Efficacy of Adjuvant Zolodronic Acid in Post Menopausal Women with Early Breast Cancer Receiving Adjuvant Aromatas Inhibitor on Improving Bone Health

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Abstract: Purpose: The introduction of aromatase inhibitors (AIs) during the last decade has opened new horizons in the successful treatment of hormone receptor-positive (HR) breast cancer. Bone mineral density (BMD) rapidly decreases with a consequent high risk of skeletal fragility due to aromatase inhibitor-associated bone loss (AIBL). For the prevention of this adverse event, antiresoptive agents such as bisphosphonates (BPs) are used in combination with AIs. This prospective study compared the bone protecting effect of adjuvant vs. no zolodronic acid (ZOL) in patients with early breast cancer (EBC) receiving adjuvant AIs at 12 and 24 months. **Patients and Methods:** One hundred postmenopausal patients with HR+ EBC in whom AIs treatment was initiated letrozole (2.5mg once daily) were randomized to no ZOL or adjuvant ZOL (4mg every 6 months) between June 2013 and June 2015. The patients were stratified by established or recent postmenopausal status, baseline T-scorees, and adjuvant chemotherapy. Our endpoint is to evaluate changes in bone health by estimation of BMD (lumber spin LS and total hip TH), for each treatment group at 12, and 24 month. **Results:** At 12 months, the LS BMD in adjuvant ZOL group was (+4.8%) which increased at 24 months to (+5.2 vs, (-1.9%) and (-1.5%) in no ZOL group. Adverse events were generally mild, transient, and consistent with the known safety profiles. **Conclusion:** Adjuvant ZOL administration effectively improves BMD in postmenopausal women with HR+EBC receiving adjuvant AIs.
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1. Introduction

The introduction of aromatase inhibitors (AIs) during the last decade has opened new horizons in the successful treatment of HR+ breast cancer. Clinical trials established the role of AIs in the adjuvant therapy of postmenopausal women with hormone-responsive breast cancer in upfront, switch, and sequential treatment settings **[1]** and this is reflected by international guidelines such as those of the American Society of Clinical Oncology **[2**], St. Gallen **[3],** the National Comprehensive Cancer Network **[4].**

Various clinical studies demonstrated that estrogen deprivation caused by AI administration has a serious negative effect on bone health **[5].** Bone mineral density (BMD) rapidly decreases with a consequent high risk of skeletal fragility due to aromatase inhibitor-associated bone loss (AIBL). For the prevention of this adverse event, antiresoptive agents such as bisphosphonates (BPs) are used in combination with AIs.

Many randomized controlled trials have evaluated the role of bisphosphonates in the adjuvant setting of breast cancer and have shown a beneficial effect on bone loss prevention **[6].**

In this prospective study, we evaluate changes in bone health by estimation of BMD for ZOL and no ZOL group at 12 and 24 month in postmenopausal women with HR+EBC receiving adjuvant AIs with tolerated toxicities

2. Patients and Methods

This study included 100 postmenopausal patients with HR+EBC who were prospectively treated in Clinical Oncology Department, Zagazig University Hospitals between June 2013 and June 2015. Patients were randomized into 2 groups: ***Group A*** patients who did not receive ZOl acid and ***Group B*** patients who receive ZOL acid.

Inclusion criteria were: female patient postmenopausal or recently menopausal from ovarian ablation or bilateral oophorectomy, completed adjuvant treatment (tumor resection, chemotherapy and or radiotherapy), Eastern Cooperative Oncology Group performance status ≤ 2, LS and TH BMD T-scores ≥- 2.0.

Exclusion criteria were: clinical or radiological evidence of distant metastases, existing LS or TH fracture, or history of fragility fracture, renal dysfunction, other malignancies, or diseases known to affect bone metabolism.

Patient Assessment

Pretreatment assessment includes: detailed history taking; full physical examination; serum

creatinine level before each dose of ZOL, BMD at baseline, 12 and 24 months.

Treatment Plan

Postmenopausal Patients with HR+EBC under hormonal therapy with AIs enrolled in this trial were randomized 1:1 into 2 groups: ***Group A*** includes patients who didn't receive ZOL acid. ***Group B*** includes patients who receive ZOl acid.

All patients were instructed to take an oral calcium supplement (1,000-1,200mg), multivitamin tablet containing vitamin D once daily during the study.

Informed consent was obtained from each patient before enrollment.

All patients received letrezole 2.5 mg orally daily until disease progression and were assigned to either on ZOL treatment or ZOL 4mg IV over 15 minutes every 6 months for 2 years.

Study endpoint and assessment

The study endpoint is to evaluate changes in bone health by estimation of LS and TH BMD for each treatment group as measured by DEXA scan at 12 and 24 months.

Adverse events (AEs) were assessed and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE).

3. Results

Beginning in June 2013 to June 2015, one hundred postmenopausal female patients with HR+EBC were enrolled and randomized into two treatment groups.

Treatment arms were well balanced in age ranged between 49-76 years in Group A and between 49-79 years in Group B.

Previous treatment with adjuvant chemotherapy was completed in 33 patients (66%) in arm 1, and 36 patients in arm 2 (72%).Ten patients in arm 1(20%), and eight patients in arm 2 (16%) give history of early menopause (≤45 years). Eighty six patients (86%) had invasive duct carcinoma, 14 patients (14%) had invasive lobular carcinoma Table (1).

Four patients (4%) had T1 tumor size, 39 patients (39%) had T2, 57 patients (57%) had T3. Thirty one patients had negative lymph nodes (31%), 27 patients (27%) were N1, and 42 patients (42%) were N2. Grade one were present in 7 patients (7%), grade II were in 85 patients (85%), and GIII were in 8 patients (8%). Table (1).

Estrogen receptors (ER) were low positive in 40 patients (40%), medium positive in 32 patients (32%), and 32 patients (32%) had high positive expression. Progesterone receptors (PR) were low positive in 45 patients (45%), medium positive in 29 patients (29%), and high positive in 26 patients (26%). Table (1).

BMD analysis:

The percentage change from baseline BMD at 12 months for group A, LS was -1.9% and +4.8 for group B, with significant absolute difference of 6.7% (P<0.02). Similarly, the percentage change from baseline BMD at 12 months for group A, TH was -0.9% and +2.6 for group B, with significant absolute difference of 3.5% (P <0.064), Table (2).

The percentage change from baseline BMD at 24 months for group A, LS was -3.9% and +5.2 for group B, with significant absolute difference of 9.2% (P<0.004). Similarly, the percentage change from baseline BMD at 24 months for group A, TH was -1.5% and +3.9 for group B, with significant absolute difference of 5.4% (P<0.02), Table (2).

Correlation between BMD shift at 12 months evaluation and age there were more patients with decline in BMD with age ≥65, 71.4% versus 69.2% and 33.3% versus 16.2% for arm 1 and 2 respectively. Such differences had on statistic significance (p= 0.77 & 0.48), Table (3).

Correlation between BMD shift at 12 months evaluation and early menopause (≤ 45y), patients of arm 1 show more decline in BMD in those without early menopause 68% versus 62.5% for those with early menopause, in arm 2 it was reported for those with early menopause 33.33% versus 20% for those without early menopause. The differences had no statistic significance (p= 0.1 & 0.39), Table (3).

Correlation between BMD shift at 12 months evaluation and previous chemotherapy, there were more BMD decline in arm 2 for previous chemotherapy administration 27.8% versus 10% for those without previous chemotherapy, in patients of arm 1 the decline was more in those without previous chemotherapy 82.4% versus 58.6% for those with previous chemotherapy. The difference had no statistic significance (p= 0.24 & 0.38), Table (3).

Toxicity was analyzed according to the NCI-Common Toxicity Criteria scale. The toxicity pattern was generally tolerable, no cases of grade 3-4 toxicity, no treatment related deaths, 26% of patients in Group A vs 36% of patients in Group B had grade 1-2 artharalgia, 20% of patients in Group A vs 58% of patients in Group B had grade 1-2 bone pain, 22% of patients in Group A vs 20% of patients in Group B had grade 1-2 myalgia, 34% of patients in Group A vs 40% of patients in Group B had grade 1-2 fatigue, 8% of patients in Group A vs 26% of patients in Group B had grade 1-2 fever, 26% of patients in Group A vs 14% of patients in Group B had grade 1-2 headache, 8% of patients in Group A vs 10% of patients in Group B had grade 1 nausea &vomiting, with on significant difference between both groups except for fever (P<0.01), Table (4).

Table (1): Clinico-pathological characteristics of patients:

Patient characteristics		**Arm-1 No (%) 50 (100%)**	**Arm-2 No (%) 50 (100%)**	***P*-value**
Age Median Range	Mean ± SD	56.3±8.4 57 49-76	57.1±9.3 58 49-79	0.91
Early menopause	≤ 45y	10(20%)	8(16%)	0.5
Pathology type ILC	IDC	42(86%) 8(16%)	44(88%) 6(12%)	0.56
Tumer size(T) T2 T3	T1	2(4%) 20(40%) 28(56%)	2(4%) 19(38%) 29(58%)	0.97
Nodal state(N) N1 N2	N0	17(34%) 12(24%) 21(42%)	14(28%) 15(30%) 21(42%)	0.73
Grade (G) G2 G3	G1	3(6%) 42(84%) 5(10%)	4(8%) 43(86%) 3(6%)	0.72
Hormone receptor ER + +++ PR + ++ +++	++	 21(42%) 16(32%) 13(26%) 26(52%) 15(30%) 9(18%)	 19(38%) 16(32%) 15(30%) 19(38%) 14(28%) 17(34%)	 0.58 0.19
Her-2 neu (-) ve	(+) ve	21(42%) 29(58%)	11(22%) 39(78%)	0.03*
Previous chemotherapy No	Yes	33(67%) 17(34%)	36(72%) 14(28%)	0.51

Table (2): BMD characteristics at baseline, 12 month and 24 month:

BMD		**Arm 1 No (%)**	**Arm 2 No (%)**	***P*-value**
Base line	Normal MMO	(n=50) 17(34%) 33(66%)	(n=50) 16(32%) 34(68%)	0.83
12 month	Normal to MMO MMO to SO Osteoporosis MMO to normal Normal to SO Kept without shift	(n=46) 12(26%) 9(20%) 7(15%) 2(4%) 3(7%) 13(28%)	(n=46) 4(9%) 2(4.5%) 3(6.5%) 9(19.5%) 1(3%) 27 (57.5%)	**0.001****
24 month	Normal to MMO MMO to SO Osteoporosis MMO to normal Normal to SO Kept without shift SO to MMO	(n=23) 1 (5%) 5(21%) 4(17%) 1(6%) 0(0%) 12(51%) -	(n=40) 1(2.5%) 3(7.5%) 1(2.5%) 9 (22.5%) 1(2.5%) 22(55%) 3(7.5%)	**0.06**

Mean % of change from base line		Arm 1	Arm 2	*P*
12 month	LS TH	(n=50) -1.9 -0.9	(n=50) +4.8 +2.6	**0.02*** 0.06
	Difference LS TH	6.7 3.5		0.31
24 month	LS TH	(n=26) -3.9 -1.5	(n=47) +5.2 +3.9	**0.004**** **0.02***
	Difference LS TH	9.2 5.4		0.31

***BMD**= bone mineral density* ***Normal BMD**= T-score > -1*
***MMO**=mild to moderate osteopenia (T-score between -1 and -2)*
***SO**= sever osteopenia (T-score less than -2 but more than -2.5* ***Osteoporosis**=T score ≤ -2.5*
***T-score** =difference in the number of standard deviations between an individuals BMD and the mean for a group of young healthy women.*

Table (3): Relation between BMD shift at 12 months evaluation and age, early menopause and previous chemotherapy:

Variable			Improve	Decline	Stable	*P*
Age	Arm 1	≥65y (n=7) < 65y (n=39)	1 (14.3%) 3 (7.7%)	5 (71.4%) 27(69.2%)	1 (14.3%) 9 (23.1%)	0.77
	Arm 2	≥65y (n=9) < 65y (n=37)	1 (11.1%) 7 (18.9%)	3 (33.3%) 6 (16.2%)	5 (55.6%) 24 (64.9%)	0.48
Early menopause	Arm 1	Yes (n=9) No (n=37)	2 (22.2%) 1 (5.3%)	5 (55.6%) 26 (68.4%)	2 (22.2%) 10(26.3%)	0.1
	Arm 2	Yes (n=6) No (n=40)	2 (33.3%) 7 (17.5%)	2 (33.3%) 8 (20%)	2 (33.3%) 25 (62.5%)	0.39
Previous chemotherapy	Arm 1	Yes (n=29) No (n=17)	3 (10.3%) 1 (5.8%)	17 (58.6%) 14 (82.4%)	9 (31.1%) 2 (11.8%)	0.24
	Arm 2	Yes (n=36) No (n=10)	9 (25%) 2 (20%)	10 (27.8%) 1 (10%)	17 (47.2%) 7 (70%)	0.38

Table (4): Toxicity pattern in both treatment arms:

	Grade	Arm 1 No.=50No. (%)	Arm 2 No.=50No. (%)	*P*value
Artharalgia	0 1 2	37 (74%) 9 (18%) 4 (8%)	32 (64%) 12 (24%) 6 (12%)	0.55
Bone pain	0 1 2	40 (80%) 9 (18%) 1 (2%)	31 (62%) 15 (50%) 4 (8%)	0.1
Myalgia	0 1 2	38 (78%) 12 (22%) 0 (0%)	40 (80%) 9 (18%) 1 (2%)	0.47
Fatigue	0 1 2	33 (66%) 11 (22%) 6 (12%)	30 (60%) 14 (28%) 6 (12%)	0.77
Fever	0 1	46 (92%) 4 (8%)	37 (74%) 13 (26%)	**0.01***

	Grade	Arm 1 No.=50No. (%)		Arm 2 No.=50No. (%)		*P*value
	2	0	(0%)	0	(0%)	
Morning stiffness	0 1 2	42 8 0	(84%) (16%) (0%)	46 4 0	(92%) (8%) (0%)	0.21
Peripheral neuropathy	0 1 2	42 8 0	(84%) (16%) (0%)	41 9 0	(82%) (18%) (0%)	0.78
Nausea & vomitting	0 1 2	46 4 0	(92%) (8%) (0%)	45 5 0	(90%) (10%) (0%)	0.72
Headache	0 1 2	37 10 3	(74%) (20%) (6%)	43 5 2	(86%) (10%) (4%)	0.31

4. Discussion

Bone health is clearly an important concern for breast cancer patients and, before the start of treatment, needs to be evaluated by oncologists by using baseline DEXA scanning and known clinical risk factors such as family history, cigarette smoking, and excessive alcohol consumption. Specific guidelines on how to evaluate and manage cancer therapy-induced bone loss were recently published by Hadji and colleagues **[7].** AI use is a major additional cancer treatment-related risk factor in postmenopausal breast cancer patients. However, our findings along with data from the ATAC study and the Intergroup Exemestane Study (IES) **[8,9]** indicate that women with normal BMD before starting endocrine therapy have a very low risk of developing osteoporosis and that only the use of general preventive measures for maintaining bone health in postmenopausal women seems to be appropriate practice. Nevertheless, a lot of patients will still have established osteopenia or osteoporosis and need some other intervention to minimize their risk of ongoing loss of bone density due to long-term AI treatment.

Prevention of continuously decreasing BMD during endocrine treatment with AIs can be achieved with the appropriate administration of BPs. Several clinical trials demonstrate that the combination of AIs with BPs has a potent effect on BMD, The Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) bone substudy assessed zoledronic acid for preventing bone loss during adjuvant endocrine therapy **[10].** The investigators concluded that hormonal treatment for 3 years without concomitant zoledronic acid caused significant bone loss at the LS and trochanter (-11.3% and -7.3%, respectively) and that the administration of BP improved BMD (LS +4.0% and trochanter +3.9%) compared with baseline at 5 years. In three Zometa-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST, and E-ZO-FAST), patients received letrozole therapy combined with either immediate or delayed (that is, after a fracture or after BMD T-score decreased to -2.0) zoledronic acid treatment **[11-13].** Patients who have been administrated immediately with zoledronic acid treatment had significant increases in BMD and had fewer fractures overall than patients who have delayed treatment ($P < 0.0001$ for all).

In our study women who did not receive zoledronic acid experienced decrease in BMD from baseline to month 12 in both the LS &TH with mean % change (- 1.9%) and, (-0.9%) respectively, whereas patients who received zoledronic acid experienced increase in BMD of the LS & TH with mean % change about (+4.8%) and (+2.6%) from baseline to month 12 ($P < 0.001$ for both), with difference 6.7 % and 3.5 % for both LS and TH respectively. The mean % change of BMD of lumbar spine (LS) with zoledronic acid (+2.6) was in agreement with results of integrated analysis of the E-Z-FAST and ZO-FAST studies which showed that upfront patients experienced significant increases in LS (+2.72%) and TH (+1.72%) BMD ($p <0.0001$, both BMD sites) **[11]**. Z-FAST and ZO-FAST integrated analysis showed difference 5.1% and 3.4 % for both LS and TH respectively between immediate versus delayed zoledronic acid **[11]**, E-ZO-FAST showed mean% difference 5.4% and 3.3% for both LS and TH respectively between immediate versus delayed zoledronic **[13]**, and our study showed difference 6.7 % and 3.5 % for both LS and TH respectively, our higher difference due to more mean % change of BMD loss.

In our study women who did not receive zoledronic acid experienced decrease in BMD from baseline to month 24 in both the LS & TH with mean % change about (-3.9%) and, (-1.5%) respectively,

whereas patients who received zoledronic acid experienced increase in BMD of the LS & TH with mean % change about (+5.2%) and (+3.9%) from baseline to month 12 (P < 0.004 for both), with difference 9.2 % & 5.4% for both LS & TH.

Z-FAST and ZO-FAST studies also showed decrease in mean % change of BMD from baseline in patients with delayed zoledronic acid at 24 months evaluation with difference for LS & TH 5.9% & 4.7% and 8.2% &4.7% for both studies respectively with p-value significant <0.0001 **[14].**

Our study showed that patients in the zoledronic acid groups had a higher incidence of bone pain, arthralgia, and fever compared with those without zoledronic acid (bone pain 58% versus 20%, arthralgia 36% versus 26% and fever 26% versus 8%). Overall, there was no significant difference in the incidence of adverse events, and this was in agreement of both Z-FAST and ZO-FAST studied separate and integrated (bone pain 12.2% versus 5.9%,arthralgia 31.7% versus 28.5% and fever12.1% versus 1% for immediate versus delayed zoledronic acid) **[11].**

Conclusion

Our results evaluated bone health by comparing BMD of both study groups and proved the benefit of adding adjuvant zoledronic acid to letrezole hormonal treatment, BMD increased in those received zoledronic acid and decreased in those on hormonal treatment only, and these changes was sustained and continuous by evaluation of BMD at both 12 and 24 months.

Our results showed that the treatment regimen in the present study was well tolerated. The most prevalent toxicity of treatment was bone pain, arthralgia and fever with no cases of renal impairment, no cases of ONJ and no treatment related mortality.

Further studies are needed to evaluate cost – benefit effect of zoledronic acid every 6 months regimen.

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