopnea, or significant dyspnea on exertion. Subclinical cardiotoxicity was defined as a change in systolic and diastolic LV function from baseline. A cardiac event was defined as a difference of 10% between the left ventricular ejection fraction (LVEF) values at each visit and the baseline value, and LVEF <50%. The parameters measured were the peak systolic velocity (Sa), early (Ea) and late (Aa) diastolic velocities, and E/Ea. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) and fraction shortening (FS) were also measured.

Study endpoints and adverse events were continuously monitored, and patients were also questioned at each visit about general and cardiac-specific adverse events.

Statistical methods. Descriptive data are expressed as mean values with standard deviations (SD) or proportions. All *p*-values are two-sided with a 0.05 type I error and 95% power. A *p*-value of <0.05 was considered statistically significant. Echocardiographic changes between the three groups were analyzed by repeated-measures

Figure 1. *Study scheme and timelines*.

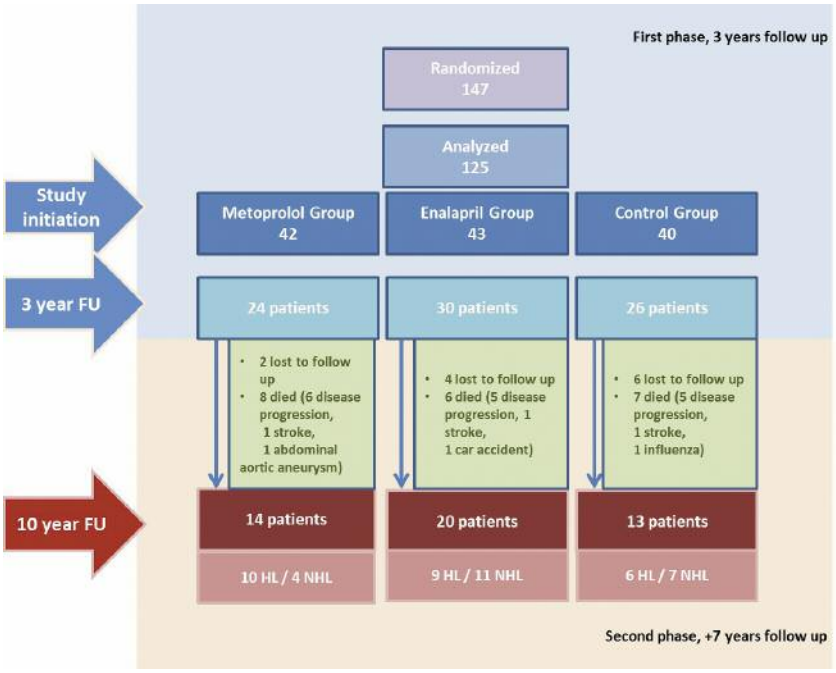

Figure 2. *Patient flow chart*.

analysis of variance. For patients lost to follow-up or those who died, the last follow-up evaluation was considered the final measurement. The analysis was performed by using Statistical Package for the Social Sciences (SPSS) v.18.

Results

As published earlier, 125 patients were enrolled in this study with similar baseline characteristics across groups (13). Of the patients, 48% (60/125) had HL and 52% (65/125) NHL. Mean follow-up was (12±1.6 years). Average doses were: (380±5.7 mg/m^2) for doxorubicin, (88.8±3.1 mg) for metoprolol, and (11±0.68 mg) for enalapril. The sample size of 125 patients is close to the estimated sample size of 107 patients under the 95% confidence level and under 5% error.

After completion of the initial three years of follow-up, 80 patients were eligible for the additional seven-years of follow-up: 24 patients from the metoprolol group, 30 from the enalapril group, and 26 from the control group. All patients had completed six or eight CT cycles, at the end of which metoprolol and enalapril were discontinued. Overall, 47 patients completed the 10-year follow-up. Twelve patients interrupted the long-term follow-up mainly because of the long distance between their homes and the clinic. Twenty-one patients died due to: disease progression (16 patients), stroke (2 patients), abdominal aortic aneurysm, influenza, car accident (a single patient each) (Figure 2).

Long-term cardiotoxicity. None of the patients developed clinical symptoms of heart failure after the 4th year from therapy initiation. The mean changes for all echocardiographic variables between groups did not differ significantly 10 years after baseline (Table II). There were also no significant differences between the baseline and 10-year values in each group (control, metoprolol, and enalapril) (LVEDD p=0.661, LVESD p=0.545, LVEF p=0.836, FS p=0.666, E/A p=0.104, E/Ea p=0.87).

Table II. *Subclinical cardiotoxicity at baseline and at 10-years follow-up.*

	Baseline				After 10 years			
	Metoprolol group	Enalapril group	Control group	*p*-Value	Metoprolol group	Enalapril group	Control group	*p*-Value
LVEDD, cm (SD)	4.7 (0.5)	4.9 (0.4)	4.8 (0.6)	0.19	4.6 (0.4)	4.4 (0.5)	4.4 (0.5)	0.45
LVESD, cm (SD)	2.9 (0.3)	3.1 (0.4)	3.0 (0.5)	0.16	3 (0.4)	2.9 (0.3)	2.9 (0.4)	0.32
LVEF, % (SD)	65.7 (5.0)	65.2 (7.1)	67.6 (7.1)	0.40	61.7 (6.2)	63.5 (6.9)	63.6 (5.1)	0.54
FS, % (SD)	36.5 (4.8)	35.7 (5.8)	37.9 (5.7)	0.33	32.5 (4.6)	34 (4.8)	34.7 (3.4)	0.09
E/A, ratio (SD)	1.1 (0.4)	1.1 (0.4)	1.0 (0.4)	0.62	1.06 (0.3)	0.9 (0.3)	0.99 (0.3)	0.70
E/Ea, ratio (SD)	4.8 (1.9)	4.6 (1.3)	4.9 (1.4)	0.73	7.3 (2.7)	7.7 (2.5)	7.21 (2.7)	0.70

Ea: Early diastolic velocity; FS: fraction shortening; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; SD: standard deviation.

Discussion

We prospectively assessed long-term cardiotoxicity in patients who had received doxorubicin for HL or NHL, and investigated possible cardioprotective effects of concomitant administration of metoprolol and enalapril. Ten years after the start of doxorubicin CT, we saw no clinical or subclinical cardiotoxicity between the 4th and 10th year in any of our study groups; also, subclinical variables were similar between groups at baseline and 10 years later.

As we reported earlier, during the first three years of follow-up in our study, we did not see differences in cardiotoxicity between the three groups, except for the E/A index for diastolic function in the metoprolol group at 30 and 42 months after the start of treatment (13). At 30 months E/A was 1,3 (standard deviation [SD]=0.5) in the metoprolol group *vs*. 1.0 (SD=0.4) in the enalapril group and 1.0 (SD=0.4) in the control group (p=0.003); at 42 months the respective ratios were 1.3 (SD=0.3), 1.1 (SD=0.5), and 0·5 (SD=0.2) (p=0.005).

As in our study, improvements in diastolic function were shown in the PRADA study, in which a 0.8 (p=0.009) difference between metoprolol and no-metoprolol groups in the diastolic function was seen after the completion of adjuvant anticancer therapy in 120 women with early breast cancer (17).

Deaths in our study were primarily caused by disease progression. Ten-year survival rate in our patients was 87% among the HL subpopulation of patients and 77% among the NHL subpopulation. This is similar to the 12-year overall survival reported by Meyer and colleagues (18) in 405 patients with previously untreated stage I-II HL who had received ABVD.

To the best of our knowledge, ours is the first study to have assessed long-term cardiotoxicity prophylaxis data in adult-onset cancer patients. These long-term findings are similar to our previously published short-term finding (13). Our short-term cardiotoxicity findings were not similar to the findings of previous trials reporting differences in short-term cardiotoxicity (15, 17, 19, 20) and indicating cardioprotective effects of carvedilol (19), enalapril (20) their combination (15), or caldesartan (17). This was probably due to our lower cumulative doxorubicin dose and the selection of patients who were not suffering from heart disease at baseline. As indicated elsewhere by Menna and colleagues (16) doxorubicin's reduced cumulative dose is the 'most obvious strategy for primary prevention'. Careful monitoring and correction of risk factors for heart disease should also be part of primary cardiovascular prophylaxis in patients considered for doxorubicin treatment (16).

The open label design of our study and the lack of a placebo cardioprotective prophylaxis in the control group are our study's main limitations. Because chemotherapy was given only by one hospital site, patients might not be representative of the general population. This central General University Hospital is, however, one of the major institutions in the National Healthcare System and attracts patients from accross the country. Principle strengths of our study are the inclusion of only one type of cancer, the prospective randomized-control design, and the long-term follow-up of 10 years. Therefore, in conclusion, low-cumulative-dose doxorubicin was not associated with long-term cardiotoxicity in our patients with HL or NHL who did not have clinical or subclinical evidence of heart disease before starting chemotherapy. Co-administration of the cardioprotective agents metoprolol and enalapril did not offer any additional benefit.

Conflicts of Interest

The Authors declare no conflicts of interest concerning this article.

Authors' Contributions

All Authors, PG, MK, AP, AK, SZ, NM and AC, conceived and designed the study. PG, MK, AP, AK, SZ, NM and AC gathered and interpreted the data. MK, AP, AK, and NM performed and analyzed

echocardiograms and analyzed electrocardiograms. SZ performed the statistical analysis. PG developed the figures and table. PG, MK, AP, AK, SZ, NM, MK and AC wrote and approved the final report.

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