Original Article

EFFECT OF AROMATASE INHIBITORS ON EARLY STAGE BREAST CANCER AND FREQUENCY OF JOINT PAIN SYMPTOMS IN POSTMENOPAUSAL WOMEN

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ABSTRACT

Objective: To find out the effect use of aromatase inhibitors on early stage breast cancer and the frequency of joint symptoms they developed.

Methods: This was a cross-sectional study on postmenopausal breast cancer women, who were receiving the different therapy for cancer. A questionnaire was used, comprises of demographic information and questions related to drug history and joint pain symptoms, and assessing the presence of joint symptoms at initial stage of cancer.

Results: Among 200 patients of this study, 93 (46.5%) reported having aromatase inhibitor-related joint pain and 89 (44.5%) with joint stiffness. Patients who received other medicines have less joint pain and stiffness (odds ratio [OR] _ 4.08, 95% CI, 1.20 to 10.43 and OR _ 4.46; 95% CI, 1.74 to 11.56, respectively).

Conclusion: Present study concluded that symptoms produced by aromatase inhibitor are more frequent in the female patients of breast cancer.

Keywords: Breast cancer, Aromatase inhibitor, Joint Symptoms, Postmenopausal women

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INTRODUCTION

There are many treatment of cancer in the world. Tamoxifen and aromatase inhibitors (AIs) are the best for the treatment of hormone-sensitive breast cancer. AIs are a common therapy for post-menopausal women with hormone positive breast cancer. Estrogen is mainly produced after menopause, by converting androgens into estrogens by aromatase. Aromatase inhibitors block this conversion, leading to less estrogen in the body.

While aromatase inhibitors are the better and effective therapy in reducing the risk of breast cancer recurrence. They increase the risk of developing osteoporosis and commonly cause joints or muscle pain. These joint symptoms (arthralgia) can interfere with quality of life [1].

Aromatase inhibitors may developed few serious side effects than tamoxifen, such as blood clots, stroke, and endometrial cancer. It was observed that these aromatase inhibitors can cause more heart complications, and bone loss, as compare to tamoxifen, when these subjects were treated in first few years of the treatment. Although these inhibitors have more side effects than other drugs, aromatase inhibitors are more effective than tamoxifen for the treatment of hormone-sensitive breast cancers. Aromatase inhibitors have a higher incidence of osteoporosis, bone fractures, and musculoskeletal symptoms, particularly joint pain and stiffness [2]. According to the previous studies the three most common sites of arthralgia, are knees, wrists, and shoulders. Aromatase inhibitors decreases estrogen levels in postmenopausal women by inhibiting the enzyme aromatase. This enzyme is responsible for the conversion of androgens to estrogens in peripheral and malignant breast tissue [3, 4].

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The exact mechanism of aromatase inhibitor-related joint pain is not clear. It is believed to be related to deficiency of this hormone [5, 6].

MATERIALS & METHODS

This cross-sectional study is conducted in university of Karachi. The sample size was calculated as 200 by open epi online calculator. The data were collected from Kiran cancer hospital Karachi. The participants are postmenopausal women with a history of stage I to III hormone receptor–positive breast cancer who were currently taking a third-generation aromatase inhibitor (anastrozole, letrozole) for three months.

The symptoms which are observe in these patients are morning stiffness and pain of the hands, knees, hips, lower back, and shoulders. The subjects were histologically confirmed with estrogen or progesterone receptor–positive primary breast cancer. Questionnaire includes the information about demographic figures, stage and diagnosis, tumor size, presence of axillary lymph node, cancer stage, status of hormone receptor, time on aromatase inhibitor therapy, and history of cancer treatment such as any surgery, chemotherapy, radiation therapy, or hormonal therapy). Joint pain and stiffness in any joint were assessed by scale from 0 to10.[7] The data were subjected to SPSS version 16.0 and analyzed for frequency and percentage of variables. The Odds ratio was also calculated with 95% confidence level.

RESULTS

In the present study 200 patients were participated. The demographic details are given in table-1. Most of the patients range from age 55 to 65 yrs. They showed joint pain (44%). While age group <55yrs expressed more joint stiffness (51%). Among them 93 (46.5%) reported with AI-related joint pain and 89 (44.5%) reported aromatase inhibitor-related joint stiffness (Figure-1). Patients who were overweight (BMI, 25 to 30 kg/m2) were less likely to have aromatase inhibitor-related joint pain as compared to those who had a normal BMI (25 kg/m2) or were obese (BMI>30 kg/m2). Both aromatase inhibitor-related joint pain and stiffness were associated with prior taxane chemotherapy (Table-2). Severity and location of aromatase inhibitor –related joint symptoms are showed in the Fig2. In multiple logistic regression analysis, patients who received taxane chemotherapy were more than four times more likely than other patients to have aromatase inhibitor-related joint pain and stiffness (odds ratio [OR] _ 4.08, 95% CI, 1.20 to 10.43 and OR _ 4.46; 95% CI, 1.74 to 11.56, respectively).

Patients who reported having either aromatase inhibitor-related joint pain and/or stiffness as well as medication relief are showing in the (Table-2). Patients were using different medicine for pain relief, among them 46% were taking NSAIDs, 26% were using acetaminophen and 6% were on opiates, while rest were on other treatments (Figure-3). The subjects who were using aromatase inhibitor -therapy, showing different levels of relief from symptoms as moderate, complete and mild (41%, 37% and 22% respectively) (Figure-4).

Table-1: Demographic parameters of patients receiving aromatase inhibitor-therapy.

Characteristics	No of Patients	Pain			Stiffness		
		No of patients	%	p	No of Patients	%	p
Total	200	93			89		
Age(years)							

<55	45	22	48	0.179	23	51	
55-65	85	38	44		35	41	0.189
>65	70	33	47		31	44	
Marital Status							
Married	135	55	41	0.356	50	37	0.317
Unmarried	65	38	58		39	60	
Employment							
Employed	60	23	38	0.621	25	42	0.613
Unemployed	140	70	50		64	46	

Table-2: Clinical characteristics and treatment of patients on AI-therapy.

Characteristics	**No of patients**	**Pain**			**Stiffness**		
		No of patients	**%**	**P***	**No of patients**	**%**	**P***
Total	200	93			89		
Entry into menopause							
Natural	125	56	41	**0.139**	54	40	0.301
Surgical	65	37	57		35	54	
Years since menopause							
<10	65	40	62		38	58	
10 to 20	50	31	62	**0.319**	29	58	0.199
> 20	53	22	42		22	41	
BMI (Kg/ m^2)							
< 25	62	38	62		36	58	
25 to 30	70	25	36	**0.037**	25	36	**0.216**
> 30	58	30	52		28	46	
Chemotherapy							
None	45	25	56		23	51	
Any	60	30	50	0.263	28	47	0.0598
Doxorubicin	55	27	49	0.143	26	47	0.0674
Texane	40	11	27	**0.0176**	12	30	**0.029**
Prior tamoxifen							
No	130	62	48	0.879	65	50	0.179
Yes	65	31	47		24	37	
Aromatase inhibitor							
Anastrozole	125	59	47	0.895	57	46	0.181
Letrozole	40	19	48		17	43	
Exenestane	34	15	44		15	44	
Duration of AI-therapy (years)							
<1	50	27	54		25	50	
1 to 3	123	58	47	0.399	55	45	0.897
>3	25	8	32		9	36	

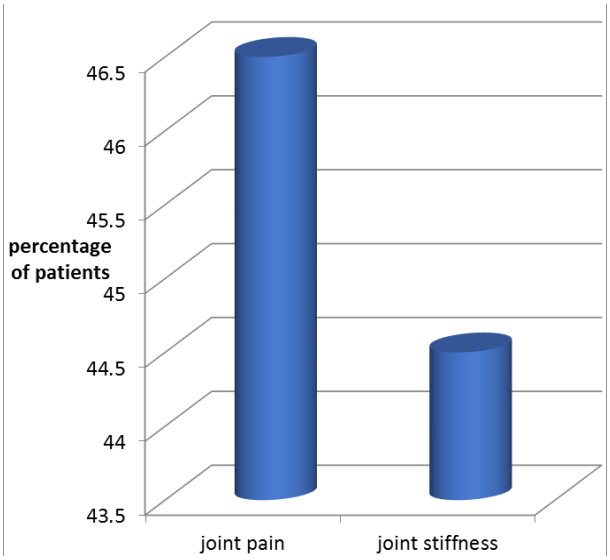

Figure-1: Percentages of AI-Related joint pain and stiffness.

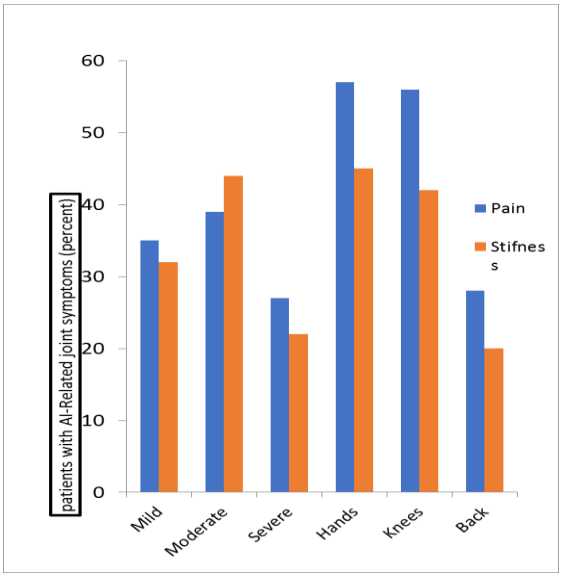

Figure-2: Location and severity of aromatase inhibitor (AI) –related joint symptoms.

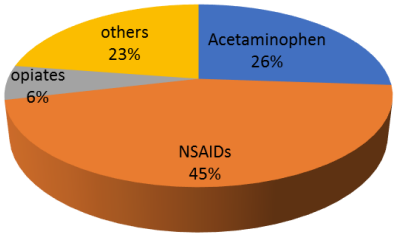

Figure-3: Other oral medications used for symptoms relief.

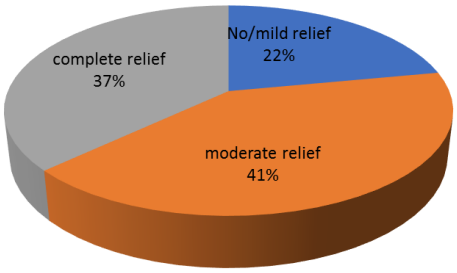

Figure-4: Symptom relief after use of aromatase inhibitors.

DISCUSSION

It is believed that aromatase inhibitor-related arthralgia is related to estrogen deficiency, but exact mechanism is not clear. We found that patients taking aromatase inhibitor therapy, they reported joint symptoms [8]. Use of Aromatase inhibitor is the standard treatment for the breast tumors [9, 10]. Aromatase inhibitors are considered to have a better adverse effect profile compared with tamoxifen. Many clinical research trials evaluated a safety profile for the aromatase inhibitors compared to tamoxifen [11]. The cartilage is sensitive to estrogens. The different observational studies of the prevalence of osteoarthritis (OA) give the strong positive and for the effect of estrogens in osteoarthritis (OA). HRT basically reduces the risk of radiologic knee osteoarthritis (OA). Various vitro studies suggest that estrogen hormone has the ability to regulate cartilage turnover and development of joint disease. It was observed in different experimental model of osteoarthritis (OA) with oophorectomized rats, that deficiency of this hormone initiate cartilage turnover. When estrogen or selective estrogen receptor

modulators are administered, they suppress the cartilage degradation significantly [12,13].

Our observation of a protective effect of prior tamoxifen therapy on aromatase inhibitor-related joint stiffness is consistent with these findings, greater than four-fold increased risk of aromatase inhibitor-related joint symptoms are observed in patients who received prior taxane therapy [14].

CONCLUSION

Joint symptoms which are produced after the medication of aromatase inhibitors is a complicated and challenging clinical problem for health care personnel. It is concluded that aromatase inhibitor-related joint symptoms are more frequent as compare to other medicines used for the cancer.

AUTHORS CONTRIBUTION

Dr Sadia: Idea and writing of article.

Dr Fauzia: Supervisor, Statistical analysis and finalized the draft.

Dr Shabnum: Clinical identification of patients and follow-up.

Dr Zia: Data collection and entry in SPSS

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