

# The Differences of Myelosuppression before and after Doxorubicin Chemotherapy in Breast Cancer Patients in Rsup. H. Adam Malik Medan

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## ABSTRACT

**Introduction:** Breast cancer is formed from breast cells, either lobule or duct epithelium, which undergoes uncontrolled growth and development. The therapy of breast cancer to reduce mortality and morbidity can be done by way of surgery, chemotherapy, and radiotherapy. Doxorubicin chemotherapy is a therapeutic option to kill cells directly or by stopping the cell division based on the tumor pathogenesis.

**Method:** This research is a paired numerical comparative analytical study using a retrospective cohort approach. This study was conducted on 56 breast cancer patients to see the differences in myelosuppression before and after doxorubicin chemotherapy at H. Adam Malik General Hospital Medan from January-December 2019. The data were obtained through recording the routine blood laboratory results listed in the patient's medical record and were analyzed with dependent t-test by using SPSS. The difference is significant if  $p < 0.05$ .

**Result:** The results showed that the average age of the research subjects was 40.79 years, 28 patients (50%) graduated from high school, 38 patients (67.9%) did not work and 53 patients (94.6%) had marital status. In a significant myelosuppression difference, anemia occurred with chemotherapy Hb levels of  $8.48 \pm 1.09$ , the Hb difference in Hb prior to and after doxorubicin chemotherapy obtained a mean of 1.28 with  $p$  value  $< 0.001$ .

**Conclusion:** Based on the demographic characteristics of patients with breast cancer, it was found that the mean age of patients with

breast cancer in women was 46.79 years; most of the subject's education level was high school, unemployed and married status. There was a very significant difference between the subject's Hb level and breast cancer before and after doxorubicin chemotherapy.

**Keywords:** myelosuppression, doxorubicin, breast cancer

## INTRODUCTION

Breast cancer is a malignant tumor formed from breast cells, either lobules or duct epithelium, which undergoes uncontrolled growth and development. Based on the data obtained by the International Agency for Research on Cancer (IARC) through GLOBOCAN 2018, breast cancer ranks fifth as the cause of cancer deaths worldwide (626,679 cases) and is second in Indonesia; there are 58,256 new cases of breast cancer in Indonesia. [1]

Breast cancer generally begins in the ductal or lobular area. Breast cancer can spread through blood vessels or lymph nodes which are known as metastasis. [2] According to the Association of Indonesian Pathology Specialists and the Indonesian Cancer Foundation, the incidence of breast cancer is generally almost 99% in women and 1% in men. [3] Determining the cancer stage and grade is a very important part in diagnosing cancer because it will then determine the most effective type of treatment. Cancer management can be in the

form of surgery, radiation and chemotherapy. In most cases, patients come at an advanced stage so the choice of treatment method is chemotherapy.<sup>[3]</sup> Cytotoxic drugs that can be used singly or in combination as chemotherapy drugs in breast cancer includes doxorubicin, epirubicin, cyclophosphamide, methotrexate, fluorouracil, paclitaxel, docetaxel, melfalan, prednisone, vinorelbine, and vincristine.<sup>[4]</sup>

Doxorubicin belongs to the anthracycline drug class which is the most active class of chemotherapy agents in the treatment of metastatic breast cancer<sup>[4]</sup>. Chemotherapy is a therapy for cancer using drugs with the aim of stopping the growth of cancer cells either by killing the cells directly or by stopping the cell division process based on the tumor pathogenesis.<sup>[5]</sup> Doxorubicin belongs to the anthracycline antibiotic class. The mechanism of action of doxorubicin is (1) inhibition of topoisomerase II, (2) intercalation of DNA resulting in inhibition of DNA and RNA synthesis, (3) binding of cell membranes which causes flow and transport of ions and (4) formation of semiquinone free radicals and oxygen free radicals through iron-dependent processes and enzyme-mediated reductive processes. Compared to other antibiotics in the anthracycline group, doxorubicin is an antibiotic that has the broadest spectrum of clinical activity. In addition, doxorubicin has hepatotoxic and myelosuppressive side effects<sup>[6]</sup>.

The production of reactive oxygen species (ROS) is an important molecule that induces oxidative stress in organisms; it plays a key role in tumorigenesis, tumor development and recurrence. Recent findings on ROS have shown that ROS is used to treat cancer because it accelerates tumor cell death. High levels of ROS do not only induce tumor cell death but also oxidative damages to normal cells, especially the hemopoietic cells in the bone marrow, leading to bone marrow suppression and other side effects. How to enhance the effects of ROS on tumor cells

while avoiding oxidative damages to normal cells has become a desperate issue. Recent studies on the role of ROS-mediated programmed death in tumor treatment and prevention and treatment of oxidative damages in the bone marrow caused by ROS.<sup>[7]</sup>

Anemia is the end result of failure of the erythropoiesis process caused by cancer or chemotherapy, called cancer-related anemia (CRA).<sup>[8]</sup> Each chemotherapy agent has a different mechanism in causing thrombocytopenia, affecting stem cells, more mature progenitor megakaryocytes, preventing the release of platelets from megakaryocytes, and other therapies that induces platelet apoptosis.<sup>[9]</sup> Chemotherapy reduces the number of leukocytes, particularly neutrophils, to about 70% of circulating leukocytes. The main function of neutrophils is to fight bacteria, viruses and other pathogens. It takes about 10 to 14 days for a mature neutrophil to leave the bone marrow and enter the bloodstream, and it survives for only 4 to 8 hours.<sup>[10]</sup>

This study analyzed the differences in myelosuppression before and after doxorubicin chemotherapy in patients with breast cancer.

## **MATERIAL AND METHODS**

### **Study Sample**

The target population was all patients with breast cancer who received doxorubicin chemotherapy and met the inclusion and exclusion criteria from January-December 2019 at RSUP. H. Adam Malik Medan.

### **Study Design**

This study was a paired numerical comparative analytical study with a retrospective cohort approach to see the differences in myelosuppression in breast cancer patients before and after doxorubicin chemotherapy. After receiving Ethical Clearance, the study subjects who met the inclusion criteria were recruited and patients with leukemia, autoimmune diseases, HIV / AIDS patients, pulmonary TB patients,

patients undergoing radiation therapy, transfusions during chemotherapy cycle were excluded from the study. The data were obtained from medical records and have routine blood laboratory results from before and after chemotherapy. Then after the data were collected, data processing and analysis were carried out.

### Statistical Methods

Data collection from complete medical records and data processing and data analysis was performed on a computer system using the SPSS program for windows version 22.0

The first step was to test the data normality using the Kolmogorov-Smirnov test because the sample size is  $\geq 50$ , if the data was not normally distributed, then the data transformation is performed with log 10. After performing the data transformation and the normality test was performed again, if the data was still not normally distributed then it is continued by performing the Wilcoxon test. If after the second normality test the data is normally distributed, it is followed by a dependent t-test to see the bivariate relationship.

### RESULTS

This study was conducted on 56 breast cancer patients who experienced myelosuppression. Demographic characteristics of breast cancer patients undergoing doxorubicin chemotherapy are shown in Table 1. Table 1 shows that the mean age of breast cancer subjects was 46.79 years and the standard deviation was 8.79 years ( $p = 0.053$ ) All research subjects for breast cancer were women, as many as 56 people (100%). Based on the variable of education level, we found 28 people (50%) had high school education level. Based on employment status variable, it was found, 38 people (67.9%) were unemployed. For the variable of marital status, 53 people (94.6%) were married, 3 people (5.4%) were not married.

**Table 1: Demographic Characteristics of Subjects with Breast Cancer**

No	Variable	Breast Cancer (n=56)
1	Age, mean $\pm$ SB, years	46.79 $\pm$ 8.79
2	Sex	
	• Male	0
	• Female	56 (100%)
3	Education Level	
	• Primary School	10(17.9%)
	• Middle School	4 (7.1%)
	• High School	28(50%)
	• Bachelor	14(25%)
4	Employment Status	
	• Civil servant	13(23.2%)
	• Farmer	39(5.4%)
	• Entrepreneur	2(3.6%)
	• Unemployed	38(67.9%)
5	Marital Status	
	• Married	53(94.6%)
	• Not married	3(5.4%)

Distribution of patients with breast cancer based on the degree of myelosuppression who undergone doxorubicin chemotherapy. 1 patient (1.7%) had anemia before grade 1 chemotherapy, 43 patients (76.7%) had anemia before grade 2 chemotherapy, 12 patients (21.4%) had anemia before grade 3 chemotherapy. As many as 43 patients experienced anemia after grade 1 chemotherapy (76.7%), grade 2 as many as 13 people (23.2%). Five patients (8.9%) had neutropenia before grade 1 chemotherapy, and consecutively 1 patient (1.7%) had neutropenia before grade 2 chemotherapy, 1 patient (1.7%) before grade 3 chemotherapy and 2 patients (3.5%) before grade 4 chemotherapy. Three patients (5.3%) had neutropenia after grade 1 chemotherapy, as for grade 2 as many as 1 patient (1.7%), grade 4 as many as 2 patients (3.5%). Five patients (8.9%) had thrombocytopenia before grade 1 chemotherapy. There were 7 patients with thrombocytopenia after grade 1 chemotherapy (12.5%).

Table 2 describes the differences in Hb levels of subjects with breast cancer before doxorubicin chemotherapy, the mean was 8.48 and the standard deviation was 1.09. The average Hb level after doxorubicin chemotherapy was 10.86 and the standard deviation was 1.11. Meanwhile, the mean Hb level difference before and after doxorubicin chemotherapy was 1.28

and the standard deviation was 1.16 ( $p < 0.001$ ). There was a very significant difference between the subject's Hb level and breast cancer before and after doxorubicin chemotherapy. The difference in platelet levels before doxorubicin chemotherapy obtained a mean of 379.04, and a standard deviation of 160.75, and a mean of 378.55 and a standard deviation of 188.68 was obtained after doxorubicin chemotherapy. Based on the Wilcoxon test it was concluded that 33 subjects had lower platelet values after chemotherapy. A total of 23 subjects with breast cancer had higher platelet values after chemotherapy, and none of the subjects did not experience changes in platelet values after chemotherapy. There

was no significant difference between the subject's platelet levels and breast cancer before and after doxorubicin chemotherapy ( $p=0.65$ ). The difference in neutrophil levels before doxorubicin chemotherapy obtained a mean of 5.63 and a standard deviation of 2.44. The mean of neutrophil values after doxorubicin chemotherapy was 6.09 and the standard deviation was 2.70. Meanwhile, the difference of neutrophil values before and after doxorubicin chemotherapy obtained a mean of 2.14 and the standard deviation was 2.84 and the value of  $P=0.58$  ( $p > 0.05$ ). There was no significant difference between neutrophil levels in subjects with breast cancer before and after doxorubicin chemotherapy.

**Table 2: The Differences of Myelosuppression Before and After Doxorubicin Chemotherapy in Subjects with Breast Cancer**

Variable		Dependent t-test				Wilcoxon test	
		Mean $\pm$ (SD)	Difference $\pm$ (SD)	CI 95%	p	Median (Min-Max)	p
Breast Cancer (n=56)	Pre Chemotherapy Hb level	8.48 $\pm$ 1.09	1.28 $\pm$ 1.16	1.22 -1.33	<0.001		
	Post Chemotherapy Hb level	10.86 $\pm$ 1.11					
	Pre Chemotherapy Platelet level					356(126-800)	0.65
	Post Chemotherapy Platelet level					349(55-945)	
	Pre Chemotherapy Neutrophil level	5.63 $\pm$ 2.44	2.14 $\pm$ 2.84	1.22 -1.43	0.58		
	Post Chemotherapy Neutrophil level	6.09 $\pm$ 2.70					

## DISCUSSION

The results showed that the age group which breast cancer occurred most was in the mean age group of 46 years. This result is in accordance to a survey by the American Cancer Society in 2017 towards American women which also showed similar results, whereas 65% occurred in the 40-69 year age group. Research conducted by the Australian Cancer Council in 2016 concluded that nearly 70% of breast cancers occur in women aged 40-69 years. This result is in accordance with research by Mohammed Khalis et al in 2018 whereas 21% for the age group <40 years. [11]

According to the ACS, the decrease in the incidence of elderly people is due to low rates of screening tests, detection using mammography or incomplete identification at previous ages. [12] Breast cancer is considered as an age related condition. This increase begins more rapidly in middle age. The multifactorial transformation process from normal cells to cancer cells includes

accumulation of DNA damage and mutations over time added by disturbances in DNA repair and growth system regulation. Aging is also associated with increased inflammation or decreased immune function that supports cell proliferation and change. [13]

Patients with breast cancer who received transfusions during the doxorubicin chemotherapy cycle were difficult to assess the degree of myelosuppression. In this study, the average patient with breast cancer received transfusions in several cycles of chemotherapy. Chemotherapy in cancer patients is often accompanied by bone marrow aplasia which manifests in the form of anemia, leukopenia, thrombocytopenia or a combination of these conditions. These complications contribute to increased morbidity and mortality and reduce the patient's quality of life. In the results of this study, the highest incidence of anemia was before grade 2 chemotherapy as many as 43

patients (76.7%), after grade 1 chemotherapy as many as 43 patients (76.7%).

Regimens in breast cancer adjuvant chemotherapy are used both in international guidelines and national guidelines. According to WHO in the WHO Handbook for Reporting Results of Cancer Treatment, evaluating the response to non-surgical cancer treatment is by evaluating the toxicity or side effects of treatment. In this study, researchers evaluated the outcome of the regimen administration in patients by looking at the potential effects of myelosuppression in breast cancer patients receiving doxorubicin chemotherapy.

The drug preparation of doxorubicin given by intravenous injection is rapidly cleared from the blood, and distributed to tissues including the lungs, liver, heart, spleen, and kidneys. This drug is rapidly metabolized in the liver into metabolites including the active metabolite doxorubicinol. Approximately 40-50% of the dose is excreted in the bile within 7 days, of which nearly half are unchanged. Only 5% of the dose is excreted in the urine within five days. Doxorubicin can penetrate the blood brain barrier membrane, it may be able to penetrate the placenta and be distributed in breast milk. The elimination of doxorubicin from bloodstream must go through three phases, namely the average half-life of 12 minutes, 3.3 hours and 30 hours. [14,15]

The occurrence of myelosuppression, especially anemia in these patients, is related to the production of ROS from doxorubicin which results in further injury to the cell membrane and mitochondria and DNA. Anthracyclines react with cytochrome P450 reductase in the presence of reduced NADPH present in the cell nucleus membrane to become semiquinone free radicals. If oxygen is present, semiquinone will give unpaired electrons to combine with oxygen molecules to form superoxide radicals, namely hydrogen peroxide and hydroxyl which attacks DNA. This reaction is known as the redox cycle that occurs in the cytoplasm,

mitochondria and sarcoplasmic reticulum. Intramolecular electron transfer reactions in semiquinone compounds also cause the formation of lipid peroxides, nitrogen monoxide and other destructive radicals. The first target of anthracycline-induced free radicals is the cell membrane, which is rich in lipids and susceptible to peroxidation. The doxorubicin metabolite, namely Doxorubicinol, will also form a cytoplasmic Fe-S complex that prevents iron absorption and increases free iron. [16] The free iron content catalyzes the redox cycle to form hydrogen peroxide. [17] In patients with malignancy, iron deficiency conditions often occur, decreased peripheral erythropoiesis due to decreased levels of vitamin B12 and decreased production of folic acid. Chemotherapy drugs stimulate apoptosis in erythroid cells and cause disturbances through damage to renal tubular cells, which will reduce endogenous erythropoietin causing anemia conditions. [18]

Based on the severity, drug interactions are divided into major interactions (fatal effects can cause death), moderate (moderate effects can cause organ damage), and minor (can be handled well) [19]. The accuracy of chemotherapy drug preparation procedures observed is the activity carried out by health workers who work in the process of preparing chemotherapy drugs. The flow of chemotherapy drug preparation services starts from the submission of the required documents (prescriptions, chemotherapy protocols, and health insurance for BPJS patients) by the inpatient/polyclinic room nurses and the submission of documents to the chemotherapy room nurse is carried out by the patient or the patient's family members, the inpatient room nurse/ Polyclinic only provides patient medical records at the time the chemotherapy schedule is implemented.

The weakness of this study is that this study was not conducted in a multicenter facility, due to limited resources. Patients with anemia, infection

and a history of receiving transfusions could not be excluded from the study because the samples studied were in the chemotherapy induction phase and many still had anemia within the study period. Research subject data were taken from the patient's medical records so that detailed data on the demographics of research subjects becomes difficult to optimize.

## CONCLUSION

Based on the results of this study it was concluded that the demographic characteristics of breast cancer patients found that the average age of breast cancer patients in women was 46.79 years, most of them had high school education level, unemployed status and married status. There was a very significant difference between the subject's Hb level and breast cancer before and after doxorubicin chemotherapy. There was no significant difference between the subject's platelet levels and breast cancer before and after doxorubicin chemotherapy. There was no significant difference between neutrophil levels in subjects with breast cancer before and after doxorubicin chemotherapy.

## SUGGESTION

Based on the results of this study, it is recommended that further research to be carried out regarding the differences in myelosuppression due to doxorubicin chemotherapy in breast cancer patients. Medical personnel are expected to carry out the treatment process in accordance with valid fixed procedures. Consider potential drug interactions and side effects that may occur in the administration of cytostatic drugs together with other drugs. Taking into account the dose of drug used according to the needs and physiology of the patient. Conduct research evaluation of chemotherapy regimens towards age groups, regimen accuracy, physical and mental condition of patients.

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