The Effect of CHOP Chemotherapy Implementation Towards Reduced Global Longitudinal Strain in Non-Hodgkin Lymphoma

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Abstract

Background: Doxorubicin in CHOP regimen is still the golden standard of first-line chemotherapy in patients with NHL (Non-Hodgkin Lymphoma); however, it has enormous cardiotoxicity side-effects.

Objective: This study aims to investigate the effect of CHOP chemotherapy implementation towards the GLS reduction in cumulative dosage of doxorubicin ≥ 100 mg/m.

Method: This study was pre experimental analysis with modified cohort. The subjects were observed for 1 month, since the first chemotherapy until 1 week after the second chemotherapy. The echocardiogram procedure with ejection fraction and global longitudinal strain was conducted twice which was before the first chemotherapy and 1 week after the second chemotherapy.

Results: The implementation of CHOP therapy with the cumulative dosage of ≥100 mg/m2 has resulted in reduced GLS from 19.62% to -18.03%. The reduction of GLS>10% was 40% while the LVEF has not been obtained any reduction > 10%. The case of subclinical left ventricular dysfunctions was attained 16%.

Conclusion: The implementation of CHOP chemotherapy with the dosage of ≥100mg/m2 has been proved to cause reduced GLS and subclinical left ventricular dysfunctions.

Keywords*: Global longitudinal strain, Left ventricular ejection fraction, anthracycline, CHOP chemotherapy*

Background

Chemotherapy is described as one of therapies which are very effective in cancer treatment. One of the serious side-effects which have been noticed by Hematology and Cardiology experts is cardiotoxicity. One of the chemotherapy drugs that have cardio-toxic effects is anthracycline. This compound can cause arrhythmia, pericarditis, myocarditis and cardiomyopathy. The cardio-toxic effects of doxorubicin have been studied by various kinds of researches. The case of heart failure because of cardiotoxicity was first found in leukemia child patient in 1967 who underwent doxorubicin therapy[1,2].

Non Hodgkin Lymphoma (NHL) is a primer malignancy which attacks lymphoid tissue and its supportive tissues, such as macrophages, histiocytes, and connective tissue. This disease comes from lymphocytes B, lymphocytes T and NK cells[3]. In 2010, it was presumed that there were 65.540 lymphoma cases that were diagnosed and caused 20.210 deaths [4]. In Indonesia, NHL was positioned on the sixth rank along with Hodgkin disease and leukemia as malignancy causes[5]. The number of malignant NHL cases in Indonesia since 1988 until 1991 was approximately 3.40% to 5.62% in males and, 79% to 3.40% in females[6].

Doxorubicin in the Cyclophosphamide, Hydroxyn-doxorubicin, Oncovin, Prednisone (CHOP) regimen is still the golden standard of first-line chemotherapy in patients with NHL. It requires more attention even though the implementation of first-line chemotherapy will cause cardiotoxicity that will affect the prognosis of patients themselves[7,8]doxorubicin, vincristin, prednisone. The case of acute cardiotoxicity after the

anthracycline chemotherapy implementation is <1%, during the therapy until 1 year 1.6-2.1% and after 1 year 1.6-5%[9]. The cardiotoxicity causes myocardium damage and continues to decreased ventricular function progressively; then, it ends up being decomposition. The cohort research in 830 patients who underwent chemotherapy for 8.5 years was found 2.5% suffered from heart failure [10].

The risk of cardiotoxicity is caused by several factors such as old age, young age, female, drug consumption duration, mediastinal radiotherapy, history of heart disease, hypertension, and specifically cumulative dose of doxorubicin [11]. The heart failure risks occur in 35% patients who obtain cumulative dose of 400 mg/m2, 7-26% in dose of 550 mg/m2, and 18-47% in dose of 700 mg/m^2. The suggested administration of maximum cumulative dose is 400-500 mg/m^2. The previous study reported that 27% patients who received doxorubicin with cumulative dose of ≥200 mg/m^2 underwent cardiomyopathy although the contraction abnormality and ventricular relaxation have occurred in doxorubicin dose of ≤200 mg/m^2 [7,9,12doxorubicin, vincristin, prednisone].

The early detection in cardiotoxicity and the preventive action of heart failure are considered as a challenge for cardiology and oncology experts. Several ways are conducted to monitor heart condition such as electrocardiography, echocardiography, radionuclide angiocardiography and endomyocardial biopsy as the golden standard [13,14].

Echocardiography is non-invasive examination that is received generally to evaluate the occurrence of cardiotoxicity[15]. This examination gives important information to recognize systolic heart function, especially left ventricular ejection fraction that is calculated by using teach method and modified simpson biplane [16]. The previous study stated that reduced global longitudinal strain in 2D-STE has occurred in doses of 200 mg/m^2 or the forth chemotherapy[17]. This study aims to investigate the effect of CHOP chemotherapy implementation towards the GLS reduction in cumulative dosage of doxorubicin ≥ 100 mg/m^2.

Method

The study was a pre experimental study with modified cohort by using one group pretest posttest group design. It was conducted in Hematology-Medical Oncology Unit Dr. Soetomo General Hospital Surabaya.

The research subjects must fulfill the inclusion criteria which were clinical diagnosis of NHL and hispathology, and EF ≥60%. Subjects who have underwent chemotherapy before, had one of the diseases such as CKD, coronary heart disease, cardiomyopathy, and non-sinus EKG rhythm were excluded from study.

Patients was examined by echocardiography and taken the parameter of LVEF and GLS. Then, the NHL patients underwent CHOP chemotherapy until two cycles (doxorubicin cumulative doses of ≥100 mg). Patients who have undergone CHOP chemotherapy twice were examined by using echocardiography and taken the parameter of LVEF and GLS 1 week after. The echocardiography test was conducted with machine, namely Echo GE vivid 7 [GE Healthcare, USA]. The examination of 2D Speckle Tracking Echocardiography [2D-STE] was conducted with 2D and Automated Function Imaging by using imaging analysis software [*EchoPac* version 11O.x.x, *GE Medical Systems*, 2010]. The offline analysis was conducted in 2D imaging (apical long axis, apical 2 - and 4 – chamber) which was kept with frame rate approximately 50-70 bps. Each image was measured PSLS per segment and evenly calculated. Afterwards, the average value of the third value was automatically measured which was called Global Longitudinal Strain GLS. The LVEF test applied the Simpson's biplane method.

The collected data in this study were analyzed descriptively and statistically. The statistical analysis to assess the different longitudinal strain parameter pre and post doxorubicin chemotherapy used paired t-test. The analysis to measure the correlation between decreased GLS and cardiotoxicity risk factors used Pearson correlation. The analysis of the data was conducted by using SPSS 17.0 program (SPSS, Inc., Chicago, IL) and it was significant if *p value* <0.05.

Results

Subject Characteristics

Most patients were males (73.3%). The average age of the subjects was 49±13 years old and the most frequent subjects based on age categorization were 61-70 years old with the total of 9 individuals (30%). The most frequent clinical stage was stage III which were 73.34% while the most frequent risk factor was smoking (50%; table 1).

Table 1. Research Subject Characteristics

Variables	N [%] or average ±SB	Min-Max
Age [year] - 11 – 20 - 21 – 30 - 31 – 40 - 41 – 50 - 51 – 60 - 61 – 70	49±13 1 [3.33] 1 [3.33] 7 [23.33] 8 [26.67] 4 [13.34] 9 [30]	15-68
Gender - Males - Females	22 [73.33] 8 [26.67]	
Stage - I - II - III - IV	1 [3.33] 6 [20.00] 22 [73.34] 1 [3.33]	
Risk factors - Hypertension - Diabetes mellitus - Smoking	9 [30.00] 3 [10.00] 15 [50.00]	

The Analysis Result

The evaluation result of 30 NHL patients showed that there was no reduced EF more than 10%; however, it was obtained that 12 patients (40%) had reduced GLS > 10%, 10-15% in 7 patients (23.3%) and >15% in 5 patients (16.6%). The reduction of GLS >15 % signified the occurrence of subclinical left ventricular dysfunctions (table 2).

Table 2. The Analysis of EF and GLS before and after Chemotherapy

Measurement	Before	After	<10%*	10-15%*	>15%*
LVEF [%]	65.5±3.1	63.9±2.8	30	0	0
Global longitudinal strain [%]	-19.62±1.4	-18.03±1.9	18	7	5

Note: * Percentage of left ventricular systolic function decrease

Discussion

In this study, it was found that the administration of CHOP chemotherapy with a cumulative dose of 100 mg / m2 had an effect of decreasing GLS and causing subclinical left ventricular dysfunction. Swain *et al.* state that

LVEF is not an accurate predictor of heart failure on chemotherapy and prove there is no relationship between the severity of heart failure and the decrease in LVEF[18]. The reverse results in the study of Nousiainen *et al.* stated a decrease in LVEF 4% after the cumulative dose of doxorubicin 200 mg / m² has a sensitivity of 90% and a specificity of 72% as predictors of cardiotoxicity. In this study, 1 sample was found which experienced a LVEF decrease of 4%[19].

In this study, there was no reduced LVEF >10% after NHL patients underwent CHOP chemotherapy with the doses of ≥100 mg/m^2. On the other hand, the maximum reduced LVEF in this study was 4%. This result was in accordance with the study of Stoodley *et al*. in which with the doxorubicin doses of ≥ 200 mg/m², it has not been obtained reduced LVEF >10%. However, Limat *et al*. showed different result in which after the giving of doxorubicin cumulative doses of ≥ 200 mg/m² or after the fourth chemotherapy in CHOP regimen, the occurrence of cardio-toxic was 27% [7,17,20]doxorubicin, vincristin, prednisone.

Chemotherapy Related Cardiac Dysfunction (CRCD) is divided into I and II. Anthracycline is considered as type I in which it can cause permanent and irreversible myocardium damage compared to type II that can cause reversible myocardium damage. Early detection is required to prevent myocardium cell damage widely and more severe. Swain et al. stated that LVEF was not accurate predictor of heart failure in chemotherapy and proved that there was no correlation between the severity of heart failure and reduced LVEF. In contrast, Nousiainen *et al*. asserted that reduced LVEF of 4% after doxorubicin cumulative doses of 200 mg/m² had the sensitivity of 90% and specificity of 72% as cardiotoxicity predictor. This study attained 1 sample that encountered reduced LVEF of 4%[12,18,19,21].

Several previous studies have showed the superiority of GLS test compared to LVEF test. Most population that was being analyzed using GLS parameter was breast cancer by employing the combination regimen of anthracycline and trastuzumab. Researches which employed GLS and NHL as their parameter are rarely conducted. Kang *et al*. used GLS parameter and high sensitivity of troponin-T as cardiotoxicity predictor in NHL. GLS monitoring is conducted on baseline, 1 day after the third cycle, and 1 day after completing chemotherapy. The GLS monitoring in this study was conducted on baseline, and 1 week after the second cycle[22].

GLS test is considered capable in detecting subclinical cardio-toxic and has good reproducibility. Expert Consensus Statement recommends GLS test to detect subclinical left ventricular dysfunctions rather than Global Radial Strain [GRS] and Global Circumferential Strain [GCS] because there has not been normal value and different variability between vendor and software. The abnormal reduced GLS value is different in several studies. Stoodley *et al*. determined abnormal reduced GLS value of >10% [17], Negishi *et al*. determined reduced GLS of >11%[23]. Banchs suggested that reduced GLS of >10% was considered in giving anti-remodeling therapy [24] and clinical monitoring strictly together with oncologist whereas Kang *et al*. determined reduced GLS of >15.9%[22]. The abnormal GLS value in this study based on Expert Consensus Statement ASE that stated reduced GLS of >15% from baseline showed that subclinical left ventricular dysfunctions[17,21–25]. In this study there was no correlation between reduced GLS and hypertension risk factors while there was no correlation between reduced GLS and other factors such as age, diabetes, and smoking. It was in accordance with the study conducted by Hershman *et al.* in which only hypertension risk factor that synergized with cardio-toxic cases [26]which improves survival for patients with non-Hodgkin's lymphoma, is often withheld from elderly patients because of its cardiotoxicity. We studied the cardiac effects of doxorubicin in a population-based sample of older patients with diffuse large B-cell lymphoma (DLBCL.

Conclusion

There was an effect in the implementation of CHOP chemotherapy towards global longitudinal strain. The giving of doxorubicin cumulative doses of ≥ 100 mg/m2 was able to cause subclinical left ventricular dysfunctions.

Ethical Clearance: The study protocol was approved by the Ethical Commission to conduct basic science/clinical research in Dr. Soetomo General Hospital Surabaya, Indonesia. The present study was carried out in accordance with the research principles. This study implemented the basic principle ethics of respect, beneficence, non-maleficence, and justice.

Conflict of Interest: The author reports no conflict of interest of this work.

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