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The prevalence of menopausal level of follicle-stimulating hormone (FSH) in peri-menopausal breast cancer patients aged between 45 and 60 years

Chanyoot Bandidwattanawong[1], M.D., Pittawat Thamsoponsakul[2], M.D.

[1]Department of Internal Medicine, Faculty of Medicine, [2]Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

ABSTRACT

Objectives: Breast cancer is the global most common cancer among women. One of the major breakthrough in systemic therapy for breast cancer is the development of an aromatase inhibitor (AI). An AI is indicated as an adjuvant treatment and a palliative therapy, specifically for hormonal-receptor positive (HR+) breast cancer women with complete loss of ovarian function. Since there are many definitions of post-menopause, an AI is commonly falsely prescribed based on either a patient's age or menstrual history alone and it may lead to unexpectedly poorer outcomes. The follicle-stimulating hormone (FSH) level of more than 40 IU/L is one of the acceptable definition of menopause. The investigators intended to determine the prevalence of menopausal level of FSH among women aged 45-60 years with breast cancer and its predictive factors.

Material and Methods: This was a cross-sectional study conducted among peri-menopausal HR+ breast cancer patients aged 45-60 years who were treated either in an adjuvant or metastatic setting in Vajira Hospital. Any patients still having regular periods, already receiving an AI, fulvestrant, or a gonadotropin hormone releasing hormone (GnRH) analogue, or not castrated either by oophorectomy or radiation were excluded.

Results: There were 90 patients in this study. FSH levels in 46 of them (51%) were menopausal. Only subgroups using tamoxifen and a history of rare or no menstruation for more than 2 years had a statistically significant trend toward having menopausal FSH levels.

Conclusion: Physicians should not rely on a patient's age or menstrual history to determine post-menopausal status. These results emphasize strict validation of menopausal status prior to prescribing an AI or fulvestrant to peri-menopausal breast cancer patients.

Keywords: Breast cancer, FSH level, Post-menopausal status

INTRODUCTION

Breast cancer is globally the most common cancer diagnosed in women.[1,2] The breakthroughs in systemic treatment lead to longer survival among patients with both locally advanced and metastatic hormonal-receptor positive (HR+) diseases. An aromatase inhibitor (AI), unlike tamoxifen, does not directly bind to the estrogen receptor, but it indirectly blocks the conversion of adrenal androgens to estrone (E_3) in peripheral (extra-ovarian) tissues, including the adipose tissue, liver, muscle, brain, and breast itself. Theoretically, estrogen deprivation produced by AI induces the secretion of gonadotrophins, which in turn stimulate functioning ovaries to produce even more estradiol (E_2). Therefore, an AI is active only in women with definite loss of ovarian function, either medically by concomitantly using a GnRH analog or surgically by oophorectomy.[3] Since 2001, the results from several pivotal trials have provided evidence that adjuvant AI therapy, either upfront or sequential (after tamoxifen), improves disease-free survival (DFS) in post-menopausal HR+ patients.[4-9] Nevertheless, the post-hoc analyses reveal that younger post-menopausal women derive less DFS benefit from AIs than older post-menopausal ones.[6,8,9] Presumably, its difference in DFS benefit may be partly explained by the fact that it was a result of no clear definition of post-menopausal status especially in younger post-menopausal women. A strict definition of menopause should be addressed

***Corresponding author:** Prof. Chanyoot Bandidwattanawong M.D., Department of Internal Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Dusit District, Bangkok, Thailand. chanyootmd@gmail.com

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to peri-menopausal women and those women who are pre-menopausal at cancer diagnosis and then appear to become menopausal after receiving chemotherapy. Although chemotherapy may induce amenorrhea by suppressing ovarian function, it cannot be extrapolated that the absence of ovarian function has occurred. Some women with chemotherapy-induced amenorrhea were still found to have pre-menopausal levels of estradiol.[10] Therefore, to maximize the benefits of an AI, a determination of the post-menopausal state is crucial. Peri-menopause is the period of the natural transition to menopause when ovarian function is gradually terminated. During this period, menstrual irregularities, such as more or less frequent periods, heavier or lighter periods, or even skipped periods, commonly occur. It usually takes around two years prior to permanent menopause. Breast cancer patients who have ever received cytotoxic chemotherapy or are taking hormonal therapy are subject to the misdiagnosis of menopause due to skipped periods. Hence, the American Association of Clinical Endocrinologists recommends that a detailed history, physical examination, and measurement of FSH are compulsory for the diagnosis of menopause. The FSH levels of more than 40 IU/L are required to determine the menopausal state.[11] This study intended to explore the prevalence of menopausal levels of FSH among peri-menopausal HR+ breast cancer patients.

MATERIAL & METHODS

This was a cross-sectional study conducted among peri-menopausal breast cancer patients aged 45-60 years who sought medical attendance either in an adjuvant or metastatic setting at Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. Baseline characteristics, including age and cancer stage at the time of breast cancer diagnosis and the movement of blood collection for FSH level and history of systemic treatment, including chemotherapy (any chemotherapy regimens ever received and numbers of cycles) and tamoxifen use (no longer used, currently using or never used) either in adjuvant or metastatic setting were recorded. Patients who were still having regular periods were excluded. Any patients who were receiving one of the AIs (anastrozole, letrozole, exemestane) or fulvestrants were excluded. Those receiving ovarian function suppression with an luteinizing hormone releasing hormone (LHRH) agonist or undergoing either surgical oophorectomy or radiation were also excluded. Medical histories were retrieved from written and electronic medical records.

The age of the participants was reported in years at the time of blood collection and subdivided into periods of 45-50, 50-55, and 55-60 years old. Menstrual statuses were divided into 1) *rare or absence of menstruation during the past two years,* if rare or absence of menstruation had been recognized during the past two years prior to the blood collection. 2) *rare or absence of menstruation for more than two years*, if rare or absence of menstruation had been recognized for more than two years prior to blood collection. The menopausal level of FSH was defined as more than 40 IU/L.[11]

Statistical analysis The primary outcome was to determine the prevalence of menopausal levels of FSH among peri-menopausal (aged 45 to 60 years) breast cancer patients. The secondary outcome was to determine the independent factors that would predict the menopausal FSH levels. The investigators calculated sample size based on the study conducted by Miglioretti, *et al.*[12] It required 90 participants. The continuous variables were reported in number and percent, median, and interquartile range (IQR), whatever was appropriate. Any factors that had a significant association with the menopausal level of FSH at a p-value of < 0.05 in the uni-variate analysis were tested by multi-variate analysis using logistic regression. Any factors with a p-value of < 0.05 in the multi-variate model were recognized as independent predictive factors. Statistical analyses were performed using SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

There were 90 participants in the study. Table 1 showed numbers and per cent (in parenthesis) of participants without and with post-menopausal level of FSH (> 40 IU/L) stratified by baseline demographics. Nearly half (44, 48.9%) of the participants were aged between 45-50 years. Around half of them were diagnosed at an early stage (42, 46.7%). At the time of blood collection, most of them (65, 72.3%) were still disease-free since diagnosis and were receiving adjuvant treatment (65, 72.2%). Most of the participants (71, 78.9%) were receiving or had received chemotherapy. Around two-third of them (66, 66.7%) had received 8 cycles or more. The median time since the last cycle of chemotherapy was 5 months (IQR 0-29.5). Only 19 participants (21.1%) received adjuvant hormonal treatment only. Thirty-nine (43.3%) had previously used tamoxifen, 18 (20%) were taking tamoxifen, and 33 (36.7%) had never used tamoxifen at the time of blood collection. Around two-third (57, 63.3%) of the participants reported rare or absence of menstruation during the past two years. Forty-six (51.1%) peri-menopausal participants had menopausal levels of FSH ($\geq$ 40 IU/L). Among participants aged 45-50, 50-55, and 55-60 years old, there were 43.2% (19/44), 63.3% (19/30), and 50% (8/16) having menopausal FSH levels, respectively. Pronouncedly, 45 of 46 (97.8%) participants who had reported rare or absence of menstruation for more than 2 years had post-menstrual levels of FSH.

Table 2 showed uni- and multi-variate analyses of factors associated with post-menopausal level of FSH (> 40 IU/L).

Table 1: Showed numbers and per cent (in parenthesis) of participants without and with post-menopausal level of FSH (> 40 IU/L) stratified by baseline demographics.

Variables	All participants (N = 90)	FSH < 40 IU/L (N = 44)	FSH ≥ 40IU/L (N = 46)
Age (at the time of blood collection) (years)			
45-50	44 (48.9)	25 (56.8)	19 (41.3)
50-55	30 (33.3)	11 (25.0)	19 (41.3)
55-60	16 (17.8)	8 (18.2)	8 (17.4)
Staging at diagnosis			
Early (stage I)	42 (46.6)	23 (52.3)	19 (41.3)
Locally advanced (stage II-III)	24 (26.7)	13 (29.5)	11 (23.9)
Metastatic	24 (26.7)	8 (18.2)	16 (34.8)
Staging at the time of blood collection			
Early (stage I)	42 (46.7)	23 (52.3)	19 (41.3)
Locally advanced (stage II-III)	23 (25.5)	13 (29.5)	10 (21.7)
Metastatic	25 (27.8)	8 (18.2)	17 (37.0)
Intention of Systemic Treatment			
Adjuvant	65 (72.2)	36 (81.8)	29 (63.0)
Palliative	25 (27.8)	8 (18.2)	17 (37.0)
Numbers of chemotherapy cycles ever received	8 (IQR 1.75-8)		
Never received	19 (21.1)	6 (13.6)	13 (28.3)
< 8 cycles	11 (12.2)	3 (6.8)	8 (17.4)
>/= 8 cycles	60 (66.7)	35 (79.6)	25 (54.3)
History of tamoxifen use			
Never using	33 (36.7)	9 (13.6)	24 (52.2)
Previously used	39 (43.3)	29 (65.9)	10 (21.7)
Now using	18 (20.0)	6 (13.6)	12 (26.1)
Menstruation history			
Rare or absence of menstruation within 2 years	33 (36.7)	32 (72.7)	1 (2.2)
Rare or absence of menstruation more than 2 years	57 (63.3)	12 (27.3)	45 (97.8)

FSH: Follicle stimulating hormone

Even though those who were receiving systemic treatment in the palliative setting, using tamoxifen and reporting rare or absence of menstruation for more than 2 years had the trend towards having post-menstrual levels of FSH; however, those who were using tamoxifen and those who had had rare or absence of menstruation for more than 2 years were significantly associated with menopausal FSH level.

DISCUSSION

Hormonal treatment is the mainstay of management of HR+ breast cancer. Besides tamoxifen, an AI, fulvestrant, a cyclin-dependent kinase (CDK) 4/6 inhibitor[13], and other novel targeted agents inhibiting the bypass tract of the endocrine pathway i.e. PI3K and AKT inhibitors[14] need pre-existing maximal estrogen-deprived conditions. To determine post-menopausal status is, therefore, the pre-requisite to commencing any subsequent lines of endocrine therapy. The definitions of post-menopausal status were nonidentical between clinical trials. According to the arimidex, tamoxifen alone, or combination (ATAC) trial, the most widely-used criteria in nowadays clinical practice defined that the post-menopausal one must have at least one of the following criteria: 1) those who had undergone surgical oophorectomy, 2) those who aged more than 60 years old, 3) those who aged between 45-59 years and had an intact uterus, amenorrhea must be documented for 12 months or more (if the duration of amenorrheic period was less than 12 months or uncertain, the menopausal status must be ascertained by determining the FSH level of within postmenopausal range).[4] The Breast International Group (BIG) 1-98 trial defined more detailed criteria. Irrespective of history of hormonal replacement therapy (HRT) or hysterectomy, the post-menopausal women were 1) those of any age who had surgical oophorectomy, 2) those of any age who had

Table 2: Showed uni- and multi-variate analyses of factors associated with post-menopausal level of FSH (> 40 IU/L).

Factors	Uni-variate analysis			Multi-variate analysis		
	OR[1]	95% C.I.	p-value	$OR^{2}_{adj.}$	95% C.I.	p-value
Intention of Systemic Treatment						
Adjuvant	1.0	(Reference)		1.0	(Reference)	
Palliative	2.64	(1.00 – 7.00)	0.051	0.923	(0.24 – 3.60)	0.908
History of tamoxifen use						
Never using	1.0	(Reference)		1.0	(Reference)	
Previously used	0.13	0.04-0.37	< 0.001	0.32	0.07-1.49	0.147
Now using	1.33	1.13-1.61	0.005	3.58	1.59-8.06	0.044
Menstruation history						
Rare or absence of menstruation within 2 years	1.0	(Reference)			(Reference)	
Rare or absence of menstruation more than 2 years	120.0	(14.85 – 969.93)	< 0.001	142.60	(11.94 – 1702.55)	< 0.001

Abbreviations: OR, odds ratio; OR_{adj}, adjusted odds ratio; 95% CI, 95% confident interval.
[1] Crude OR was estimated by binary logistic regression.
[2] Adjusted OR estimated by multiple logistic regression

radiotherapy-induced castration must have amenorrhea for at least 3 months or 3) those with ages of more than 45 years who had not been postmenopausal at the initiation of adjuvant cytotoxic therapy and recently received at least six cycles cyclophosphamide-methotrexate-fluorouracil (CMF) or four cycles doxorubicin-cyclophosphamide (AC) regimen regimens must be ascertained with follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E_2) levels. In case of no history of hormonal replacement therapy (HRT), 1) those with ages of less than 55 years who had undergone hysterectomy must be ascertained with hormonal levels (FSH, LH, and E_2) prior to initiation of chemotherapy, while in 2) those with ages of more than 55 years who had undergone hysterectomy, ascertainment with hormonal levels was not necessary. In case of those who had never used HRT and never undergone hysterectomy, 1) those who aged less than 50 years must have had amenorrhea for at least 1 year, while 2) those who aged more than 50 years must have had amenorrhea for at least 6 months. In case of those who had ever used HRT with or without a history of hysterectomy, 1) if patients aged less than 55 years, HRT must be discontinued for at least 1 month, and ascertainment with hormonal levels was required prior to initiation of chemotherapy, while 2) if patients aged more than 55 years, ascertainment with hormonal levels was not necessary. Those who did not fit in any mentioned categories, ascertainment with hormonal levels was required prior to initiation of chemotherapy.[5]

The kind of cytotoxic therapy ever used in the adjuvant setting, higher cumulative doses of cytotoxic agents, and older ages at the initiation of adjuvant chemotherapy were the most powerful predictors of both chemotherapy-induced amenorrhea (CIA) and chemotherapy-induced menopause (CIM).[15,16] Furthermore, higher cumulative doses of alkylating agents in older pre-menopausal patients and a period of CIA of more than 12 months were remarkably associated with CIM as well.[16,17] Tamoxifen, used sequentially after chemotherapy, led to a significant increase in the chance and/or duration of CIA[18] and resulted in a slight but statistically significant increase in the chance of CIM.[19] However, how tamoxifen affects CIA/CIM remains unelucidated. The investigators deduced from the results of this study that a physician should not rely on menstrual history, age, or history of systemic treatment.

Even though the odds of resuming ovarian function reduce as a woman approaches the mean age of natural menopause (usually at 51 years old) and when more ovarian-damaging agents are included in a chemotherapy regimen, the diagnosis of menopause still remains cumbersome in a pre-menopausal woman presenting with amenorrhea following adjuvant chemotherapy for early breast cancer. Torino F, *et al.* suggested that women aged between 40 and 50 years who had developed CIA should preferably be biochemically evaluated where a highly sensitive assay of E_2 was available.[20] Moreover, serial monitoring of E_2 and FSH levels was required to document the most accurate diagnosis of menopause. If hormonal levels indicated the emergence of a post-menopausal status (i.e. FSH > 40 IU/L and E_2 < 10 pmol/L), the anti-Mullerian hormone (AMH) assessment may be worthwhile in order to ascertain residual ovarian function.[21] If the AMH level is still below the lower limits of the normal range, an AI, a selective estrogen receptor degrader (SERDs e.g. fulvestrant), and other novel hormonal targeted agents should be prescribed cautiously. Likewise, if a woman is a candidate for switching to an AI because she has developed amenorrhea during tamoxifen treatment, without regard to a history of previous adjuvant chemotherapy, it is more logical to obtain serial highly sensitive assays of E_2 concomitant with FSH and AMH levels.[21] Primary endocrine resistance is not unusual in those receiving an AI in both adjuvant and palliative settings. The most widely-accepted definition is the relapse during the first 2 years of adjuvant endocrine therapy or progressive disease within the first 6 months of first-line endocrine therapy for metastatic breast cancer.[22] Provocatively, the investigators speculate that some of the peri-menopausal patients with primary hormonal resistance occurred as a result of mis-validation of menopausal status. The investigators suggest that for peri-menopausal women with unreliable menstruation history or inconclusive hormonal levels, castration by either surgical oophorectomy or concomitant use of a GnRH analogue is the safer choice prior to commencing any subsequent hormonal therapy. These results emphasize strict validation of menopausal status prior to prescribing an AI or a SERD to peri-menopausal breast cancer patients.

CONCLUSION

Among peri-menopausal breast cancer women, only half of them had post-menopausal levels of FSH. Physicians should not rely on a patient's age or menstrual history to determine post-menopausal status.

Author contributions: CB: Conceptualization, methodology, data curation, supervision, data analysis, manuscript writing, PT: Data collection and analysis.

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