THE RISK FACTOR OF NEUTROPENIA ON LOCALLY ADVANCED BREAST CANCER PATIENTS TREATED WITH FIRST CYCLE CYCLOPHOSPHAMIDE, DOXORUBICINE, 5- FLUOROURACIL CHEMOTHERAPY AT SANGLAH GENERAL HOSPITAL DENPASAR, BALI-INDONESIA

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Objective: Breast cancer is the most common type of cancer found in women, in the United States breast cancer is the number one cancer in women and the second highest cause of cancer deaths after lung cancer. This study aims to determine the incidence of neutropenia and tested several clinical risk factors of neutropenia in locally advance breast cancer/LABC patients who obtain first cycle cyclophosphamide, doxorubicine, 5-fluorouracil neoadjuvant chemotherapy at Sanglah Hospital in Denpasar. **Method**: The study was a prospective cohort involving 62 LABC patients conducted between February to June 2012. Clinical factors such as age, chronic obstructive pulmonary disease, hypertension, nutritional status, and hemoglobin levels in patients were recorded. Neutrophil level were recorded on day 7 and 12 of first cycle neoadjuvant chemotherapy. Bivariate analysis was done to see the strengths of each risk factor for neutropenia followed by multivariate logistic regression analysis to determine the most significant risk factor for the occurrence of neutropenia. Relative risk with 95% confidence interval was recorded. The level of significance was set at value of less than 0,05. **Results**: Neutropenia was found in 17 patients (27,4%). Bivariate analysis showed that age older than 60 years old, hypotensive, under nourished, and anemic are significant risk factors of neutropenia. However, in multivariate logistic regression age (RR 20,225; 95% CI 1,804-226,776) and nutritional status (RR 35,328; 95% CI 3,108-401,524) remained significant clinical risk factors of neutropenia. **Conclusion:** Neutropenia incidence was 27,4%. Patients older than 60 years old and under nourished status are the significant clinical factors causing neutropenia and can be used as a predictor to predict neutropenia.
Keywords: LABC, clinical risk factors, CAF chemotherapy, first cycle, neutropenia.

INTRODUCTION

Breast cancer is the most common type of cancer found in women, in the United States breast cancer is the number one cancer in women and the second highest cause of cancer deaths after lung cancer. Every year estimated that more than 250.000 new cases of breast are diagnosed in Europe, and more over than 175.000 cases in the United States.[1] Data from the Indonesian Ministry of Health showed that Case Fatality Rate from breast cancer have increased from 1992-1993, ie from 3,9 to 7,8. This incidence seems minimal because not all cases are reported or get medical treatment.[2] Data from Departement of Oncology Surgery, Faculty of Medicine/Sanglah General Hospital Denpasar, Bali-Indonesia 2009-2010, showed that 50% of breast cancer patients have already in the locally advanced stadium (stadium IIIa or more), and 45% are over 50 years.[3] The main goal in locally advanced breast cancer patients is to reduce the size of an unresectable tumor, improve local control and reduce the spread of metastases by neoadjuvant chemotherapy.

The use of chemotherapy can induce neutropenia, chemotherapy-induced neutropenia (CIN), which could end with febrile neutropenia (FN). FN decreases the patient's immune system to a very low point. Factors that contribute to the incidence of FN are tumor type[4], old age[5], advanced illness[6], comorbidity[7], hypotension, malnutrition[8], and low hemoglobin levels[9]. Demographic conditions such as like bady mass index (BMI) were related with lower nutritional status, hence increasing the probability of FN.

In this study we want to see the incidence of neutropenia and the role of each risk factors in LABC patients who received chemotherapy Cyclophosphamide, Doxorubicine, 5-Fluorouracil (CAF) in Denpasar Sanglah Hospital.

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MATERIALS AND METHOD

This is a prospective cohort study involving 62 LABC patients from February to June 2012 admitted in Sanglah Hospital that will receive neoadjuvant chemotherapy CAF for the first cycle, and had not received previous chemotherapy before. Patients with comorbidities (cardiovascular, liver diseases, Diabetes Mellitus, and other malignancies), pregnant patients, and patients with a Karnofsky score less than 70 were excluded from this study. Patients who meet the inclusion and exclusion criteria noted risk factors are age neutropenia, presence or absence of chronic obstructive pulmonary disease, hypotension, nutritional status, hemoglobin and neutrophil levels. After that patients received CAF chemotherapy regimen with doses according to body surface area of the sample. On the seventh and twelveth day after receiving the first cycle of neoadjuvant chemotherapy neutrophil values were recorded. Bivariate analysis was done to see the strength of each risk factor for neutropenia followed by multivariate logistic regression analysis to determine the most significant risk factor for the occurrence of neutropenia. The relationship between risk factors with neutropenia using relative risk with 95% confidence intervals and risk factors are significant with the p value less than 0.05

RESULTS

During the period of February to June 2012 we recorded 287 breast cancer patients undergoing chemotherapy, and 62 patients fulfilling the study. Subject characteristic of all patients was presented in Table 1.

Table 1
Subject Characteristics

Characteristics	Details
Sex: Male	0 (0%)
Female	62 (100%)
Age: <40 year	8 (12.9%)
40 – 60 year	45 (72.6%)
>60 years	9 (14.5%)
Clinical predictors	
Age	
>60 years	9 (14.5%)
≤ 60 years	53 (85.5%)
Blood pressure	
Hypotension	12 (19.4%)
Normal	50 (80.6%)
Nutrition	
Poor	32 (51.6%)
Normal	30 (48.4%)
Hemoglobin	
Anemia	34 (54.8%)
Normal	28 (45.2%)

The average patient age was 49 years, the youngest age is 32 years and the oldest 67 years of age.

Blood tests performed on days 7 and 12 after the first cycle of chemotherapy CAF obtained 17 patients (27.4%) experienced neutropenia.

Univariate analysis shows that **age > 60 years old** (RR, 15.050; 95%CI, 2.707-83.671), **hypotension** (RR, 5.6; 95%CI, 1.465-21.4), **malnutrition** (RR, 29,0; 95%CI, 3.514-239.313), and **anemia** (RR, 5,833; 95%CI, 1.470-23.155) are risk factors of neutropenia.

The relative risk of each component to the occurrence of neutropenia and relation between risk factors and neutropenia were presented in Table 2 and 3.

Multivariate analysis shows that only **old age** (RR, 20.225; 95%CI, 1.804-226.776) and **poor nutrition** (RR, 35.328; 95%CI, 3.108-401.524) is a risk factor for the occurrence of neutropenia.

DISCUSSION

Management of patients with advanced breast cancer is aimed at reducing the size of the tumor, improve local control and reduce the spread of metastasis by means of neoadjuvant chemotherapy.[10] Currently, the provision of multi-drug chemotherapy due to breast cancer is heterogeneous, it has shape of cells and cell properties are diverse, including in and sensitivity resistance to chemotherapy drugs that are also different.[11] From the many combinations of chemotherapy drugs for breast cancer according to PERABOI 2010, Sanglah Hospital uses first-line regimen of anthracycline-based chemotherapy that is CAF as it is widely available, affordable, and easy to apply to people with breast cancer.

Chemotherapy drugs can not distinguish between normal cells and cancer cells. The effect on normal cells, especially in cells that are actively proliferating / mitosis, such as blood cells. Blood cells that have the shortest life will experience "Penia" first, in this case the leukocytes, particularly neutrophils, followed by platelets and erythrocytes. Neutrophil is the first line of defense against infection is characterized by Absolute Neutrophil Count (ANC) less than 1500/μL. The risk of infection begins to appear when ANC values are less than 1000/μL and increases dramatically when ANC levels are less than 500/μL. 10-20% of patients with ANC less than 100/μL would experience bakteremia.[12,13]

Cyclophosphamide and 5-fluorouracil neutropenia appears after 7 days of chemotherapy. Neutropenia occurs after administration of cyclophosphamide on days 8-15, days 10-14 doxorubicine, and 5-fluorouracil on day 9-14.[14] On that basis of two examinations were conducted for ANC values, i.e., on days 7 and 12 after chemotherapy. Examination on day 7 is a routine inspection carried out on all breast cancer patients who received chemotherapy in Sanglah General Hospital. Evaluation on the 12th day aims to see

Table 2
The Relative Risk of Each Component to the Occurrence of Neutropenia

Clinical Factors	Neutropenia Positive	Neutropenia Negative	amount	p	RR	95% CI Lower	Upper
Age							
> 60 years old	7	2	9	0.001**	15.05	2.70 – 83.67	
≤ 60 years old	10	43	53				
Total	17	45	62				
Blood Pressure							
Hypotension	7	5	12	0.013**	5.60	1.47 – 21.40	
Normal	10	40	50				
Total	17	45	62				
Nutrition							
Poor	16	16	32	0.001*	29.00	3.51 – 239.3	
Normal	1	29	30				
Total	17	45	62				
Hemoglobin							
Anemia	14	20	34	0.007*	5.83	1.47 – 23.16	
Normal	3	25	28				
Total	17	45	62				

Table 3
Relation Between Risk Factors and Neutropenia (multivariate)

Risk Factors	p	RR	95%CI Lower	Upper
Age> 60 years	0.015*	20.225	1.804	226.776
Poor nutrition	0.004*	35.328	3.108	401.524

Logistic regression. *Significance $p < 0.005$

the severity of neutropenia. In this study, 27.4% of breast cancer patients experienced neutropenia after first series CAF chemotherapy. Some research data between 35-50% FN episodes occurs in first cycles chemotherapy.[4,9,15,16] This is higher due possibly because of aggressive chemotherapy with high doses hence side effects are more common. The research was conducted in the first cycle of chemotherapy to reduce the bias that may result from chemotherapy patients, as well as the possibility of change by the clinician's next cycle of chemotherapy regimens. ANC average patient before chemotherapy is given at 4.0/mL, seven days after administration of chemotherapy decreased to 2.2/mL, and after 12 days, giving a 1.3/mL.

Risk factors for the occurrence of neutropenia, which can be grouped into four therapeutic effect is obtained, the patient's own factors, types of cancer, and comorbid illnesses. Of the many risk factors are taken some risk factors such as age over 60 years, chronic obstructive pulmonary disease, hypotension, malnutrition, and anemia with consideration of risk factors is easily applied clinically in patients, and the few studies that have been done before has significant value predictors.[5,6,8,9]

Bivariate analysis found that all of these risk factors have a significant relationship to the occurrence of neutropenia. However, after multivariate was done, it turned out to be just over 60 years of age and malnutrition posed as a significant risk factor for the occurrence of neutropenia. Other risk factors were not significant may lose strength, the opposite direction, or as a confounding factor in this study.

Age over 65 years had a higher risk for the occurrence of neutropenia. The increase in the elderly patients is likely related to immunosenescence (progressive remodeling of the immune system to decrease the ability of immune cells to respond to stimuli and increased response to tolerogenic signals). Immunosenescence significantly influence the effectiveness of cancer chemotherapy. However, no evidence of increased risk of neutropenia correlation with age after 65 years.[9] Perhaps this is because in these patients a lower dose of chemotherapy or chemotherapy in the elderly patients are less aggressive. However, research conducted by Balducci found elderly patients can benefit equally from such aggressive chemotherapy as do younger patients.[17] In this research, nine patients over the age of 65 years and 7 of them experienced neutropenia (77.8%) with

RR 20.2 95% CI 1.8 to 226.[7] Although in this study using chronological age in the study sample due to easy retrieval of data, preferably in patients with cancer using physiological age to better reflect the biological and physiological condition of the patient.

Three previous studies found that poor performance status is a significant risk factor for the occurrence of CIN.[5,8,18] This can be assessed using the Karnofsky score, in which patients with values less than 70 are not given chemotherapy. In this study, poor performance status has an analogy with malnutrition. The average BMI of patients with breast cancer who have neutropenia was 16.63 and included into the group under weight. A high number of patients came with malnutrition because these patients are from low socio-economic levels. Obtained 50% of 32 patients with malnutrition had neutropenia. Patients with malnutritionare more susceptible to neutropenia due to the decrease in the body's ability to produce stem cells in the bone marrow. In this research, 32 patients with malnutrition and 50% had neutropenia with RR 35.3, 95% CI 3.1 to 401.5. Use of BMI as an indicator of nutritional status in this study was caused to facilitate retrieval of clinical data in the field, but there are other tests that better assess the nutritional status in patients with cancer, by using the Patient Global Assessment Generated-wiki. However, these methods require trained personnel and a longer time to collect data.

CONCLUSION

In this research, 27.42% of patients with locally advanced breast cancer experienced neutropenia after chemotherapy CAF obtained in the first series. Age over 60 years, and poor nutrition are the most significant risk factors for the occurrence of neutropenia in patients with locally advanced breast cancer treated with CAF chemotherapy.

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