Open Access

Original Article

Osteoporosis/Osteopenia in Post-Menopausal Breast Cancer Patients Receiving Hormonal Therapy

Rahimullah Khattak, Riaz Ahmad, Muhammad Nadeem, Umair Tufail, Amjad Khan, Assam Ahmad

Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To analyze the presence of osteoporosis and osteopenia in post-menopausal breast cancer patients receiving hormonal therapy.

Study Design: Comparative Cross-sectional Study.

Place and Duration of Study: Oncology Department, Combined Military Hospital Rawalpindi Pakistan, from Dec 2020 to May 2021.

Methodology: This study was conducted on 200 post-menopausal female breast cancer patients who had been taking Aromatase inhibitors for more than six months. All the study participants underwent a dual-energy X-ray absorptiometry (DEXA) scan to measure bone mineral density. As a result, they were classified as having osteoporosis or osteopenia based on bone mineral density. In addition, age, duration of therapy, tumour stage and molecular subtypes of breast cancer were correlated with the presence of osteopenia/osteoporosis in the study participants.

Results: A total of 200 post-menopausal patients with breast cancer using hormonal therapy for more than six months were included in the final analysis. The mean age of the patients was 56.331 ± 6.744 years. In addition, 55 (22.5%) patients had normal bone mineral density, 92 (46%) had osteopenia, while 53 (26.5%) had osteoporosis on a dual-energy X-ray absorptiometry (DEXA) scan. Molecular subtypes of the tumour, the advancing age of patients and the long duration of hormonal therapy were statistically significantly associated with the presence of osteopenia/osteoporosis (p-value <0.05) in our study participants.

Conclusion: Considerable number of post-menopausal patients with advanced breast cancer taking hormonal therapy showed the presence of osteopenia and osteoporosis. Molecular subtyping, the advanced age of patients and the long duration of hormonal therapy significantly predicted osteopenia/osteoporosis in patients included in our study.

Keywords: Breast cancer; Hormonal therapy; Osteopenia; Osteoporosis.

How to Cite This Article*: Khattak R, Ahmad R, Nadeem M, Tufail U, Khan A, Ahmad A. Osteoporosis/Osteopenia in Post-Menopausal Breast Cancer Patients Receiving Hormonal Therapy. Pak Armed Forces Med J 2022; 72(4): 1474-1477. DOI: https://doi.org/10.51253/pafmj.v72i4.6784*

INTRODUCTION

Cancer has been a common non-communicable disease diagnosed by physicians in all parts of the world.[1] Breast cancer is a predator that takes the lives of thousands of women across the globe.[2] Number of factors at the time of diagnosis determine the short-term and long-term prognosis in patients suffering from breast cancer.[3] Depending upon the stage and hormonal profile of the disease, physicians devise a strategy right from the start, and aggressive management of this life-threatening illness may prone the patient towards multiple adverse effects.[4] Advanced disease usually requires a combination of chemotherapy and surgical resection with an aggressive approach to reducing the chances of mortality and better outcome.[5] Management modalities, especially hormonal treatment offered for advanced breast cancer, are associated with several side effects, including musculoskeletal side effects.[6]

Correspondence: Dr Rahimullah Khattak, Department of Medical Oncology, Combined Military Hospital, Rawalpindi, Pakistan

Received: 26 May 2021; revision received: 25 Jul 2021; accepted: 28 Jul 2021

Many breast cancer patients have reported various musculoskeletal adverse effects using aromatase inhibitors, including osteoporosis and osteopenia. Ramaswamy *et al,* in 2003 highlighted that osteoporosis has been prevalent among post-menopausal women and those taking adjuvant chemotherapy are more at risk of these problems. They also concluded that after five years of follow-up, women with breast cancer treated with anastrozole experience increased fractures compared to those treated with tamoxifen.[7] Musalmani *et al*, in 2009 published data from the United States of America regarding the role of osteoporosis in predicting musculoskeletal problems among breast cancer patients and using aromatase inhibitors for management. They concluded that patients on aromatase inhibitors who develop osteoporosis were at increased risk of musculoskeletal symptoms and bone fracture, and managing osteoporosis can prevent musculoskeletal problems effectively.[8] Perez in 2007 studied the safety profile of aromatase inhibitors and concluded that these medications were associated with many side effects, including musculoskeletal side

effects, such as arthralgia, myalgia and bone loss. However, these events were preventable or manageable with appropriate and timely interventions.[9]

Weighing the risks and benefits of treatment options for malignant conditions like breast cancer has been the primary role of the treating team. Clinicians worldwide have different opinions regarding the efficacy and safety profile of aromatase inhibitors used to treat breast cancer. Shaikh *et al,* in 2012 published a local paper highlighting that Anastrozole, Tamoxifen, and Letrozole were preferred options of oncologists among the aromatase inhibitors keeping in view safety and efficacy.[10] We planned this study with the rationale of analyzing the presence of osteoporosis and osteopenia in post-menopausal breast cancer patients receiving hormonal therapy.

METHODOLOGY

This Comparative Cross-sectional study was conducted at the Oncology Department of Combined Military hospital Rawalpindi Pakistan from December 2020 to May 2021. The sample was gathered by using the non-probability consecutive sampling technique. The sample size was calculated using the WHO sample size calculator by using the population prevalence of osteoporosis/osteopenia in advanced breast cancer as 55.4%,[11] and precision of 10%.

Inclusion Criteria: All female patients between the age of 40 and 70 years having menopause (confirmed via history and relevant investigations) and suffering from non-metastatic advanced carcinoma of the breast with positive hormonal status taking hormonal treatment for more than six months were included in the study.

Exclusion Criteria: The patients less than 18 or more than 65 years of age or those with electrolyte imbalance or compromised renal and liver function. Patients who were pregnant or had a history of lumpectomy or those with metastatic disease were also excluded from the study. Patients with a history of bone disease before starting hormonal therapy were also excluded from the study. Patients who were taking bisphosphonates or other bone replacement therapies or those who refused to undergo a DEXA scan were also not included in the study.

Ethical approval (a.158/5/21) was taken from the ethical review board committee of Combined Military Hospital Rawalpindi before the start of this study. After written informed consent from the participants, menopausal patients presenting with advanced hormonal positive breast cancer and fulfilling the criteria of inclusion and exclusion were included in the study. Diagnosis of advanced hormonal positive breast cancer was made by a consultant oncologist based on clinical, radiological and pathological criteria.[12] Hormonal therapy was given to all the patients for more than six months in the Oncology Department under the supervision of a consultant oncologist based on their hormonal status (molecular subtype) as per the current international guidelines.[13] DEXA bone scan was performed on all the patients and findings of bone mineral density were interpreted based on T-score. T-score of -1.0 or above was normal bone density, T-score between -1.0 and -2.5 was osteopenia, and a T-score of -2.5 or lower was osteoporosis.[14]

All statistical analysis was performed using the Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Mean and standard deviation was calculated for the age of patients. Frequency and percentages were calculated for the qualitative variables described in the study. Pearson chi-square test was applied to look for the association of age, duration of therapy, tumour stage and molecular subtypes of breast cancer with the presence of osteoporosis or osteopenia among post-menopausal patients who have breast cancer and taking hormonal therapy. The *p*-values less than or equal to 0.05 were taken as significant to establish a correlation among the study variables.

RESULTS

A total of 200 post-menopausal patients with breast cancer using hormonal therapy for more than six months were included in the final analysis. The mean age of the patients was 56.331 ± 6.744 years. In addition, 55 (22.5%) had normal bone mineral density, 92 (46%) had osteopenia, while 53 (26.5%) had osteoporosis on a dual-energy X-ray absorptiometry (DEXA) scan. Table-I showed the general characteristics of patients. Out of 200 patients, 85 (42.5%) had stage II disease, while 115 (57.5%) had stage III disease.

Table-II showed that molecular subtypes of the tumour (*p*-value-0.007), advancing age of patients (*p*-value-<0.001) and long duration of hormonal therapy (*p*-value-0.005) were statistically significantly associated with the presence of osteopenia/osteoporosis (*p*-value<0.05) in our study participants.

DISCUSSION

Novel treatment options have always haunted the oncologists worldwide to offer better management to their patients. Hormonal therapy was considered a breakthrough in the treatment of advanced breast cancers. However, physicians usually face problems

with patients who are already at high risk, like patients at extreme age or with multiple comorbid. Post-menopausal women are otherwise at high risk for multiple skeletal problems, which may increase when they suffer from a malignant condition. We planned and conducted this study intending to analyze the presence of osteoporosis and osteopenia in post-menopausal breast cancer patients receiving hormonal therapy for more than six months. We used a DEXA bone scan to look for osteopenia and osteoporosis.

Table-I: Characteristics of patients with hormonal receptor positive advanced breast cancer included in the study.

Parameters	n (%)
Age (Years)	
Mean ± SD	56.331 ± 6.744
Range (min-max)	43 - 69
Pathological Sub Type	
Infiltrative ductal carcinoma	172 (86%)
Infiltrative lobular carcinoma	16 (8%)
Others	12 (6%)
Staging of Tumor at Time of Diagnosis	
II	85 (42.5%)
III	115 (57.5%)
Molecular Subtypes	
ER+ PR +	70 (35%)
ER+ PR –	80 (20%)
ER- PR +	50 (25%)
DEXA Scan Interpretation	
Normal Bone Mineral Density	55 (27.5%)
Osteopenia	92 (46%)
Osteoporosis	53 (26.5%)

Table-II: Association of various factors with presence of osteopenia/osteoporosis to neo-adjuvant therapy (pearson chi-square test).

Factors	Normal Bone Mineral Density	Osteopenia	Osteoporosis	*p*-value
Age				
<55 years	36 (65.4%)	39 (42.4%)	11 (20.7%)	<0.001
>55 years	19 (34.6%)	53 (57.6%)	42 (79.3%)	
Stage of Tumor				
Stage II	24 (43.6%)	32 (34.8%)	29 (54.7%)	0.064
Stage III	31 (56.4%)	60 (65.2%)	24 (45.3%)	
Molecular Sub Types				
ER+ PR +	10 (18.2%)	39 (42.4%)	21 (39.6%)	0.007
ER+ PR-	24 (43.6%)	32 (34.8%)	24 (45.3%)	
ER- PR+	21 (38.2%)	21 (22.8%)	08 (15.1%)	
Duration of Hormonal Therapy				
<12 months	36 (65.4%)	57 (61.9%)	20 (37.7%)	0.005
>12months	19 (34.6%)	35 (38.1%)	33 (62.3%)	

Henning Mouridsen in 2006 summarized the adverse events reported in third-generation Aromatase inhibitor trials.[15] He concluded that these medications increased the chances of deranged lipid metabolism, cardiovascular abnormalities and osteoporosis. Increased chances of osteoporosis also lead to more fractures in these patients. Our results supported the findings generated by Henning Mouridsen, as more than 2/3rd of our study participants showed the presence of osteoporosis or osteopenia. We did not study other abnormalities or adverse effects in our target population.

Cepa *et al.*[16] published an interesting paper in 2015 regarding the management of bone loss in post-menopausal breast cancer patients treated with aromatase inhibitors. They recommended that all women treated with aromatase inhibitors should be evaluated for their fracture risk before initiation of treatment, taking into consideration individual bone mineral density and several risk factors. We did not study the fracture risk, but bone mineral density was reduced in many patients included in our study, and the duration of hormonal therapy had a significant relationship with bone loss.

A sub-study of the DATA trial was published by Van Hellemond *et al.*[17] in 2020, focusing on breast cancer outcomes with bone mineral density and bisphosphonate use. It was concluded that 49.5% of patients had osteopenia while 12.3% had osteoporosis. However, we only studied the hormonal therapy patients and found that 46% of patients had osteopenia, and 26.5% had osteoporosis. The difference in statistics may be because of the difference in the dataset, as Van Hellemond *et al*, included all the patients with breast cancer under treatment, and we only included patients of advanced disease receiving hormonal treatment.

Heery *et al,*[18] in 2020 published an informative paper analyzing precautions required by the patients using Aromatase Inhibitors for the management of breast cancer. They concluded that multiple adverse effects might need to be catered for in these patients, but increased risk of fracture and bone loss should be emphasized.[18] Our findings supported their opinion as around 75% of our patients had either osteoporosis or osteopenia after the hormonal therapy.

LIMITATIONS OF STUDY

Menopausal women are a high-risk group for osteoporosis and osteopenia. A cohort or case-control study design may have yielded better results in establishing the cause-and-effect relationship between hormonal therapy and bone loss. This remained one of the main limitations of our study. Doing a DEXA scan before the start of therapy and then doing scans at various therapy intervals may establish a reliable association.

CONCLUSION

Many post-menopausal patients with advanced breast cancer taking hormonal therapy showed the presence of osteopenia and osteoporosis. Molecular subtyping, the advanced age of patients and the long duration of hormonal therapy significantly predicted osteopenia/osteoporosis in patients included in our study.

Conflict of Interest: None

Author's Contribution:

RK: Overall responsibility for the manuscript, patients selection, treatment and followup, collection of data, RA:, MN: Over supervision, conception of article, UT: Data analysis, AK: Drafting and designing of article, AA: Applying statistic.

REFERNCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021; 71(1): 7-33.
2. Alkabban FM, Ferguson T. Breast Cancer. StatPearls. Treasure Island (FL): StatPearls Publishing; 2021, [Internet] availiable at: https://www.ncbi.nlm.nih.gov/books/NBK482286/
3. Lüftner D, Schneeweiss A, Hartkopf AD, Muller V, Wockel A. Update Breast Cancer 2020 Part 2-Advanced Breast Cancer: New Treatments and Implementation of Thera-pies with Companion Diagnostics. Geburtshilfe Frauenheilkd 2020; 80(4): 391-398.
4. Maajani K, Jalali A, Alipour S, Khodadost M, Tohidinik HR, Yazdani K. The Global and Regional Survival Rate of Women with Breast Cancer: A Systematic Review and Meta-analysis. Clin Breast Cancer 2019; 19(3): 165-177.
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365(9472): 1687-717.
6. Heery M, Farley S, Sparkman R, Healy J, Eighmy W, Zahrah G, et al. Precautions for Patients Taking Aromatase Inhibitors. J Adv Pract Oncol 2020; 11(2): 184-189.
7. Ramaswamy B, Shapiro CL. Osteopenia and osteoporosis in women with breast cancer. Semin Oncol 2003; 30(6): 763-75.
8. 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(1): 34-38.
9. Perez EA. Safety profiles of tamoxifen and the aromatase inhibitors in adjuvant therapy of hormone-responsive early breast cancer. Ann Oncol 2007; 18(Suppl 8): 26-35.
10. Shaikh AJ, Kumar S, Raza S, Mehboob M, Ishtiaq O. Adjuvant Hormonal Therapy in Postmenopausal Women with Breast Cancer: Physician's Choices. Int J Breast Cancer 2012; 2012(1): 849592-849596.
11. Hellemond IEGV, Smorenburg CH, Peer PGM, Swinkels ACP, Seynaeve CM, van-der Sangen MJC, et al. Assessment and management of bone health in women with early breast cancer receiving endocrine treatment in the DATA study. Int J Cancer 2019; 145(5): 1325-1333.
12. Nounou MI, ElAmrawy F, Ahmed N, Abdelraouf K, Goda S, Syed-Sha-Qhattal H. Breast Cancer: Conventional Diagnosis and Treatment Modalities and Recent Patents and Technologies. Breast Cancer (Auckl) 2015; 9(Suppl-2): 17-34.
13. Awan A, Esfahani K. Endocrine therapy for breast cancer in the primary care setting. Curr Oncol 2018; 25(4): 285-291.
14. Krugh M, Langaker MD. Dual Energy X-ray Absorptiometry. Stat Pearls. Treasure Island (FL): StatPearls Publishing; 2021, [Internet] availiable at: https://www.ncbi.nlm.nih.gov/books/NBK519042/.
15. Mouridsen HT. Incidence and management of side effects associated with aromatase inhibitors in the adjuvant treatment of breast cancer in postmenopausal women. Curr Med Res Opin 2006; 22(8): 1609-1621.
16. Cepa M, Vaz C. Management of bone loss in postmenopausal breast cancer patients treated with aromatase inhibitors. Acta Reumatol Port 2015; 40(4): 323-330.
17. Van-Hellemond IEG, Smorenburg CH, Peer PGM, Swinkels ACP, Seynaeve CM. Breast cancer outcome in relation to bone mineral density and bisphosphonate use: a sub-study of the DATA trial. Breast Cancer Res Treat 2020; 180(3): 675-685.
18. Heery M, Farley S, Sparkman R, Healy J, Eighmy W, Zahrah G, et al. Precautions for Patients Taking Aromatase Inhibitors. J Adv Pract Oncol 2020; 11(2): 184-189.