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Effect of Zoledronic Acid Therapy on Aromatase Inhibitor Induced Bone Loss

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Abstract

Background: In postmenopausal hormone responsive early breast cancer, adjuvant aromatase inhibitor (AI) therapy improves disease free survival; however, it also produces bone loss. There are currently no approved modalities for prevention or treatment of this bone loss.

***Objectives*:** this study was carried out to study the effects of zoledronic acid on aromatase-inhibitors-induced bone loss (AIBL) in postmenopausal hormone-receptor-positive early-breast-cancer in Indian patients.

***Methods*:** The study included 20 postmenopausal hormone receptor positive early breast cancer (stage I-IIIA) patients. All patients had undergone primary surgery, did not have recurrent or metastatic disease and were receiving adjuvant aromatase inhibitor therapy for variable duration. Lumbar spine BMD (LSBMD) and serum bone turnover markers [C-telopeptide crosslinks (CTX) and alkaline phosphatase (ALP)] were measured at baseline and repeated after zoledronic acid infusion (bone turnover markers at 6 months and LSBMD at 12 months). The primary endpoint was the average percentage change in bone turnover markers at 6 months while the secondary endpoint was average percentage change in LSBMD after one year from baseline.

***Results*:** The mean age of the patients was 60.15±4.29 years. Six months after zoledronic acid, mean serum CTX level decreased from 0.76±0.40 ng/ml to 0.49± 0.27ng/ml (Δ= -35%; p <0.001). Similarly ALP decreased from 194.75±24.44 IU/L to136.20±12.12 IU/L (Δ= -30%; p <0.001). At one year follow-up, LSBMD could be done in 7 patients; the mean LS T-score increased from -2.75±0.37 to -2.64±0.35 (p-value = 0.01; Δ= 4.6%), and mean LS BMD increased from 0.788±0.041 gm/cm^2 to 0.816±0.032 gm/cm^2 (p-value = 0.016; Δ= 3.6%). There were no adverse events recorded during the study.

***Conclusion*:** The zoledronic acid is safe and effective for the treatment of AIBL in postmenopausal hormone responsive early breast cancer patients. This can be potentially used for prevention of AIBL.

Introduction

The survival from breast cancer has increased over the past decades due to improved breast cancer screening, diagnosis and treatment. One of the major advances has been the introduction of aromatase inhibitors for the treatment of hormone receptor positive (HR$^+$)

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breast cancer. Aromatase inhibitors (AI) increase the disease-free survival rates in postmenopausal women significantly alone or in sequence with tamoxifen [1]. AI therapy is superior to tamoxifen and is now the drug of choice as adjuvant therapy in postmenopausal women with receptor positive breast cancer patients [2-6].

Peripheral conversion of androgens to estrogen (estrone) is the main source of estrogen for postmenopausal women to maintain bone density [7]. Aromatase inhibitors potently suppress estrogen production by inhibiting the p450 cytochrome enzyme aromatase (CYP 19). So use of aromatase inhibitors causes estrogen deficiency and thus increases bone resorption, decreases bone mineral density and increases risk of fractures [8].

There is currently no approved treatment or prevention of aromatase inhibitors induced bone loss. Estrogen replacement therapies are contraindicated in patients with hormone dependent breast cancer. Three studies evaluated the efficacy of zoledronic acid for prevention of aromatase inhibitor induced bone loss in postmenopausal women. These three large parallel design studies (Zometa / Femara Adjuvant Synergy Trials: Z-FAST [9], ZO-FAST [10] and E-ZO-FAST randomized patients who received letrozole 2.5 mg/day to zoledronic acid 4 mg every 6 months either at initiation of letrozole treatment (upfront group) or to a delayed phase of treatment based on changes in BMD. Result of these studies support the use of zoledronic acid to potentially manage the aromatase inhibitors induced bone loss.

Till date there have been no studies on use of zoledronic acid therapy for management of aromatase inhibitor induced bone loss (AIBL) in postmenopausal hormone responsive early breast cancer patients from our country. We studied the bone changes (BMD and bone turnover markers) after single zoledronic acid infusion in aromatase inhibitors treated Indian postmenopausal women with hormone responsive breast cancer.

Material and Methods

The study was conducted between March 2011 and October 2012 in the Department of Endocrinology and Metabolism, Department of Surgical Oncology, and Department of Radiotherapy and Radiation Medicine of Institute of Medical Sciences, Banaras Hindu University, Varanasi.

Study Population

Twenty postmenopausal women with hormone receptor positive (ER and/or PR) early breast cancer (stage I-IIIA), operated and without recurrent or metastatic disease, were included. Written informed consent was obtained from all participants. The study was approved by institute ethics committee. At the time of inclusion, patients were on adjuvant aromatase inhibitor therapy [letrozole 2.5 mg/day (n=10), or exmestane 25 mg/day (n= 8), or anostrozole 1 mg/day (n=2)] for variable duration. None of them had received prior oral or intravenous bisphosphonate therapy.

Patients with other malignancy within the past 5 years, non-malignant systemic diseases like uncontrolled infection, diabetes mellitus, thyroid dysfunction, renal dysfunction, diseases affecting bone metabolism like hyperparathyroidism, hypercortisolism, Paget's disease, osteogenesis imperfecta, malabsorption syndrome, uncontrolled seizure disorders, known hypersensitivity or prior use of zolendronate or other bisphosphonates, aromatase inhibitors, calcium or vitamin D were excluded. The patients with current active dental problems, current or prior diagnosis of osteonecrosis of the jaw (ONJ), recent or planned dental or jaw surgery, recent treatment with any drugs known to affect the skeleton, prior exposure (within the prior 6 months) to anabolic steroids or growth hormone were also excluded.

Study Design

This was an open label prospective study design to assess the effect of zoledronic acid in postmenopausal hormone receptor positive early breast cancer patients on adjuvant aromatase inhibitor therapy. The detailed medical history and vital signs were obtained at baseline, 6 months, and 12 months. The data collected include age, sex, height, weight, BMI, blood pressure.

Fasting serum samples were taken at baseline and at 6 months after the treatment; and were stored frozen until analysis. All samples were tested in same run at the end of study for serum calcium, phosphorus, alkaline phosphatase (ALP), albumin, creatinine, and C-telopeptide crosslinks (CTX). Serum calcium, phosphorus, ALP, albumin, and creatinine were measured by autoanalyzer. Serum CTX was measured by electrochemiluminescensce assay.

Bone mineral density at L1-L4 lumbar spine (LSBMD) was measured by Dual Energy X-ray absorptiometry (DXA; Lunar DPX-NT, GE Medical System, USA) at baseline and at 12 months. The DXA scan was done by a single trained and experienced technician by proper calibration of machine and positioning of patient. At baseline, all the patients had T-score ≤ -2. The patients were classified as per WHO classification[11] as either osteoporosis or osteopenia. The follow-up DXA was feasible for 7 patients only.

All patients received Zoledronic acid 4 mg intravenous infusion over 15-30 minutes. Serum CTX and ALP were measured at 6 months and LSBMD was repeated at 12 months. The primary endpoint of this study was the average percentage change in serum bone turnover markers at 6 months. The secondary endpoint was average change in LSBMD from baseline to 1 year, expressed as a percentage of the baseline value. The patients were monitored for adverse events.

Table 1: Baseline Anthropometric and Biochemical Characteristics

Variables	Mean ± SD	Minimum	Maximum
Age (year)	60.15±4.29	50	67
Height (meter)	1.60±0.06	1.48	1.73
Weight (kg)	56.00±6.98	45	67
BMI (kg/m^2)	21.60±1.60	17.80	24.65
Systolic BP (mm Hg)	131.30±5.99	120	140
Diastolic BP (mm Hg)	83.80±4.04	74	90
Fasting Serum Calcium (mg/dl)	9.09±0.40	8.50	9.80
Fasting Serum Phosphate (mg/dl)	3.40±0.38	2.80	4.10
Serum Albumin (gm/dl)	3.47±0.38	2.80	4.00
Serum Creatinine (mg/dl)	0.88±0.08	0.72	0.98
eGFR (ml/min) (MDRD)	70.03±9.50	60.7	90.4

Results

The study included 20 women aged 60.15±4.29 years. The baseline anthropometric and biochemical characteristics are outlined in table 1. None of the patients had obesity, hypertension. The baseline calcium, phosphate and serum creatinine were normal. There was no renal dysfunction in study subjects (mean eGFR =70ml/min).

The effect of zoledronic acid infusion on bone turnover markers and LSBMD is shown in table 2. Serum CTX levels decreased in the study population by 35% and the decrease was similar in patients with baseline osteopenia and osteoporosis. Serum ALP similarly decreased by 30% in study group and the decrease in levels were similar in patients with baseline osteopenia and osteoporosis. The zoledronic acid infusion improved the BMD in the subgroup studied.

Table 2. Effect of Zoledronic acid infusion on bone turnover markers and LSBMD

Variable		Pre-treatment	Post treatment	Percentage change	p value
Serum C-telopeptide crosslinks (CTX)ng/ml	Overall (n=20)	0.76±0.40	0.49±0.27	35	<0.001
	Osteopenia (n= 9)	0.56±0.32	0.37±0.22	34.6	0.008
	Osteoporosis (n=11)	0.92±0.41	0.60±0.26	35.4	0.003
Serum alkaline phosphatase (ALP)IU/L	Overall (n=20)	194.75±24.44	136.20±12.12	30	<0.001
	Osteopenia (n= 9)	186.11±23.11	134.00±11.29	28	0.008
	Osteoporosis (n=11)	201.82±24.19	138.00±13.02	31.62	0.003
LS BMD gm/cm^2	Overall (n=7)	0.788±0.041	0.816±0.032	3.6	0.016
LS T Score	Overall (n=7)	-2.75±0.37	-2.64±0.35	4.6	0.01

The table 3 shows changes in bone turnover markers in patients taking letrozole or exmestane or anastrazole. Zoledronic acid infusion decreased the mean ALP and CTX in all three therapies. The effect was significant in patients on letrozole and exmestane while the anastrazole treated patients did not show significant benefit.

Discussion

Aromatase inhibitors cause profound estrogen deficiency in postmenopausal women, decrease bone mineral density and increase the risk of fractures. Bone mineral density decreases as a result of decreased osteoclast apoptosis and increased osteoclast differentiation. This bone effect is a class effect; all AIs have potentially deleterious effect on bone (decrease in BMD and an increase in bone turnover markers). In LEAP (Letrozole, Exmestane and Anastrozole Pharmacodynamics) trial, the three AIs had similar effect on bone [12].

The biochemical evaluation at baseline was performed in all subjects. The patients had normal serum creatinine and estimated GFR was above 60 ml/min in all patients. The normal renal function is an important pre-requisite for full dose zoledronic acid therapy. The serum calcium, phosphate and albumin were estimated in fasting serum sample of these patients and were found to be normal. Corrected calcium was also within the normal range.

Bone markers may be useful as an indication for pharmacotherapy in patients whose bone density is not sufficiently low; high level of a bone resorption marker may suggest that antiresorptive therapy might be beneficial, whereas a low level of the same marker might suggest a continued observation without pharmacotherapy [13]. The biochemical bone turn-over markers were studied at baseline in all patients. The mean alkaline phosphatase level was 194.75±24.44 IU/L. These levels were on higher side of the normal. The osteoporotic patients had significantly higher alkaline phosphatase levels than osteopenic patients (201.82±24.19 IU/L vs 186.11±23.11 IU/L). In study done by Lonning PE *et al*., (2005) [14], there was significant increase in bone-specific alkaline phosphatase (BSAP) by 52% from baseline in exemestane-treated women for 1 year. In ATAC study [2, 15],1 year of treatment with anastrozole increased bone-specific alkaline phosphatase (BSAP) by 20%. Thus, as our study group was on AI therapy for variable periods, this may have resulted in increased alkaline phosphatase levels.

Serum C-terminal telopeptide of type I collagen (CTX), as a marker of bone resorption, was also estimated at baseline. The baseline CTX levels were 0.76±0.40 ng/ml. These levels were on higher side of normal range. The

Table 3. Change in Bone Turnover Markers after Zoledronic Acid in Individual Drug users

Therapy	N	Mean Alkaline phosphatase (IU/L)				Mean CTX (ng/ml)			
		Pre-treatment	Post-treatment	% change	P value	Pre-treatment	Post-Treatment	% change	P value
Letrozole	10	199.50±23.80	137.30±11.78	31.1%	0.005	0.849±0.376	0.563±0.245	33.7%	0.005
Exmestane	8	187.25±27.97	133.62±14.15	28.6%	0.012	0.713±0.470	0.463±0.304	35.1%	0.012
Anastrozole	2	201.00±4.24	141.00±5.65	29.9%	0.180	0.530±0.353	0.315±0.205	40.6%	0.180

osteoporotic patients had significantly higher CTX levels than osteopenic patients (0.93±0.41 ng/ml vs 0.56±0.32 ng/ml). Use of AI increases CTX as shown in ATAC study (26% at 1 year) [2, 15],bone subprotocol of MA-17 study (17% at 1 year) [16], and another study done by Lonning PE *et al*., (35% at 1 year) (2005) [14]. In the present study, the patients were on AI therapy for variable duration (6 months to 2 years).

Bone mineral density (BMD) (DXA) was measured at lumbar spine (L1 to L4). Spine BMD may be useful in younger postmenopausal women, because it is likely to reveal bone loss earlier than the hip. All patients included in the study had T score below -2. The baseline mean T score of the group was -2.55±0.31 and BMD was 0.807±0.038 gm/cm^2. Out of 20 patients, at baseline, 9 were osteopenic (T-score between -2.1 and -2.4) and 11 osteoporotic (T-score between -2.5 and -3.2). The mean T score and BMD in osteopenic group were-2.27±0.13 and 0.835±0.02 gm/cm^2 respectively; while in osteoporotic group were -2.77±0.23 and 0.784±0.034 gm/cm^2 respectively. The mean T score and BMD were significantly lower in osteoporosis than osteopenia group.

In the bone subprotocol of MA-17 study [16], patients receiving letrozole had a significant decrease in BMD at 24 months at both the lumbar spine (–5.35 vs. –0.7%, P= 0.008) and hip (–3.6% vs. –0.71%, P= 0.044). In Breast International Group (BIG) 1–98, the incidence of clinical fracture was significantly higher in the letrozole group than tamoxifen group; both at 51 months (8.6% vs. 5.8%, P < 0.001) [17], and at 60 months (9.3% vs.6.5%, p <.001) [18].

In bone sub-protocol of the IES study [19], patients who remained on tamoxifen showed no significant change from baseline in BMD, the mean bone change was 0.2% at the spine after both 6 and 12 months (P < 0.0001 as compared with the exemestane group). In patients on sequential regimen, 6 months after tamoxifen cessation, the mean rates of bone loss were 2.7% and 1.2% at the spine and hip, respectively. The change in BMD from baseline was 3.6% at the spine and 2.4% at the hip at the end of 2 years. In another trial by Lonning PE *et al*., (2005) [14], exemestane-treated woman showed significant (P< 0.01) decrease in BMD by 2.17% and 2.72% at the spine and hip, respectively at 1 year.

Other application of bone turnover markers is in monitoring the response of therapy. Effective treatment may reduce bone turnover markers within 3 to 6 months or less, whereas to detect a significant increase in BMD, at-least 1 to 2 years may be required [15].

Zoledronic acid may counter-act the bone loss caused by AI therapy because bisphosphonates are potent inhibitors of bone resorption and produce their effect by reducing the recruitment and activity of osteoclasts and increasing their apoptosis. The results of HORIZON-PFT [20] showed that zoledronic acid significantly reduces the level of serum CTX as early as 6 months and BSAP, and NTX as early as 1 year after zoledronic acid; and at the end of 1 year, the level

decreased by 59%, 30%, and 58% respectively in post-menopausal patients. BMD was increased significantly at the lumbar spine (6.71%), total hip (6.02%), and femoral neck (5.06%) in the zoledronic acid group versus the placebo group over three years (P <0.001 for all comparisons).

The patients in our study were followed up for a mean period of 8 months (range 6-12 months) and only 7 patients could be followed at 1 year. The rest of the patients were either lost to follow-up or withdrew from study. The biochemical parameters (alkaline phosphatase and CTX) were re-evaluated at 6 months after zoledronic acid therapy in all of 20 patients. Serum alkaline phosphatase decreased significantly (30%), 6 months after zoledronic acid therapy. Serum CTX decreased significantly from 0.76±0.40 ng/ml to 0.49±0.27 ng/ml (35%) after 6 months of zoledronic acid therapy. The decrease in CTX was slightly more in osteoporotic than osteopenic patients (35.4% vs 34.6%).

The reduction in serum bone turnover markers (alkaline phosphatase and CTX) were almost similar in both osteoporosis and osteopenia groups. This is in consonance with the earlier studies showing that zoledronic acid prevents bone loss associated with aromatase inhibitors in postmenopausal women (Z-FAST study, 2007; ZO-FAST and E-ZO-FAST studies, 2008) [10]. In Z-FAST study [10], in the upfront group (Zoledronic acid at start of AI therapy), mean serum NTX and BSAP concentrations decreased by 15.1% (P < 0.0001) and 8.8% (P = 0.0006), respectively, at month 12, whereas concentrations increased significantly in the delayed group (Zoledronic acid after AI therapy) by 19.9% (P = 0.013) and 24.3% (P < 0.0001), respectively.

The difference in mean percent change of bone turnover markers at month 12 between the upfront and delayed groups was -35% for serum NTX and -33% for serum BSAP. In both ZO-FAST and E-ZO-FAST [10] studies, levels of biochemical markers of bone metabolism increased in the delayed group, but were reduced with zoledronic acid therapy.

The post-treatment evaluation for changes in BMD could be done in 7 patients. One year after zolendronic acid infusion, the LS T-score and LS BMD improved by 4.6% and 3.6% respectively. These results are similar to the result of Z-FAST [10] study. Similar results were seen in the ZO-FAST and E-ZO-FAST studies. In ZO-FAST study, the differences between treatment groups in LS was 5.7% (95% CI: 5.2–6.1%; P = 0.0001) at the end of 1 year. At 1 year in the E-ZO-FAST study, the difference between treatment groups in lumbar spine was 5.4% (P < 0.0001).

Another study done was conducted by Mayo Clinic Cancer Research Consortium (MCCRC) on similar patients to evaluate the effect of Zoledronic acid for treatment of osteopenia and osteoporosis in women with primary breast cancer undergoing adjuvant aromatase inhibitor therapy [21]. After 1 year of zoledronic acid, the LS BMD improved significantly by 2.66% (p < 0.01) from baseline.

In the present study there is similar significant reduction in bone turnover markers with zoledronic acid in all patients regardless of type of aromatase inhibitor used. There was significant improvement in LS T-score or LS BMD following zoledronic acid therapy.

Limitations of the study

Limitations of the present study include its relatively small size and shorter duration of follow-up. Instead of bone specific alkaline phosphatase, serum total alkaline phosphatase was done.

The follow-up DXA scan for BMD at spine was possible only in 7 out of 20 patients. However, the present study could highlight the benefit achievable with zoledronic acid therapy in aromatase inhibitor induced bone loss.

Conclusions

The present study shows that the aromatase inhibitor treated post-menopausal patients with early breast cancer have higher bone resorption (higher c-terminal telopeptide) and lower bone mineral density. The use of zoledronic acid will help in reducing the effect of aromatase inhibitors in such patients.

Conflict of Interests

The authors declare that there are no conflicts of interests

Authors' Contribution

NKA: Study design, concept, editing of manuscript

VP: Preparation of manuscript, literature search and data collection

MP: Concept and design, carrying out of the study and editing the final manuscript

UPS: Design and data collection, preparation of manuscript

Ethical Considerations

The study was approved by the Institute Ethics Committee

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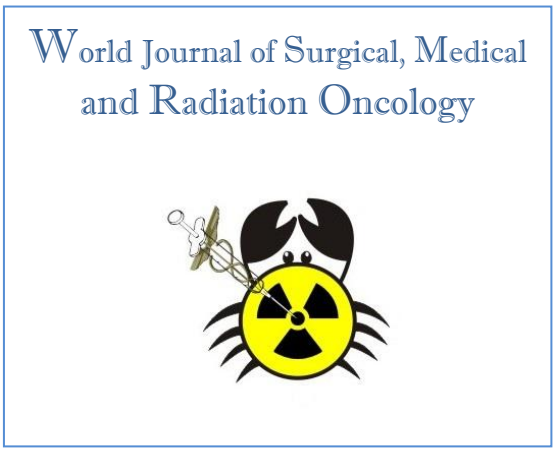

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