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Post-Chemotherapy Monocytopenia as a Predictor of Chemotherapy – Induced Neutropenia in Breast Cancer Patients

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ABSTRACT

Background: Chemotherapy-induced neutropenia (CIN) is chemotherapy's most frequent myelosuppression effect. Previous studies have examined static prognostic factors to assess dynamic neutrophil changes in each cycle. This study focuses on post-chemotherapy monocytopenia as a more dynamic predictor of CIN. This research aimed to know whether post-chemotherapy monocytopenia can be used as a predictor of CIN in breast cancer patients undergoing the chemotherapy cycle.
Methods: This research used a prospective and a retrospective longitudinal cohort of breast cancer patients undergo a CAF regimen at Sanglah Hospital Denpasar. The research was conducted on 30 samples for three cycles (90 total cycles). Monocyte data is taken in the first week (days 4 to 9), and neutrophil data is taken in the second week (days 10 to 16).
Results: From statistical analysis with interval data scale, we obtained that p 0.001 with Pearson correlation 0.613 for cycle 1, p 0.001 with Pearson correlation 0.611 for cycle 2, and p 0.003 with Pearson correlation 0.522 for cycle 3.
Conclusions: In conclusion, post-chemotherapy monocytopenia can be used to predict the occurrence of chemotherapy-induced neutropenia (CIN) with the strongest positive correlation in the first cycle.

Keywords: Monocytopenia, predictor, chemotherapy-induced neutropenia, Cancer, Benign neoplasm of Breast.
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INTRODUCTION

Breast cancer is the most common type of cancer suffered by women in Indonesia and even the world. The latest data in 2020, the number of new breast cancer cases in women is 24.5% in the world with a mortality rate of 6.9%, which is ranked 4th in the world.[1] The number of new breast cancer cases in women was 30.8% in Indonesia in 2020, which made it the highest cancer case in Indonesia, with the highest death rate number 2, which is 9.6%.[2] Sanglah Hospital Denpasar is a type B teaching hospital and a Referral Hospital for Bali, NTB, NTT, East Timor (SK Menkes RI No.134/1978).[3] In the 2019 hospital profile, breast cancer was ranked number 6 in the ten most hospitalized diseases at Sanglah Hospital Denpasar.[4]

Chemotherapy-induced neutropenia (CIN) is one of chemotherapy's most common myelosuppressive effects. The incidence of neutropenia varies between 6-50% and the CIN incidence is 15% of all chemotherapy cycles[5], and in sanglah general hospital was 27.4% incidence.[6] The heaviest complication of this side effect is febrile neutropenia (FN), which carries the consequences of inpatient hospitalization costs, broad-spectrum antibiotics, delayed chemotherapy, and surgery schedules, reduced doses of chemotherapy drugs, morbidity even mortality.[7,8] In the United States, the incidence of mortality associated with neutropenia grades 3 and 4 ranges from 3.4% to 10.5%.[9]

Research on the risk factors of CIN has been carried out and depend on the factors that have been studied, most of them are qualitative results in predicting the occurrence of neutropenia.[10,11] One of the most studied components is monocytes, because monocytes are the component of peripheral blood closest to neutrophils in the process of hematopoiesis.[12,13] Some study said that the percentage of pre-chemotherapy monocytes with a decrease in the number of neutrophils.[14–16] Ouyang et al. found that the trend of monocyte changes after chemotherapy was similar to neutrophils. Still, it occurred earlier, both at the beginning of the decline, the nadir point, and at the end of the rise.[12,17]

This study aims to determine whether the decrease in monocytes after chemotherapy can be used to predict chemotherapy-induced neutropenia. This study took monocyte value as a predictor because it originates from the same myelocytic pathway as neutrophils. Basophils and eosinophils, which also originate from the myelocytic pathway, have a narrow range of expected values with a lower limit on the value of 0 so that it is challenging to study. Ouyang's previous study only used data on neutropenic patients, whereas in this study, data from patients with or without neutropenia had either. This study uses post-chemotherapy monocyte data to provide more actual data and minimize other prognostic factors such as G-CSF administration. It is expected to be generalized to patients, cancer cases, and other chemotherapy regimens. Research on other prognostic factors showed inconsistent results with the incidence of neutropenia in each cycle, so we conducted a study for three

cycles to see the reliability of monocytes as a predictor of neutropenia. With more specific and quantitative predictors, such as monocytes, it is hoped that they can become a consideration for giving G-CSF as a prophylactic for neutropenia, including in the JKN era.

METHODS

This study used a prospective and retrospective longitudinal cohort study design. The affordable population is all breast cancer patients who undergo CAF chemotherapy, and their laboratory tests are recorded at SIMARS Sanglah Hospital. The sample size was 30 people followed up to 3 cycles for each person.

The inclusion criteria of this study were female breast cancer patients undergoing chemotherapy. The exclusion criteria were male breast cancer patients, breast cancer with other histopathology types besides adenocarcinoma, the patient with bone metastasis, the patient that the laboratory examination not listed at SIMARS RSUP Sanglah Denpasar, the patient that experienced early neutropenia (less than ten days after chemotherapy) and obtained G-CSF therapy, and also the patient that only undergoes complete blood count examination once after chemotherapy.

Patient data were taken from medical records, chemotherapy records, and SIMARS data at Sanglah Hospital. Patients undergoing chemotherapy will undergo a complete blood count twice after chemotherapy, in the first and second weeks after chemotherapy. Monocyte data (independent variables) were taken from blood tests at the first week (day 4 to 9), while neutrophil data (dependent variable) were taken from blood tests at the second week (day 10 to 16).

This study uses a linear regression statistical test because the dependent variable uses quantitative data (interval scale). Statistical significance was seen through the p-value with a significance limit of 0.01. If a significant p-value is obtained, then statistical analysis can continue to show the magnitude of the correlation between variables and compare cycles. Correlation analysis used is using Pearson correlation for quantitative data.

RESULT

Table 1 describes the characteristics of the research sample. The mean age of the patients in this study sample was 52.5 years. The average body surface area (BSA) is 1.625 m^2. The most cancer stages were stage II and III as many as 14 people (46.7%). Stage IV was obtained by two people (6.7%) and no stage I. In these 30 samples, 15 people (50%) had an exemplary operation and received adjuvant chemotherapy. While tumors that were still intact were found in 15 people (50%) and 13 people (43.3%) received neoadjuvant chemotherapy and 2 (6.7%) primary chemotherapy. From 16 samples with intact tumors, the mean primary tumor size was 7.73 cm. The most histopathological grade of cancer in the sample was grade II with 17 people (56.7%), then grade III with ten people (33.3%), and grade I as many as three people (10%).

In the first cycle of this study, 18 patients had monocytopenia with a mean monocyte value of 162.3/µL. Neutropenia was found in 18 patients with mean neutrophil values of 2519/µL. In the first cycle, the p-value was 0.001 from regression analysis with a Pearson correlation of 0.613. Table 2 and Figure 1 describe the statistical analysis in cycle 1.

In the second cycle, 11 patients had monocytopenia with a mean value of 172.3/µL monocytes. Neutropenia was found in 14 patients with mean neutrophil values of 2352/µL. In the second cycle, the p-value was 0.001 from regression analysis with a Pearson correlation of 0.611. Table 3 and Figure 2 describe the statistical analysis in cycle 2.

In the third cycle, 16 patients had monocytopenia with a mean monocyte value of 136.3/µL. Neutropenia was found in 16 patients with a mean neutrophil value of 2690/µL. In the third cycle, the p-value was 0.003 from regression analysis with a Pearson correlation of 0.522. Table 4 and Figure 3 describe the statistical analysis in cycle 3.

DISCUSSION

The age of the patients in this study ranged between 39 and 74 years, with a mean age of 52 years. The incidence of breast cancer in Indonesia is also widely

Table 1. Patient characteristic.

Characteristic	Mean Value	n (%)
Age	52.467 ± 7.619	
BSA	1.625 ± 0.132	
Primary tumor size	7.73 ± 1.486	
Stadium		
I		0
II		14 (46.7%)
III		14 (46.7%)
IV		2 (6.7%)
Chemotherapy		
Adjuvant		15 (50%)
Neoadjuvant		13 (43.33%)
Primary		2 (6.7%)
Histopathology Grading		
I		3 (10%)
II		17 (56.7%)
III		10 (33.3%)

Table 2. Regression analysis and Pearson correlation cycle one.

	Unstandardized coefficient		Standardized coefficient beta	T	Sig.
	B	Std. error			
Constant	1439.205	411.883		3.494	0.002
Monocytecycle 1	6.652	1.620	0.613	4.106	0.000

Dependent variable: neutrophils cycle 1

Table 3. **Regression analysis and Pearson correlation cycle two.**

	Unstandardized coefficient		Standardized coefficient beta	T	Sig.
	B	Std. error			
Constant	1269.734	357.152		3.555	0.001
Monocyte cycle 2	6.280	1.538	0.611	4.083	0.000

Dependent variable: neutrophils cycle 2

Table 4. **Regression analysis and Pearson correlation cycle three.**

	Unstandardized coefficient		Standardized coefficient beta	T	Sig.
	B	Std. error			
Constant	1361.301	515.342		2.642	0.013
Monocytecycle 3	9.746	3.013	0.522	3.234	0003

Dependent variable: netrophils cycle 3

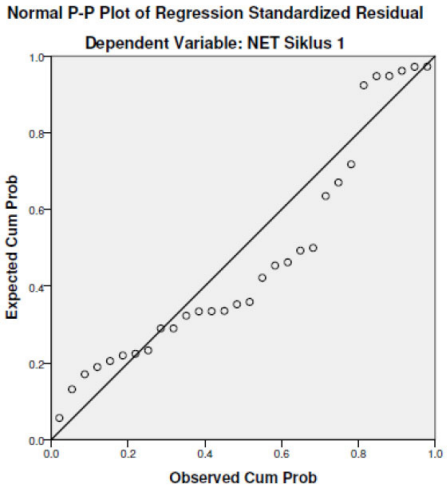

Figure 1. Regression analysis cycle one.

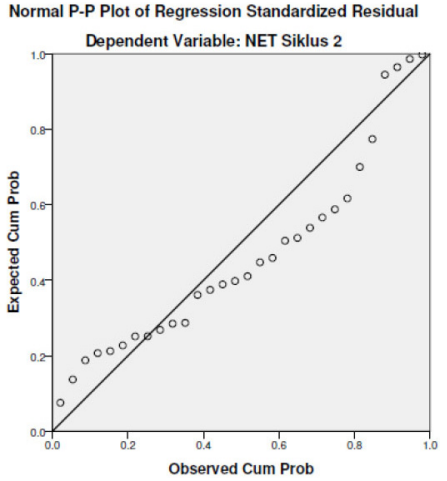

Figure 2. Regression analysis cycle two.

found in the 4th and fifth decades of age, classified as productive age.[18] There are several cut-off points for risk factors for chemotherapy-induced chemotherapy-induced neutropenia in terms of age in the literature, most of which use the ages

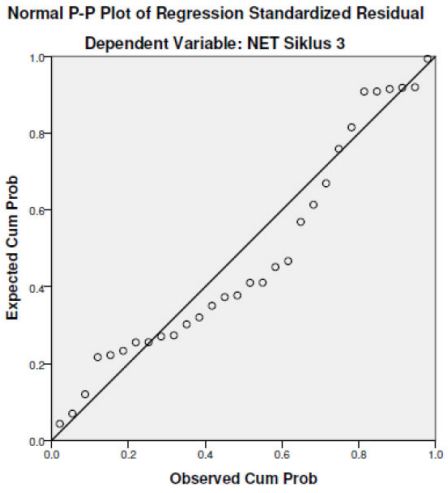

Figure 3. Regression analysis of cycle 3.

of 60 and 65 years.[10] The BSA in our study ranged between 1.3 m^2 and 1.9 m^2 with a mean of 1.625 m^2. Relevance with our study, in the literature, the risk factors for chemotherapy-induced neutropenia were more at BSA <2.0 m^2.[19]

The most cancer stages were stage II and III, each with 46.7%. Data at Dharmais Cancer Hospital showed that the highest stage was stage III as much as 44%.[20] In this study, 50% of the patients had undergone surgery so that there were no more tumors and received adjuvant chemotherapy. At the same time, the intact tumors were found in 15 people (50.0%) who underwent neoadjuvant chemotherapy as many as 13 samples (43.3%) and primary chemotherapy in 2 samples (6.7%). Of the 16 samples, the average size of the primary tumor was 7.73 cm, with the smallest size of 6 cm and the largest size of 10 cm. Advanced tumor stage or bone marrow involvement significantly predicts febrile neutropenia.[10] Most cancer histopathology grade was grade II as much as 56.7%. The breast cancer stage by the patient is also a determinant of the patient's survival rate. It is evident that most patients who come to the hospital are already in a high stage, and the treatment is not working optimally.[21] The lower-stage breast cancer patients had the best 3-year survival rates compared to the end-stage breast cancer patients.[22]

This study examined 30 breast cancer patients who underwent CAF chemotherapy for three cycles to obtain a total of 90 cycles. Of the 30 patients, 24 people (80%) had neutropenia and 6 (20%) without neutropenia. Of the 24 people who experienced neutropenia, eight people continuously experienced neutropenia in all three cycles, and 16 people who experienced neutropenia varied in each cycle. This study shows that one individual with relatively the same prognosis factors for pre-chemotherapy can experience a variety of neutropenic incidence. Someone who has neutropenia in the first cycle will not always have neutropenia in the next cycle. Likewise, someone who does not experience neutropenia in the first cycle may experience neutropenia in the next cycle. Chen has explained that these risk factors broadly do not directly reflect the granulocyte reservoir or stem cell pool in the bone marrow.[11]

Neutropenia that occurred in the first cycle was 18 patients. In the second cycle, there were 14 patients, and in the third cycle, there were 16 patients. The neutropenia data here is the neutropenia data occurring in the second week after chemotherapy. Meanwhile, patients who experienced neutropenia in the first week (less than ten days) and received G-CSF therapy would experience exclusion. Wolff

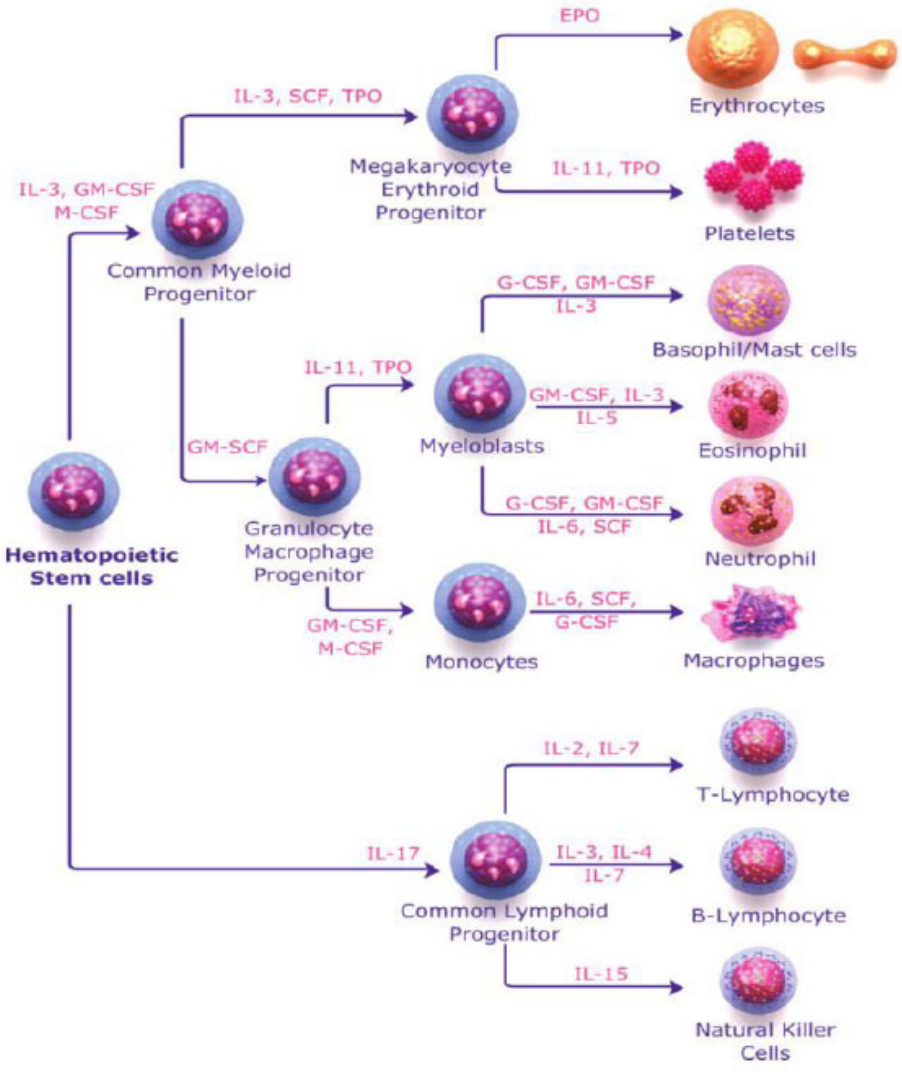

Figure 4. Hematopoietic process.

et al.'s research on 2.222 cancer patients also found that half of the neutropenia cases occurred in the first cycle, especially in breast cancer cases.[23] Monocytopenia was found in the first cycle of 18 patients, the second cycle of 11 patients, and the third cycle of 16 patients. From these results, it also appears that monocytopenia also occurs in the first cycle and neutropenia. The mean neutrophil and monocyte values in the three cycles in this study were average, even though neutropenia and monocytopenia were found in approximately half of the samples. It is because the range of expected values and values below normal are not equivalent. The standard value of monocytes is 100 - 1200/µL (11 times the value below average), while the standard value of neutrophils is 2500 - 7500/µL (twice the value below normal).[12]

The monocyte and neutrophil data were then processed with linear regression with an interval scale. After going through statistical analysis, for post-chemotherapy monocytopenia as a predictor of chemotherapy-induced neutropenia in the first cycle, it was obtained p of 0.001. In the second cycle, it was obtained p of 0.001. In contrast, in the third cycle, it was obtained p of 0.003. There were significant results from the three cycles ($p < 0.01$) between post-chemotherapy monocytopenia and chemotherapy-induced neutropenia. These results answer the problems in other studies of prognosis factors for neutropenia, where a static prognosis factor cannot predict the dynamic occurrence of neutropenia for each cycle.[11] In this study, a dynamic post-chemotherapy monocytopenia variable was used so that it was able to predict the event of dynamic neutropenia.

After statistical calculations with Pearson's correlation, positive results were obtained between monocytopenia and neutropenia, which means that the lower the monocyte value, the lower the neutrophil value. In the first cycle, the Pearson correlation was 0.613, the second cycle was 0.611, and the third cycle was 0.522. This data shows that monocytopenia has the strongest correlation to predict neutropenia in the first cycle compared to the second and third cycles. The Pearson correlation between 0.5 and 0.7 has a moderate interpretation. This correlation value may be increased by using the combined value or the ratio of neutrophils to monocytes to produce better predictions. Lymphocytes have a different formation pathway from neutrophils, namely the lymphocytic pathway, so that changes in lymphocyte value are not related to neutrophil values. Moreau, in his research, also did not include lymphocytes as a factor influencing the incidence of neutropenia.[24] Although basophils and eosinophils originate from the myeloblastic pathway, their range of values is too small, and the lower limit is at point 0, making it impossible to observe them as predictive factors.

From the comprehensive statistical analysis data for the three cycles, there were significant results ($p < 0.01$) between post-chemotherapy monocytopenia that occurred in the first week and chemotherapy-induced neutropenia that occurred in the second week after chemotherapy with the strongest correlation in the first cycle. It is consistent with the study of Ouyang et al., which states that post-chemotherapy neutrophil changes follow the pattern of changes in monocytes that occur earlier (Figure 4).[17] Because monocytes are located in a position upstream than neutrophils, changes in monocytes will occur earlier than neutrophils (Figure 5).[12] Monocytes also have a crucial role in triggering the proliferation, differentiation, survival, and activation of neutrophils and monocytes themselves by producing GM-CSF, G-CSF, macrophages-CSF, and other cytokines through paracrine or autocrine. Ouyang's

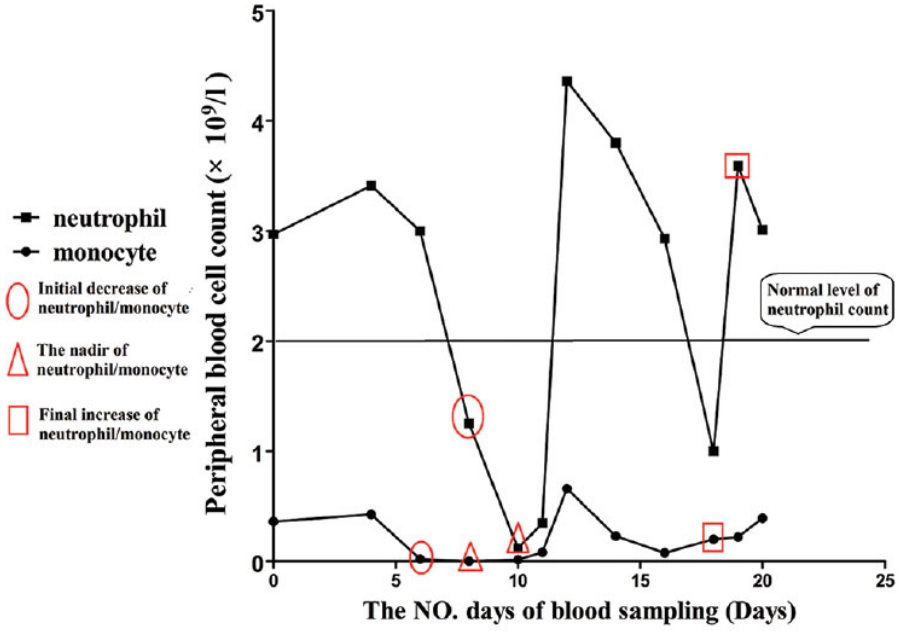

Figure 5. Monocyte and neutrophils after chemotherapy.

study took all samples from patients with neutropenia, while our study took samples from patients without neutropenia and patients with neutropenia. From these results, it can be concluded that post-chemotherapy monocytopenia can be a predictor of chemotherapy-induced neutropenia (CIN).

The limitation of this study is that it has been done only with a breast cancer patient at one center. So it is necessary to do this study with a systematic review and randomized control trial at multiple centers with cancer type and chemotherapy regiment variation so it can be generalized to the broader population.

CONCLUSION

In conclusion, post-chemotherapy monocytopenia can predict chemotherapy-induced neutropenia (CIN) with the strongest positive correlation in the first cycle. Furthermore, monocytes as a more specific and quantitative predictor, are expected to be considered giving G-CSF as prophylaxis for neutropenia, including in the JKN era.

DISCLOSURES

Funding

The source of funds for blood tests in this study came from JKN (Jaminan Kesehatan Nasional) because this blood test was already a routine procedure for the implementation of chemotherapy.

Conflict of Interest

None of the author have any conflicts of interest to disclose.

Ethical Statement

This study has approved by Research Ethical Committee, Faculty of Medicine Universitas Udayana/Sanglah Hospital Denpasar with number 2066/UN14.2.2.VII.14/LP/2019.

Author Contributions

All Authors involved in concepting, designing and supervising the manuscript and Dimas Ryan Desetyaputra conducted the research. All authors analized the data. All authors prepare the manuscript and agree for this final version of manuscript to be submitted to this journal.

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