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Original Article

The Effect of Coenzym Q10 on Doxorubicin-induced Cardiotoxicity in Non Hodgkin's Lymphoma Patients

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Abstract

Background : Non-Hodgkin's Lymphoma is a primary malignancy in the Lymph Nodes and lymphoid tissue originating from B lymphocytes, T lymphocytes and Natural Killer (NK) cells. Therapy for Non-Hodgkin's Lymphoma chemotherapy can be given alone or combined with radioactive therapy. Doxorubicin is a chemotherapy drug used for lymphoma with side effects, one of which is cardiotoxic effects. The aims of this study was to prove that coenzyme Q10 can reduce the cardiotoxic effect of doxorubicin chemotherapy in non-Hodgkin's lymphoma patients

Methods : Intervention study with a randomized pre and post test double blind control group design with 34 NHL patients undergoing chemotherapy. The treatment group received additional therapy with coenzyme Q10 300mg/day for 12 weeks while the controls received placebo. The cardiotoxic effects examined were assessed based on the results of Electrocardiography and Echocardiography.

Results : The treatment group with coenzyme Q10 supplementation after the 4th chemotherapy showed a decrease in echocardiography results in 3 patients (18%) and in the control group 17 patients (100%). There was a significant difference in the echocardiography results of the treatment and control groups (p=0.001). There were no drug side effects in both groups

Conclusion : Coenzyme Q10 supplementation provides an improvement in the cardiotoxic effects of doxorubicin in non-Hodgkin's lymphoma patients, on echocardiography, but not on Electrocardiography.

Keywords : Hodgkin's non lymphoma, Doxorubicin, Cardiotoxicity, Coenzym Q10

INTRODUCTION

Malignant tumors in lymph nodes and lymphoid tissues arising from B lymphocytes, T cells, and NK cells are known as non-Hodgkin's lymphoma (NHL).[1] Non-Hodgkin's lymphoma accounts for 90% of lymphoma cases worldwide, and 509 new cases of NHL are recorded worldwide.[2] NHL ranks sixth among the most common malignancies in Indonesia.[2] Chemotherapy is the treatment of choice for LNH, the management of patients with NHL, according to the clinical practice guidelines adapted to the National Comprehensive Cancer Network (NCCN),[3] mainly using first-line chemotherapy namely cyclophosphamide, doxorubicin, oncovin/vincristine and prednisone + rituximab (CHOP ± R).[1,3]

An anthracycline chemotherapy drug, doxorubicin, has a side effect that is considered serious for the heart, dilated cardiomyopathy. This side effect can lead to treatment discontinuation and increased morbidity.[4,5]

Hequet *et al*. reported that 27.65% of patients receiving doxorubicin at an average cumulative dose of 300 mg/m^2 met the criteria for subclinical cardiomyopathy, and only one of these patients developed congestive heart failure.[6] Research by Khattry *et al*. showed that 27% of patients experienced a decrease in left ventricular ejection fraction >10% with the use of doxorubicin 300–450 mg/m^2.[7] Chung *et al*. reported that as many as 29 of 174 patients (16.7%) experienced a decrease in ejection fraction >10% or a decrease in left ventricular ejection fraction below 55% of the normal limit without symptoms of heart failure. Research by Kamelia at Cipto Mangunkusumo Hospital shows an average decrease in left ventricular ejection fraction.[4]

Coenzyme Q10, also known as ubiquinone, is an important nutrient in the regulation of enzyme activities to carry out various biochemical reactions that have an effect on the decrease in ATP production through inhibition of glycolysis. Coenzyme Q10 (CoQ10) or ubiquinone is a lipophilic molecule commonly found in cell membranes, known as a cofactor that transfers electrons from complexes I and II to complex III during ATP formation in the inner mitochondrial membrane. In addition, CoQ10 may also act as an antioxidant in the cell membrane. The underlying pathophysiology of cardiotoxicity is increased free radical production, lipid peroxidation, and reactive oxygen species (ROS) accumulation can damage myocardium, and CoQ10 may prevent myocardial damage by inhibiting oxidative stress and lipid peroxidation.[8]

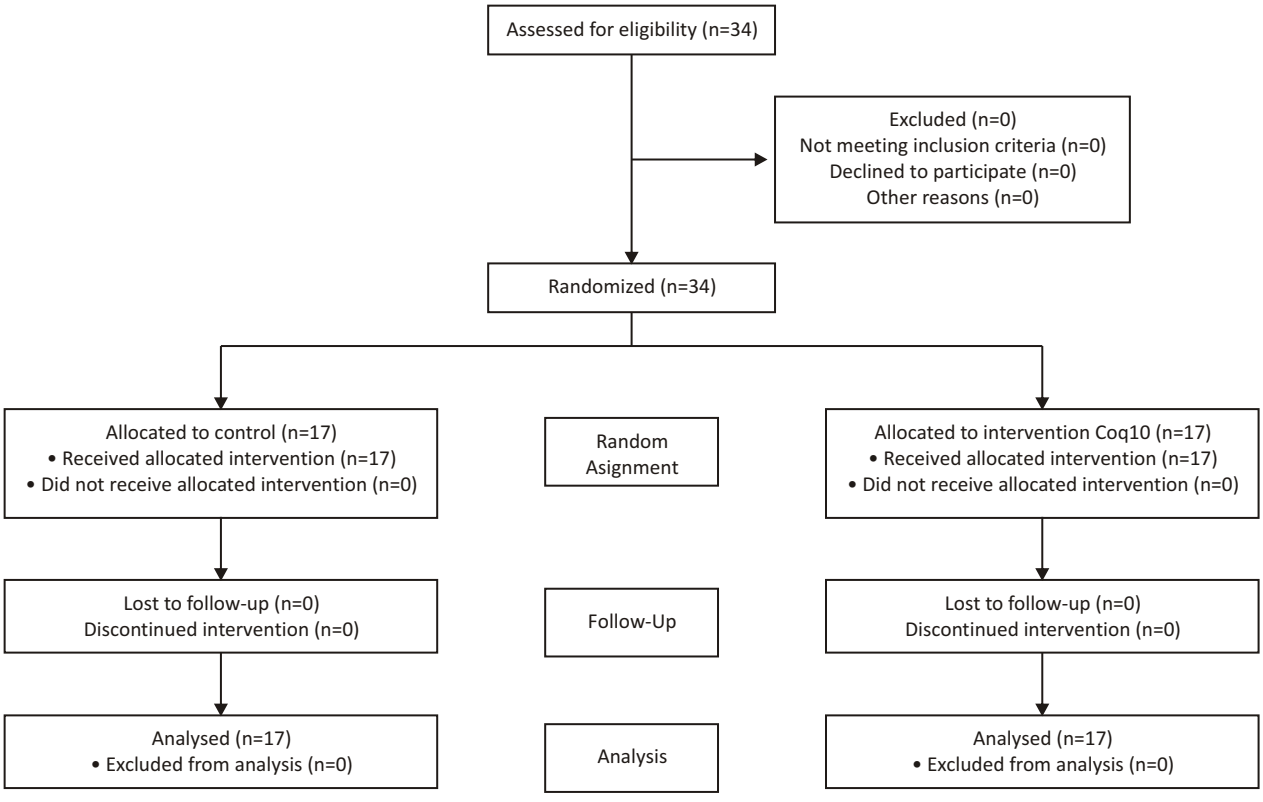
Coenzyme Q10 supplementation on cardiotoxic effects in NHL patients receiving doxorubicin chemotherapy at Dr. Kariadi Hospital, Semarang has never been studied before.

METHODS

This study is an interventional research with randomized pre- and post-test double-blind control group design. The research subjects were LNH patients who received chemotherapy with 12 weeks of therapy. The sample that has been determined is 34 samples. The data was collected from December 2022 to May 2023. The research group was divided into 2 groups, namely the treatment group (NHL patients who received chemotherapy and coenzyme Q10 300 mg/day) and the control group (NHL patients who received chemotherapy and placebo in the same capsule form). The study sample size was calculated using the intervention-test sample size formula, paired numerical, with an error rate of $\alpha = 5\%$, two-way hypothesis testing, then $Z\alpha = 1.65$. The study power is 80%, $Z\beta = 0.84$, the significant difference in value is 1.9. Therefore, N = 17 patients were obtained for each group.

Electrocardiographic examination prior to chemotherapy and echocardiography after the fourth cycle of chemotherapy. Inclusion criteria were all NHL patients with normal sinus rhythm and normal systolic function (>50%) or left ventricular ejection fraction. Chemotherapy-appropriate laboratory values were obtained and patients agreed to participate in this study. Exclusion criteria included history of antioxidant use, comorbidities (diabetes mellitus, hypertension, previous heart disease), and history of left chest irradiation. The independent variable was coenzyme Q10, while the dependent variable was left ventricular ejection fraction on echocardiography and the first negative wave deflection whose width exceeded 0.04 seconds accompanied by inverted T or pathological Q waves. The dependent variables were the echocardiographic left ventricular ejection fraction and the pathological Q wave, and the independent variable was coenzyme Q10. The coenzyme Q10 treatment group received 300 mg capsules/24 h for 12 weeks starting one week before chemotherapy, the control group received placebo capsules/24 h for 12 weeks starting one week before chemotherapy. The subjects received doxorubicin chemotherapy with an interval of three weeks before a second blood sample was taken one week after the second series of doxorubicin chemotherapy.

Subject characteristics were presented descriptively consisting of gender, age, type of NHL and type of chemotherapy. The relationship between variables was analyzed using normality test, Chi-Square test, Shapiro-Wilk test and normality data, then hypothesis testing on pre-post test using paired t-test. This study was approved by the Health Research Ethics Commission of Dr. Kariadi Hospital Semarang .



Picture 1. Consort Flow Diagram

RESULTS

This study included 34 NHL patients receiving doxorubicin chemotherapy divided into 17 control and 17 coenzyme Q10 treatment groups, sample characteristics shown in Table 1.

Table 1 shows that the majority of the control and treatment groups were male. There were no differences in the basic clinical characteristics between the control and coenzyme Q10 groups in terms of medical history, symptoms and signs, physical examination, laboratory results, and medical therapy.

Table 1 shows that the majority of the control and treatment groups were male. The ages under 60 years with the most type of NHL is DLBC and chemotherapy received CHOP.

Table 2 shows the results of ECG data analysis before and after the 4th chemotherapy, comparing two variables. There was an insignificant relationship between the two groups of NHL patients who received doxorubicin and coenzyme Q10 chemotherapy (p >0.05), which means that the confounding variables were homogeneous.

Table 3 in treatment group, echocardiographic changes pre and post chemotherapy using paired T-test, obtained significant results (p<0.05). Similarly, in control group, echocardiographic changes pre and post chemotherapy fourth cycle obtained significant results (p<0.05). The results of data analysis showed that treatment group pre chemotherapy had echo results around 67.65±5.44 and post chemotherapy fourth cycle around 61.06±5.03, so the difference between pre chemotherapy and post chemotherapy fourth cycle in treatment group was around 6.58±4.07. The control group pre chemotherapy with echo results 69.65 ± 6.38 and echo results post chemotherapy fourth cycle were about 55.18 ± 4.69. So the difference between pre and post chemotherapy fourth cycle in the control group was about 14.47 ± 6.66. The difference results in the control group were greater than the treatment group. This showed significant results that the control group had a greater difference.

The results of the Saphiro-Wilk normality test showed normal distribution of all data. In the treatment group before chemotherapy amounted to 0.063 (p>0.05), control amounted to 0.377 (p>0.05). In the treatment group after the 4th chemotherapy was 0.923 (p>0.05) and control was 0.10 (p>0.05).

The results of unpaired t-test showed no significant difference in the treatment and control groups pre chemotherapy, while there was a significant difference in the treatment and control groups post

TABLE 1
Subject Characteristics

Variable		n	%
Group	Intervention	17	50
	Control	17	50
Gender	Man	19	55.9
	Woman	15	44.1
Age	≤ 60	27	79.4
	≥ 60	7	20.6
Histopathology	DLBCL	20	58.9
	NKT, Nasal type	6	17.6
	Burkitt Lymphoma	2	5.9
	Diffuse Follikuler	6	17.6
Type of Chemotherapy	CHOP	22	68
	RCHOP	12	32
	ECG before Chemotherapy		
	No pathological Q waves	34	100

TABLE 2
The Relationship between ECG Results in the Chemotherapy Group with Coenzyme Q10 Supplementation and the Control Group after the Fourth Chemotherapy Session

Variable	ECG Result post fourth chemotherapy				*p*
	Pathological Q waves		No pathological Q waves		
Group	n	%	n	%	
Intervention	3	9	14	41	0.128
Control	7	21	10	29	

*Significant ($p < 0.05$), Chi Square test

chemotherapy fourth cycle and the difference between the groups pre and post chemotherapy fourth cycle. The results of the paired t-test showed significant differences in the treatment and control groups pre and post chemotherapy fourth cycle.

DISCUSSION

Non-Hodgkin lymphoma is a malignancy of the lymphatic tissue and is the sixth most common malignancy in Indonesia.[9] Based on histological type, it is divided into two major groups, namely Non-Hodgkin lymphoma, which is the most common case in head and neck cancer, and Hodgkin lymphoma.[1] NHL can originate from B lymphocytes, T lymphocytes, and, although it is very rare, from natural killer (NK) cells in the lymphatic system.[9] NHL is the seventh most common cancer and the ninth most common cause of cancer death in Indonesia.[10] The incidence of LNH at Dr. Kariadi Central General Hospital (RSUP), Semarang in January 2015 to May 2017 recorded the highest incidence, which was 60 cases.

The most common gender was male in both control and treatment groups in this study, less than 60 years of age was the largest age group. The most common histopathology in this study was DLBCL, consistent with a previous study in Southeast Asia (2017) that the most common histopathology in LNH was

TABLE 3
Difference in Echo results pre chemotherapy and post chemotherapy fourth cycle

Echo Result	Intervention	Control	*p*
Pre Chemotherapy	Mean 67.65 ± 5.44	Mean 69.65 ± 6.38	0.333‡
Post Chemotherapy	Mean 61.06 ± 5.03	Mean 55.18 ± 4.69	<0.001‡
p	0.000†	0.000†	

*Significant (p<0,05); ‡ unpaired t-test; † paired t test

DLBCL.[11]

Chemotherapy is the treatment of choice for NHL according to Clinical Practice Guidelines (CPG) and the National Comprehensive Cancer Network (NCCN),[3] involving first-line chemotherapy with Cyclophosphamide, doxorubicin, Oncovin/Vincristine, and Prednisone+ Rituximab (CHOP ± R).[1,3] Chemotherapy drugs, such as doxorubicin, are known to have serious side effects on the heart (cardiotoxicity). These side effects can lead to treatment discontinuation and increased morbidity.[4,5] Chung *et al*. reported that out of 174 patients, 29 (16.7%) experienced a decrease in ejection fraction >10% or a decrease in left ventricular ejection fraction below 55% of the normal limit without symptoms of heart failure.[4,10] Heart damage due to doxorubicin results from oxidative production in the heart, mainly in cardiac mitochondria. In mitochondria, the formation of oxygen radicals occurs through the auto-oxidation of doxorubicin semiquinone. Hydrogen peroxide is also a cause of oxidative stress and is responsible for inducing apoptosis by doxorubicin in endothelial and cardiac muscle cells. Hydrogen peroxide is inactivated by two enzymes, catalase, and glutathione peroxidase. Cardiac muscle contains a small amount of catalase, so the activity of glutathione peroxidase plays an important role in neutralizing the effects of anthracycline and free radicals formed.[12] The main mechanism of doxorubicinol toxicity occurs due to its interaction with iron and the formation of reactive oxygen species (ROS) that damage cellular macromolecules.[13] Heart damage caused by doxorubicin is due to oxidation in the heart. Mitochondria are the primary target of cardiotoxicity in the heart. Increased production of oxygen radicals. Hydrogen peroxide also causes oxidative stress and apoptosis induction by doxorubicin in endothelial and cardiomyocyte cells.[14] Damage to heart cell organs leads to myocardial damage, resulting in myocardial dysfunction. Examinations that can be performed include electrocardiography, angiography, echocardiography, and cardiac enzyme tests, but the examination recommended by the European Society for Medical Oncology (ESMO) is echocardiography.[15,16]

Coenzyme Q10 is the primary coenzyme for ATP in mitochondria and functions as an intracellular antioxidant, protecting mitochondrial protein membranes and phospholipids from free radicals. CoQ10 also acts as a membrane antioxidant. The pathophysiology underlying cardiotoxicity involves increased production of free radicals, lipid peroxidation, and accumulation of reactive oxygen species (ROS) that can damage the myocardium. CoQ10 is expected to prevent myocardial damage by inhibiting oxidative stress and lipid peroxidation.[8]

Based on this research, coenzyme Q10 can be used as an adjunctive therapy to mitigate cardiotoxic effects in patients undergoing Doxorubicin chemotherapy. This is evidenced by the significant improvement in echocardiographic findings in the treatment group before and after the fourth chemotherapy cycle with additional coenzyme Q10 therapy. Furthermore, this is reinforced by the comparison of echocardiographic results between the treatment and control groups, revealing significant disparities. Although the nonsignificant findings in the Electrocardiogram (ECG) are attributable to reversible changes, often observed within 24 hours of drug administration and subsequently resolving spontaneously.

The findings of this study align with prior research, suggesting that pretreatment with Coenzyme Q10 at a dosage of 100 mg/kg for 18 days exhibits protection against cardiac hypertrophy and cardiotoxicity, while also reducing lipid peroxidation in rats. Al Qahtani Abdullah *et al*. reported that out of the initial search yielding 11,303 articles, 14 were included. Among these 14 articles, 10 indicated that Coenzyme Q10 offers protective effects against doxorubicin-induced cardiotoxicity.[17]

CONCLUSION

Coenzyme Q10 can be considered as an adjunctive therapeutic option for NHL patients undergoing doxorubicin chemotherapy to prevent myocardial damage, thereby reducing cardiotoxic effects and lowering morbidity. However, this study requires further investigation with a longer duration, extending to the completion of 6 cycles of chemotherapy, to provide a clearer understanding of the cardiotoxic effects in NHL

patients receiving standard doxorubicin chemotherapy combined with Coenzyme Q10 therapy. Given that cardiotoxic assessments are not limited to EKG and ECHO, further research using cardiac enzymes is necessary to comprehensively evaluate cardiotoxic effects.

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