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Aromatase inhibitor-associated musculoskeletal symptoms: incidence and associated factors

Jin Young Park*, Se Kyung Lee*, Soo Youn Bae, Jiyoung Kim, Min Kuk Kim, Won Ho Kil, Jeong Eon Lee, Seok Jin Nam

Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Purpose: Arthralgia is the most common side effect in breast cancer patients receiving aromatase inhibitor (AI) therapy. Few studies have evaluated the risk factors, onset, and incidence of musculoskeletal pain in these patients. This study identifies the risk factors of AI-related severe arthralgia and their prevalence.

Methods: All the clinical and pathological records of postmenopausal patients diagnosed with invasive breast cancer using AI at Samsung Medical Center from January 2005 to November 2007 were reviewed. Multivariate logistic regression analyses were performed to evaluate the risk factors of AI-associated musculoskeletal symptoms (AIMSS) and factors associated with AI discontinuance.

Results: Among 299 patients, 69 patients (23%) experienced musculoskeletal symptoms attributed to AI use. In multivariate logistic regression analysis, no statistically significant outcome was found to confirm the risk factors for the development of AIMSS. Among the 69 patients who experienced AI-associated musculoskeletal symptoms, 29 (39.7%) discontinued AI use. Multivariate logistic regression analyses revealed an association of prior tamoxifen use with discontinuance of AI ($P < 0.01$; odds ratio, 4.27; 95% confidence interval, 1.74 to 10.50).

Conclusion: Prior use of tamoxifen is related to discontinuation of AI due to AI-associated severe arthralgia. Special monitoring and proper pain control for these patients should be considered during the treatment period.

Corresponding Author
Seok Jin Nam
Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-3478
Fax: +82-2-3410-6982
E-mail: seokjin.nam@samsung.com

*These authors contributed equally to this study and should be considered co-first authors.

Key Words
Aromatase inhibitors, Aromatase inhibitor-associated musculoskeletal symptoms, Prior tamoxifen

INTRODUCTION

Aromatase inhibitors (AIs) have become a necessary part of standard adjuvant hormonal therapy that significantly reduces the risk of recurrence for postmenopausal women with hormone receptor positive invasive breast cancer. However, breast cancer patients receiving AI therapy show a higher incidence of AI-associated musculoskeletal symptoms (AIMSS). The incidence of AIMSS in phase III clinical trials of anastrozole, letrozole, and exemestane has been recently reviewed; women receiving these drugs experienced significantly higher rates of arthralgia than women who received tamoxifen [1]. In a study investigating arthralgia in 200 patients receiving AI therapy, 47% of the patients reported AI-related joint pain and 44% reported stiffness [2]. Typically, patients experience stiffness, achiness, or pain, which is frequently symmetric, occurring in the hands, arms, knees, feet, and pelvic and hip bones [3]. The few studies that have assessed the risk factors for the development of AIMSS (regardless of whether patients were on anastrozole or tamoxifen) looked into previous chemotherapy, previous hormone replacement

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Table 1. Analysis of risk factors for the development of AIMSS

Variable	Univariate analysis			Multivariate analysis	
	Symptom	Asymptomatic	P-value	OR (95% CI)	P-value
Total	69	230			
Age (yr)			0.52		
<55	19 (28)	54 (74)		1.00	-
≥55	50 (72)	176 (76)		1.26 (0.60–2.64)	0.54
Body mass index (kg/m^2)			0.90		
<23	25 (36)	82 (36)		1.09 (0.54–2.19)	0.82
≥23, <30	18 (26)	55 (24)		1.13 (0.55–2.32)	0.74
≥30	26 (38)	93 (40)		1.00	-
Femur T score			0.02		
Normal (T ≥ –1.0)	41 (59)	94 (41)		1.388 (0.34–5.75)	0.65
Osteopenia (–2.5 < T < –1.0)	25 (36)	125 (54)		0.644 (0.16–2.66)	0.54
Osteoporosis (T ≤ –2.5)	3 (4)	11 (5)		1.00	-
Radiotherapy			0.88		
Yes	50 (72)	162 (70)		1.041 (0.51–1.80)	0.90
No	19 (28)	68 (30)		1.00	-
Chemotherapy			0.19		
Yes	58 (84)	174 (76)		1.00	-
No	11 (16)	56 (24)		1.503 (0.67–3.39)	0.33
Chemotherapy regimen			0.27		
Taxane	37 (53)	141 (61)		1.00	0.10
None taxane	32 (46)	89 (39)		1.293 (0.70–2.41)	-
Prior tamoxifen			0.07		
Yes	25 (36)	57 (25)			
No	44 (64)	173 (75)			
Trastuzumab			0.20		
Yes	1 (1)	13 (5)		4.388 (0.55–34.87)	0.16
No	68 (99)	217 (95)		1.00	-
TNM			0.50	NA	NA
I	30 (43)	85 (37)			
II	31 (45)	107 (47)			
II	8 (12)	38 (16)			
Histology			0.86	NA	NA
IDC	60 (87)	199 (87)			
ILC	2 (3)	10 (4)			
Mucinous	2 (3)	9 (3)			
Others	5 (7)	12 (6)			
Estrogen receptor			0.23	NA	NA
Positive	67 (97)	228 (99)			
Negative	2 (2)	2 (1)			

(Continued to the next page)

Table 1. Continued

Variable	Univariate analysis			Multivariate analysis	
	Symptom	Asymptomatic	P-value	OR (95% CI)	P-value
Progesterone receptor			0.56	NA	NA
Positive	61 (88)	195 (84)			
Negative	8 (12)	35 (15)			
HER2			0.04	NA	NA
Positive	4 (6)	35 (15)			
Negative	65 (94)	195 (85)			
LV invasion			0.02	NA	NA
Positive	16 (23)	88 (38)			
Negative	53 (77)	142 (62)			
Multiplicity			1.00	NA	NA
Single	58 (84)	192 (83)			
Multiple	11 (16)	38 (17)			
Nuclear grade			0.15	NA	NA
Low	17 (25)	64 (28)			
Intermediate	39 (57)	101 (44)			
High	13 (19)	65 (28)			

Values are presented as number (%).
AIMSS, aromatase inhibitor associated musculoskeletal symptom; OR, odds ratio; CI, confidence interval; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HER2, human epidermal growth factor 2; LV, lymphovascular; NA, not analyzed.

therapy, hormone receptor positivity, obesity, and prior taxane therapy [1,2].

AIMSS could appreciably affect quality of life, adherence behavior, and potential survival benefit derived from AIs; further research is needed to better define the characteristics of AIMSS to help guide interventions. Thus, the objective of our study was to identify the clinical and pathological risk factors for the development of AIMSS and associated factors with severe AIMSS that prompt cessation of AI therapy.

METHODS

Patients and characteristics

The medical records of 299 postmenopausal women patients with hormone receptor-positive invasive breast cancer treated with AI at the Breast Division of the General Surgery Department from January 2005 to November 2007 were retrospectively reviewed. Patients were taking a third generation nonsteroidal AI (anastrozole or letrozole) for 5 years, or were switched to an AI after 2 to 3 years of tamoxifen treatment. Patients with no evidence of metastatic or recurrent disease, previous or concurrent cancer, and prior/current cancer treatment including chemotherapy and radiation therapy were excluded. Severe AIMSS was defined as a pain level where patients desired to ease of AI use. Bone mineral density (BMD) needed to have been performed within 3 months before or after reporting of AIMSS. Body mass index (BMI: calculated as weight in kilograms divided by height in square meters) and T score of femur head or shaft were analyzed. Patients with a BMI between 18.5 and 22.9 kg/m^2 were considered to be of normal weight, between 23 and 24.99 kg/m^2 overweight, and over 25 kg/m^2 obese, according to Korean Society for The Study of Obesity. Information concerning AIMSS and AI discontinuation was collected from the medical records. The pathological data were collected by a pathological chart review. Pathological records included stage at diagnosis, operation name, laterality, performance of axillary lymph node dissection, hormone receptor status, lymphovascular invasion, multiplicity, and nuclear grade.

Statistical analyses

All statistical analyses were performed with IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). Categorical variables were compared by using the chi-square or Fisher exact test: Discontinuation of AI therapy due to AIMSS, clinical characteristics and pathological status. Probability values <0.05 were considered significant. Multivariate logistic regression while controlling for all confounding variables was used to

evaluate the risk factors for the development of AIMSS and discontinuation of AI therapy due to severe AIMSS.

RESULTS

Incidence of AIMSS

From January 2005 to November 2007, 299 patients were enrolled. Baseline clinical and pathological characteristic are summarized in Tables 1 and 2. The median age of the women enrolled was 60 years (range, 47 to 87 years). Of the total patients, 69 patients (23%) reported having AIMSS. Among these 69 patients, 29 (39.7%) discontinued AI therapy due to severe AIMSS.

Onset of AIMSS

Among the 69 patients, the onset of AIMSS was noted in six patients (9%) within a month of starting therapy, 18 (26%) within the first 3 months, 11 (16%) within the first 6 months, and 34 (49%) after 6 months. Thus, approximately 50% of the patients experienced AIMSS within 6 months after the onset of therapy.

Risk factors for the development of AIMSS

In univariate analysis, the presence of AIMSS was associated with femur T score and negative human epidermal growth factor receptor 2 (HER2) receptor status. However, there was no association with age, BMI, BMD, operation type and laterality, axillary lymph node dissection, adjuvant chemotherapy and radiotherapy, TNM stage, hormonal receptor (estrogen receptor [ER], progesterone receptor [PR]) status, lymphovascular invasion, multiplicity, nuclear grade, and prior tamoxifen use. AIMSS was associated with normal femur T score and negative HER2 receptor status (Table 1). Multivariable logistic regression analysis with clinical factors for presence of AIMSS did not reveal any significant associations (Table 1).

Risk factors for discontinuation of AI therapy due to severe AIMSS

Univariate analysis indicated that discontinuance of AI therapy was not associated with age, BMI, BMD, adjuvant chemotherapy and radiotherapy, TNM stage, hormonal receptor (ER, PR, and HER2) status, lymphovascular invasion, multiplicity, and nuclear grade. Women with prior use of tamoxifen displayed a significant tendency toward AI discontinuation due to AIMSS (P = 0.01) (Table 2). Multivariate logistic regression with clinical factors showed a relation between prior tamoxifen use and discontinuation of AI (P < 0.01; odds ratio, 4.27; 95% confidence interval, 1.74 to 10.50) due to severe AIMSS (Table 2).

DISCUSSION

Large clinical trials evaluating AI (anastrozole in Arimidex, Tamoxifen, Alone or in Combination [ATAC] [4], letrozole in Breast International Group1-98 [5], and exemetane in the International Exemestane Study [2]) have reported arthralgia rates ranging from 5.4% to 35.6%. A small study carried out before the routine use of AI as an adjuvant treatment reported an incidence of pain ranging from 10% to 15% [6]. Our study showed a similar result (69 patients, 23%). A retrospective analysis of 600 patients who received adjuvant AI therapy showed 20% self-reported arthralgia/arthritis; notably, 17% of the patients discontinued AI therapy, which was attributable to arthralgia in 46% of the cases [7], and 45.4% developed AIMSS, which met the criterion for rheumatology referral [1]. Our study showed similar results (29 patients, with 39.7% discontinuing AI therapy due to severe AIMSS).

In several studies the majority of patients (75%) developed symptoms within 3 months of starting therapy [8,9]. In a prospective evaluation of AIMSS that developed in women treated with AI, the median time to onset of symptoms was 1.6 months and 13% of patients discontinued AI therapy after a median of 6.1 months secondary to musculoskeletal toxicity [8]. Also, The ATAC trial reported that the peak occurrence for AIMSS was 6 months [1]. Our study was consistent with previously published studies that have demonstrated 50% experienced AIMSS within 6 months after the onset of therapy.

Several studies have evaluated the risk factors associated with AIMSS. The results have not been consistent. Part of the ATAC trial was carried out looking for risk factors for development of AIMSS in 1,921 patients. Prior use of hormone replacement therapy, obesity (BMI > 30 kg/m^2), prior chemotherapy, geographic region (higher in North America, lower in the United Kingdom), and positive hormone receptor status are all associated with a higher risk of AIMSS [1]. Another study examined 200 patients of consecutive postmenopausal women receiving adjuvant AI therapy for early stage hormone sensitive breast cancer. The authors reported an increased risk of AIMSS in patients who received prior taxane chemotherapy (four-times more likely to develop symptoms) and associated with BMI [2]. In this study, BMI, prior chemotherapy and hormone receptor status were not related with AIMSS. Our study showed that AIMSS was associated with HER2 negative status in univariate analysis. HER2 status was just a pathologic result which was not related with clinical outcome. Therefore, we analyzed with the factor of trastuzumab use in multivariate analysis. In this analysis, there was not associated with administered trastuzumab.

The significant association between AIMSS and BMD has

Table 2. Analysis of risk factors for discontinuation of AI therapy due to severe AIMSS

Variable	Univariate analysis			Multivariate analysis	
	Stop (+)	Stop (-)	P-value	OR (95% CI)	P-value
Total	40	29			
Age (yr)			0.60		
<55	9 (31)	10 (25)		1.00	-
≥55	20 (69)	30 (75)		1.59 (0.56–4.482)	0.38
Body mass index (kg/m^2)			0.50		
<23	13 (45)	12 (30)		1.00	-
≥23, <30	7 (24)	11 (28)		1.30 (0.46–3.64)	0.62
≥30	9 (31)	17 (42)		1.15 (0.89–3.40)	0.80
Femur T score			0.15		
Normal (T ≥ –1.0)	16 (55)	25 (62)		1.00	-
Osteopenia (–2.5 < T < –1.0)	10 (35)	15 (38)		0.57 (0.23–1.38)	0.21
Osteoporosis (T ≤ –2.5)	3 (10)	0 (0)		2.47 (0.50–12.22)	0.27
RTx			1.00		
Yes	21 (72)	29 (72)		1.00	-
No	8 (28)	11 (28)		1.07 (0.43–2.68)	0.88
CTx			1.00		
Yes	24 (83)	34 (85)		1.00	-
No	5 (17)	6 (15)		0.71 (0.22–2.34)	0.63
Chemotherapy regimen			1.00		
Taxane	16 (55)	21 (52)		1.25 (0.51–3.06)	0.63
None taxane	13 (45)	19 (48)		1.00	-
Prior tamoxifen			0.01		
Yes	16 (55)	9 (22)		4.27 (1.74–10.50)	<0.01
No	13 (45)	31 (78)		1.00	-
Trastuzumab			0.38		
Yes	0 (0)	1 (3)		1.88 (0)	0.99
No	29 (100)	39 (97)		1.00	-
TNM			0.43	NA	NA
I	19 (48)	11 (38)			
II	18 (45)	13 (45)			
III	3 (7)	5 (17)			
Histology			0.28	NA	NA
IDC	37 (94)	23 (80)			
ILC	1 (2)	1 (3)			
Mucinous	1 (2)	1 (3)			
Others	1 (2)	4 (14)			
Estrogen receptor			1.00	NA	NA
Positive	28 (97)	39 (98)			
Negative	1 (3)	1 (2)			

(Continued to the next page)

Table 2. Continued

Variable	Univariate analysis			Multivariate analysis	
	Stop (+)	Stop (-)	P-value	OR (95% CI)	P-value
Progesterone receptor			1.00	NA	NA
Positive	26 (90)	35 (88)			
Negative	3 (10)	5 (12)			
Estrogen receptor			0.13	NA	NA
Positive	0 (0)	4 (10)			
Negative	29 (100)	36 (90)			
LV invasion			0.39	NA	NA
Positive	11 (28)	5 (17)			
Negative	29 (72)	24 (83)			
Multiplicity			0.04	NA	NA
Single	37 (92)	21 (72)			
Multiple	3 (8)	8 (28)			
Nuclear grade			0.32	NA	NA
Low	10 (25)	7 (24)			
Intermediate	25 (63)	14 (48)			
High	5 (12)	8 (28)			

Values are presented as number (%).
AIMSS, aromatase inhibitor associated musculoskeletal symptom; OR, odds ratio; CI, confidence interval; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HER2, human epidermal growth factor 2; LV, lymphovascular; NA, not analyzed.

been reported with severe degree of symptoms [10]. AIMSS is related with a significantly increased likelihood of having abnormal BMD [10]. Worsening bone health including osteopenia and osteoporosis is increased by AI treatment [11,12]. In our study, while AIMSS was associated with normal BMD range in univariate analysis, there was no association with BMD in multivariate analysis.

We found a greater than four-fold increased risk factor for discontinuance of AI due to severe AIMSS in patients who received prior tamoxifen therapy. The present study is the first report that discontinuation of AI therapy may be exacerbated by prior tamoxifen therapy. Prior tamoxifen use could be a real cause of severe AIMSS. However, this might cause an easy change to another drug (e.g., tamoxifen). There are various ongoing studies in progress at ClinicalTrial.gov (http://clinicaltrials.gov/). Further associated factors of AIMSS will hopefully be revealed soon.

A limitation of this study is the retrospective design, which introduced the possibility of selection bias. Due to the limitation of a measurement tool for AIMSS, we relied on self-reporting for measurement of AIMSS. Therefore, the measurement of AIMSS of our study could not be standardized.

In conclusion, there is no significant result concerning risk factors for the development of AIMSS. Furthermore, prior use of tamoxifen was related to discontinuance of AI due to severe AIMSS. Special monitoring and proper pain control for these patients should be considered during the treatment period.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Sestak I, Cuzick J, Sapunar F, Eastell R, Forbes JF, Bianco AR, et al. Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis. Lancet Oncol 2008;9:866-72.
2. Crew KD, Greenlee H, Capodice J, Raptis G, Brafman L, Fuentes D, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol 2007;25:3877-83.
3. Din OS, Dodwell D, Wakefield RJ, Coleman RE. Aromatase inhibitor-induced arthralgia in early breast cancer: what do we know and how can we find out more? Breast Cancer Res Treat 2010;120:525-38.

4. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60-2.
5. Coates AS, Keshaviah A, Thurlimann B, Mouridsen H, Mauriac L, Forbes JF, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol 2007;25:486-92.
6. Donnellan PP, Douglas SL, Cameron DA, Leonard RC. Aromatase inhibitors and arthralgia. J Clin Oncol 2001;19:2767.
7. Dent SF, Hopkins S, Di Valentin T, Verreault J, Vandermeer L, Verma S. Adjuvant aromatase inhibitors in early breast cancer - toxicity and adherence. Important observations in clinical practice. Breast Cancer Res Treat 2007;106:S111.
8. Henry NL, Giles JT, Ang D, Mohan M, Dadabhoy D, Robarge J, et al. Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. Breast Cancer Res Treat 2008;111:365-72.
9. Mao JJ, Stricker C, Bruner D, Xie S, Bowman MA, Farrar JT, et al. Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors. Cancer 2009;115:3631-9.
10. Muslimani AA, Spiro TP, Chaudhry AA, Taylor HC, Jaiyesimi I, Daw HA. Aromatase inhibitor-related musculoskeletal symptoms: is preventing osteoporosis the key to eliminating these symptoms? Clin Breast Cancer 2009;9:34-8.
11. Mincey BA, Duh MS, Thomas SK, Moyneur E, Marynchencko M, Boyce SP, et al. Risk of cancer treatment-associated bone loss and fractures among women with breast cancer receiving aromatase inhibitors. Clin Breast Cancer 2006;7:127-32.
12. Confavreux CB, Fontana A, Guastalla JP, Munoz F, Brun J, Delmas PD. Estrogen-dependent increase in bone turnover and bone loss in postmenopausal women with breast cancer treated with anastrozole. Prevention with bisphosphonates. Bone 2007;41:346-52.