Original Article

The Incidence and Clinical Risk Factors of Anthracycline-Induced Cardiomyopathy in Adult Patients with Lymphoma

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Background: Anthracycline-induced cardiomyopathy is one of the major complications that increase mortality in patients receiving anthracycline-based chemotherapy.

Objective: To determine the incidence and risk factors of anthracycline-induced cardiomyopathy in patients with lymphoma.

Materials and Methods: A prospective study was conducted in adult patients with lymphoma at Srinagarind Hospital, Khon Kaen University. Anthracycline-induced cardiomyopathy was defined as the presence of clinical signs of congestive heart failure or the decrease of left ventricular ejection fraction [LVEF], or LVEF shortening, or the presence of abnormal wall motion by echocardiography. Echocardiography was evaluated at baseline, after accumulating anthracyclines doses of at least 100 mg/m^2 and after the last cycle of chemotherapy. The clinical parameters which literature has indicated as risk factors for cardiomyopathy were collected and analyzed by using the logistic regression method.

Results: In 104 patients, anthracycline-induced cardiomyopathy was found in 38 patients (36.5%). Accumulating doses of anthracyclines exceeding 300 mg/m^2 and systemic hypertension were significant risk factors statistically associated with cardiomyopathies in patients with lymphoma.

Conclusion: The incidence of anthracycline-induced cardiomyopathy is modest in adult patients with lymphoma. A moderate accumulated dose of anthracyclines and systemic hypertension were important risk factors. High-risk patients should be closely monitored by echocardiography.

Keywords: Anthracycline-induced cardiomyopathy, Risk factors, Lymphoma

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Anthracyclines are a class of drugs in the topoisomerase II inhibitor group of chemotherapeutic agents. The common drugs in this group of chemotherapeutic agents are doxorubicin, idarubicin, epirubicin, and daunorubicin. The anthracycline drugs are widely used in many cancer chemotherapy regimens e.g., lymphoma, leukemia, breast cancer, and soft tissue sarcomas. The mechanism of action of anthracycline drugs is inhibition of topoisomerase II enzyme resulting in blocking DNA transcription and DNA replication leading to promoting DNA breaks[1]. The cardiotoxic mechanisms of anthracycline-induced cardiomyopathy include the formation of reactive oxygen species leading to the myocardial damage, inhibition of specific muscle gene expression for contraction of myocardium, and alteration of molecular signaling pathways[2,3]. Anthracycline-induced cardiomyopathy is divided into 4 subgroups according to the clinical course and prognosis including: 1) acute cardiotoxicity, 2) subacute cardiotoxicity, 3) chronic cardiotoxicity and 4) late cardiotoxicity[4]. Previous studies reported the incidence of anthracycline-induced cardiomyopathy that varied from 2.2% to 57% according to the differences in definitions of anthracycline-induced cardiomyopathy and study populations[4-7].

Literature has shown various clinical risk factors for anthracycline-induced cardiomyopathy. The high cumulative anthracycline dose was the most important risk factor followed by a history of thoracic

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irradiation, advanced age, malnutrition, and presence of existing cardiovascular risk factors[3-14]. The present study was aimed to determine the incidence and clinical risk factors for predicting anthracycline-induced cardiomyopathy in adult patients with lymphoma.

Materials and Methods

A prospective study was conducted in patients with lymphoma at Srinagarind Hospital, Khon Kaen University from January 2012 to July 2013. Eligible participants were patients aged ≥18 years old with a diagnosis of Hodgkin's lymphoma or non-Hodgkin's lymphoma. All participants underwent trans-thoracic echocardiography 3 times (AlokaProSound F75 sonographic system; Hitachi-Aloka Medical, Ltd, Tokyo, Japan) by one cardiologist. The first echocardiography was performed at baseline, the second echocardiography was performed after accumulating doses of anthracyclines >100 mg/m^2, and the last echocardiography was performed after the last cycle of chemotherapy. The study flow is shown in Figure 1. Clinical characteristics and laboratory data that literature indicated as risk factors for anthracycline-induced cardiomyopathy were collected.

All participants gave consent, and the research protocol was approved by the Ethics Review Board for Human Research of the Faculty of Medicine, Khon Kaen University Diagnosis of anthracycline-induced cardiomyopathy Anthracycline-induced cardiomyopathy included the presence of the following:

1) Congestive heart failure defined as the presence of clinical symptoms of congestive heart failure according to the Framingham criteria[15] or

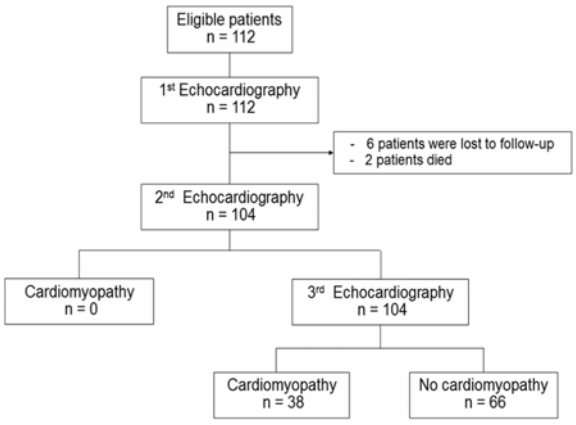

Figure 1. The study flow.

2) Subclinical cardiomyopathy defined as the presence of left ventricular ejection fraction [LVEF] <40% or the decrease of LVEF >15% from baseline or LVEF shortening (fractional shortening) <28% or presence of abnormal wall motion by the two-dimensional Teichholz M-mode echocardiography[16,17].

Cardiovascular risk factors are the presence of the following risk factors including;

1) Diabetes mellitus defined as the fasting plasma glucose >126 mg/dl[18].

2) Hypertension defined as systemic blood pressure >140/90 mmHg[19].

3) Dyslipidemia defined as total cholesterol >200 mg/dl, LDL-cholesterol >100 mg/dl, HDL-cholesterol <40 mg/dl for men or <50 mg/dl for women, and triglycerides >150 mg/dl[20].

4) Significant smoking defined as a history of smoking >10 pack-year.

Statistical analysis

Categorical parameters are reported as numbers and percentages. Continuous parameters are reported as means and standard deviations [SD]. Clinical risk factors for anthracycline-induced cardiomyopathy were analyzed by using the univariate and multivariate logistic regression methods. All statistical analyses were performed by the STATA program version 10 (StataCorp, College Station, TX). A probability value less than 0.05 was considered statistically significant.

Results

One hundred twelve patients (69 females, 35 males) were enrolled in the study. Six patients were lost to follow-up and 2 patients died from disease progression before performing the second echocardiography. A total of 104 patients were therefore included in the present study. Anthracycline-induced cardiomyopathy was found in 38 patients (36.5%). Of the 38 patients with anthracycline-induced cardiomyopathy, 4 patients developed congestive heart failure (10.5%) and 34 patients had subclinical cardiomyopathy (89.5%). Baseline clinical characteristics data of all patients are shown in Table 1. The mean age was 51.9±14.4 years. The mean dose of anthracycline chemotherapy was 317.3±89.6 mg/m^2. A history of thoracic radiation was found in 9 patients (7.7%). The most common type of lymphoma in this cohort was diffuse large B cell lymphoma (62 patients, 59.6%) followed by T-cell lymphoma (16 patients, 15.4%) and Hodgkin's lymphoma (13 patients, 12.5%).

Significant smoking was the most common cardiovascular risk factor (43 patients, 41.3%) followed by hypertension (16 patients, 15.4%) and diabetes mellitus (12 patients, 11.5%).

Univariate analyses of the clinical risk factors for the anthracycline-induced cardiomyopathy in patients with lymphoma are shown in Table 2. A total accumulating dose of anthracycline chemotherapy >300 mg/m^2 was the only clinical risk factor that was statistically significantly associated with the anthracycline-induced cardiomyopathy in patients with lymphoma (odds ratio, OR = 2.8, 95% CI 1.1 to 7.2 and *p*-value = 0.03).

Multivariate analyses of the clinical risk factors for the anthracycline-induced cardiomyopathy in patients with lymphoma are shown in Table 3. Total accumulating doses of anthracycline chemotherapy

Table 1. Demographic and clinical characteristic data of 104 patients with lymphoma

Characteristics	Total patients (n = 104)
Mean age ±SD, years	51.9±14.4
Hemoglobin ±SD, g/dl	11.9±1.8
Mean total dose of anthracycline chemotherapy ±SD, mg/m^2	317.3±89.6
Gender, n (%)	
Female	69 (66.3)
Male	35 (33.7)
Anthracycline-induced cardiomyopathy	
No	66 (63.5)
Yes	38 (36.5)
Thoracic radiation, n (%)	
No	95 (92.3)
Yes	9 (7.7)
Total dose of doxorubicin >300 mg/m^2, n (%)	
No	44 (42.3)
Yes	60 (57.7)
Cardiovascular risks, n (%)	
Diabetes mellitus	12 (11.5)
Dyslipidemia	10 (9.6)
Hypertension	16 (15.4)
Significant smoking	43 (41.3)
Type of lymphoma, n (%)	
Diffuse large B-cell lymphoma	62 (59.6)
T-cell lymphoma	16 (15.4)
Hodgkin's lymphoma	13 (12.5)
Mantle cell lymphoma	8 (7.7)
Other	5 (4.8)
Stage of lymphoma, n (%)	
Stage 1	10 (9.6)
Stage 2	25 (24)
Stage 3	16 (15.4)
Stage 4	53 (51)
Performance status, n (%)	
ECOG 0	22 (21.2)
ECOG 1	67 (64.4)
ECOG 2	14 (13.5)
ECOG 3	1 (0.9)
ECOG 4	0 (0)

Table 2. Univariate analysis of clinical risk factors for anthracycline-induced cardiomyopathy in 104 patients with lymphoma

Variables	OR	95% CI of OR	*p*-value
Age >60 years			
Yes	1.4	0.6 to 3.3	0.4
No	1	-	-
Gender			
Male	1.3	0.4 to 3.9	0.6
Female	1	-	-
Total dose of anthracycline >300 mg/m^2			
Yes	2.8	1.1 to 7.2	0.03
No	1	-	-
Hypertension			
Yes	2.6	0.8 to 7.7	0.08
No	1	-	-
Dyslipidemia			
Yes	1.8	0.5 to 6.8	0.3
No	1	-	-
Diabetes mellitus			
Yes	0.9	0.2 to 3.1	0.8
No	1	-	-
Significant smoking			
Yes	0.8	0.5 to 1.2	0.4
No	1	-	-
Thoracic radiation			
Yes	1.4	0.3 to 5.7	0.6
No	1	-	-
Hemoglobin <8 g/dl			
Yes	3.5	0.3 to 40.6	0.3
No	1	-	-
Advanced stage			
Yes	1.4	0.6 to 3.3	0.4
No	1	-	-
Performance status			
ECOG 0	1	-	-
ECOG 1	0.9	0.3 to 2.6	0.9
ECOG 2	1.3	0.3 to 5.6	0.7
ECOG 3	-	-	-
ECOG 4	NA	NA	NA

OR = odds ratio; 95% CI = 95% confidence interval

Table 3. Multivariate analyses of risk factors for anthracycline-induced cardiomyopathy in 104 patients with lymphoma

Variables	AOR	95% CI of AOR	*p*-value
Age >60 years	1.0	0.9 to 1.1	0.3
Advanced stage	1.2	0.4 to 3.3	0.6
Doxorubicin dose >300 mg/m^2	2.7	1.1 to 7.1	0.04
Hemoglobin <8 g/dl	2.8	0.2 to 34.8	0.4
Thoracic irradiation	2.5	0.5 to 11.9	0.2
Female gender	1.4	0.5 to 3.7	0.4
Hypertension	5.3	1.2 to 23.9	0.03
Dyslipidemia	1.7	0.3 to 11	0.5

AOR = adjusted odds ratio, 95% CI = 95% confidence interval

>300 mg/m^2 remained significantly associated with the anthracycline-induced cardiomyopathy with an adjusted odds ratio (95% CI) of 2.7 (1.1 to 7.1) and a *p*-value of 0.04. Systemic hypertension was also statistically proven to be associated with anthracycline-induced cardiomyopathy (AOR = 5.3, 95% CI 1.2 to 23.9 and *p*-value = 0.03).

Discussion

The incidence of anthracycline-induced cardiomyopathy is modest in adult patients with lymphoma. In the present study, the incidence of anthracycline-induced cardiomyopathy is slightly higher than the highest of previous studies in adult patients (36.5% vs. 4.7% to 29%)[21-25]. The high incidence of anthracycline-induced cardiomyopathy in this cohort might be explained by the definition of anthracycline-induced cardiomyopathy in the present study because the present study included both patients with clinical congestive heart failure and those patients with subclinical cardiomyopathy.

It is well established that large accumulated doses of anthracycline chemotherapy is an important risk factor for developing anthracycline-induced cardiomyopathy. Previous studies demonstrated that a cumulative dose of doxorubicin exceeding 500 to 550 mg/m^2 is the most serious risk factor for developing cardiomyopathy[26-29]. A study of periodic echocardio graphic surveillance in childhood cancer survivors showed lower accumulating doses of anthracyclines for developing cardiomyopathy. They found that a cumulative dose of anthracyclines >300 mg/m^2 was significantly associated with subclinical cardiomyo pathy in young patients receiving anthracycline-based chemotherapy (hazard ratio [HR] 3.00; 95% CI 1.51 to 5.98)[30]. A previous retrospective study in adult patients treated with doxorubicin[21] found that older patients experienced congestive heart failure after a cumulative dose of 400 mg/m^2. This study also demonstrated that accumulating doses of anthracyclines >300 mg/m^2 was an independent risk factor for anthracycline-induced cardiomyopathy (adjusted odds ratio 2.7, 95% CI 1.1 to 7.1, $p = 0.04$). This finding suggested that anthracycline-induced cardiomyopathy could be developed in adult patients at a lower cumulative dose than previous studies. Therefore, early echocardiographic surveillance should be performed, especially in high-risk patients for early diagnosis and management in these patients.

An interesting finding is that systemic hypertension was a significant risk factor for anthracycline-induced cardiomyopathy in this cohort. This finding is similar to a large study in adult patients with diffuse large B cell lymphoma by Hershman DL et al. They found that hypertension intensified the effect of doxorubicin on risk of congestive heart failure (hazard ratio = 1.8, *p*-value <0.01)[25].

The findings herein could have clinical implications as guidelines for early screening echocardiography in hypertensive patients who have received accumulating doses of anthracyclines >300 mg/m^2. Early detection and early treatment of cardiotoxicity in these patients may reduce the mortality and prevent long-term morbidity.

In conclusion, the incidence of anthracycline-induced cardiomyopathy is modest in adult patients. Accumulating doses of anthracyclines exceeding 300 mg/m^2 and systemic hypertension are important risk factors for developing cardiomyopathy in patients receiving anthracycline-based chemotherapy. Early screening by echocardiography should be performed in high-risk patients.

What is already known on this topic?

Anthracycline-induced cardiomyopathy is one of the major complications in patients receiving anthracycline-based chemotherapy. High accumulated doses of anthracycline drugs is believed to be the most important risk factors for the development of anthracycline-induced cardiomyopathy.

What this study adds?

The present study demonstrated accumulating doses of anthracyclines exceeding 300

mg/m^2 and hypertension are the important risk factors for anthracycline-induced cardiomyopathy in adult patients. The findings could have a clinical implication as a guideline for early screening echocardiography in hypertensive patients who have received a moderate accumulating dose of anthracyclines.

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Potential conflicts of interest

The authors declare no conflict of interest.

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