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The effects of *cyclophosphamide, adriamycin* and *5-fluorouracil* chemotherapy on blood cells and cardiac hemodynamics in breast carcinoma patients: a case study at Dr. Kariadi General Hospital, Semarang, Indonesia

Sibin Chandra[1*], Djoko Handojo[2]

[1]Resident of Department of Surgery, Medical Faculty, Universitas Diponegoro, Dr. Kariadi Hospital, Semarang, Indonesia.
[2]Staff of Oncology Surgery, Department of Surgery, Medical Faculty, Universitas Diponegoro, Dr. Kariadi Hospital, Semarang, Indonesia.

*Corresponding author:
Sibin Chandra;
Resident of Department of Surgery, Medical Faculty, Universitas Diponegoro, Dr. Kariadi Hospital, Semarang, Indonesia;
sibinjuli2016@gmail.com

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ABSTRACT

Background: One of the treatment modalities for breast malignancy is chemotherapy. Chemotherapy could kill cancer cells as well as normal cells, including blood cells and cardiac cells. Early detection of adverse events includes myelosuppression and cardiotoxicity could reduce morbidity and mortality rates. This study aims to determine a decrease in blood cells and cardiac hemodynamics in breast carcinoma patients who underwent *Cyclophosphamide, Adriamycin,* and *5-Fluorouracil* (CAF) chemotherapy.

Methods: Analytical prospective observational study with breast carcinoma. The measurements were Haemoglobin (Hb), Hematocrit (Ht), Erythrocyte (Ery), Leukocyte (Leu), Platelet (Plt), Left Ventricle Ejection Fraction (LVEF), Stroke Volume (SV), and Cardiac Output (CO) until 3rd cycles of chemotherapy. Data were analyzed using SPSS version 17 for Windows.

Results: There were 35 subjects enrolled in this study. Decreases in Hb, Ht, Ery, Leu, and Plt after the 1st, 2nd, and 3rd cycles of chemotherapy were statistically significant ($p<0.05$). There was a statistically significant decrease in LVEF, SV, and CO after the 1st, 2rd and 3rd cycles of chemotherapy ($p<0.05$). Besides, the SV and CO after the 2nd and 3rd cycles of chemotherapy were also decreased significantly ($p<0.05$).

Conclusions: There is a decrease in blood cells (Hb, Ht, Ery, Leu, Plt) and cardiac hemodynamics (LVEF, SV, and CO) in breast carcinoma patients who underwent CAF chemotherapy.

Keywords: Chemotherapy, Myelosuppression, Cardiotoxicity, Breast Carcinoma.
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INTRODUCTION

Breast Cancer (BC) is a malignant tumor in the breast tissue that can originate from the ductal epithelium or lobule.[1] This BC mortality rate is the number 1 cause of female gender worldwide based on WHO in 2018.[2] In Southeast Asia, the number of new breast cancer cases is also ranked first in 2018, namely 13.5% of all new cancer cases.[3] In Indonesia in 2018, breast cancer's incidence was still in the first rank, namely 42.1 per 100,000 population with an average death rate of 17 per 100,000 population.[4] Reducing the mortality rate by administering the antineoplastic drug (chemotherapy). It is proven that chemotherapy can improve cancer patients' survival and save more than 12 million people.[5]

Chemotherapy is still an option for cancer management.[6] Chemotherapy regimens are most often used in clinical practice today since they improve survival and reduce recurrence, especially breast cancer.[6] Doxorubicin (also known as Adriamycin) is a class of anthracyclines used as a foundation for breast cancer therapy combined with 5-Fluorouracil (5-FU) and Cyclophosphamide (CP).[1,7] This combination is known as the CAF regimen and is given at a dose of 500/500/50 mg/m^2 intravenously (iv), given every 3 weeks, as long as 6 cycles.[1] This regimen has a good survival rate for the breast cancer survivor.[6]

The mechanism action of cyclophosphamide, adriamycin, and 5-Fluorouracil is killing cancer cells by directly damaging the DNA in cancer cells.[8] The side effect of chemotherapy produces free radicals and myelosuppressive properties, characterized by decreased production of erythrocytes, leukocytes, and platelets.[8] In addition, this CAF regimen was also reported to have cardiotoxic side effects.[9,10]

Because of the myelosuppressive and cardiotoxic effects due to the CAF regimen, this study aims to monitor blood cells (erythrocytes, leukocytes, and platelets) and more comprehensive cardiac

Table 1. Baseline Characteristics of Pre Chemotherapy CAF (F = 35)

Variables	Frequency (N=35)	Mean ± SD	Median (min – max)
Age (Years)		51.94±10.55	51.00 (31.00–79.00)
Weight (kg)		58.17± 13.52	58.00 (35.00–90.00)
Height (cm)		1.51± 0.07	1.53 (1.35–1.62)
Body Mass Index (BMI)(kg/m^2), n (%)		25.35 ± 4.75	24.89 (18.13–35.52)
Underweight	2 (5,7)		
Normoweight	17 (48,6)		
Overweight	9 (25,7)		
Obesity	7 (20.0)		
Age of menarche (Years)			
Age of menopause (Years)		12.35 ± 1.87	12.00 (10.00–17.00)
Diagnosis, n (%)		50.17 ± 4.06	50.00 (45.00–60.00)
Invasive Ductal	24 (68,6)		
Invasive Lobular	5 (14,3)		
Mixed	2 (5,7)		
Mucinous	2 (5,7)		
Others	2 (5,7)		
Mammae location, n (%)			
Right	21 (60.00)		
Left	14 (40.00)		
Operation, n (%)			
MRM	31 (88.60)		
Biopsy	4 (11.40)		
Chemotherapy, n (%)			
Adjuvant	31 (88.60)		
Neoadjuvant	4 (11.40)		
Body Surface Area (BSA) (m^2)		1.53±0.18	1.52 (1.23–1.93)
Hb pre (g/dL)		12.06±1.32	12.40 (9.50–15.20)
Haematocrit pre-chemotherapy (%)		37.12±4.07	37 (28.70–47.60)
Erythrocyte pre-chemotherapy (mm^3)		4,370,571.00±516,509	4,490,000 (3,180,000-5,550,000)
Leucocyte pre-chemotherapy (mm^3)		8,426±2,712	8,400 (2,300– 14,500)
Platelet pre-chemotherapy (mm^3)		399,029±120,849	401,000 (218,000-738,000)
LVEF (%)		68.49±4.97	68.00 (59.00–79.00)
Stroke Volume (SV) (ml)		53.49±8.23	55.00 (37.00– 70.00)
Cardiac Output (CO) (L/minute)		4.45±0.88	4.20 (2.60–5.90)
Cyclophosphamide dose		741.14±86.82	765.00 (600.00-1,000.00)
Adriamycin dose		72.90±7.32	75.00 (60.00–80.00)
Fluorouracil dose		714.57±133.95	750.00 (70.00–810.00)

Hb: Haemoglobin; MRM: Modified Radical Mastectomy; LVEF: Left Ventricle Ejection Fraction

hemodynamics due to cyclophosphamide, adriamycin, and 5-fluorouracil chemotherapy.

METHODS

The research method was a prospective observational analytic cohort that examined the values of blood cells (Hb, Hematocrit, Erythrocyte, Leukocytes And Platelets) and cardiac haemodynamics (LVEF, stroke volume (SV) and cardiac output(CO)) in breast carcinoma patients treated with CAF. The research took place at the Kasuari Installation and Eagle Installation at Kariadi Hospital Semarang, Central Java, Indonesia. The study was conducted in March-July 2020, patients were followed up 2 weeks after the first cycle of CAF chemotherapy until the third cycle and required sample size was met.

The sample of this study were breast carcinoma patients who had been proven malignant histopathologically and indicated CAF chemotherapy at the Kasuary Installation of Dr. Kariadi Semarang during the research period. The sampling was consecutive sampling method who fulfilled inclusion criteria and did not meet the study exclusion criteria. The inclusion criteria were patients aged ≥ 18 years, the patient was diagnosed with breast carcinoma and was confirmed by histopathological examination, patients who are given CAF antineoplastic, and willing to be included in research by signing an informed consent. In addition, the exclusion criteria were patients who have previously been given antineoplastic therapy, radiotherapy in the thorax region, decreased left ventricular systolic function, significant valvular heart disease (more than moderate degrees), diabetes mellitus, hypertension, congenital heart disease, and echocardiographic image quality is not clear (inappropriate acoustic windows). Data were analyzed using SPSS version 17 for Windows.

RESULTS

The mean age of patients was 51.94±10.55, followed by the mean age of menarche

Table 2. Descriptive data and normality of laboratory parameters

Variables	Groups	Mean ± SD	Median (minimum – maximum)	p
Haemoglobin	Pre	12.06±1.32	12.40 (9.50– 15.20)	0.471
	Post 1	11.47±1.28	11.70 (9.20– 14.80)	0.567
	Post 2	11.18±1.18	11.20 (8.10– 13.20)	0.361
	Post 3	10.99±1.08	11.10 (8.00–13.00)	0.075
Haematocrit	Pre	37.12±4.07	37.00 (28.70–47.60)	0.561
	Post 1	35.06±3.61	35.20 (28.30–46.00)	0.400
	Post 2	34.02±3.72	34.60 (24.60–40.60)	0.435
	Post 3	33.23±3.23	33.80 (24.90–39.00)	0.450
	Pre	4,370,571±516,509	4,490,000 (3,180,000-5,550,000)	0.802
Erythrocyte	Post 1	4,148,571±454,294	4,140,000 (3,280,000-5,480,000)	0.301
	Post 2	4,029,714±497,378	4,110,000 (2,790,000-5,110,000)	0.966
	Post 3	3,957,143±458,787	3,940,000 (3,100,000-4,850,000)	0.540
	Pre	8,425±2,712	8,400 (2,300–14,500)	0.942
Leukocyte	Post 1	4,309±1,822	4,000 (1,300– 8,800)	0.021*
	Post 2	3,634±2,385	3,000 (400–12,000)	0.000*
	Post 3	3,589±1,731	3,500 (900–9,200)	0.028*
	Pre	399,029±120,849	401,000 (218,000–738,000)	0.942
	Post 1	318,571±105,742	329,000 (80,000–508,000)	0.314
Platelet	Post 2	288,657±121,228	277,000 (89,000–604,000)	0.000*
	Post 3	255,143±89,274	248.000 (104,000–557,000)	0.028*
	Pre	68.49±4.97	68.00 (59.00–79.00)	0.891
	Post 1	64.20±4.00	64.00 (58.00–72.00)	0.073
LVEF	Post 2	62.26±3.54	62.00 (57.00–69.00)	0.081
	Post 3	59.06±2.92	59.00 (55.00–68.00)	0.040*
	Pre	53.49±8.23	55.00 (37.00–70.00)	0.400
	Post 1	50.57±11.48	55.00 (24.00–74.00)	0.088
Stroke volume	Post 2	50.14±7.69	50.00 (32.00–61.00)	0.055
	Post 3	47.06±9.52	45.00 (30.00–69.00)	0.276
	Pre	4.45±0.88	4.20 (2.60–5.90)	0.039*
	Post 1	4.24±0.99	4.40 (1.60–6.10)	0.001*
Cardiac output	Post 2	4.11±0.66	4.30 (2.50–5.10)	0.022*
	Post 3	4.07±0.73	4.20 (2.70–5.70)	0.250

*Data were considered not normally distributed based on the Shapiro Wilk test if p-value less than 0.05

(12.35±1.87 years) and menopause (50.17±4.06 years) (Table 1). The baseline characteristics based on anthropometry showed that the subjects' height was 1.51 ± 0.07 m and the body weight was 58.17 ± 13.52 kg. Calculation of Body Mass Index (BMI) obtained 2 patients (5.7%) with underweight, 17 patients (48.6%) with normoweight, 9 patients (25.7%) with overweight, and 7 patients obese (20%). The mean body surface area (BSA) of patients in this study was 1.53 ± 0.18 m^2 (Table 1).

Baseline characteristics were 21 patients (60.00%) had breast cancer on the right side and 14 patients (40.00%) on the left side. The most common type of breast cancer in this study was Invasive Ductal Carcinoma (68.60%). Most of the subjects of this study were performed Modified Radical Mastectomy (MRM) as many as 31 people (88.60%) and 4 people (11.40%) performed biopsy incisions. There were 31 patients (88.60%) who received Adjuvant Chemotherapy and 4 people (11.40%) received Neoadjuvant Chemotherapy (Table 1).

The baseline characteristics based on laboratory parameters in this study showed that the mean haemoglobin was 12.06±1.32 g/dL, followed by haematocrit (37.12±4.07%), erythrocyte (4,370,571±516,509/mm^3), leukocytes (8,426±2,712/mm^3), platelet count (399,029±120,849/mm^3) (Table 1). Based on echocardiographic parameters, a mean LVEF was 68.49±4.97%, followed by a Stroke Volume (SV) value of 53.49±8.23 ml and a mean Cardiac Output (CO) of 4.45±0.88 L/minute (Table 1).

Table 2 shows the decrease in mean Hb, haematocrit, erythrocyte, leucocyte, and platelet values each cycle of chemotherapy. After doing the normality test using Saphiro Wilk, the results of normal data distribution were obtained with a value of p>0.05 at haemoglobin value S0 (baseline), S1 (first cycle), S2 (second cycle), S3 (third cycle); haematocrit S0, S1, S2, S3; erythrocytes S0, S1, S2, S3; S0 leukocytes; platelets S0, S1 and abnormal data distribution on leukocytes S1, S2, S3; platelets S2, S3 (Table 2).

The assessment of Hb, Haematocrit, Erythrocyte, Leukocyte, and Platelet at each cycle of chemotherapy compared to baseline (Table 3) was tested by Paired t-test (if normal distribution) and Wilcoxon (if the distribution was not normal). These results show significant values ranging from the 1st cycle of chemotherapy (S1) until the 3rd cycle of chemotherapy (S3) (p<0.05) (Table 2). Table 2 shows the mean reduction in LVEF, SV, and CO values at each chemotherapy cycle. After the normality test using Saphiro Wilk, the normal data distribution results were obtained with at LVEF S0, S1, S2; SV at S0, S1, S2, S3; and CO at S3 (p>0.05). Whereas the abnormal data distribution at LVEF S3; Co at S0, S1, S2 (p<0.05) (Table 2).

The assessment of LVEF, SV, and CO at each cycle of chemotherapy compared to baseline was tested with the Paired t-test (if normal distribution) and Wilcoxon (if the distribution was not normal) (Table 3). These results indicate a significant decrease in value LVEF after 1st cycle of chemotherapy (S1) until 3rd cycle of chemotherapy (S3) (p<0.05), as well as a significantly decreased in SV and CO values after 2nd until 3rd cycle of chemotherapy (S3) with (p<0.05) (Table 3).

Table 4 shows the mean reduction in Hb, Haematocrit (Ht), Erythrocyte (Ery), LVEF, SV, and CO after the 1st, 2nd, and 3rd cycle of chemotherapy compared with baseline values. After the normality test using Saphiro Wilk, the results of the normal data distribution were obtained with a value of p> 0.05 on the decrease at Hb S1, S3; Ht at S1, S3; Ery at S3; LVEF S3; SV at S1, S2, S3; CO at S1, S2, S3, and abnormal data distribution on decreased Hb at S2; Ht at S2; Ery at S1, S2, and LVEF at S1, S2.

The relationship between the decrease in Hb, Ht, Ery on the reduction in LVEF, SV, and CO was tested with Pearson's Correlation (if normally distributed) and Spearman's Correlation (if the distribution was not normal) (Table 5). This study shows a significant reduction in Hb, Ht, Ery at SV after the 2nd and 3rd cycle of chemotherapy (S2, S3) with a p-value <0.05 (Table 5).

The echocardiography follow-up results at each cycle of chemotherapy in 35 study subjects using the LVEF parameter, the first (S1), second (S2), and third (S3) post-chemotherapy LVEF values were compared with baseline LVEF values (S0). If there was a decrease ≥ 10% and LVEF value below 55% is considered as cardiotoxicity. Table 6 shows that in S1 there were 8 patients whose decrease was more than 10%, but the mean value of LVEF was 64.00 ± 2.62%. At S2, 11 people whose decrease was more than 10%, but the mean value of LVEF was 61.55 ± 2.16% (Table 6). In S3, there were 27 people whose decline was more than 10%, but the mean value of LVEF was 58.41 ± 2.31%. Thus, although some patients with DLVEF ≥ 10% had a value below 53%, all samples in this study did not meet the criteria for cardiotoxicity (Table 6).

Table 3. The results of the decrease laboratory parameters in each cycle of chemotherapy compared to baseline

Variable	Pre – post 1	Pre – post 2	Pre – post 3
Haemoglobin	0.002[a]*	<0.001[a]*	<0.001[a]*
Haematocrit	<0.001[a]*	<0.001[a]*	<0.001[a]*
Erythrocyte	0.002[a]*	<0.001[a]*	<0.001[a]*
Leukocyte	<0.001[b]*	<0.001[b]*	<0.001[b]*
Platelet	<0.001[a]*	<0.001[b]*	<0.001[b]*
LVEF	<0.001[a]*	<0.001[a]*	<0.001[a]*
Stroke volume	0.130[a]	0.041[a]	<0.001[b]*
Cardiac output	0.313[b]	0.040[b]	0.040[b]*

[a]Paired T-Test; [b]Wilcoxon; *statistically significant if p-value less than 0.05

Table 4. Descriptive and normality test for delta Hb, Ht, LVEF, SV, and CO

Variable	Category	Mean ± SD	Median (minimum–maximum)	P
Haemoglobin	Post 1	-0.59±1.02	-0.60 (-3,5 – 1,5)	0.524
	Post 2	-0.88±1.11	-1.20 (-2,7 – 1,6)	0.010*
	Post 3	-1.07±1.25	-1.10 (-3,4 – 1,4)	0.747
Haematocrit	Post 1	-2.07±3.14	-2.00 (-11,4 – 3,2)	0.072
	Post 2	-3.10±3.58	-3.80 (-9,1 – 3,9)	0.028
	Post 3	-3.89±4.01	-3.70 (-11,3 – 4,1)	0.691
Erythrocyte	Post 1	-222,000±399,425	-250,000 (-1,470,000-370,000)	0.047*
	Post 2	-340,857±451,268	-500,000 (-1,040,000-610,000)	0.040*
	Post 3	-413,429±541,436	-420,000 (-1,710,000-480,000)	0.595
LVEF	Post 1	-4.29±3.37	-3.00 (-14.00–0.00)	0.010*
	Post 2	-6.23±4.51	-6.00 (-21.00–0.00)	0.003*
	Post 3	-9.43±5.86	-9.00 (-24.00–3.00)	0.672
Stroke volume	Post 1	-2.91±11.12	-2.00 (-33.00–14.00)	0.132
	Post 2	-3.34±9.33	-3.00 (-25.00–20.00)	0.866
	Post 3	-6.43±9.54	-7.00 (-28.00–10.00)	0.654
Cardiac output	Post 1	-0.20±1.09	-0.30 (-3.10–2.10)	0.775
	Post 2	-0.34±0.96	-0.40 (-2.90–1.80)	0.880
	Post 3	-0.37±0.93	-0.20 (-2.70–1.50)	0.105

*Data were considered not normally distributed based on the Shapiro Wilk test if p-value less than 0.05

Table 5. The results of correlation test for decreasing in Hb, Ht, and Ery on the decrease in LVEF, SV and CO

Delta	Category	Delta LVEF		Delta SV		Delta CO	
		p	r	p	r	p	r
Haemoglobin	Post 1	0.209[b]	0.218	0.479a	0.124	0.321[a]	0.173
	Post 2	0.950[b]	0.011	0.008b*	-0.443	0.323[b]	-0.172
	Post 3	0.991[a]	-0.002	0.015[a]*	-0.407	0.219[a]	-0.213
Haematocrit	Post 1	0.185[b]	0.229	0.620[a]	0.087	0.453[a]	0.131
	Post 2	0.745[b]	-0.057	0.006[b]*	-0.457	0.211[b]	-0.217
	Post 3	0.984[a]	0.004	0.027[a]*	-0.375	0.169[a]	-0.238
Erythrocyte	Post 1	0.286[b]	0.186	0.632[b]	0.084	0.454[b]	0.131
	Post 2	0.370[b]	-0.156	0.018[b]* 0.031[a]*	-0.399	0.248[b]	-0.200
	Post 3	0.957[a]	-0.010		-0.366	0.054[a]	-0.328

*Data were considered significant if p-value less than 0.05 on [a]Pearson or [b]Spearman's correlation test

Table 6. The mean reduction in LVEF values which are <10% and ≥ 10% in each cycle of CAF chemotherapy S1, S2, S3 compared to baseline values before chemotherapy

Variable	F	%	Mean ± SD	Median (minimum– maximum)
LVEF post 1				
< 10%	27	77.1	64.26±4.36	63.00 (58.00–72.00)
≥ 10%	8	22.9	64.00±2.62	64.00 (60.00–69.00)
LVEF post 2				
< 10%	24	68.6	62.58±4.02	61.50 (57.00–69.00)
≥ 10%	11	31.4	61.55±2.16	62.00 (58.00–65.00)
LVEF post 3				
< 10%	8	22.9	61.25±3.81	61.50 (56.00–68.00)
≥ 10%	27	77.1	58.41±2.31	58.00 (55.00–64.00)

DISCUSSION

This study's baseline characteristics were 35 patient samples; all of them were female (100%). The mean age of breast cancer patients was 51.94 ± 10.55 years. Aging is associated with a reduced immune system. Many cancers are associated with aging. Although age is not an important determinant of cancer risk, it does suggest prolonged exposure to carcinogens, particularly in breast cancer.[11] The most significant changes in the world's population in the next 50 years are changes in the proportion of older people (over 65 years); 7% in 2000 to 16% in 2050.[12] By 2050, 27 million people are projected to have cancer. More than half of the estimated number will be residents of developing countries. Enhancing immune status is key in preventing cancer.[12]

The baseline characteristics based on anthropometry obtained that the height of the research subjects in meters was 1.51 ± 0.07 and the bodyweight of the research subjects in kilograms (kg) was 58.17 ± 13.52. Calculation of Body Mass Index (BMI) according to WHO criteria for Asia Pacific population found 2 patients (5.7%) with underweight status (<18.5 kg/m^2), 17 patients (48.6%) with normoweight status (18,5-22.9 kg/m^2), 9 patients (25.7%) were overweight (23-27.5 kg/m^2) and obese (> 27.5 kg/m^2) as many as 7 patients (20%).[13] This was common because an increase of 5 kg/m^{2}BMI would increase breast cancer risk by 2% (SRR: 1.02, 95% CI: 1.01-1.04, p <0.001).

The mean age of menarche in this study was 12.35 ± 1.87 years. This is consistent with the previous study, which states that the risk of breast cancer increases at the age of menarche earlier than the age of menarche 14 years and over (RR 1.05, 95% CI 1.044-1.057; p <0.0001).[14] The mean age of menopause in this study was 50.17 ± 4.06 years. The results of this study are in line with the epidemiological study of Collaborative Group on Hormonal Factors in Breast Cancer which stated that the risk of breast cancer increases at the older menopausal age (> 50 years) and premenopausal women (aged 45-54 years) have a higher risk of developing breast cancer (RR 1.43, 95% CI 1.33-1.52, p <0.001).[14]

This study's most common type of breast cancer was Invasive Ductal Carcinoma, with 24 patients (68.6%). In accordance with the study of Fujimoto RHP et al., which studied for 5 years from 2007-2012 in Brazil, there were 129 samples (77%) with a type of diagnosis of Invasive Ductus Carcinoma in breast cancer.[15] Most of the subjects of this study were performed Modified Radical Mastectomy (MRM) as many as 31 people (88.6%) and 4 people (11.4%) performed biopsy incisions. This is related to the type of chemotherapy received by this study sample, namely Adjuvant Chemotherapy. As many as 31 patients (88.6%) and 4 people (11.4%) received Neoadjuvant Chemotherapy (Table 1). Neoadjuvant chemotherapy is a therapy given before primary treatment, which aims to reduce the tumor's size. Meanwhile, adjuvant chemotherapy is a therapy given after the primary treatment, which aims to kill the remaining cancer cells.[6]

The mechanism of CAF action (5-Fluorouracil, Adriamycin Cyclophosphamide) in killing cancer cells is by directly damaging the DNA in cancer cells. A study by Tecza K et al. showed that there was no interaction in CAF combination, but there were side effects such as cardiotoxicity and myelosuppression.[9,16,17]

Cell DNA damage causes apoptosis

which produces free radicals. Free radicals can also kill cancer cells as a side mechanism.[18] Free radicals from these by-products can also damage healthy cells, including erythrocytes, leukocytes, and platelets. Cell membranes become more susceptible to oxidative stress, which can induce lysis and cause side effects of depressing bone marrow in producing erythrocytes, leukocytes, and platelets.[18] Our study shows a decrease in the mean Hb, Ht, Ery, Leu, and Plt values after the 1st cycle of CAF chemotherapy and also decreased after the 2nd and 3rd cycle of CAF chemotherapy, where this decrease was statistically significant compared to the mean Hb, Ht, Ery, Leu and Plt prior to CAF chemotherapy.

The most frequently used combination chemotherapy, namely CAF (Cyclophosphamide, Adriamycin, 5-Fluorouraiyl), can cause mild to moderate anemia with an incidence of less than 43-47%. Approximately 11% of those receiving CAF therapy had severe anemia.[19,20] A previous study by Lyman GH et al., revealed that about one-third of outpatients with potentially curable breast cancer received less than 85% of the optimal minimum dose for treatment, and 1/4 of patients experienced delays.[21] Treatment for more than a week. Overall, about 56% of patients received less than 85% of the dose intensity targeted for therapy because of leukopenia's side effects.[8]

The decrease in platelet counts in the control group that only received CAF occurred due to the depressive effect of colony factor unit-megakaryocyte (CFU-Meg) in bone marrow due to free radicals resulting from cell damage caused by chemotherapy.[22] Decreased platelet production due to administration of antineoplastic agents has the potential to require dose reduction or delay in further therapy because it increases the risk of life-threatening spontaneous bleeding.[22] The prevention and management of chemotherapy-induced thrombocytopenia require platelet transfusion as the mainstay of therapy and thrombopoietin receptor agonists as options currently being examined.[22]

In this study, there was a decrease in the value of LVEF, SV, and CO after the 1st (S1), 2nd (S2), and 3rd (S3) cycles of CAF chemotherapy. The statistical test results of decreased LVEF value, stroke volume, and cardiac output after the 1st (S1), 2nd (S2), and 3rd (S3) cycle of CAF chemotherapy were compared with baseline, which resulted in a statistically significant decrease in LVEF ($p < 0.05$) after 1st, 2nd, and 3rd cycle of CAF chemotherapy. The reduction in SV and CO was statistically significant ($p<0,05$) after the 2nd and 3rd CAF chemotherapy cycles. This study's results are in concordance with research previously conducted by Grip EA et al., where there was a decrease in the value of LVEF in the 3rd cycle.[23] In the study by Grip EA et al., a baseline echocardiography examination was carried out with a mean value of LVEF S0 64 ± 4,8%, post 3rd cycle (mid) with a mean LVEF S3 value of 57.6±12,3% and post 6th cycle (end of chemotherapy) with the mean value of LVEF S6 was 52± 5,1%.[23] This shows that the LVEF value has not decreased significantly after the 3rd cycle (S3). This is in line even earlier in this study that after the first cycle of CAF chemotherapy (S1), there was a decrease in the value of the LVEF until after the third cycle of chemotherapy CAF (S3). However, the mean value of LVEF was still within normal limits. This may occur because the age of this study's subjects was relatively older than the Grip study (49,7±12.2%).[23]

The mechanism of decreasing LVEF, SV, and CO is through oxidative stress because chemotherapy activates apoptotic signals that cause apoptosis in cardiomyocytes, which are involved in both the extrinsic and intrinsic pathways.[24] Cellular and extracellular factors play an important role in the complex process of myocardial remodeling. Significant changes in the structure and composition of the extracellular matrix contribute to the development of heart failure.[25] Besides, doxorubicin also inhibits transcription and translation of the matrix metalloproteinase (MMP-1) in tumor cells, thereby decreasing tumor cells' mobility. On the other hand, doxorubicin increases the production of MMP-2 and MMP-9 in the myocardium.[24] This contributes to cardiomyopathy because it can reduce the collagen matrix that fights cardiomyocytes and contributes to cardiac remodeling. Both the MMP-2 and MMP-9 increase the production of ROS. In a state of inflammation and injury, the body's adaptive response will produce a Tissue Inhibitor of Metalloproteinase-3 (TIMP). TIMP is useful for antiapoptosis, and this process is also related to the synthesis of collagen, which forms the final product in the form of connective tissue.[24,25]

After exposure to doxorubicin, caspase-3 activation causes apoptosis. Apoptosis will result in decreased number and contractile function of the cardiomyocytes.[26] Remodeling of the extracellular collagen matrix plays a vital role in left ventricular hypertrophy. Fibrosis may be involved in cardiac dysfunction, leading to increased collagen synthesis by invading fibroblasts and displacing apoptotic myocytes. This increase in collagen in the myocardium results in dysfunction and stiffness of the left ventricular muscles, reducing LVEF, stroke volume, and cardiac output.[26]

A decrease in Hb, Ht, and Ery creates a compensatory mechanism by increasing venous return, thereby increasing preload and decreasing left ventricular afterload, which increases SV. The SV is multiplied by the number of heartbeats per minute to produce CO (typically 4-8 L/minutes). If the heart compensation is still adequate, the CO will increase to supply blood and oxygen to peripheral tissues when the SV increases.[27] In patients receiving CAF chemotherapy, there is dysfunction and stiffness of the left ventricular muscle; thus, the heart cannot compensate, so the stroke volume decreases and the heart rate per minute increases.[26,27]

Based on the consensus of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI), cardiotoxicity is defined as a decrease in LVEF≥10% and LVEF value <53% (biplane) in asymptomatic women.[28] This study shows that in S1, it already exists 8 patients had a decrease of more than 10%, but the mean LVEF was 64,0 ± 2,62%. At S2, 11 people whose decline was more than 10%, but the mean value of LVEF was 61,55 ± 2,16%. In S3, 28 people whose LVEF decreased by more than 10%, but the mean value of LVEF was 58,41 ± 2,31%. The paired-t test shows that p significant

(<0.001) in each cycle (S1, S2, S3) was compared to the baseline. Although some patients with ≥10% had a value below 53%, all samples in this study did not meet the criteria for cardiotoxicity.[28] These results are consistent with research by Grip EA et al., who assessed that LVEF in S3 had occurred decrease ≥10% compared to baseline, but the value is not below 53% (biplane).[23]

CONCLUSION

Based on those explain above, this study indicates a significant decrease in blood cells (Hb, Ht, Ery, Leu, Plt) and cardiac hemodynamics (LVEF, SV, and CO) in breast carcinoma patients who underwent CAF chemotherapy.

CONFLICT OF INTEREST

There is no conflict of interest regarding the manuscript.

ETHICS CONSIDERATION

Ethics approval has been obtained from the Health Research Ethics Committee of Dr. Kariadi Hospital, Semarang, Indonesia, with number 471/EC/KEPK-RSDK/2019 prior to the study being conducted.

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AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, data gathering, data analysis until reporting the study results through publication.

REFERENCE

1. Richie RC, Swanson JO. Breast cancer: a review of the literature. J Insur Med. 2003;35(2):85-101.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
3. Saxena N, Hartman M, Bhoo-Pathy N, et al. Breast cancer in South East Asia: comparison of presentation and outcome between a middle income and a high income country. World J Surg. 2012;36(12):2838-2846.
4. Anwar SL, Raharjo CA, Herviastuti R, Dwianingsih EK, Setyoheriyanto D, Avanti WS, et al. Pathological profiles and clinical management challenges of breast cancer emerging in young women in Indonesia: a hospital-based study. BMC Womens Health. 2019;19(1):28.
5. Henley SJ, Singh SD, King J, Wilson RJ, O'Neil ME, Ryerson AB. Invasive Cancer Incidence and Survival - United States, 2013. MMWR Morb Mortal Wkly Rep. 2017;66(3):69-75.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, Gray R, Pan HC, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379(9814):432-44.
7. Martin M, Villar A, Sole-Calvo A, Gonzalez R, Massuti B, Lizon J, et al. Doxorubicin in combination with fluorouracil and cyclophosphamide (i.v. FAC regimen, day 1, 21) versus methotrexate in combination with fluorouracil and cyclophosphamide (i.v. CMF regimen, day 1, 21) as adjuvant chemotherapy for operable breast cancer: a study by the GEICAM group. Ann Oncol. 2003;14(6):833-42.
8. Cummings FJ, Gelman R, Horton J. Comparison of CAF versus CMFP in metastatic breast cancer: analysis of prognostic factors. J Clin Oncol. 1985;3(7):932-940.
9. Lenneman CG, Sawyer DB. Cardio-Oncology: An Update on Cardiotoxicity of Cancer-Related Treatment. Circ Res. 2016;118(6):1008-1020.
10. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(36):2768-2801.
11. Wiranata S, Anjani IAW, Saputra IPGS, Sadvika IGAS, Prabawa IPY, Supadmanaba IG, et al. Pretreatment Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as a Stage Determination in Breast Cancer. Open Access Maced J Med Sci. 2020;8(B):1058-1063.
12. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.
13. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-163.
14. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012;13(11):1141-1151.
15. Fujimoto RHP, Koifman RJ, Silva IFD. Survival rates of breast cancer and predictive factors: a hospital-based study from western Amazon area in Brazil. Cien Saude Colet. 2019;24(1):261-273.
16. Tecza K, Pamula-Pilat J, Lanuszewska J, Butkiewicz D, Grzybowska E. Pharmacogenetics of toxicity of 5-fluorouracil, doxorubicin and cyclophosphamide chemotherapy in breast cancer patients. Oncotarget. 2018;9(10):9114-9136.
17. Iqubal A, Iqubal MK, Sharma S, et al. Molecular mechanism involved in cyclophosphamide-induced cardiotoxicity: Old drug with a new vision. Life Sci. 2019;218:112-131.
18. Das UN. Free radicals: biology and relevance to disease. J Assoc Physicians India. 1990;38(7):495-498.
19. Buck I, Morceau F, Grigorakaki C, Dicato M, Diederich M. Linking anemia to inflammation and cancer: the crucial role of TNFalpha. Biochem Pharmacol. 2009;77(10):1572-1579.
20. Cella D, Kallich J, McDermott A, Xu X. The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials. Ann Oncol. 2004;15(6):979-986.
21. Lyman GH, Greenlee H, Bohlke K, Bao T, DeMichele AM, Deng GE, et al. Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline. J Clin Oncol. 2018;36(25):2647-2655.
22. Parameswaran R, Lunning M, Mantha S, Devlin S, Hamilton A, Schwartz G, et al. Romiplostim for management of chemotherapy-induced thrombocytopenia. Support Care Cancer. 2014;22(5):1217-22.
23. Gripp EA, Oliveira GE, Feijó LA, Garcia MI, Xavier SS, Sousa AS. Global Longitudinal Strain Accuracy for Cardiotoxicity Prediction in a Cohort of Breast Cancer Patients During Anthracycline and/or Trastuzumab Treatment. Arq Bras Cardiol. 2018;110(2):140-150.

24. Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, Crijns HJ, Moens AL. Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. J Mol Cell Cardiol. 2012;52(6):1213-1225.
25. Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. Physiol Rev. 2007;87(4):1285-1342.
26. Hong YM, Lee H, Cho MS, Kim KC. Apoptosis and remodeling in adriamycin-induced cardiomyopathy rat model. Korean J Pediatr. 2017;60(11):365-372.
27. Metivier F, Marchais SJ, Guerin AP, Pannier B, London GM. Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol Dial Transplant. 2000;15 Suppl 3:14-18.
28. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014;27(9):911-39.