The relationship of vitamin d serum pre-chemotherapy with myeloid toxicity in locally advanced breast cancer received cyclophosphamide, doxorubicin, and 5-fluorouracil neoadjuvant

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Abstract

Background: Myeloid toxicity is one of the effects caused by patients undergoing chemotherapy and potentially life-threatening. This study aimed to determine the relationship between serum vitamin D levels in pre-cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) chemotherapy, and the occurrence of myeloid toxicity in patients with locally advanced breast cancer (LABC) undergoing neoadjuvant chemotherapy.

Methods: A cohort study design was enrolled in patients with LABC undergoing CAF neoadjuvant chemotherapy. The independent variable was the level of vitamin D in the blood, and the dependent variable was chemotherapy myeloid toxicity.

Results: In this study, 70% of patients had low vitamin D levels. There were significant differences in hemoglobin (p = 0.000), leukocytes (p = 0.028), platelets (p = 0.018), neutrophil (p = 0.003) after chemotherapy. Moreover, there were relationship between changes in hemoglobin levels (p = 0.006), leukocytes (p = 0.024), platelets (p = 0.03), and neutrophils (p = 0.02) after chemotherapy with low levels of vitamin D before chemotherapy. Low levels of pre-chemotherapy vitamin D of LABC patients was statistically correlated with myeloid toxicity after CAF neoadjuvant chemotherapy (p = 0.014).

Conclusion: Pre-chemotherapy serum vitamin D levels are associated with the occurrence of myeloid toxicity in LABC patients undergoing CAF neoadjuvant chemotherapy.

Keywords: advanced breast cancer, vitamin D, myeloid toxicity

INTRODUCTION

Breast cancer is one of the most common types of cancer in Indonesia. There are some risk factors related to breast cancer incidence, such as the use of hormonal contraceptive and age of menarche (Bustan et al. 1993, Dewi et al. 2015, Sarmila et al. 2018). The mortality rate of breast cancer is also high among women in Indonesia (Mursyidah et al. 2019). Based on Pathological Based Registration in Indonesia, breast cancer ranks first with a frequency of 18.6%. In 2010, there was an incidence of 12 per 100,000 women. More than 80% of cases are found to be at an advanced stage with a mortality rate of around 18%. Therefore, it requires good prevention, early diagnosis, and curative and palliative treatment (World Health Organization 2006). Patients with locally advanced breast cancer (LABC) need to be considered for neoadjuvant chemotherapy. Previous study mentioned neoadjuvant chemotherapy caused down-staging of disease in LABC, making more conservative surgery feasible (Iqbal et al. 2014). Therefore, many studies discuss the factors influencing the success of chemotherapy, including antioxidants as unique external factor agents because they can provide potentiation effects from chemotherapy agents while reducing their side effects (Ellisen et al. 2010). The incidence of breast cancer decreases by around 50% by maintaining 25(OH)D levels of 52 ng/ml related to women taking vitamin D 2000 IU per day (Garland et al. 2007).

Myeloid toxicity, such as myeloid cytopenia, is one of the effects caused by patients undergoing chemotherapy and potentially life-threatening occurring in the form of febrile neutropenia, anemia, and thrombocytopenia (Garland et al. 2007). Previous study states that there is an increased incidence of myeloid toxicity in the group of subjects in the winter. It turns out that after analyzing, there is a relationship with low levels of vitamin D in the blood against the incidence of myeloid toxicity (Lee et al. 2011). In addition, there was affective psychopathological comorbidities affecting on the quality of life of patients undergoing radiotherapy (Catherine et al. 2019). This study aimed to determine relationship between serum vitamin D (Luo, 2020) levels in pre-cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) chemotherapy and the occurrence of myeloid toxicity in patients with LABC undergoing neoadjuvant chemotherapy (Sittisom, 2020).

METHODS

This was a cohort study located at the Center for Cancer Services and Development Center and the Clinical Pathology Laboratory of Dr. Soetomo General Hospital, Surabaya, Indonesia. The study was conducted from September 2018 to February 2019. The study population was female patients with LABC who underwent cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF)'s first-line neoadjuvant chemotherapy at Dr. Soetomo General Hospital, Surabaya from September 2018 to December 2018. The study subjects were all female patients with LABC undergoing CAF first-line neoadjuvant chemotherapy at Dr. Soetomo General Hospital, Surabaya from September 2018 to December 2018 who met the inclusion and exclusion criteria. The inclusion criteria included female patients with LABC who received CAF first-line neoadjuvant chemotherapy, postmenopausal women, and agreed to follow the study by signing informed consent. Exclusion criteria were patients with kidney failure, chronic liver disease, residual breast cancer, weak general conditions described in the performance status with a measurement scale Karnofsky value ≤70%, and had received chemotherapy/radiotherapy before.

The study subjects then underwent examination of vitamin D levels in the blood 1 day before undergoing neoadjuvant chemotherapy. Subjects underwent chemotherapy according to the CAF regimen administration procedure. The CAF administration cycle was repeated every 3 weeks until reaching the third cycle. Determination of CAF dose was based on body mass index (BMI), with a dose of cyclophosphamide 500 mg/m² i.v, doxorubicin 50 mg/m² i.v, 5FU 500 mg/m². Furthermore, the patient's clinical response was measured after undergoing the third chemotherapy.

Table 1. Frequency of demographic characteristics of research subjects

Characteristics	Categories	n (%)
Sex	Male	0 (0)
	Female	30 (100)
Age (years)	35-45	10 (33.3)
	46-55	8 (26.7)
	56-65	10 (33.3)
	>65	2 (6.7)
Occupation	Housewife	7 (23.3)
	Teacher	6 (20)
	Merchant	9 (30)
	Farmer	8 (26.7)

Table 2. Characteristics of vitamin D levels pre- and post-chemotherapy

Variables	n (%)	Median
Vitamin D pre-chemotherapy	16.51 ng/ml*	17.41 ng/ml
Deficiency (<20 ng/ml)	17 (56.7)	
Insufficiency (21-29 ng/ml)	13 (43.3)	
Normal (30-54 ng/ml)	0 (0)	
High (>55 ng/ml)	0 (0)	
Vitamin D post-chemotherapy	14.37 ng/ml*	15.57 ng/ml
Deficiency (<20 ng/ml)	24 (80)	
Insufficiency (21-29 ng/ml)	6 (20)	
Normal (30-54 ng/ml)	0 (0)	
High (>55 ng/ml)	0 (0)	

*Mean

RESULTS

The frequency of demographic characteristics of subjects is shown in **Table 1**. The subjects were homogeneous data of women (100%) with menopausal status (100%). Menopausal status was based on history taking where the patient has not menstruated for at least 1 year (Shah et al., 2016). The youngest patient was 35 years old, and the oldest was 69 years old (Haseeb et al., 2020). The mean age of the subjects was 51.1 years. Data on subjects' occupation showed four sample jobs with the most occupation being a merchant in 9 patients (30%). These data are displayed because researchers want to observe the relationship between sun exposure and vitamin D levels.

Table 2 presents the vitamin D levels pre- and post-chemotherapy of subjects. The mean of vitamin D level before chemotherapy was 16.5 ng/ml and 14.3 ng/ml in post-chemotherapy. The data showed that 56.7% of the subjects had low vitamin D levels. Vitamin D levels of subjects were decreasing after chemotherapy, and 80% of subjects experienced vitamin D deficiency.

Table 3 shows there are significant differences in hemoglobin (p = 0.000), leukocytes (p = 0.028), platelets (p = 0.018), and neutrophil (p = 0.003) after chemotherapy in this study.

Table 4 displays relationship between pre-chemotherapy vitamin D levels with changes in hemoglobin, leukocyte, platelet and neutrophil levels after chemotherapy. There were relationship between changes in hemoglobin levels (p = 0.006), leukocytes (p = 0.024), platelets (p = 0.03), and neutrophils (p = 0.02) after chemotherapy with low levels of vitamin D before chemotherapy.

Table 3. Differences in Hemoglobin, Leukocyte, Thrombocyte and Neutrophil Pre-Chemotherapy and Post-Chemotherapy Levels

Parameters	Pre-Chemotherapy	Post-Chemotherapy	p-value
Hemoglobin (g/dL)			
Mean	12.46	11.84	
Minimal	10.30	10.30	0.00
Maximal	14.70	13.20	
Leukocyte			
Mean	7273	6181	
Minimal	2400	3040	0.028
Maximal	23400	16700	
Thrombocyte			
Mean	300800	276060	
Minimal	120000	120000	0.018
Maximal	450000	380000	
Neutrophil (%)			
Mean	62.53	51.60	
Minimal	2.54	4.87	0.003
Maximal	82.70	77.20	

Table 4. Relationship between pre-chemotherapy vitamin D levels with changes in hemoglobin, leukocyte, platelet and neutrophil levels after chemotherapy

Changes in Levels after Chemotherapy	n (%)	p-value
Hemoglobin		
Decreasing	24 (80%)	0.006
Increasing	6 (20%)	
Leucocyte		
Decreasing	18 (60%)	0.024
Increasing	12 (40%)	
Thrombocyte		
Decreasing	21 (70%)	0.03
Increasing	9 (30%)	
Neutrophil		
Decreasing	20 (66.7%)	
Increasing	7 (23.3%)	0.02
Stable	3 (10%)	

Table 5. Relationship of vitamin D pre-chemotherapy levels with the incidence of myeloid toxicity

Vitamin D levels	Positive Myeloid	Negative Myeloid	p-value
Deficiency of Vitamin D	19 (90.4%)	2 (0.96%)	0.014
Insufficiency of Vitamin D	4 (44.4%)	5 (55.6%)	

Table 5 shows that pre-chemotherapy vitamin D deficiency levels experience myeloid toxicity as much as 90.4%, while 0.96% do not experience myeloid toxicity. Other data showed that patients with pre-chemotherapy vitamin D insufficiency have an incidence of myeloid toxicity as much as 44.4%, while those without myeloid toxicity are 55.6%. Data on serum vitamin D levels of pre chemotherapy were analyzed in association with the incidence of myeloid toxicity; it was found that there was a correlation significant with p = 0.014 with odds ratio of 1.66 - 84.51. This explains the low pre-chemotherapy serum vitamin D levels can increase the occurrence of myeloid toxicity.

DISCUSSION

Women with LABC with low levels of serum vitamin D pre-chemotherapy/deficiency have a risk for the occurrence of myeloid toxicity compared to women with insufficient vitamin D levels. This study also revealed the significant difference vitamin D levels in female patients who had not undergone neoadjuvant chemotherapy and after undergoing neoadjuvant chemotherapy for three cycles. In patients with breast cancer, systemic administration of neoadjuvant chemotherapy provides an opportunity for a rapid assessment of the success of the therapy regimen (Siregar et al. 2017). The high serum vitamin D levels can reduce the process of inflammation. The results of this study indicate that low serum vitamin D levels prior to chemotherapy will affect the decrease in blood component levels in the form of hemoglobin, leukocytes, platelets, and neutrophils post-chemotherapy so as to cause worse outcomes in patients with vitamin D deficiency. This is in line with a study showing that pre-chemotherapy vitamin D levels have a significant relationship with Platelet to Lymphocyte Ratio (PLR) and Neutrophil to Lymphocyte Ratio (NLR) (Akbas et al. 2016; Clausen, 2018).

The research data showed that 56.7% of the sample had low vitamin D levels, where the post-chemotherapy level of vitamin D patients decreased, and 80% of subjects experienced vitamin D deficiency. The study further wrote that normal vitamin D levels were 48.9% in urban areas, and 49.5% in rural areas with high vitamin D levels only reach 5.7% of the urban population and 3.3% of the rural population (Poh et al. 2016). Supporting research in Indonesia also shows that the prevalence of vitamin D deficiency is 50% in women aged 45-55 years (Rimahardika et al. 2017). Another study stated that women who live in a tropical country can have vitamin D deficiency if they have sun-avoiding lifestyles, work indoors, and have a low dietary intake of vitamin D (Sari et al. 2014).

Complete blood examination on the sample before and after receiving chemotherapy showed that the study sample's hemoglobin showed a normal average result of pre-chemotherapy 12.46 while post-chemotherapy 11.84. Compared with pre-chemotherapy hemoglobin values with post-chemotherapy, there was a statistically significant decrease (p = 0.000). This can be caused by the chemotherapy regimen that affects erythroid progenitor cells so that the eryptosis process occurs and inhibits the release of hemoglobin. Some chemotherapy regimens can also inhibit erythropoietin producing cells in the kidneys so that the production of red blood cells is slow and anemia occurs. This is in line with another study stating that patients with stage II and III breast cancer with normal hemoglobin levels prior to chemotherapy using Doxorubicin and Cyclophosphamide had decreased hemoglobin levels after chemotherapy using the regimen (Kirshner et al. 2004).

Thrombocyte samples of pre-chemotherapy studies showed an average of 300800, and post-chemotherapy were 276060. From these results, there were significant differences in the values of pre-chemotherapy and post-chemotherapy platelets. These results are in accordance with other studies that mentioned platelets could decrease 10-25% of cancer patients who received

intensive chemotherapy (Hassan 2013). Leukocytes in the pre-chemotherapy study sample showed a mean of 7273 and in post-chemotherapy of 6181. From these results, there were significant differences in the values of pre-chemotherapy and post-chemotherapy (p = 0.028). This decrease is in line with a study that showed that the administration of chemotherapy could provide the effect of myeloid suppression so that neutropenia could occur. Chemotherapy-induced neutropenia is an aspect that needs attention because it can increase the morbidity and mortality of patients, one of which is the occurrence of febrile neutropenia (Ashour Badawy et al.

2014). In this study, the occurrence of a decrease in neutrophils may indicate the administration of anthracycline-based chemotherapy agents to have major side effects for neutropenia.

CONCLUSION

There was a relationship between pre-chemotherapy serum vitamin D levels with the occurrence of myeloid toxicity in female patients with LABC undergoing CAF neoadjuvant chemotherapy for three cycles with clinical response after chemotherapy.

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