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Age as an Independent Factor in the Permanent Chemotherapy-Induced Amenorrhea Incidence in Breast Cancer Patients at Dr. Moewardi Hospital, Surakarta, Indonesia

Mudib Mudib[1], Kristanto Yuli Yarso[2]*, Henky Agung Nugroho[2]

[1]Department of Surgery, Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia; [2]Department of Surgery, Division of Oncology, Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia

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***Correspondence:** Kristanto Yuli Yarso, Department of Surgery, Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia. E-mail: yarsaonko@gmail.com
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Abstract

BACKGROUND: Chemotherapy-induced amenorrhea (CIA) is one common side effect of chemotherapy in breast cancer patients. Some who have CIA may experience menstruation return while others experience permanent CIA.

AIM: This study aims to examine the factors that contribute to the incidence of persistent CIA in breast cancer patients.

METHODS: The population of this retrospective study was new breast cancer patients with premenopausal status when they started receiving chemotherapy at Dr. Moewardi Hospital, Surakarta, Indonesia, from January 2019 to July 2021. To determine the relationship, the Chi-square/Fisher's exact test was performed. Risk factor analysis on the incidence of permanent CIA was carried out using a bivariate logistic regression test followed by multivariate analysis.

RESULTS: A number of 105 premenopausal breast cancer patients who received chemotherapy were found. Of these patients, 97 (93.38%) patients experienced CIA and 8 patients (6.62%) continued to menstruate. Of all the subjects having CIA, 49 patients (46.67%) menstruated again while the other 48 (45.71%) had persistent CIA. Age factor has a significant relationship with the incidence of permanent CIA (p □ 0.001), where patients aged >45 years tend to have permanent CIA incidence with a proportion of 42 patients (87.5%) (p < 0.05). The multivariate analysis showed that age >45 years (OR = 75.117; 95% CI = 12.671–445.311; p = < 0.001) was the most dominant risk factor associated with the incidence of permanent CIA, while other variables as risk factors for permanent CIA based on multivariate analysis were Stage III (R = 6.677; 95% CI = 1.370–32,545; p = 0.019) compared to Stages I and II, and body mass index (BMI) in the normal category (OR = 5.485; 95% CI = 1.083–27.786; p = 0.040) compared to excess BMI. The other variables were not found to be associated with the incidence of permanent CIA.

CONCLUSION: Age is a major factor associated with permanent CIA incidence. Other factors related to this study are staging and BMI.

Introduction

Breast cancer is the most common cancer in women worldwide [1]. It has a high incidence rate in all countries, developing and least developed countries [2]. In developing countries, breast cancer cases account for more than half of new cancer cases and a quarter of all cancers [3]. One of the main concerns today is the trend of breast cancer in young women. GLOBOCAN 2018 reported that the number of breast cancer women younger than 45 years is 13.4/100,000 people/year. In Indonesia, women with breast cancer are diagnosed at a younger age, having premenopause, and at an advanced stage [4], [5].

The increasing incidence of breast cancer and better management has led to an increase in the prevalence of breast cancer patients [6]. In addition to surgery as the main therapy for breast cancer, other therapeutic modalities include chemotherapy, radiotherapy, hormonal therapy, and targeted therapy according to the characteristics of the patient and cancer [7], [8]. Chemotherapy has increased the survival of breast cancer [9], but the effects of chemotherapy on the reproductive system, especially chemotherapy-induced amenorrhea (CIA), can cause menopause, infertility, and psychological distress [10], [11]. CIA incidence can be permanent or reversible [11], [12]. Several factors have been reported to be associated with the incidence of permanent amenorrhea [13], [14], [15]. At present, there is no CIA research on breast cancer patients in Indonesia. This study aims to find out the factors related to menstruation return in the CIA of breast cancer chemotherapy at Dr. Moewardi General Hospital, Surakarta.

Materials and Methods

The population of this study was new breast cancer patients with premenopausal status when

they started receiving chemotherapy at Dr. Moewardi Hospital, Surakarta, Indonesia, from January 2019 to July 2021. This retrospective study was conducted with the approval of the Ethics Committee of Dr. Moewardi General Hospital, Surakarta. The criteria for the subjects of this study were Stage I–IV breast cancer patients, having premenopause, no history of chemotherapy, no history of oophorectomy/hysterectomy therapy, no history of radiation therapy to the pelvis, and not receiving gonadotropin-releasing hormone analogs.

All patients who met the criteria and gave informed consent to participate were included in this study. Demographic data, breast cancer characteristics, and details of anti-cancer treatment were reviewed and recorded from medical records. Menstrual status was obtained from the patient's anamnesis; the patient was declared premenopausal if, during the diagnosis, they still had regular menstruation in the past 3 months and did not receive hormone replacement therapy. The patient was declared to have CIA if they experienced a period of amenorrhea for more than or equal to 3 months after receiving chemotherapy; CIA was declared persistent if, in the 12-month follow-up period after the completion of chemotherapy, there was no return of menstruation [16].

The research variables include age, education, marital status, occupation, stage, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her-2), body mass index (BMI) as classified by the Ministry of Health of Indonesia, parity, and menarche. Research variables in the form of categorical data are presented in the distribution of frequency and percentage values. To determine the relationship, the Chi-square/Fisher's exact test was performed. Risk factor analysis on the incidence of permanent CIA in this study was carried out using a bivariate logistic regression test then followed by multivariate analysis on variables that had p < 0.2 in bivariate analysis. All data were processed and analyzed using SPSS 22.

Results

In this study, 105 premenopausal breast cancer patients who received chemotherapy were found. Of these patients, 97 (93.38%) patients experienced chemotherapy-induced amenorrhea and 8 patients (6.62%) continued to menstruate. Of all the subjects having CIA, 49 patients (46.67%) menstruated again while the other 48 (45.71%) had persistent CIA.

A total of 44 breast cancer patients (45.5%) who had CIA were ≤45 years old, and 53 patients (54.6%) were >45 years old; most of the education was elementary school by 34 patients (35.1%); most of the patients (92 patients or 94.8%) were married; based on the occupation, most of the patients worked, that is, 59 patients (60.8%) with mostly Stage-III cancer, namely, 56 patients (57.7%). Based on the CPI, 28 patients (28.9%) had positive ER, 38 patients (39.2%) had positive PR, and 12 patients (12.4%) had positive Her-2. The BMI of most patients (57 patients or 58.8%) was in the normal category. For parity, most of them (92 patients or 94.8%) had given birth. The age at menarche was mostly >12 years (93 patients or 95.9%). For more details, refer to Table 1.

Table 1 shows that age has a significant relationship with the incidence of permanent CIA (p =< 0.001), where patients aged >45 years tend to have permanent CIA incidence with a proportion of 42 patients (87.5%) (p < 0.05). Meanwhile, education level (p = 0.240), marital status (p = 362), occupation (p = 0.184), staging (p = 0.294), ER (p = 0.063), PR (p = 0.184), Her 2 (p = 0.203), BMI (p = 0.276), parity (p = 0.362), and menarche (p = 0.362) did not show a significant relationship with the incidence of amenorrhea (p > 0.05).

Risk factor analysis on the incidence of permanent CIA in this study was carried out using a bivariate logistic regression test followed by multivariate analysis on variables that had p < 0.2 in bivariate analysis. The OR value is used to determine the level of risk for permanent CIA incidence and significant if p < 0.05. The analysis of risk factors for the incidence of permanent CIA is shown in Table 2 as follows.

The multivariate analysis showed that age >45 years (OR = 75.117; 95% CI = 12.671–445.311;

Table 1: Description of research data by type of amenorrhea

Variable	Chemotherapy-induced amenorrhea (%)		Total	p-value
	Reversible (n = 49)	Permanent (n =48)	(n=97) (%)	
Age				
≤45 years	38 (77.6)	6 (12.5)	44 (45.4)	<0.001
>45 years	11 (22.4)	42 (87.5)	53 (54.6)	
Education				
Elementary school	14 (28.6)	20 (41.7)	34 (35.1)	0.240
Junior high school	12 (24.5)	10 (20.8)	22 (22.7)	
Senior high school	18 (36.7)	10 (20.8)	28 (28.9)	
University	5 (10.2)	8 (16.7)	13 (13.4)	
Married				
Yes	45 (91.8)	47 (97.9)	92 (94.8)	0.362
No	4 (8.2)	1 (2.1)	5 (5.2)	
Occupation				
Not working	16 (32.7)	22 (45.8	38 (39.2)	0.184
Working	33 (67.3)	26 (54.2)	59 (60.8)	
Staging				
Stages I and II	17 (34.7)	10 (20.8)	27 (27.8)	0.294
Stage III	25 (51.0)	31 (64.6)	56 (57.7)	
Stage IV	7 (14.3)	7 (14.6)	14 (14.4)	
ER				
Negative	39 (79.6)	30 (62.5)	69 (71.1)	0.063
Positive	10 (20.4)	18 (37.5)	28 (28.9)	
PR				
Negative	33 (67.3)	26 (54.2)	59 (60.8)	0.184
Positive	16 (32.7)	22 (45.8)	38 (39.2)	
Her-2				
Negative	45 (91.8)	40 (83.3)	85 (87.6)	0.203
Positive	4 (8.2)	8 (16.7)	12 (12.4)	
BMI				
Underweight (≤18.4)	4 (8.2)	2 (4.2)	6 (6.2)	0.276
Normal (18.5–25)	25 (51.0)	32 (66.7)	57 (58.8)	
Overweight (>25)	20 (40.8)	14 (29.2)	34 (35.1)	
Parity				
Nullipara	4 (8.2)	1 (2.1)	5 (5.2)	0.362
Multiparity	45 (91.8)	47 (97.9)	92 (94.8)	
Menarche				
≤12 years	1 (2.0)	3 (6.3)	4 (4.1)	0.362
>12 years	48 (98.0)	45 (93.8)	93 (95.9)	

Chi-square test/Fisher's exact test; *significant if a = 5%. ER: Estrogen receptor, PR: Progesterone receptor, Her-2: Human epidermal growth factor receptor 2, BMI: Body mass index.

p = < 0.001) was the most dominant risk factor associated with the incidence of permanent CIA, while other variables as risk factors for permanent CIA based on multivariate analysis were Stage III (R = 6.677; 95% CI = 1.370–32,545; p = 0.019) compared to Stages I and II, and BMI in the normal category (OR = 5.485; 95% CI = 1.083–27.786; p = 0.040) compared to excess BMI. Demographic factors such as education, occupation, and marital status did not show a relationship with permanent CIA. Likewise, ER, PR, Her-2, parity, and menarche were not found to be associated with the incidence of permanent CIA.

Discussion

In this study, the CIA incidence of breast cancer patients was found in 97 patients (92.38%); 8 patients (7.62%) continued to menstruate regularly or did not experience CIA. Of all the subjects having CIA, 49 CIA patients (46.67%) experienced reversible CIA while the other 48 (45.71%) had persistent CIA. The incidence of amenorrhea in premenopausal patients receiving breast cancer chemotherapy is common. Various reports show the CIA incidence varies from 10% to 93% [12], [17]; the incidence of CIA in our study is similar to the report of Koga *et al*.; the incidence of CIA in Japanese women is 96% [18]. The study by Jeon *et al*. reported the incidence of CIA in Korean women as 88% [10] while the Suprasert *et al*. study reported the incidence of CIA in Thai women by 92.2% [14]. The high CIA incident range is due to differences in CIA definitions, length of follow-up, and patient characteristics in each study [17]. In many studies, the factor most associated with the incidence of CIA is age [10], [11], [17], [18]. However, the study by Pourali *et al*. reported no relationship between age and the incidence of CIA [19].

Table 2: Bivariate and multivariate analysis of risk factors on permanent CIA incidence

Variable	Bivariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Age				
≤45 years	Ref.	Ref.	Ref.	Ref.
>45 years	24.182 (8.153–71.723)	<0.001	73.144 (12.628–423.680)	<0.001*
Education				
Elementary school	0.893 (0.241–3.308)	0.865		
Junior high school	0.521 (0.129–2.107)	0.360		
Senior high school	0.347 (0.089–1.351)	0.127	0.230 (0.026–2.005)	0.183
University	Ref.	Ref.	Ref.	Ref.
Married				
Yes	Ref.	Ref.		
No	0.239 (0.026–2.224)	0.362		
Occupation				
Not working	Ref.	Ref.	Ref.	Ref.
Working	0.573 (0.251–1.306)	0.184	0.334 (0.087–1.284)	0.110
Staging				
Stages I and II	Ref.	Ref.	Ref.	Ref.
Stage III	2.108 (0.822–5.408)	0.121	6.576 (1.371–31.538)	0.019*
Stage IV	1.700 (0.460–6.280)	0.426		
ER				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	2.340 (0.944–5.801)	0.063	5.947 (0.775–45.651)	0.086
PR				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	1.745 (0.766–3.978)	0.184	2.886 (0.457–18.239)	0.260
Her-2				
Negative	Ref.	Ref.		
Positive	2.250 (0.630–8.040)	0.203		
BMI				
Underweight (≤18.4)	0.714 (0.115–4.451)	0.719		
Normal (18.5–25)	1.829 (0.774–4.323)	0.169	5.093 (1.072–24.197)	0.041*
Overweight (> 25)	Ref.	Ref.	Ref.	Ref.
Parity				
Nullipara	Ref.	Ref.		
Multiparity	4.178 (0.450–38.818)	0.362		
Menarche				
≤12 years	Ref.	Ref.		
>12 years	0.313 (0.031–3.115)	0.362		

ER: Estrogen receptor, PR: Progesterone receptor, Her-2: Human epidermal growth factor receptor 2, BMI: Body mass index.

Based on age group, the incidence of CIA at the age group of 45 years occurred in 44 patients (45.4%) and the age group of >45 years occurred in 53 patients (64.6%), where the incidence of menstruation return in the age group of 45 years was in 38 patients (77.6%), and only 11 patients (22.4%) got menstruation return in the age group of >45 years. In multivariate analysis, age over 45 years was associated with permanent CIA. Pérez-Fidalgo *et al*. reported that the incidence of CIA in the age group of >45 years reached 95%; the proportion of CIA decreased to 52% in the age group of <40 years [20]. The age limit of 45 years is also a significant factor in predicting the irreversible incidence of CIA [14]. Meng *et al*. reported that the age group of under 45 years rarely experiences post-CIA menopause and has a high probability of menstruation return; thus, age is a predictor factor for the incidence of reversible CIA and the occurrence of menopause. Likewise, Suprasert *et al*. and Koga *et al*. reported that older age increases the risk of permanent CIA [14], [18]. The decrease in the number and quality of oocytes in the ovarian cortex follicles is a physiological aging process of the reproductive system [21]. Additional chemotherapy has a toxic effect that makes the elderly more susceptible to permanent CIA.

In the multivariate analysis, the relationship between BMI and permanent CIA was found. Some studies have reported that BMI is associated with the CIA while others found no relationship. Likewise, Zaccarelli *et al*. reported that BMI was not associated with CIA in breast cancer patients receiving anthracycline and cyclophosphamide chemotherapy [22]. Abusief *et al*. reported in their study that BMI was not associated with permanent CIA [15], [19]. The study by Lee *et al*. demonstrated that higher BMI showed more recovery of ovarian function [23]. Another study by Jeon *et al*. reported that CIA was associated with age, instead of BMI and tamoxifen therapy [10]. In this study, higher

BMI was more protective against CIA permanent incidence. This may be related to the cutoff value of BMI for Indonesians based on the classification of the Ministry of Health of Indonesia. In addition, there are differences in the relationship between BMI, percentage, and distribution of fat in the population due to different CIA effects. Changes in the pharmacokinetics of chemotherapy drugs in patients with higher BMI may lead to reduced gonadal toxic effects. Another possibility is the tendency of giving lower chemotherapy doses in patients with high BMI due to concerns about the side effects of chemotherapy.

There was also an association between permanent CIA incidence and disease stage. Pourali *et al*. found no association of amenorrhea with stage, hormone receptor status, and BMI [19]. The previous study by Di Cosimo *et al*. also found no significant association between CIA and tumor size, involvement of axillary nodes, stage of disease, and receptor status [24]. The relationship between persistent CIA at an advanced stage may be related to the number of regimens and the duration of chemotherapy given.

In this study, the chemotherapy regimen and tamoxifen therapy with the incidence of permanent CIA were not analyzed. Pérez-Fidalgo JA *et al*. reported no significant association between CIA chemotherapy regimens [20]. The study by Suprasert *et al*. stated that tamoxifen therapy was not associated with persistent CIA [14]. A meta-analysis study also stated that there was no significant relationship between tamoxifen and the incidence of persistent CIA [17]. This is in contrast to Meng *et al*. reporting an association between CIA and tamoxifen therapy [4]. The mechanism of cytotoxic agents causing CIA was described by Luo *et al*. through experiments in experimental animals (C57BL/6 mice) which found the role of inflammation regulation, SDF-1/CXCR4, and cellular apoptosis in the ovarian tissue that played a role in premature ovarian failure [25]. However, Yarso *et al*. found that chemotherapy abolished the effects of SDF1a/CXCR4 in breast cancer patients [26]. This indicates that other factors play a role in the mechanism of ovarian damage due to chemotherapy through complex interactions.

With the limit of CIA for 12 months, we assessed as permanent CIA, CIA reversible was found in 46.67% of patients from 93.38% who experienced CIA. Sukumvanich *et al*. reported that 41% of BC survivors had amenorrhea during therapy, but menstruation returned within 3 years of chemotherapy in 48% of patients [13]. On the other hand, Jeon *et al*. in their study revealed that within 5 years, the rate of menstruation return was found in 48.6% of patients [10]. This finding suggests that prolonged periods of amenorrhea may decrease the patient's chances of getting menses again.

Conclusion

This study showed that the incidence of CIA in premenopausal breast cancer patients reached 93.38%; 45.71% of patients had persistent CIA, and age was the main factor associated with this incident. Other factors related to this study are staging and BMI.

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