

EFFECTS OF FAC CHEMOTHERAPY ON ANTI MULLERIAN HORMONE IN PREMENOPAUSAL BREAST CARCINOMA

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Abstrak:

Breast cancer is the most common carcinoma in women in the world. Anti-Mullerian Hormone (AMH) is a hormone secreted by primary, secondary, and small antral ovarian follicles of <4mm. The chemotherapy regimen toxic to ovarian follicles is 5-fluorouracil-doxorubicin-cyclophosphamide (FAC). In Indonesia, there had been no study on the effect of FAC chemotherapy on AMH in premenopausal breast carcinoma patients. This study aims to determine the effect of FAC chemotherapy on AMH in premenopausal breast carcinoma patients. This study employed a prospective cohort *study design*. Inclusion criteria were breast carcinoma, premenopausal, and history of chemotherapy (-). Exclusion criteria were history of ovarian surgery, pelvic radiation, GnRH-agonist therapy, smoking for ≥ 10 years, obesity, and chemotherapy dropout. Subjects were examined for AMH before the 1st chemotherapy and after the 4th chemotherapy. Statistical test was done with Wilcoxon test, significant if $p \leq 0.05$. The average AMH level before FAC chemotherapy was 1.51 ± 1.957 ; the average AMH level after the 4th FAC chemotherapy was 0.24 ± 0.587 . The result of the Wilcoxon test comparing AMH levels before and after 4th FAC chemotherapy was $p < 0.0001$. FAC chemotherapy reduces AMH patients with premenopausal breast carcinoma.

Keywords: Breast carcinoma, chemotherapy, AMH.

Introduction

Breast cancer is a carcinoma with the highest number of cases in women in the world. Based on data from the Global Burden of Cancer Study (GLOBOCAN) released by the International Agency for Research on Cancer (IARC) in 2018, the incidence of breast cancer is 2.1 million people in the world.¹ In Indonesia, breast carcinoma also ranks first of all carcinomas in women. In 2018, there were 58,256 new cases of breast carcinoma, with a mortality rate of 22,692, 11% of all breast cancer patients.²

Based on global data, around 1.7 million women in the world are diagnosed with breast cancer at the age of <50 years old every year, and the characteristics of young breast cancer patients abroad are different from those in Indonesia. Abroad, there are 30% of women diagnosed with breast cancer at the age of < 50 years old.^{3,4} Meanwhile in Indonesia, 52.6% of women were diagnosed with breast cancer at the age of <50 years old.^{5,6} Breast cancer therapy consists of surgery, radiotherapy, and systemic therapy which includes chemotherapy. Chemotherapy has an effect on fertility in premenopausal breast carcinoma patients. Patients with premenopausal status have more concerns about fertility after therapy, and some of them still want to have children.⁷

According to the American Society of Clinical Oncology (ASCO), education about the preservation of reproductive function is part of informed consent in breast cancer patients before the first treatment. Oncologists should discuss the possibility of reproductive dysfunction and infertility in patients undergoing treatment, as well as discuss options for the preservation of reproductive function in these patients.⁸ Many efforts can be made to prevent unwanted effects of chemotherapy on ovarian follicles, including

freezing the ovarian cortex, freezing embryos or oocytes. Another effort that is not invasive is the use of gonadotropin agonists.⁹

Currently, there are several markers of decreased ovarian function, including estradiol, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), inhibin B, and Anti-Mullerian Hormone (AMH).¹⁰⁻¹³ FSH and LH are polypeptide gonadotropin hormones produced and secreted by gonadotropic cells in the anterior pituitary gland. FSH stimulates the growth of large preovulatory follicles that enter the menstrual cycle and the production of estradiol. LH is responsible for dominant ovarian follicle growth and ovulation, estradiol secretion, and corpus luteum formation.¹⁴ Estradiol is a hormone secreted by the granulosa cells of the developing follicles in the ovaries in the follicular phase of the menstrual cycle. Inhibin B is a growth factor produced by the granulosa cells of the developing ovarian follicle. Inhibin B is secreted by the larger ovarian follicles i.e. ovarian follicles measuring 5mm to 10mm. Inhibin B reaches its maximum value in the follicular phase of the menstrual cycle and inhibits FSH secretion.¹⁴

Anti-Mullerian Hormone (AMH) is a *homodimeric glycoprotein* belonging to the *Transforming Growth Factor- β* (TGF- β) *superfamily*. AMH is a hormone that is exclusively secreted by primary ovarian follicles, secondary ovarian follicles, and small antral follicles of <4mm.^{10,11}

There is controversy over the use of markers of decreased ovarian function. FSH and LH only describe ovarian follicular reserves indirectly, because cyclic fluctuations in FSH and LH influenced by the hypothalamic-pituitary-gonadal axis tend to make the determination of ovarian reserves difficult.¹⁵ Estradiol is mostly produced by the ovaries but is also produced by several other tissues

such as adipose tissue which contributes significantly to extragonadal sources of circulating estrogens in the blood. Thus, it does not describe specifically the decline in ovarian function. Inhibin B has limitations as a marker of decreased ovarian function because inhibin B is also influenced by the hypothalamic-pituitary-gonadal axis.¹⁴

In contrast to the above markers, AMH was not affected by the hypothalamic-pituitary-gonadal axis and better described the pattern of decreasing ovarian follicle numbers over time. In various studies of premenopausal breast carcinoma patients, it was proven that there was a significant decrease in AMH levels after chemotherapy. AMH has recently become the most reliable marker of the ovarian follicular reserve.^{12-14,15}

The mechanism of chemotherapy toxicity in ovarian follicles is caused by direct DNA damage to the dividing and developing ovarian follicles, direct damage to the ovarian stroma, direct or indirect damage that alters the development of growing follicles, and disruption of steroidogenesis.³ An example of a chemotherapy regimen that is toxic to ovarian follicles and is often used in breast cancer is 5-fluorouracil-doxorubicin-cyclophosphamide (FAC). Cyclophosphamide has a high-risk gonadotoxic effect, doxorubicin has a medium risk gonadotoxic effect, and 5-fluorouracil has a low-risk gonadotoxic effect.¹⁶

Currently, there has been no study on the effect of FAC chemotherapy on AMH levels in premenopausal breast carcinoma patients in Indonesia. Based on the above background, it is necessary to conduct a study on the effect of FAC chemotherapy on AMH levels in premenopausal breast carcinoma patients in Indonesia.

Research Method

This study is a prospective analytic observational study with a cohort study design employed and a comparative analysis carried out. The study was conducted on surgical oncology patients at RSUP Dr. Hasan Sadikin Bandung. Inclusion criteria were patients with breast carcinoma, perimenopause, and not perimenopause before chemotherapy was given, and had never had chemotherapy before. Exclusion criteria were history of ovarian surgery, history of pelvic radiation, history of GnRH agonist therapy, smoking for ≥ 10 years, obesity (IMT ≥ 30), and chemotherapy dropouts. Subjects who met the inclusion criteria were examined for serum AMH levels before the 1st cycle of chemotherapy and after the 4th cycle of chemotherapy. The statistical test used was the Wilcoxon test, with a significance criterion used was the p -value, $p \leq 0.05$ indicates statistically significant. This study obtained approval and recommendation (Ethic Approval) from the Research Ethics Committee of RSUP Dr. Hasan Sadikin Bandung number LB.02.01/X.6.5/29/2021.

Results

A study on the effect of FAC chemotherapy on serum Anti Mullerian Hormone (AMH) levels in premenopausal breast carcinoma patients had been conducted on 32 patients. All subjects who met the inclusion criteria were recorded with characteristic data, examination of AMH levels before the first cycle of chemotherapy, and AMH levels after the fourth cycle of chemotherapy. The characteristics of the subjects of this study are presented in Table 1.

Table 1. Description of Research Subject Characteristics

Variable	n = 32
Age	
≤ 40 years old	9 (28.1%)
Median	38 y.o.
> 40 years old	23 (71.9%)
Median	45 y.o.
Marriage Status	
Married	32 (100.0%)
Single	0 (0.0%)
Parity	
0	3 (9.4%)
1-2	17 (53.1%)
>2	12 (37.5%)
BMI	
Mean±Std	24.10±2.284
Median	24.40
Range (min-max)	19.80-28.60
Stage	
I	0 (0,0%)
II	3 (9,4%)
III	29 (90,6%)
IV	0 (0,0%)
Subtype	
Luminal A	2 (6,3%)
Luminal B Her2 (-)	6 (18,8%)
Luminal B Her2 (+)	12 (37,5%)
<i>Her-2 type</i>	7 (21,9%)
<i>Triple Negative</i>	5(15,6%)
Menstrual Status Post 4 th Chemotherapy	
<i>Amenorrhea</i>	29 (90.6%)
Menstruating	3 (9.4%)

Note: Categorical data are presented with number/frequency and percentage, while numerical data were presented with mean, median, standard deviation, and range. BMI = Body Mass Index, y.o. = years old, Std = Standard deviation

The average BMI of the subjects was 24.10±2.284. There were no subjects who were in stage I (0.0%) or stage IV (0.0%). Subjects who were in stage II were 3 patients (9.4%), and most of the subjects were in stage III, 29 patients (90.6%). Subjects with luminal A subtype were 2 patients (6.3%), those with luminal B Her2(-) were 6 patients (18.8%), those with luminal B Her2 (+) were 12

patients (37.5%), those with *Her-2 type* were 7 patients (21.9%) and those with *Triple Negative* were 5 patients (15.6%). Most of the research subjects experienced amenorrhea after chemotherapy, 29 patients (90.6 %), while the rest, 3 patients (9.4 %) were still menstruating after 4 cycles of chemotherapy.

Table 2 Comparison rate AMH serum based on age ≤ 40 Year dan > 40 Year

Age	Rate AMH serum (ng/MI)		<i>p</i>
	Before Chemotherapy FAC	After Chemotherapy FAC	
≤ 40 Year (n=9)			
Mean±Std	3,34±2,816	0,75±0,954	0.008*
Median	2,50	0,17	
Range (min-max)	0,17-8,70	0,01-2,19	
>40 Year (n+23)			
Mean±Std	0,79±0,777	0,04±0,078	0.0001**
Median	0,50	0,01	
Range (min-max)	0,03-3,00	0,01-0,33	

Note : Std = The standard deviation, for numerical data, the *p* value was tested by the Wilcoxon test, because the data were not normally distributed. The significance value is based on the *p* value <0.05 . The sign * indicates the value of $p < 0.05$, which means that it is statistically significant or significant. Significance <0.05 ** significance <0.0001

Table 2 presents the description of serum AMH levels by age. In the group of patients aged ≤ 40 years old, serum AMH levels before FAC chemotherapy had an average of 3.34 ± 2.816 , while serum AMH levels after 4 cycles of FAC chemotherapy had an average of 0.75 ± 0.954 . In the group of patients aged > 40 years old, the serum AMH levels before FAC chemotherapy had an average of 0.79 ± 0.777 , while the serum AMH levels after 4 cycles of FAC chemotherapy had an average of 0.04 ± 0.078 .

Wilcoxon test was conducted to analyze the numerical data since the data were not normally distributed, serum AMH levels. The results of the statistical test in the age group ≤ 40 years old above obtained information on the *p*-value of the serum AMH levels variable less than 0.05 (*p*-value <0.008) indicating statistically significant. Thus, it can be explained that there is a statistically

significant difference in mean statistics between variables of serum AMH levels before and after 4 cycles of FAC chemotherapy at age of ≤ 40 years old. The results of statistical tests in the age group of > 40 years old obtained information on the *p*-value of the serum AMH level variable less than 0.05 (*p*-value <0.0001), indicating statistically significant. Therefore, it can be explained that there is a statistically significant difference in mean statistics between variables of serum AMH levels before and after 4 cycles of FAC chemotherapy at > 40 years old.

Table 3 describes the comparison between serum AMH levels before and after 4 cycles of FAC chemotherapy. Serum AMH levels before FAC chemotherapy had an average of 1.51 ± 1.957 while serum AMH levels after 4 cycles of FAC Chemotherapy had an average of 0.24 ± 0.587 .

Table 3 Comparison rate AMH serum before and after chemotherapy FAC 4 cycle

Variable	Group		Value <i>p</i>
	Before Chemotherapy FAC n=32	After Chemotherapy FAC n=32	
Rate AMH serum (ng/mL)			
Mean±Std	1,51±1,957	0,24±0,587	0.0001**
Median	0,80	0,01	
Range (min-max)	0,003-8,70	0,01-2,19	

Note : Wilcoxon tested the p-value for numerical data because the data were not normally distributed. The significance value is based on the p value <0.05. The * sign indicates the value of p<0.05, which means that it is statistically significant or significant. *Significance <0.05, **significance <0.0001

Table 4 Overview of serum AMH levels based on menstrual status after chemotherapy

Menstrual status after chemotherapy	Rate AMH serum (ng/MI)	
	Before Chemotherapy FAC	After Chemotherapy FAC
Amenorrhea (n=29)		
Mean±Std	0,98±0,940	0,06±0,093
Median	0,69	0,01
Range (min-max)	0,03-3,65	0,01-0,33
Still menstruating (n=3)		
Mean±Std	6,63±1,888	2,01±0,163
Median	6,20	1,98
Range (min-max)	5,00-8,70	1,87-2,19

Note : Std = Standar Deviation

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Wilcoxon test was conducted to analyze numerical data since the data were not normally distributed, serum AMH levels. The results of statistical tests in the study group above obtained information on the *p*-value of the serum AMH level variable less than 0.05 (*p* value < 0.0001), indicating statistically significant. Hence, it can be explained that there is a statistically significant mean difference between serum AMH levels before and after 4 cycles of FAC chemotherapy.

Table 4 describes serum AMH levels based on menstrual status after chemotherapy. In the group of patients who did not menstruate (amenorrhea) after chemotherapy, the serum AMH levels before FAC chemotherapy had an average of 0.98±0.940, while the serum AMH levels after

cycles of FAC chemotherapy had an average of 0.06±0.093.

The serum AMH levels before FAC chemotherapy of post-chemotherapy menstruating patients had an average of 6.63±1.888, while the serum AMH levels after 4 cycles of FAC chemotherapy had an average of 2.01±0.163.

Discussion

Table 1 presents a description of the characteristics of this study. Most of the patients were in stage III, 29 patients (90.6%). This supports data in Indonesia that most breast cancer patients, 70-80% of cases, are found at an advanced stage.¹⁷

Table 1 also presents the comparison of serum AMH levels by age ≤ 40 years old and > 40 years old, showing that both groups had a significant decrease in AMH levels after undergoing 4 cycles of FAC chemotherapy. In the age group > 40 years old, the decrease in AMH levels after 4 cycles of FAC chemotherapy showed $p < 0.0001$. This shows a more significant decrease compared to the age group ≤ 40 years with a p -value < 0.008 . This supports a study conducted by Silvia et al. which showed that breast cancer patients aged > 40 years old would have a worse recovery of ovarian function after chemotherapy than ≤ 40 years old breast cancer patients.¹⁸

Serum AMH levels of research subjects before being given chemotherapy differed between age ranges. The highest was 8.70 to the lowest was 0.03. This can be explained that according to a study by Du et al, normal AMH levels have different values according to age, even women of the same age might have different AMH values. Based on the AMH nomogram of healthy women, all subjects in this study had AMH before chemotherapy within normal limits.¹⁹

Table 3 shows the average serum AMH level before FAC chemotherapy of 1.51 ± 1.957 , while the average serum AMH level after 4 cycles of FAC chemotherapy of 0.24 ± 0.587 . By using the Wilcoxon statistical test, there was a significant mean difference between serum AMH levels before and after 4 cycles of FAC chemotherapy, with $p < 0.0001$ (p -value less than 0.05). This proves that FAC chemotherapy reduces serum AMH levels in patients with premenopausal breast carcinoma. This supports a study by Anderson et al which proved that there was a significant decrease in serum AMH levels in patients with premenopausal breast carcinoma after chemotherapy was given.²⁰ The same result was also obtained in the study of Henry et al, namely a significant decrease in serum AMH levels after chemotherapy in premenopausal breast carcinoma patients.¹³

The percentage decrease in the mean serum AMH level after chemotherapy in this study was 84.1%. It is similar to the study conducted by Anderson et al where there was a decrease in the mean serum AMH level after chemotherapy by 88%.²⁰ A study by Henry et al also showed similar results, namely the percentage decrease in the mean serum AMH level after chemotherapy was 88.1%.¹³

This study is the first study in Indonesia to evaluate the decrease in serum AMH levels due to FAC chemotherapy in premenopausal breast carcinoma patients. A similar study in Asia that has been done is the study by Kim et al in South Korea. Their study proved that there was a significant decrease in serum AMH levels after chemotherapy in premenopausal breast carcinoma patients.¹⁴ A study on African-American women suffering from breast carcinoma was conducted by Su et al. The results showed a significant decrease in serum AMH levels after chemotherapy.⁴⁴

AMH is mainly secreted by primary ovarian follicles, secondary ovarian follicles, and small antral follicles of < 4 mm. AMH secretion is gradually decreased by follicles measuring between 4-8 mm. Larger granulosa cells, such as pre-ovulatory follicles up to 10 mm in size, do not secrete AMH.^{10,11} The decrease in serum AMH levels between before chemotherapy and after chemotherapy indicates toxicity to ovarian follicles during chemotherapy.²⁰ The mechanism of chemotherapy toxicity in ovarian follicles is caused by direct DNA damage to the dividing and developing ovarian follicles, direct damage to the ovarian stroma, direct or indirect damage that alters the development of growing follicles, and disruption of steroidogenesis.³

Concerning menstrual status after chemotherapy, most patients were in a state of post-chemo amenorrhea, 19 patients (90.6%). This is similar to the study by Ruddy

et al which showed that the majority of patients (82%) with premenopausal breast carcinoma who received chemotherapy would experience post-chemotherapy amenorrhea, where the study subject of Ruddy et al received 4 cycles of doxorubicin-cyclophosphamide followed by 4 cycles of paclitaxel.²¹

Table 4 describes serum AMH levels based on menstrual status after chemotherapy. The post-chemotherapy amenorrhea group had an average serum AMH level before chemotherapy of 0.98 ± 0.94 , and an average serum AMH level after chemotherapy of 0.06 ± 0.093 . This is different from the post-chemotherapy menstruating group, which had an average serum AMH level before chemotherapy of 6.63 ± 1.888 , and an average serum AMH level after chemotherapy of 2.01 ± 0.163 .

It can be explained that the post-chemotherapy amenorrhea condition may be associated with the average serum AMH level before chemotherapy in the lower range compared to the post-chemotherapy menstruating group. Based on the research of Anderson et al, the lower the serum AMH level before chemotherapy, the greater the risk of post-chemotherapy amenorrhea.²² This is also consistent with the study of Rudy et al which showed that the lower the serum AMH level before chemotherapy, the greater the risk of post-chemotherapy amenorrhea.²¹

Since the number of primordial follicles decreases with age, the follicles that secrete AMH also decrease. This is what explains in normal women's menopause conditions, serum AMH levels are at very low or even undetectable levels.²³ Menopause-like conditions such as amenorrhea in patients who have undergone chemotherapy are caused by low AMH levels after chemotherapy. This proves that chemotherapy has a toxic effect on ovarian follicles that manifests clinically in the form of post-chemotherapy amenorrhea.^{4,20}

In this study, no follow-up was conducted on whether patients who experienced post-chemotherapy amenorrhea would progress to permanent amenorrhea or otherwise experience recovery of ovarian function as indicated by the return of menstruation (temporary amenorrhea). This is a drawback of this study due to the limited time of the study. Based on the study by Anderson et al and Kim et al, evaluation of the return of menstruation as a sign of long-term recovery of ovarian function requires follow-up of 6 months to 5 years after chemotherapy.^{14,20,22,24}

Conclusions

FAC chemotherapy reduces levels of Anti-Mullerian Hormone in patients with premenopausal breast carcinoma in Indonesia.

Further research is suggested to include research with long-term follow-up on patients who experience amenorrhea after chemotherapy whether to experience permanent amenorrhea or temporary amenorrhea. Therefore, a cut-off point for AMH levels before chemotherapy can predict the recovery of ovarian function. Furthermore, studies can be carried out with subjects in the group of breast cancer patients who were given GnRH agonists (such as *goserelin*) before chemotherapy compared with groups not given GnRH agonists before chemotherapy, examining serum AMH levels 6 months after chemotherapy, and examining AMH levels when the patient is menstruating again.

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