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Correlation Between Pre-Chemotherapy AMH Level, Menstrual Status, and Prediction of Ovarian Function Recovery after FAC Chemotherapy AMH in Breast Cancer Patients

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Abstract

Around 52.6% of women aged <50 years in Indonesia are diagnosed with breast cancer. One of the chemotherapy regimens with a toxicity effect on reproductive function, especially ovarian follicles, is 5-fluorouracil-doxorubicin-cyclophosphamide (FAC). Anti-Mullerian Hormone (AMH) is a biomarker that can be used to assess the ovarian function. This study aimed to determine the correlation between pre-chemotherapy AMH serum level, menstrual status, and whether the AMH serum level can predict ovarian function recovery in pre-menopausal women receiving FAC chemotherapy. This was an analytical observational study with a prospective cohort design performed in Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, during 2021–2022. Data were analyzed using correlation analysis. Subjects were breast cancer patients aged ≤45 years, still of reproductive age, with no prior history of chemotherapy, and were undergoing the FAC chemotherapy. All 32 patients who met the inclusion criteria were included in this study. There was a significant difference (p 0.0001) between pre- and post-6 cycles of chemotherapy AMH levels. Post-6 cycles of chemotherapy showed lower AMH levels. There was a high correlation (p 0.0034) between pre-chemotherapy AMH level and menstrual status six months after six cycles of chemotherapy. The correlation test between post-chemotherapy AMH level and menstrual status showed a non-significant result. Thus, there is a high statistical correlation between pre-chemotherapy anti-Mullerian hormone levels in pre-menopausal women with breast cancer and the menstrual status after FAC chemotherapy which demonstrates that the AMH level could also be used to predict ovarian function recovery.

Keywords: Anti-Mullerian hormone, breast neoplasms, chemotherapy

Introduction

Breast carcinoma is the world's fifth leading cause of cancer death, with 685,000 deaths.[1] The International Agency for Research on Cancer (IARC) reported that in 2020, 2.26 million (11.7%) cases of total new cases of breast carcinoma.[2] Statistics in Indonesia also showed breast carcinoma as the first with the number of new cases of 65,858 (30.8%) of all carcinomas in women.[3]

Breast carcinoma can occur at any age, in developed countries, with many cases in post-menopausal women; however, in Indonesia, there are many cases in women aged <50.[4.] Global data shows approximately 1.7 million women worldwide are diagnosed with breast carcinoma at <50 years each year. In other countries, 30% of women are diagnosed with breast carcinoma by the age of <50 years.[3.4] In Indonesia, as many as 52.6% of women are diagnosed with breast carcinoma at the age of <50.[5.6] The data shows that cases of breast carcinoma in women of pre-menopausal age in Indonesia are higher than those in Central Africa.

The management of breast carcinoma consists of various modalities, including breast surgery, radiotherapy, and systemic treatment (cytotoxic chemotherapy, endocrine treatment, and targeted agents).[7] Chemotherapy has a gonadotoxic effect and a drastic decrease in ovarian follicles, affecting female reproductive function.[8] One of the chemotherapy regimens that have a toxicity effect on ovarian follicles and is often used as a therapeutic option in breast carcinoma is *5-fluorouracil-doxorubicin-cyclophosphamide* (FAC).[9]

Ovarian function can be described by looking

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at the menstrual cycle and assessed with several *markers*. One of the hormone biomarkers that can be used to assess the function of the ovaries in women is anti mullerian hormone (AMH).[10,11,12] AMH hormone is easier to use clinically because it is not affected by the menstrual cycle.[11]

Previous studies have shown AMH's effectiveness in examining ovarian follicle reserves. This biomarker is trusted and widely chosen for application AMH value of more than 2.1 indicates sufficient ovarian follicle reserves and thus could be used as a predictor of return to menstruation after chemotherapy.[12] Some previous studies showed a decrease in AMH levels in patients with breast carcinoma after performing chemotherapy.[13]

The study focused on pre-menopausal women aged <45 who received FAC chemotherapy because researchers thought women aged <45 were still productive and likely to get pregnant again. This gave rise to the idea for researchers to look at AMH levels of patients with breast carcinoma before and after chemotherapy to examine their ovarian function.

Methods

This study is an analytical observational study with a prospective cohort design. Correlative analysis was performed to gain insight into the association of the variables. Subjects were breast cancer patients in Dr. Hasan Sadikin General Hospital in 2021–2022. Inclusion criteria are patients with stage III breast cancer, aged ≤45 years old, still of reproductive age, no history of chemotherapy, and receiving FAC chemotherapy regardless of any subtype. Subjects are excluded if patients have undergone bilateral oophorectomy procedure, have a history of exposure to bilateral ovarian radiation, have a history of receiving hormonal therapy for breast cancer, and haven't or did not complete six cycles of FAC regardless of reason, including stable and progressive response to FAC chemotherapy.

Data regarding AMH pre and postchemotherapy were collected. Prechemotherapy serum levels were analyzed 1-3 weeks before the first cycle using the ELISA method. The patient would then receive FAC 60mg/m^2 and cyclophosphamide 600mg/m^2 for six cycles with an interval of 21 days. The patient's menstrual cycle was observed during chemotherapy, and six months after the 6th cycle of chemotherapy, AMH serum postchemotherapy was also analyzed this time.

The study obtained informed consent from the patient and received ethical clearance from the Health Research Ethics Committee of Hasan Sadikin Hospital (LB.02.01/X.6.5/358/2021).

Results

Thirty-seven patients were admitted as subjects. Two patients passed away before the completion of the research, two patients refused to undergo chemotherapy, and one was lost to follow-up. The remaining 32 patients were documented as the research subject. Documentation of the patient's characteristics was made. Data on patients' age, marital status, parity, body mass index (BMI), cancer stage, cancer subtype, and postchemotherapy menstrual status were described.

Characteristics of the subjects are summarized in Table 1. The average age of the subjects was 41.5 years, with the youngest subject at 22 years old and the oldest at 45 years old. In this study, most patients were married, namely 29 study subjects or 90.6%. Parity status was distributed relatively evenly, with four people, or 12.5%, not having children, while those with 1–2 children were 17 people, or 43.1%, and those with children more than 2 were 11 people or 34.4%.

In this study, all subjects had stage III breast cancer, mostly stage IIIB, with as many as 28 study subjects or 87.5%. While the study subjects had diverse breast cancer subtypes, the most common subtype found was Luminal B Her2 (-) in 50% of 16 research subjects.

This study found all subjects have experienced amenorrhea while undergoing chemotherapy. Twelve patients stopped menstruating after the first cycle of chemotherapy, 14 stopped menstruating after the second cycle of chemotherapy, five stopped menstruating after the third cycle of chemotherapy, and one stopped menstruating after the fourth cycle. Then observation was carried out for six months after the 6th cycle of chemotherapy; 21 patients continued to have amenorrhea, one patient had menstruation three months after the sixth cycle of chemotherapy, five patients returned to menstruation four months after the sixth cycle of chemotherapy, two patients returned to menstruation five months after the sixth cycle of chemotherapy, three patients returned to menstruation six months after the sixth cycle of chemotherapy.

It was found that the average value of pre-

Table 1 Characteristics of Subjects

Variables	n=32	%
Age (years)		
20–30	2	6.3
31–40	16	50
>40	14	43.8
Marital status		
Married	29	90.6
Not married	3	9.4
Parity		
0	4	12.5
1–2	17	43.1
>2	11	34.4
Cancer stage		
IIIA	4	12.5
IIIB	28	87.5
Subtype		
Luminal A	1	3.1
Luminal B		
Luminal B Her2 (-)	16	50
Luminal B Her2 (+)	9	28.1
Her-2	4	12.5
Triple Negative	2	6.3

chemotherapy AMH was 2.16, with a median value of 1.15. The lowest pre-chemotherapy AMH level was 0.02, and the highest was 6.6. In contrast, the average post-chemotherapy AMH value is 0.46, with a median value of 0.15. The lowest post-chemotherapy AMH level was 0.01, and the highest pre-chemotherapy AMH level was 1.67. A numerical analysis test was carried out on the results obtained so that the results of the p-value of 0.0001 appeared, which stated

Table 2 Comparison of Serum AMH Level Pre and Postchemotherapy

Variables	Group		P value
	Prechemo-therapy	postchemo-therapy	
	n=32	n=32	
Serum AMH (ng/mL)			
Mean±Std	2.16±1.95	0.46±0.52	0.0001**
Median	1.15	0.15	
Range (min-max)	0.02-6.6	0.01-1.67	

** P value tested with Wilcoxon test; very significant results obtained

that there was a significant difference in the value of pre-chemotherapy AMH and the post-chemotherapy AMH value in the subjects of this study. This data is presented in Table 2.

In this study, an analysis of the relationship of pre-chemotherapy AMH to the incidence of menstruation six months after 6-cycle FAC chemotherapy was carried out in paired study subjects. Statistical tests were conducted to determine whether there was a relationship between pre-chemotherapy AMH and the incidence of menstruation again after FAC chemotherapy in breast cancer patients, as displayed in Table 3.

Discussion

The incidence of breast cancer in pre-menopausal women continues to increase in various

Table 3 Correlation between Pre and Postchemotherapy Serum AMH Level with Menstruation Six Months After 6-cycle FAC Chemotherapy

Variables	Menstruation		Total	P value
	Amenorrhea	Menstruation		
AMH prechemotherapy (ng/mL)				
Low (<2,1)	14	3	17	0.0034*
High (>=2,1)	7	8	15	
Total	21	11	32	
AMH postchemotherapy (ng/mL)				
Low (<0,8)	15	5	20	0.149*
High (>=0.8)	6	6	12	
Total	21	11	32	

P value tested with Chi-square test; very significant results obtained

countries. This increasing incidence rate leads to an increase in the incidence of chemotherapy-related amenorrhea, which occurs as a side effect of cancer treatment in the form of chemotherapy. AMH is one of the hormones that can be assessed to see the condition of ovarian function, where the condition of the ovaries is known to affect menstrual status after chemotherapy. AMH is affected by age, sex, BRCA-1 and BRCA-2 mutation, chemotherapy, and history of radiation.

Previous studies have shown a significant decrease in serum AMH before and after chemotherapy. The author found similar results with a significant difference between pre-chemotherapy and post-chemotherapy AMH levels. This is in accordance with previous studies conducted by Dezellus et al., which showed a drastic decrease during chemotherapy, even to the level of not being detected at the end of chemotherapy.[14]

Another study conducted by Malisic et al.[15] showed results that there was a decrease in AMH levels detected from the first month of chemotherapy, which then decreased significantly until the end of chemotherapy; this study also found results where there was a gradual increase in AMH after chemotherapy was completed which was gradual in pre-menopausal women. This is in line with this research, where the author found results of a decrease in AMH after chemotherapy in six months. The author also followed the patient for the next six months, assessed their menstrual status, and found that 11 study subjects returned to menstruation; this showed that ovarian function improved again after the administration of anthracycline chemotherapy. In this study, ovarian function improved after 3 to 6 months.

Chemotherapy in breast cancer is known to have a cytotoxic effect on the ovaries, resulting in cell damage, so it cannot produce FSH, LH, and estradiol to trigger menstruation. The study showed that anthracycline has a lower level of toxicity than taxans when given to pre-menopausal women.[15] This is in accordance with our study, where the subjects were given anthracycline chemotherapy, namely FAC, for six cycles and six months, after which 11 subjects had menstruation. A previous study by Koga et al. reported that in anthracycline chemotherapy, the menstrual status would return to normal in all women under 30 years old, generally within one year.[16]

In this study, the author also tried to find the association between the value of prechemotherapy AMH to the incidence of menstruation after chemotherapy. We compared both groups of prechemotherapy AMH (high and low) with both menstrual status groups (amenorrhea and menstrual). The results showed an association between pre-chemotherapy AMH and menstrual events. This is in accordance with a study conducted by Dezellus et al., which states that patients with low pre-chemotherapy AMH will experience amenorrhea compared to patients who continue their menstruation. This shows that pre-chemotherapy AMH can also function as a predictor of menstrual events after chemotherapy.[14]

Previous literature by Cosgrove et al.[13] concluded that patients with high levels of prechemotherapy AMH have a higher chance of having menstruation again due to the recovery of ovarian function. In contrast, in women with low levels of prechemotherapy AMH, the ovarian function will not return to normal.This suggests that AMH can be a good predictor for assessing ovarian function and re-menstruation in patients after chemotherapy. Rudi et al. reported the same thing when a pre-chemotherapy AMH assessment was carried out on the incidence of amenorrhea in patients after chemotherapy, and the results were obtained that there was a significant association in patients with low AMH of less than 0.11 ng/ml with the incidence of amenorrhea for 18 months after chemotherapy.[17]

A study by Decanter et al. tried to compare the level of prechemotherapy AMH between two groups of slow and rapid restoration of ovarian function. This study showed no significant difference in the value of prechemotherapy AMH levels between the two groups. Contrary to it, the author found that prechemotherapy AMH levels were significantly associated with re-menstruation incidence. This difference may be because the research by Decanter et al. tried to assess the group with slow and rapid restoration of ovarian function. At the same time, there is a high probability of no restoration of ovarian function in low prechemotherapy AMH.[18]

The limitation of this study is that the author determined a follow-up period of 6 months after the patient completed the 6th chemotherapy cycle. This is relatively short compared to other studies that reported a return in ovarian function after 12–24 months. Factors affecting AMH have been controlled in inclusion and exclusion criteria. All chemotherapy was given on time, with no delay. In addition, the author gathered no data on hormonal therapy and the type of hormonal therapy used in postchemotherapy that may

affect the menstrual cycle in postchemotherapy patients.

It concluded that there is an association between prechemotherapy AMH levels in patients with pre-menopausal breast carcinoma and menstrual events after FAC chemotherapy. The author has also reported that prechemotherapy serum AMH levels can predict ovarian function recovery.

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