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Increase of Carotid Intima-Media Thickness and Reduction of Carotid Artery Lumen Diameter in Breast Cancer Patient Before and After Chemotherapy

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ABSTRACT

Background: Increasing the number of cancer survivors motivates clinical practitioners to focus on the chronic effect of chemotherapy agents, especially those with vascular toxicity effects, which may attenuate the incidence of thrombosis and atherogenesis. Ultrasonography examination on carotid intima-media thickness (C-IMT) provides accurate results in evaluating atherosclerotic. The purposes of this research are to find out any structural changes of the carotid artery, especially atherosclerosis changes in breast cancer patients after chemotherapy. **Methods**: Analytic cross-sectional study using a pre-post test group design in breast cancer patients. Eligible subjects undergo carotid ultrasonography examination before chemotherapy and after completing the three cycles of chemotherapy for the second exam. The examination was performed with the same USG machine, high-frequency linear transducer (>7mHz) in B-mode under the auspices of two reputable radiologist consultants. **Results:** Total patients are 26, mean of age (year) is 47.15 ± 8.11. The most dominant histopathology finding is invasive carcinoma nonspecific type, in 24 patients (92.4%), and the disease stage is in stadium III in 14 patients (53.9%). Mean C-IMT (mm) prior chemotherapy is 0.51 ± 0.06 and after chemotherapy is 0.58 ± 0.05, there is an increase of 0.07 ± 0.06 ($p<0.0001$). Carotid artery lumen diameter (mm) before chemotherapy is 4.05 ± 0.66 and after chemotherapy is 3.90 ± 0.73, so there is a decrease of 0.16 ± 0.40 ($p = 0.057$). **Conclusion:** There is a statistically significant increase in intintima-mediaickness of the carotid wall of breast cancer patients after chemotherapy, consisting of chemotherapy-induced atherosclerosis.

Keywords: ultrasonography, C-IMT, chemotherapy, breast cancer.

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INTRODUCTION

The survival of cancer patients is currently an interesting topic to be studied, researched, and developed. There is a noticeable increase in cancer survival rates internationally, supported by early detection, better chemotherapy regimens, and especially collaborative multidisciplinary management approaches. In January 2016, more than 2.5 million women living in the US with a history of breast cancer, with a lower life expectancy than the general healthy population.[1,2] These findings increase the vigilance of clinicians for advanced chronic effects of breast cancer therapy, especially chemotherapeutic agents.

One distinct consequence of current cancer therapy is cognitive dysfunction after chemotherapy often referred to as “chemobrain.”[3] It is estimated that about 18 to 78% of breast cancer patients have this cognitive dysfunction after the initiation of chemotherapy therapy, but the certain pathophysiology is not fully understood. [4]Cognitive dysfunction in the general population is closely related to various cerebrovascular disorders, the especially microvascular disruption that causes hypoperfusion, demyelination and ischaemic lession in white matter.[5] Carotid atherosclerosis is also a major risk factor for the cerebrovascular disorder, and it can be used to predict the risk of cognitive impairment.[6]

The main undesirable well-known side effects of chemotherapy is vascular toxicity in which endothelial dysfunction can occur, loss of vasorelaxant ability, suppression of anti-inflammatory function and vascular reparation.[7] These impairments are able to accelerate the occurrence of hypertension, thrombosis and atherogenesis, which are risk factors for cardiovascular disease. The prevalence of arterial thromboembolism in cancer patients who undergo chemotherapy is 1.7.[8] However, it must be understood that chemotherapy works systemically; it is not possible to attack only the cardiovascular course exclusively. Certainly, it will also interfere with the cerebrovascular course.

Atherosclerosis, alteration in carotid artery wall intima-media thickness (C-IMT), can be used as an early marker for cognitive dysfunction in breast cancer patients receiving chemotherapy. Color Doppler ultrasound examination is proficient in non-invasive evaluation of carotid arteries by assessing C-IMT and the stenosis of the internal carotid artery as well as the common carotid artery.[9,10] In this study, the author intends to prove whether there are structural changes in the carotid arteries, especially atherosclerosis, in breast cancer patients who received chemotherapy through measurement and examination of carotid ultrasound.

METHODS

This study uses an analytic cross-sectional study with a pre-post test group design from April to September 2019 at RSUP Sanglah Denpasar. The research subjects were breast cancer patients who underwent chemotherapy. Patients with uncontrolled diseases or comorbidity such as hypertension, dyslipidemia, stroke and refuse to participate after informed consent were excluded from the study. We calculated the sample size with estimated standart deviation difference of mean C-IMT thickness pre and post test was 0.13,[11,12] and we got an estimate of the minimum sample size needed is 26 people.

After obtaining ethical clearance and permission from the Research and Development Unit of Faculty of Medicine Udayana University / Sanglah Hospital, No.161/UN14.2.2.VII.14/LP/2019, we continued with subject collecting and explained the whole process of this study, including the aims and benefits for the subjects, possible complications, and ended with signing the informed consent.

Carotid ultrasound examination is done twice, before and after chemotherapy, on the right and left carotid arteries, using the GE LOGIC™ S7 ultrasound machine, with high-frequency (>7 MHz) linear transducer in B-mode by radiology specialist consultant. Measurement of the carotid intima-media thickness (C-IMT) is done semiautomatic at 3 spots on both sides of the carotid artery in the supine position and the head-turning contralaterally from the examined site. The three spots are the common carotid artery (10 mm before the bulb), the bulb (5-10 mm cranial bulb), and the internal carotid artery (10 mm after carotid branching) at the free plaque part. The mean C-IMT is calculated from the mean value of the six points measured. The maximum C-IMT is the largest value among the six points. The second carotid ultrasound measurement is performed after the third cycle of chemotherapy take place with the same measurement procedure as explained.

Statistical analysis is done using IBM SPSS statistics 23.0. For numerical data, data normality analysis was performed using the Shapiro-Wilk test. The data is normally distributed if p>0.05. Bivariate analysis was used to find the risk factor affecting the C-IMT before and after chemotherapy. We use T-Paired test for analysis of C-IMT before and after chemotherapy.

Since there are several variables that affect the C-IMT, a multivariate analysis test was carried out, namely covariance analysis (ANCOVA) for age, cancer stage, histopathology type and pre-post chemotherapy group. Statistical test results were significant if p<0.05.

RESULTS

This study engaged 26 breast cancer patients who underwent chemotherapy treatment. We also studied an interobserver of the C-IMT measurement result for conformity value between the two operators. There is no difference (bias) between operator 1 and 2 with all p values >0.05 for the thickness measurement of the common carotid artery, bulbous and internal carotid artery. The characteristics of the subjects are described in **Table 1**.

Table 1. Characteristics of research subjects (n=26)

Variable	Characteristics of research subjects	
Age (years) [a]	47.15 ± 8.11	
Body mass index (kg/ m^2) [a]	24.38 ± 3.36	
Types of chemotherapy [b]		
CAF	9 (34.6%)	
CEF	5 (19.2%)	
Paclitaxel Doxorubicin	8 (30.8%)	
Paclitaxel Epirubicin	3 (11.5%)	
Doxorubicin cyclophosphamide	1 (3.8%)	
Histopathology [b]		
Invasive carcinoma non-specific type	24 (92.4%)	
Adenocarcinoma	1 (3.8%)	
Mixed type invasive and lobular carcinoma	1 (3.8%)	
Stadium [b]		
I	1 (3.8%)	
II	7 (26.9%)	
III	14 (53.9%)	
IV	4 (15.4%)	
	C-IMT before chemotherapy (mm)	**C-IMT after chemotherapy (mm)**
Right common carotid artery [a]	0.49 ± 0.061	0.54 ± 0.072
Right bulb [a]	0.54 ± 0.085	0.65 ±0.133
Right internal carotid artery [a]	0.49 ± 0.089	0.52 ± 0.128
Left common carotid artery [a]	0.49 ± 0.087	0.58 ± 0.079
Left bulb [a]	0.55 ± 0.138	0.63 ± 0.118
Left internal carotid artery [a]	0.52 ± 0.706	0.57 ± 0.101
C-IMT average [a]	0.51 ± 0.496	0.56 ± 0.055
Internal carotid artery diameter [a]	4.05 ±0.660	3.9 ± 0.731

[a] Mean ± standard deviation; [b] Frequency (%); CAF: cyclophosphamide doxorubicin 5-fluorouracil; CEF: cyclophosphamide epirubicin 5-fluorouracil

All subjects who participated in this study underwent doppler carotid ultrasound examination twice, before and after chemotherapy. Data characteristic is shown in **Table 1**. The values of C-IMT average and internal carotid artery diameter were normally distributed in the Shapiro-Wilk normality test (p>0.05), so we continued with the bivariate analysis of T-paired test.

In **Table 2**, the mean of average C-IMT before chemotherapy was 0.51 ± 0.06 mm, after chemotherapy 0.58 ± 0.05 mm with a significant increase of 0.68 ± 0.06 mm (p<0.0001). The reduction in diameter of the internal carotid artery before chemotherapy was 4.05 ± 0.66 mm, after chemotherapy, it became 3.90 ± 0.73 mm, resulting in decreased in diameter by 0.16 ± 0.40 mm, but statistically, it was not significant with p=0.057.

To determine which variables (chemotherapy type, age, histopathology, and cancer stadium) affects the C-IMT and internal carotid diameter before and after chemotherapy, multivariate analysis was performed with covariance analysis (ANCOVA) (**Table 3**).

Analysis of covariance (ANCOVA) on the C-IMT thickness before and after chemotherapy shows that chemotherapy regiment and age affect the thickening of C-IMT thickness (p <0.05). ANCOVA also shows that the reduction in internal carotid artery lumen diameter is not affected by chemotherapy, age, histopathology, and cancer stadium. This might be influenced by other variables that cannot be identified in this study.

Table 2. Average C-IMT and diameter of internal carotid artery values

	Chemotherapy		difference	p-value
	Before	**After**		
C-IMT average (mm)	0.51 ± 0.05	0.58 ± 0.06	0.07 ± 0.06	<0.0001
Internal carotid artery diameter (mm)	4.05 ± 0.66	3.90 ± 0.73	0.16 ± 0.40	0.057

C-IMT: carotid intima-media thickness

Table 3. Covariance analysis of C-IMT and diameter of internal carotid artery

	Variable	F	p-value
C-IMT	Chemotherapy type	23.11	<0.0001*
	Age (years)	4.954	0.031*
	Histopathology	0.370	0.546
	Cancer stadium	0.064	0.802
Internal carotid artery diameter	Chemotherapy type	0.686	0.412
	Age (years)	0.350	0.557
	Histopathology	3.585	0.064
	Cancer stadium	1.015	0.319

C-IMT: carotid intima-media thickness

DISCUSSION

The subjects collected in this study is 26 sample with diagnosis of breast cancer. The average age of the patients is 47.15 ± 8.11 years, consistent with the result of a previous study conducted by Karima, et al who reported that the average age of women with breast cancer in Dr. Cipto Mangunkusumo National Public Hospital Jakarta is 47.53 ± 10.21 years old. [13]

The distribution of subjects based on histopathological type showed the dominance of Invasive Carcinoma of no special type (NST) in 24 subjects (92.4%), followed by adenocarcinoma and mixed types of invasive-globular carcinoma, each of which consisted of 1 person (3.8%). This data is in line with the findings of two previous studies at Sanglah Hospital in 2002-2012 (81.9%) and 2014-2016 (96.2%), that Invasive Carcinoma of no special type (NST) is the most common histopathology type that occurs in cancer patient, especially in the Balinese population.[14,15]

These previous studies also find that most of the breast cancer patients seeking treatment at Sanglah Hospital were patients who had been diagnosed with stage III B cancer. The most common stage of breast cancer in this study is stage III, amounting to 14 patients (53.9%) with 9 patients in stage III b, 5 patients in stage IIIa. The same finding was also obtained by Kusumadjayanti, et al who stated that from the year 2010 until 2011, dr. Hasan Sadikin Public hospital's breast cancer patients are often diagnosed at stage III.[16]

The type of chemotherapy most widely used in this study was CAF (Cyclophosphamide Doxorubicin 5-Fluorouracil), amounting to 34.6%, followed by CEF (Cyclophosphamide Epirubicin 5-Fluorouracil). Chemotherapeutic agents cause an increased incidence of cardiovascular disturbance and atherosclerotic[17], but there are no available studies that state which agents greatly affect the process of atherosclerotic, whereas doxorubicin is widely known to have cardiotoxic effect so that electrocardiographic examination should be examined inpatient receiving treatment with doxorubicin.[18]

The mean C-IMT before chemotherapy is 0.51 ± 0.05 mm, after chemotherapy is 0.58 ± 0.06 mm, with a significant increase of 0.07 ± 0.06 mm ($p<0.0001$). Whereas in the analysis of the reduction in internal carotid artery lumen diameter before chemotherapy is 4.05 ± 0.66 mm, after chemotherapy is 3.90 ± 0.73 mm, the reduction in lumen diameter is 0.16 ± 0.40 mm, however, this finding is not statistically significant ($p = 0.057$).

Covariance analysis (ANCOVA) of the C-IMT thickness before and after chemotherapy with controlled variables such as age, histopathology and cancer stage were also carried out. There was a significant effect on the group of before and after chemotherapy, also on the group of age. As for the diameter of the internal carotid lumen, it does not appear to be affected by these variables. This can be caused by other variables that were not identified in this study.

To date, to the best of the author's knowledge, there have been no other studies that have focused on the increase of C-IMT thickness, which is assessed by ultrasound semiautomatic B-mode that can directly demonstrate atherosclerotic changes of blood vessel wall of breast cancer patients after chemotherapy. The existing publication only states a relation of new atherosclerotic formation and heart problems after chemotherapy treatment, in line with the findings in our study.[17]

In our study, an increase in the C-IMT thickness seemed to be influenced by chemotherapy. In practice, several journals also state that 5-Fluorouracil and Cisplatin have an effect on vascular toxicity due to endothelial dysfunction, loss of vasorelaxant effect and suppression of anti-inflammatory function and reparation function, these cause an increase in thrombosis and atherogenesis.[19,20] Atherosclerosis of the carotid artery is a major risk of cerebrovascular disorder and can be used to predict the risk of cognitive impairment.[6]

Age was also found to be a variable that affected the increase in C-IMT thickness. As we know, atherosclerosis is one of the degenerative signs that increases with age. This finding is in line with the study of a large cohort group which found that there was a projected increase in C-IMT of 0.01 mm/year in men and women.[21]

CONCLUSION

From the results described above, all findings confirm the occurrence of chemotherapy-induced atherosclerosis, where there is an increase in the C-IMT thickness of breast cancer patients after chemotherapy, which is statistically significant.

For further research, we recommend that the research be conducted with more subjects, more variables, a longger period of time, one type of chemotherapy regimen, and a narrower age range. Doppler carotid ultrasound can be added as a routine follow up examination in breast cancer patients undergoing chemotherapy to reduce morbidity and mortality from related atherosclerotic disease.

DISCLOSURE

There are no financial conflicts of interest to disclose.

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