Protective Effect of Carvedilol in Cardiomyopathy Caused by Anthracyclines in Patients Suffering from Breast Cancer and Lymphoma

Rezvanie Salehi, MD,[1] Bijan Zamani, MD,[2] Ali Esfehani, MD,[3] Samad Ghafari, MD,[2] Mohsen Abasnezhad, MD[4] and Mohamad Goldust, MD[5]

Objective: Anthracyclines can damage the left ventricle, causing cardiomyopathy. This study evaluated the protective effect of carvedilol in cardiomyopathy caused by anthracyclines in patients suffering from breast cancer and lymphoma. **Methods:** In this clinical trial, patients undergoing chemotherapy were randomly divided into three groups. The first group received placebo and the second and third groups received, respectively, 12.5mg and 25mg of apo-carvedilol 24 hours before starting the study. The patients underwent echocardiography and tissue Doppler to look for cardiomyopathy. After four months the efficacy of carvedilol was evaluated. **Results:** Sixty-six patients were evaluated. No meaningful difference was observed among the groups in terms of mortality, age, gender, type of malignancy, chemotherapy regimen, and cumulative dose of doxorubicin and epirubicin. No statistically significant differences were observed between control and case groups considering the frequency of systolic cardiomyopathy (p=0.284) or the frequency of diastolic cardiomyopathy (p=0.284). **Conclusion:** Carvedilol at a daily dose of 12.5mg has a protective effect against diastolic disorder and at a daily dose of 25mg has a protective effect against both systolic and diastolic disorders.

Anthracyclines are effective drugs for the treatment of malignancies. However, the use of anthracyclines is accompanied by irreversible dilatory cardiomyopathy in 5–20 % of cases. Drug treatment for such cardiomyopathy is ineffective and the condition has a mortality rate of over 50 %. Therefore, the prevention of cardiomyopathy is clinically important.[1,2]

Acute intoxication appears as myocarditis and may lead to transient hyperemia. Delayed cardiomyopathy is characterized by fatigue, activity dyspnea, orthopenia, bradicardia, S3 gallop, and lung edema.[3,4] Cardiotoxic symptoms may be subclinical but can be identified using various methods of cardiac function assessment in asymptomatic subjects. Generally, cardiac symptoms resulting from anthracyclines may be premature and observed during treatment or within the first year after beginning treatment.[5,6] A high cumulative dose of the prescribed drug, radiotherapy, female gender, and young age at the time of suffering from the background malignancy are the most important risk factors for cardiac complications caused by anthracycline treatment.[7,8]

The main mechanism of the cardiotoxic effects of anthracyclines is not completely known but two factors are suspected: lipid peroxidation and production of free radicals by ferrous–anthracycline complexes.[9,10]

Several possible methods have been suggested to reduce the adverse cardiac effects of anthracycline treatment, including avoidance of anthracyclines (especially in tumors with a poor prognosis), reduction of the prescribed cumulative dose, use of liposome anthracyclines, immediate and early identification of subclinical cardiac symptoms, and use of cardioprotective agents such as dexrazoxane.[2,11] Prescribing cardioprotective agents together with

• 1. Associate Professor in Cardiology; 2. Assistant Professor in Cardiology; 3. Associate Professor in Oncology; 4. Assistant Professor in Cardiology; 5. Medical Student, Tabriz University of Medical Sciences, Iran
• Correspondence: Mohamad Goldust, Tabriz University of Medical Sciences, 5166614711, Iran. E: Drmgoldust@yahoo.com

Table 1: Patients' Demographic Information

	Placebo	12.5 mg Carvedilol	25 mg Carvedilol	Carvedilol (both groups)
Gender (p=0.569)				
Male	8	7	5	5
Female	14	15	17	17
Age (years) (p=0.098)				
	43.50±15.27	45.70±14.16	52.52±11.00	43.50±15.27
Type of malignancy (p=0.140)				
Lymphoma	9	5	5	6
Breast	13	17	17	16
Chemotherapy regimen				
CHOP	6	3	2	4
ABVD	2	1	2	2
CAF	10	16	17	15
Mortality (p=0.210)				
	4	2	1	1

ABVD = adriamycin, bleomycin, vinblastine, dacarbazine; CAF = cyclophosphamide, doxorubicin, fluorouracil; CHOP = cytoxan, hydroxyrubicin (Adriamycin), oncovin (Vincristine), prednisone.

anthracyclines leads to a reduction of cardiac complications. Apparently, dexrazoxan hinders the development and activity of ferrous–anthracycline complexes by binding the ferrous particles; this leads to reduced free radical production and, thus, reduced historrhexis.[12] Carvedilol obstructs β-1, β-2, and α-1 receptors and has strong antioxidant and antiapoptotic effects,[13] which are highly important for cardioprotection. Also, carvedilol can suppress sarcoplasmic reticulum Ca2- ATPase. The effects of carvedilol in suppressing apoptosis signaling routes may play a role in cardioprotection.[14]

The aim of the research presented in this article was to study the protective effect of carvedilol in cardiomyopathy caused by anthracyclines in patients suffering from breast cancer and lymphoma.

Methods

Over the course of one year, patients with a diagnosis of breast malignancies and lymphoma who were under treatment with anthracyclines and who were referred to Shahid Ghazi Clinic entered the study and were followed up for four months. The following patients were excluded from the study: patients with records of chemotherapy, radiotherapy, symptoms of hyperemia, and cardiac insufficiency; patients with approved restrictive and hyperemia cardiomyopathy; patients with coronary vessel disease; those with moderate to severe insufficiency of the mitral and aortic valves in early echocardiography; patients with ramous blocks; patients with thyroid dysfunction; patients in whom carvedilol was contraindicated; patients with serious concurrent disease; patients taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or beta-blockers; and patients under 12 years of age.

In this clinical trial, 66 patients undergoing chemotherapy were randomly divided into three groups, each containing 22 patients. The first group received placebo and the second and third groups received, respectively, 12.5 mg and 25 mg of apo-carvedilol 24 hours before starting the study. The study lasted for four months. Doxorubicin and epirubicin were prescribed at 50–60 mg and 100 mg per square meter of body area, respectively. The patients in this study underwent echocardiography and tissue Doppler using Vingmed System 7 to look for cardiomyopathy. Left ventricular function was measured during systole and diastole before starting chemotherapy and during the acute phase (in cases where clinical symptoms of cardiomyopathy appeared) and during the chronic phase in the fourth month. Anolous movement of the mitral valve was used to calculate the ejection fraction. A questionnaire was used to collect the required information: age, gender, mortality, type of malignancy, type of chemotherapy regimen and cycle, cumulative dose of doxorubicin and epirubicin, echocardiography results (left ventricular ejection fraction, diastolic end diameter of the left ventricle, systolic end diameter of the left ventricle, E-wave velocity, E/A ratio), results of tissue Doppler (including maximum systolic velocity of the mitral valve, Ei/Ea ratio, inferior–posterior movement of the mitral valve, speed development), and pure systolic and diastolic cardiomyopathy.

The obtained data were analyzed using SPSSTM-15 statistical software. Quantitative variables were compared using the Student t-test (independent samples, paired samples t-test). Categorical variables were compared using contingency tables and the chi-squared test or Fisher's exact test. In all cases, the results were seen as statistically significant if $p \leq 0.05$.

Results

No significant differences were observed among the groups in terms of mortality, age, gender, type of malignancy, chemotherapy regimen, and cumulative dose of doxorubicin and epirubicin (see *Table 1*). The average cumulative dose of doxorubicin was 540.28±31.17 mg/m^2 in the control group, 531.50±29.98 mg/m^2 in the group receiving 12.5 mg carvedilol, and 521.14±38.97 mg/m^2 in the group receiving 25 mg carvedilol; taking the two groups receiving carvedilol together (case group), the average cumulative dose of doxorubicin was 540.28±31.17 mg/m^2. In this regard, no statistically significant difference was observed between the control and case groups (p=0.218). The average cumulative dose of epirubicin was 768.44±26.78 mg/m^2 in the control

group, 764.25±31.21 mg/m^2 in the group receiving 12.5 mg carvedilol, 770.90±25.17 mg/m^2 in the group receiving 25 mg carvedilol, and 768.44±26.87 mg/m^2 in the case group. In this regard, no statistically significant difference was observed between the control and case groups (p=0.744).

Five patients in the control group, five patients in the group receiving 12.5 mg carvedilol, and one patient in the group receiving 25 mg carvedilol (a total of six patients in the case group) developed systolic cardiomyopathy. In this regard, no statistically significant difference was observed between the control and case groups (p=0.284). Also, there was no statistically significant difference in the frequency of systolic cardiomyopathy between the control group and the group receiving 12.5 mg carvedilol (p=1), between the control group and the group receiving 25 mg carvedilol (p=0.077),and between the two groups receiving carvedilol (p=0.093).

Five patients in the control group, three patients in the group receiving 12.5 mg carvedilol, and three patients in the group receiving 25 mg carvedilol (a total of six patients in the case group) developed pure diastolic cardiomyopathy. In this regard, no statistically significant difference was observed between the control and case groups (p=0.284). Also, there was no statistically significant difference in the frequency of diastolic cardiomyopathy between the control group and the group receiving 12.5 mg carvedilol (p=0.438), between the control group and the group receiving 25 mg carvedilol (p=0.432), and between the two groups receiving carvedilol (p=1) (see *Table 2*).

Table 2: Inter- and Intra-group Comparison of Echocardiography and Tissue Doppler Variables

	Placebo	12.5 mg Carvedilol	25 mg Carvedilol	Carvedilol (Both Groups)
Left ventricular mutation fraction (p=0.375)				
Baseline	58.56±3.62	60.5±5.07	61.00±7.06	58.56±3.62
4 months later	53.94±3.80	53.15±7.76	56.81±6.20	53.94±3.80
Diastolic end diameter of left ventricle (mm) (p=0.226)				
Baseline	4.13±0.61	4.17±0.39	3.93±0.34	4.13±0.61
4 months later	4.56±0.57	4.50±0.46	4.09±0.37	4.56±0.57
Systolic end diameter of left ventricle (mm) (p=0.069)				
Baseline	3.00±0.35	2.92±0.44	2.73±0.29	3.01±0.35
4 months later	3.24±0.44	3.00±0.55	2.85±0.35	3.24±0.44
E wave velocity (cm/s) (p=0.086)				
Baseline	68.5±14.67	75.5±13.71	67.38±5.04	67.38±5.04
4 months later	63.1±10.71	71.35±12.68	66.43±5.03	63.06±10.71
E/A ratio (p=0.087)				
Baseline	0.99±0.45	7.03±0.21	0.83±0.17	0.99±0.45
4 months later	0.86±0.33	1.00±0.38	0.81±0.17	0.86±0.33
Maximum systolic velocity of mitral valve (p=0.939)				
Baseline	17.56±2.38	17.25±2.77	17.33±2.92	17.56±2.38
4 months later	16.61±1.50	17.05±3.24	15.38±4.34	16.61±1.50
Ei/Ea ratio (p=0.518)				
Baseline	3.53±1.02	3.37±0.97	3.69±0.66	3.53±1.02
4 months later	3.88±0.78	3.51±0.80	3.79±0.66	3.88±0.78
Interior–posterior movement of mitral valve (mm) (p=0.061)				
Baseline	16.94±3.11	17.00±2.36	18.81±2.29	16.94±3.11
4 months later	15.44±1.89	16.36±1.42	18.67±2.44	15.44±1.86
Speed development (cm/s) (p=0.053)				
Baseline	58.72±8.17	65.90±10.78	66.38±12.09	58.72±8.17
4 months later	52.17±8.83	62.95±9.58	64.90±9.80	52.17±8.83

Discussion

This study considered the effects of carvedilol in preventing cardiomyopathy resulting from anthracycline treatment in patients suffering from breast cancer and lymphoma. Carvedilol was prescribed at either 12.5 mg or 25 mg per day for four months. At the end of the study, although the frequency of pure systolic and diastolic cardiomyopathy was lower in the group receiving carvedilol than in the control group (27.8 % versus 14.6 %), the difference was not statistically significant. On the other hand, studies using 2D echocardiography and color Doppler have demonstrated that carvedilol at a daily dose of 12.5 mg has a protective effect against diastolic disorders and at a daily dose of 25 mg had a protective effect against both systolic and diastolic disorders.

In 2002, Santos et al. demonstrated that prophylactic prescription of carvedilol may prevent mitochondrial cardiomyopathy caused by doxorubicin.[15] In 2007, Cruz et al., using a hamster model, suggested that carvedilol at a daily dose of 1 mg/kg body weight may lead to improved cardiac function.[16] Thus, these two studies confirm the protective effect of carvedilol in animal models. In a study in Turkey in 2006, Kalay et al. randomized 50 patients suffering from breast cancer or lymphoma to receive placebo or carvedilol. This study showed that carvedilol (at the mentioned dose) had a protective effect on systolic and diastolic disorders of the left ventricle resulting from anthracycline treatment.[17] As discussed above, our study observed a protective effect on both systolic and diastolic disorders with the 25 mg dose of carvedilol daily, while the 12.5 mg daily dose maintained diastolic (but not systolic) function of the left ventricle.

There are two main limitations in the study by Kalay et al., including the low-density sample and failure to study the long-term effects of anthracycline in cardiac cases. According to the results of this study, a daily dose of 25 mg of carvedilol may play a protective role in preventing systolic and diastolic disorders of the left ventricle, although there was no statistically significant difference in the frequency of clinical cardiomyopathy between the groups studied. Kalay et al. reported mortality rates in the control and case groups of 16 % and 4 %, respectively. The result was not statistically significant; however, the study concluded that, although the

difference is not statistically significant owing to the low-density sample, it is considerable.[17]

In 2004, Mukai et al. verified the effects of carvedilol at an initial dose of 2 mg per day increasing to 10–20 mg per day in five patients suffering from cardiomyopathy caused by anthracyclines. The study showed that carvedilol was successful in improving patients' symptoms and maintaining ventricular function and diastolic and systolic diameters.[12] This finding contradicts the results of studies showing that cardiomyopathy caused by anthracyclines is irreversible.[18] Therefore, it is necessary to study the role of carvedilol in treating clinical cases, considering its possible effect in treating and preventing cardiomyopathy resulting from chemotherapy.

It should be noted that the suggested dose of carvedilol in patients with heart failure is 12.5–50 mg, according to the MOCHA study.[19] There is no general agreement on the appropriate dose of carvedilol in cardiovascular patients because the protective effect of the drug on cardiomyopathy caused by chemotherapy has not yet been comprehensively studied and further studies are required.[20]

It should also be noted that a daily dose of 12.5 mg carvedilol may lead to decrease of echocardiography and tissue Doppler in favor of diastolic disorders, and a daily dose of 25 mg carvedilol may lead to decrease of echocardiography and tissue Doppler in favor of diastolic and diastolic disorders. ■

1. Kurihara C, Nishimura T, Nawata K, et al., Successful bridge to recovery with VAD implantation for anthracycline-induced cardiomyopathy, *J Artif Organs*, 2011;14:249–52.
2. Christiansen S, Recovery from anthracycline cardiomyopathy – how can it be explained?, *J Heart Lung Transplant,* 2009;28:751.
3. Cardinale D, Colombo A, Lamantia G, et al., Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy, *J Am Coll Cardiol,* 2010;55:213–20.
4. Richter R, Grumpelt U, Mittler U, et al., [Echocardiography studies for detection of cardiotoxic side effects of anthracycline therapy in childhood], *Monatsschr Kinderheilkd,* 1990;138:823–7. Article in German.
5. Simmons A, Vacek JL, Meyers D, Anthracycline-induced cardiomyopathy, *Postgrad Med*, 2008;120:67–72.
6. Pihkala J, Sariola H, Saarinen UM, Myocardial function and postmortem myocardial histology in children given anthracycline therapy for cancer, *Pediatr Hematol Oncol,* 1994;11:259–69.
7. Keefe DL, Anthracycline-induced cardiomyopathy, *Semin Oncol,* 2001;28:2–7.
8. Godoy LY, Fukushige J, Igarashi H, et al., Anthracycline-induced cardiotoxicity in children with malignancies, *Acta Paediatr Jpn*, 1997;39:188–93.
9. Amigoni M, Giannattasio C, Fraschini D, et al., Low anthracyclines doses-induced cardiotoxicity in acute lymphoblastic leukemia long-term female survivors, *Pediatr Blood Cancer,* 2010;55:1343–7.
10. Hauser M, Gibson BS, Wilson N, Diagnosis of anthracycline-induced late cardiomyopathy by exercise-spiroergometry and stress-echocardiography, *Eur J Pediatr,* 2001;160:607–10.
11. Florenzano F, Salman P, Carvedilol for anthracycline cardiomyopathy prevention, *J Am Coll Cardiol,* 2007;49:2142–3.
12. Mukai Y, Yoshida T, Nakaike R, et al., Five cases of anthracycline-induced cardiomyopathy effectively treated with carvedilol, *Intern Med,* 2004;43:1087–8.
13. Yeoh T, Hayward C, Benson V, et al., A randomised, placebo-controlled trial of carvedilol in early familial dilated cardiomyopathy, *Heart Lung Circ,* 2011;20:566–73.
14. Pereira GG, Silva AM, Diogo CV, et al., Drug-induced cardiac mitochondrial toxicity and protection: from doxorubicin to carvedilol, *Curr Pharm Des,* 2011;17:2113–29.
15. Santos DL, Moreno AJ, Leino RL, et al., Carvedilol protects against doxorubicin-induced mitochondrial cardiomyopathy, *Toxicol Appl Pharmacol,* 2002;185:218–27.
16. Cruz N, Arocho L, Rosario L, et al., Chronic administration of carvedilol improves cardiac function in 6-month-old Syrian cardiomyopathic hamsters, *Pharmacology,* 2007;80:144–50.
17. Kalay N, Basar E, Ozdogru I, et al., Protective effects of carvedilol against anthracycline-induced cardiomyopathy, *J Am Coll Cardiol,* 2006;48:2258–62.
18. Yoshikawa E, Marui A, Tsukashita M, et al., Carvedilol may alleviate late cardiac remodelling following surgical ventricular restoration, *Eur J Cardiothorac Surg,* 2010;37:362–7
19. Fan Y, Lin JH, Dong G, et al., [The effect of carvedilol on coronary flow reserve in patients with dilated cardiomyopathy], *Zhonghua Nei Ke Za Zhi,* 2010;49:217–9. Article in Chinese.
20. Erdogan I, Ozer S, Karagoz T, et al., Treatment of dilated cardiomyopathy with carvedilol in children, *Turk J Pediatr.* 2009;51:354–60.