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Correlation of Serum Estradiol and Duration of Anastrazole Therapy with Treatment Related Adverse Effects Among Postmenopausal Breast Cancer Women: A Cross-sectional Study

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Summary: Although anastrozole (Anas) plays a key role in the management of endocrine sensitive post-menopausal (PM) breast cancer (BC), there is much variability in its efficacy and tolerability. Anas-associated musculoskeletal symptoms (MS) and other adverse reactions, such as hot flashes (HF) and vaginal dryness/dyspareunia (VDD), are common and can affect the quality of life of BC patients, even sometimes leading to treatment withdrawal. The aim of this study was to determine the clinical and demographic factors associated with these adverse events. This is a cross-sectional study in estrogen receptor (ER) positive PM women (n = 92) with stages I to III BC receiving Anas. Multivariate analyses were performed to investigate the factors associated with Anas-induced adverse effects such as MS, HF and VDD. A serum estradiol concentration was undetectable (< 36.7 pmol/L) in 68.1% of patients but was detectable within a normal range (>36.7-88.1 pmol/L) in the other 31.9% of patients, and this group was found to have a lower odds of having at least one adverse effect (AE) compared to those with undetectable levels [adjusted odds ratio (AOR) 0.12, 95% confidence interval (CI) 0.02 to 0.64, p = 0.013]. Women with grades II and III tumors and a family history of BC had a higher odds of AE (grade II: AOR 12.22, CI 1.48 to 100.80, p = 0.020; grade III: AOR 12.95, CI 1.25 to 134.33, p = 0.032) and VDD (AOR 5.99, CI 1.30 to 27.52, p = 0.021), respectively. Patients who received Anas treatment for more than one year had a higher odds of VDD (one to three years: AOR 34.57, CI 3.86, 309.50, p = 0.002; more than 3 years: AOR 27.90, CI 2.21 to 351.84, p = 0.010). Advanced age also lowered the odds of HF (AOR 0.90, CI 0.83 to 1.00, p = 0.049). In conclusion, patients' hormonal environments and durations of Anas treatment may play a role in developing Anas-induced adverse effects.

Keywords: Estradiol, Anastrozole, Postmenopausal, Breast cancer

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INTRODUCTION

Breast cancer is the leading cause of cancer deaths in women (GLOBOCAN, 2012) and its development is the result of complex interactions between the genome and the environment (Hankinson *et al.*, 2004). The American Cancer Society has reported that a high percentage of breast cancer in postmenopausal women is ER positive (Society, 2009). Because these receptors are abundantly present on the cell surface of ER positive tumors, thus facilitating the proliferation of cancer cells, suppressing the circulating and tissue levels of estrogen or inhibiting estrogen's cellular effects by blocking the estrogen receptors have been recommended as effective approaches to minimize tumor growth (Osborne, 1998; Smith and Dowsett, 2003). The final step in estrogen synthesis is catalysed by the aromatase enzyme (CYP19A1) (Simpson *et al.*, 1994), the main target of aromatase inhibitors drugs such as anastrozole (Anas).

Anas is a selective third-generation aromatase inhibitor (AI) that has been established as one of the drugs of choice in the adjuvant therapy of postmenopausal breast cancer (Ingle, 2006) as well as advanced-stage malignancy (Ingle and Suman, 2005). Anas has also been investigated in studies for prevention of breast cancer in women who are at high risk of developing the disease (Ingle, 2005). A panel of American Society of Clinical Oncology recommended that optimal adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer should include an AI as an initial therapy or after treatment with tamoxifen (Winer *et al.*, 2005).

Anas, a non-steroidal AI, is an achiral triazole derivative known as 2,2-[5-(1H-1,2,4-triazol-1-yl methyl)-1,3-phenylene] bis (2-methylpropiononitrile) that suppresses plasma estradiol (E2) levels at doses of 1-10 mg/day; both doses are able to completely suppress E2 serum levels (Plourde *et al.*, 1994; Smith and

Dowsett, 2003). Its mechanism of action is through inhibiting or inactivating the aromatase enzyme, resulting in reduced conversion of androgens into estrone (E1) and E2 in peripheral tissues and in many other central nervous system locations (Simpson, 2003; Smith and Dowsett, 2003). Anas has been proven to be more efficacious and less toxic compared with tamoxifen (Forbes *et al.*, 2008). Its use has shown good potential in initial therapeutic assessments after 2-3 years of tamoxifen therapy as well as in the extended adjuvant therapy for 3 years following the completion of 5 years of tamoxifen treatment (Boccardo *et al.*, 2005; Jakesz *et al.*, 2005; Jakesz *et al.*, 2007; Kaufmann *et al.*, 2007; Forbes *et al.*, 2008).

Even though Anas has been shown to be superior and more effective than tamoxifen (Forbes *et al.*, 2008), a significant number of patients still present with large inter-individual variability in tolerability, resulting in serious adverse effects, such as musculoskeletal complaints and hot flashes, occasionally leading to patients' withdrawal from treatments (Mouridsen, 2006; Ingle *et al.*, 2010). The inconsistency has been attributed to inter-individual variability in Anas pharmacokinetics and/or pharmacodynamics, partly attributable to genetic variations (Abubakar *et al.*, 2014) and undetermined factors.

Large variation exists in the types and severities of AI-associated adverse reactions, which may affect patients' quality of life as well as their adherence to medication (Kyvernitakis *et al.*, 2014). To date, most studies conducted on AI-associated adverse events have been randomized clinical trials and have focused more on AI-induced musculoskeletal symptoms. Because most patients in our Oncology Center treated with Anas and other AIs report AI-related arthralgia, including other symptoms such as bone pain, hot flashes and vaginal dryness/dyspareunia upon Anas intake, further research is needed to better explain the risk factors associated with these debilitating symptoms and guide interventions. We therefore aim to investigate clinical and demographic factors that may be associated with these adverse events.

MATERIALS AND METHODS

Study Design and Study Population

This was a cross-sectional study conducted between April 2014 to June 2015 at the department of Nuclear Medicine, Radiotherapy and Oncology, Universiti Sains Malaysia, Kelantan, Malaysia. The study population consisted of postmenopausal women between 44 and 83 years of age. The eligibility criteria included histologically confirmed hormone receptor positive stage I to III breast cancer based on the American Joint Committee on Cancer (AJCC) staging manual (sixth Edition) and who were on 1 mg/day Anas treatment. Patients who were previously on tamoxifen were also included. The medical records were screened, and patients were then approached for study enrolment at their regular follow-up appointments. Informed consent was obtained, and a case report form was completed. Peripheral blood was collected for hormonal assay. The study was approved by the Human Research Ethical Committee of the Universiti Sains Malaysia.

Clinical and Demographic Data

The anastrozole-associated adverse events were evaluated in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Symptoms were characterized through a pro forma modified from the North American Menopause Society (NAMS) Menopause Health Questionnaire. Subjects were first asked whether they experienced on-going MS (joint pain/stiffness and bone pain), hot flashes (HF) or VDD because these symptoms in postmenopausal women population can be multifactorial. The subjects were then specifically asked to attribute their symptoms to factors such as age, anastrozole use, underlying medical conditions and other medications. Those who attributed their current symptoms to anastrozole were considered to have anastrozole-associated adverse effects (AAAE).

Patient demographic variables, such as age, race, ethnicity, marital status, occupational status, educational level, age of menopause, years since menopause, age at diagnosis of breast cancer, family history of breast cancer and history of contraceptive use, were ascertained. Other demographic data such as weight and height were taken at the clinic during the routine follow up visit. Clinical variables, such as cancer stage, tumor grade, ER/progesterone receptor (PR) status, human epidermal growth factor (HER2) status, current Anas use, and time since Anas, were first derived from the patient's case folder and then verified by an oncologist for quality control.

Laboratory Data

The latest routine laboratory reports of liver and kidney functions were ascertained from the patients' medical record. Serum E2 and Follicle stimulating hormone (FSH) levels were measured using one- and two-step quantitative immunoassay (using chemiluminescent microparticle immunoassay) technology, respectively, with flexible assay protocols referred to as chemiflex. ER/PR status was determined by immunohistochemistry.

Dependent and Independent Variables

The dependent variables (outcome) consisted of the presence of at least one adverse effect (AE), MS, HF and VDD. The independent variables included marital status, race, educational status, cancer stage, tumor grade, human epidermal growth factor (HER2) status, years since menopause, age of menopause, age of menarche, family history of breast cancer, history of contraceptive, body mass index (BMI), time since starting Anas, and E2 levels

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp). We conducted a simple logistic regression between each of the four dependent variables (AE, MS, HF and VDD) and the investigated covariates, including clinical and demographic variables. Covariates with p-value < 0.25 or

those with >0.25 but were clinically significant in simple logistic regression modelling were fit in the multiple logistic regression models. A p value of < 0.05 was considered as statistically significant in the multivariate analyses.

RESULTS

Socio-demographic and Clinical Data

Between April 2014 and June 2015, 92 total patients were screened for the study. The mean age of the participants was 58.3 years (SD, 7.3), with a range of 44 to 83 years. The most frequent cancer stage and tumour grade in this study were stage II (51.8%) and grade II (41.6%), respectively. Patients with a normal BMI (≤ 25 kg/m^2)

Table 1. Socio-demographic and clinical variables (n = 92)

	n	%
Age, years (mean± SD)	58.3±7.30	-
Marital status		
Married	85	92.4
Not married	7	7.6
Race		
Malays	72	78.3
Chinese	19	20.7
Indians	1	1.0
Educational status		
No formal Education	11	12.0
Primary and high school	68	73.9
Tertiary	13	14.1
Cancer stage		
I	8	8.7
II	43	46.7
III	41	44.6
Tumour grade		
I	16	17.4
II	37	40.2
III	25	27.2
Unknown	14	15.2
HER2 status		
Negative	48	52.1
Positive	34	37.0
Unknown	10	10.9
Years since menopause		
>10 years	22	23.9
5-10 years	34	37.0
<5 years	32	34.8
Unsure	4	4.3
Family history of breast cancer		
No	73	79.3
Yes	19	20.7
History of contraception		
No	59	64.1
Yes	33	35.9
BMI		
≤25	39	42.3
>25 to ≤30	34	37.0
>30	19	20.7
Time since beginning Anas		
< 1 year	47	51.0
1-3 years	34	37.0
>3 years	11	12.0

Table 2: Clinical and demographic variables and odds ratios of having at least one adverse effect (AE).

	simple logistic regression	
Variables	*OR (95% CI)*	*p* value
Grade		
I	1	
II	4.23 (1.10, 16.19)	0.035
III	1.56 (0.42, 5.72)	0.506
Age	0.95 (0.89, 1.01)	0.130
Age of menopause	0.92 (0.81, 1.04)	0.185
Estrogen levels (pmol/L)		
Undetectable*	1	
Detectable**	0.82 (0.23, 2.38)	0.715
	Multivariable analyses	
	AOR (95% CI)[b]	*p* value
Grade		
I	1	
II	12.22 (1.48, 100.80)	0.020
III	12.95 (1.25, 134.33)	0.032
Estrogen levels (pmol/L)		
Undetectable*	1	
Detectable**	0.12 (0.02, 0.64)	0.013

OR, odds ratio, AOR, adjusted OR, 95%CI, 95% confidence interval *Estrogen level <36.7pmol/L**Detectable but within normal range (>36.7 to 88.1 pmol/L)

BMI (≤ 25 kg/m^2) constituted the most frequent group (42.4%) (Table 1). Three of the subjects were unsure whether their symptoms were associated with Anas intake and were therefore excluded from the analysis. For logistical reasons, the blood samples for 20 of the subjects were not available for analysis.

Adverse Effects

Among the study subjects, 64 (69.6%) reported at least one adverse effect (overall adverse effects), whereas 3 (3.3%) were unsure of whether their symptoms were associated with Anas treatment. The odds of having at least one adverse effect was higher in grade II [adjusted odds ratio (AOR) 12.22, 95% confidence interval (CI) 1.48, 100.80, p = 0.020] and grade III (AOR 12.95, CI 1.25, 134.33, p = 0.032) tumors compared with grade I (Table 2). On the other hand, the risk of developing at least one adverse effect was reduced in patients with detectable but within normal range serum E2 levels (>36.7 to 88.1 pmol/L) compared with those with undetectable levels (<36.7 pmol/L) (AOR, 0.12, CI, 0.02, 0.64, p = 0.013).

Musculoskeletal Symptoms

A total of 38 (42.7%) participants reported MS. Clinical predictors, such as years since menopause, time since the start of Anas treatment, and serum E2 levels, were not significantly associated with the development of MS in the univariate analysis (results not shown). Covariates with p value < 0.25 in the univariate analysis were also not significantly associated with MS after multivariable adjustment (Table 3).

Table 3: Simple logistic regression: clinical and demographic variables and odds of MS

Variables	OR (95% CI)	*p value*
HER2		
Negative		
Positive	1.853 (0.75, 4.57)	0.181
Body mass index	1.05 (0.96, 1.14)	0.240
Waist circumference	1.02 (0.99, 1.05)	0.250
History of contraception		
No		
Yes	0.50 (0.20, 1.26)	0.141
Years since menopause		
>10 years		
5-10 years	1.06 (0.36, 3.18)	0.911
<5 years	1.35 (0.45, 4.08)	0.590
FSH	0.98 (0.96, 1.00)	0.096

OR, odds ratio, 95%CI, 95% confidence interval, SD, standard deviation, HER2, human epidermal growth factor receptor 2, FSH, follicle stimulating hormone. Note: None of the variables fit into the multiple logistic regression model using both forward selection and backward elimination methods.

Table 4: Clinical and demographic variables and odds of hot flashes

	simple logistic regression	
Variables	*OR (95% CI*	*p* value
Age	0.92 (0.85, 0.99)	0.020
Age of menopause	0.90 (0.79, 1.01)	0.083
FSH	0.97 (0.95, 1.00)	0.059
Years since menopause		
>10 years	1	
5-10 years	1.52 (0.47, 4.94)	0.483
<5 years	1.93 (0.59, 6.26)	0.776
	Multivariable analyses	
	AOR (95% CI)	*p* value
Age	0.91 (0.82, 1.00)	0.049

OR, adjusted odds ratio, AOR, adjusted OR, 95%CI, 95% confidence interval

Hot Flashes

There were only three covariates (age of the patients, age of menopause and FSH) with p value < 0.25 in the univariate analysis. However, after correcting for multiple testing, only age was significantly associated with decrease odds of developing hot flashes (AOR, 0.91, CI, 0.82, 1.00, $p = 0.049$) (Table 4).

Vaginal Dryness and Dyspareunia

The multivariable analyses of demographic and clinical variables and risk of VDD are shown in Table 5. Eighteen (20.2%) patients reported having VDD during anastrozole treatment. Five of the tested covariates (cancer stage, years since menopause, family history of breast cancer and time since anastrozole) had p values < 0.25 and were thus analysed in further multivariable logistic regression analysis. However, after correcting for multiple testing, only family history of breast cancer (AOR 5.99, CI 1.30 to 27.52, $p = 0.021$) and time since beginning anastrozole (one to three years: AOR 34.57, CI 3.86, 309.50, $p = 0.002$; more than 3 years: AOR 27.90, CI 2.21 to 351.84, $p = 0.010$) were significantly associated with having higher odds of VDD.

Table 5: Clinical and demographic variables and odds of vaginal dryness/dyspareunia

	simple logistic regression	
Variables	OR (95% CI)	*p* value
Stage		
I	1	
II	0.23 (0.05, 1.15)	0.074
III	0.18 (0.03, 0.93)	0.041
Years since menopause		
>10	1	
5-10	3.20 (0.61, 16.78)	0.169
<5	2.92 (0.54, 15.65)	0.212
Family history of breast cancer		
No	1	
Yes	4.13 (1.27, 13.38)	0.018
Time since beginning Anas		
<1 year	1	
1-3 years	15.05 (3.09, 73.29)	0.001
>3 years	8.25 (1.18, 57.48)	0.033
	Multivariable analyses	
	AOR (95% CI)	*p* value
Family history of breast cancer		
No	1	
Yes	5.99 (1.30, 27.52)	0.021
Time since beginning Anas		
<1 year	1	
1-3 years	34.57 (3.86, 309.50)	0.002
>3 years	27.90 (2.21, 351.84)	0.010

AOR, adjusted odds ratio, 95%CI, 95% confidence interval

DISCUSSION

Our study is the first to report the association between the major Anas-induced adverse effects and clinical/laboratory and demographic data among PM breast cancer women receiving Anas. The majority of studies on Anas and other AIs-associated adverse effects mainly focused on arthralgia and/or other musculoskeletal symptoms (Burstein, 2007; Burstein and Winer, 2007; Josse, 2007; Mackey and Gelmon, 2007; Coleman *et al.*, 2008; Goss *et al.*, 2014; Liu *et al.*, 2014; Stearns *et al.*, 2015). However, because other adverse effects such as hot flashes and vaginal dryness/dyspareunia from AIs use (especially Anas) are commonly encountered, investigating the factors associated with the adverse events enables more detailed knowledge regarding symptoms and provides important further guidance in intervention management.

The results of this study indicated that 27.2% of the studied patients did not report any adverse effects related to Anas intake. This finding is similar to that of Kyvernitakis and colleagues who reported that 28.9% of their subjects were symptomless (Kyvernitakis *et al.*, 2014). Thus, the present study suggests that the majority of patients receiving Anas experienced menopausal adverse events. Although the pathophysiology of some of the adverse effects such as joint pain or arthralgia (classified as MS) is yet to be fully elucidated, estrogen suppression has been postulated to play a key role, owing to the inhibition by anas, of aromatase which is required in the final step in the synthesis of estradiol (Felson and Cummings, 2005). Interestingly, our study found that patients with detectable but within normal limit serum E2 levels have reduced odds of developing at least one Anas-associated adverse effect compared to those with completely undetectable E2 concentrations. Therefore, this finding further suggests that E2 withdrawal may play an important role in some of the adverse effects associated with Anas and other AIs treatment.

In the present study, no significant association was detected between MS and a clinically important variable, the time since beginning Anas. This finding is similar to two previously reported studies in which no association was established between aromatase inhibitor-associated arthralgia (one of the components of MS in the present study) and time since Anas treatment administration. However, contrary to our findings on years since menopause, which showed a non-statistically significant similar trend (Table 3), these studies reported significantly higher odds of developing AI-associated arthralgia in breast cancer patients within less than five years of menopause compared to those who were more than 10 years from menopause (Mao *et al.*, 2009; Mao *et al.*, 2011). The reason for this discrepancy may be due to the nature of classification of the symptoms, the later used arthralgia as the only main outcome and also investigating all three AIs. In contrast, our study categorized both joint pain/stiffness and bone pain as a single outcome and only focused on Anas. In addition, this difference may also be attributable to different sample sizes or some underlying population differences, such as demographic or genetic factors.

In our study, the age of the patients was inversely related to the risk of having hot flashes. i.e. older patients tend to have lower odds of having hot flashes. This finding agrees with Morales and colleagues' findings, reporting that younger patients tend to have higher risks of hot flashes (Morales *et al.*, 2004). Mao and colleagues have suggested that those women who most recently attained menopause may present with higher residual circulating estrogen levels; thus, when they are treated with AIs, they are more likely to have a drop in estrogen, leading to greater symptom experiences (Mao *et al.*, 2009). The decreased odds of hot flashes with age in our study may also be explained by this hypothesis, although further clarifying research is needed because years since menopause was not significantly associated with higher risk of having hot flashes in our study (see Table 4).

A number of studies have suggested that estrogen suppression following treatment with AIs may be a plausible mechanism responsible for some of their adverse effects including arthralgia (Burstein, 2007; Burstein and Winer, 2007; Josse, 2007; Coleman *et al.*, 2008). In our study, a clinically important variable (especially the duration of Anas treatment) was shown to be associated with vaginal dryness/dyspareunia. Patients with more than one year of treatment with Anas have very high odds of having vaginal dryness/dyspareunia compared with those who were within less than one year of treatment. One of the reasons for this may be due to the long-term depletion of estrogens, leading to the development of adverse effect over time. However, this finding requires further investigation because postmenopausal women who have recently attained menopause have been suggested to be more likely to have more residual estrogen and, as a result, are more likely to develop adverse effects at the early onset of menopause when exposed to AIs treatment (Mao *et al.*, 2009).

A major limitation of the present study is the relatively small sample size that may render some of the established associations to be statistically insignificant. A larger multicentre study is thus suggested in future studies

In conclusion, our results indicate that the majority of patients treated with Anas experienced at least one adverse event. The data also suggest that host hormonal environments play a role in developing Anas-associated adverse effects. Although not life threatening, adverse events may affect patients' quality of life or patients' adherence to treatment. Therefore, patients' age and E2 levels as well as duration of Anas treatment may be considered when trying to improve the quality of life of postmenopausal breast cancer women receiving Anas.

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