ORIGINAL ARTICLE

Cytotoxic chemotherapy is associated with decreased bone mineral density in postmenopausal women with early and locally advanced breast cancer

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Abstract

Purpose The burden and mechanisms of endocrine therapy-related bone loss have been studied in detail. However, there is limited data regarding cytotoxic chemotherapy's impact on bone health. There are no definitive guidelines for bone mineral density (BMD) monitoring and treatment with bone-modifying agents during cytotoxic chemotherapy. The study's primary objective was to evaluate the changes in BMD and fracture risk assessment tool (FRAX) scores among breast cancer women on cytotoxic chemotherapy.

Methods One hundred and nine newly diagnosed early and locally advanced postmenopausal breast cancer patients planned for anthracycline and taxane-based chemotherapy were recruited prospectively during the study period from July 2018 to December 2021. BMD of the lumbar spine, the femoral neck, and the total hip were assessed by dual-energy X-ray absorptiometry scan. BMD and FRAX scores were evaluated at baseline, end of chemotherapy, and 6 months of follow-up.

Results The median age of the study population was 53 (45–65) years. Early and locally advanced breast cancers were seen in 34 (31.2%) and 75 (68.8%) patients, respectively. The duration of follow-up between two BMD measurements was 6 months. The percentage of decrease in BMD at the lumbar spine, femoral neck, and total hip were -2.36 ± 2.90, -2.63 ± 3.79, and -2.08 ± 2.80, respectively (P-value $= 0.0001$). The median risk of major osteoporotic fracture (MOF) at 10 years (FRAX score) increased from 1.7 (1.4) to 2.7% (2.4) (P-value $= 0.0001$).

Conclusion This prospective study in postmenopausal breast cancer women shows a significant association of cytotoxic chemotherapy with the worsening of bone health in terms of BMD and FRAX score.

Keywords Breast cancer · Bone mineral density · Chemotherapy · Osteoporosis

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Introduction

Breast cancer (BC) is the most common malignancy in women, and with advancements in treatment, the survival rates have increased. The current focus is to limit the treatment toxicity and improve the quality of life. Bone health is one of the critical areas impacting the quality of life, including musculoskeletal pain and fractures [1]. Studies show that women with BC on hormonal treatment are at higher risk for osteoporosis later in life [2]. Osteoporosis and its worst outcomes, such as chronic pain and fractures, are associated with increased morbidity and mortality [3]. Bone loss occurs when there is an imbalance between bone formation and bone resorption. Skeletal turnover rates appear 85% higher in elderly women with low bone mass than in women with normal bone mineral density (BMD), as patients with advancing age have high bone resorption

compared to the formation [4]. In India, osteoporosis is grossly underdiagnosed, even in high-risk individuals such as postmenopausal women, older adults, and subjects with diseases causing secondary osteoporosis [5]. Accelerated bone loss occurs in up to 80% of BC survivors on long-term follow-up. The rate of loss of BMD among women receiving hormonal treatment for BC is 2–8% per year, while that of healthy postmenopausal women is only 1% per year [6].

Chemotherapy agents directly affect bone cells, leading to increased bone resorption and decreased BMD in women with BC [7]. Chemotherapeutic drugs, such as cyclophosphamide, methotrexate, 5-fluorouracil, and doxorubicin, have been shown to damage the ovary and cause a reduction in bone volume [8–10]. Several studies have reported significantly decreased BMD after treatment [7]. Most of the study populations were heterogeneous, and there was non-uniformity in the chemotherapy regimen protocol. It was difficult to conclude which chemotherapy combination causes decreased BMD. There is limited data available on bone health in women with non-metastatic BC on chemotherapy. None of the previous studies addressed the particular chemotherapy's effect on BMD among postmenopausal women with non-metastatic BC over a period of time. If osteoporosis is left undiagnosed and untreated, it will add to lower quality of life, morbidity, and mortality. Our study aimed to evaluate BMD, FRAX scores, and fracture among postmenopausal women with non-metastatic BC on chemotherapy at various time points. The time points were before the start of chemotherapy, the end of chemotherapy, and after 6 months.

Material and methods

Study subjects

The study was carried out in a tertiary cancer center, which caters to the population from southern India. This study was a prospective cohort study involving that enrolled postmenopausal women with newly diagnosed early and locally advanced BC from June 2018 to December 2021 and was screened for their eligibility based on the inclusion and exclusion criteria described below. Informed consent was obtained from the participants. This study was approved by the institute's ethics committee (IEC No: JIP/IEC/2018/0176). Bone scans and contrast-enhanced computed tomography of the abdomen and pelvis were done to rule out distant metastatic disease at baseline.

Objectives and endpoints

The primary objective of the study was to evaluate the change in BMD and FRAX scores among postmenopausal women

with non-metastatic BC on chemotherapy. The secondary objective was to assess the incidence of fractures in them.

Inclusion criteria

All newly diagnosed early and locally advanced postmenopausal women (aged between 45 and 65 years) with non-metastatic BC planned for anthracycline and taxane chemotherapy were recruited for the study. Postmenopausal status is defined as spontaneous amenorrhea for at least 12 months. Postmenopausal status was confirmed in all patients under 50 years with FSH levels of more than 40 mIU/ml.

Exclusion criteria

Patients with Paget's disease, osteomalacia, hyperparathyroidism, active metabolic bone disease, bronchial asthma on steroid medication, rheumatoid arthritis, major surgery or substantial traumatic injury, conditions deemed to affect vitamin D metabolism, and prior history of malignancy were excluded from the study. Baseline osteoporotic patients were excluded because these patients received zoledronic acid and calcium, which could be potential confounders. The age-related fall of BMD is higher in older patients, which could be a confounding factor. The percentage of patients with normal or osteopenia BMD would be lesser in patients with older age. Hence, we restricted the age group to 45–65 years.

Treatment

Patients received three cycles of FEC (5 fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), cyclophosphamide (500 mg/m^2)) 3 weekly followed by four cycles of docetaxel (75 mg/m^2) 3 weekly. Dexamethasone (4 mg) is an antiemetic drug, with each cycle of chemotherapy as prophylaxis at a cumulative dose of 256 mg. After completion of chemotherapy, patients with hormone receptor-positive received letrozole at 2.5 mg per day for a period of 5 years as maintenance therapy with a 6-monthly zoledronic acid injection. The minimum follow-up for patients in this study was 6 months post-chemotherapy.

Sample size calculation

The sample size was calculated using the statistical formula as the minimum expected difference in the percentage decreased of BMD at the lumbar spine as − 1.5% (baseline vs end of chemotherapy which is 6 months chemotherapy duration) with a standard deviation (SD) of 4% at a 5% level of significance, and 80% of the power was 112.

$$n = 2\left(Z_a + Z_\beta\right)^2 \sigma^2 / \delta^2 = 2(1.96 + 0.84)^{2*} 4^2 / (-1.5)^2 = 112$$

Methodology

Population

Patient data were collected using a standardized case record proforma thorough medical history, including fragility fractures, detailed physical examination, BC characteristics (histology, hormonal status, stage, and grade), body mass index (BMI), treatment details, complete blood count, routine biochemistry (renal and liver function tests), viral markers, 2D ECHO, and ECG.

Estimation of bone mineral density

BMD was measured by dual-energy x-ray absorptiometry (DXA) using a Hologic Discovery Wi, Serial No: 85297. BMD was assessed at baseline, end of chemotherapy, and 6 months post-chemotherapy at the lumbar spine (LS), femoral neck (FN), and total hip (TH). The second DXA scan was performed after completing the 7th cycle of chemotherapy within a range of 10 days. It was expressed as absolute BMD (in g/cm^2), T-score (SD from the mean for young women), or Z-score (SD from the mean for age-matched women adjusted for body mass index). Osteoporosis was defined as a T-score of more than -2.5 SD at any single mentioned site (LS, FN, and total hip).

The least significant change (LSC) for LS, FN, and TH were 0.01, 0.035, and 0.012 g/cm^2, respectively. The precision for BMD measurements at LS, FN, and TH was 1.24%, 1.72%, and 1.49%, respectively.

Fracture risk assessment tool model

FRAX predicts the 10-year probability of hip fracture and major osteoporotic fracture (i.e., hip fracture, vertebra (clinical), forearm, and proximal humerus). FRAX score is calculated based on nine clinical risk factors: age, BMD, BMI, prior fragility fracture, use of oral glucocorticoids, parental history of hip fracture, current smoking, alcohol intake, and rheumatoid arthritis.

Vertebral fracture assessment

Lateral spine imaging was done to look for any morphometric fractures. Genant's classification (vertebral anterior, middle, or posterior height reduction of more than 20%) was used to identify and interpret the fractures. The vertebral fracture (VF) grade was classified as mild if the relative height reduction was between 20 and 25%, moderate for 25–40% reduction, and severe for $> 40\%$ reduction [11]. Radiologists were blinded to the clinical diagnosis and treatment of the study subjects. Two radiologists independently reported, wherever there was discordant, it was confirmed by the third radiologist.

Assessment of baseline parameters

Serum alkaline phosphatase, creatinine, calcium, inorganic phosphate, total protein, and albumin levels were estimated at baseline using Olympus 400 Clinical chemistry analyzer,
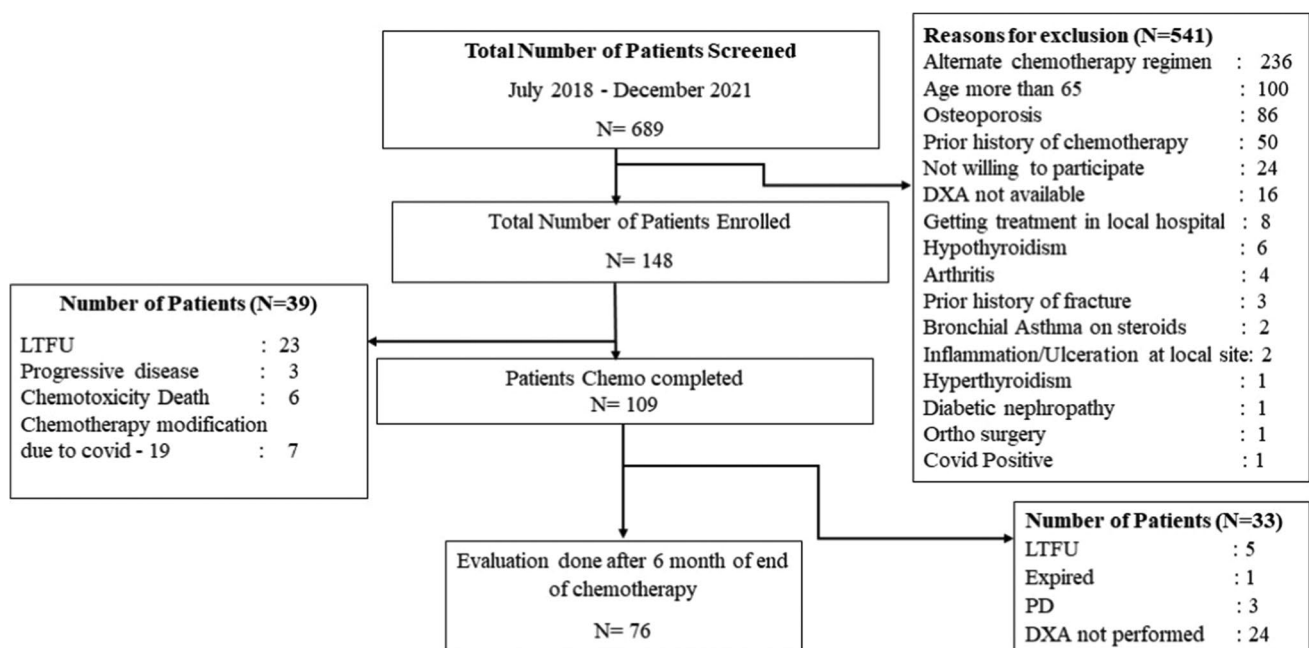

Fig. 1 Consort of the study population

Beckman Coulter, the USA. Serum 25 hydroxy Vitamin D and plasma iPTH levels were assessed at baseline using the Siemens Advia Centaur XP analyzer. The CDC has certified the Siemens ADVIA Centaur XP Vitamin D total assay and iPTH. The assay range of serum vitamin D Total: 4.2–150 ng/ml. The within-run and total coefficient of variation (CV) of this assay were 7.0% and 11.1%, respectively. The assay range of plasma iPTH was 2.5–1900 pg/ml. The within-run and total CV of this assay were 8.0% and 10.0%, respectively. A level less than 12 ng/ml indicates vitamin D deficiency. Vitamin D levels ≥ 20 to < 20 ng/ml are considered insufficiency, and ≥ 20 ng/ml is sufficient.

Statistical analyses

Continuous variables such as BMD levels and biochemical parameters were expressed in mean $\pm$ SD or median with a range based on the data distribution. The duration of menopause, age at diagnosis, and menopause were expressed in the median with range. Categorical variables such as comorbidities, stage, grade of the tumor, receptor status, TNM staging, performance status, and hormonal therapy were expressed in percentage. Percentage change in BMD was calculated as (BMD at follow-up − BMD at baseline)/BMD

Table 1 Baseline characteristics and clinicopathological features of the study population

S.No	Characteristics		$N=109$ $n\,(\%)$
1	Age at diagnosis (years)	Median (range)	53 (45–65)
2	Age at menopause	Median (range)	48 (39–57)
3	Time since menopause (years)	Median (range)	5 (1–22)
4	BMI (kg/m^2)	Mean $\pm$ SD	27.0 $\pm$ 4.82
		Underweight (<18.5)	2 (1.8)
		Normal (18.5–24.9)	39 (35.8)
		Overweight (25–29.9)	46 (42.2)
		Obese (>30)	22 (20.2)
5	Comorbidities	Hypertension	28 (25.7)
		Diabetes	34 (31.2)
6	Clinical nodal status	Positive	89 (81.7)
		Negative	20 (18.3)
7	*T* status	cTx	1 (0.9)
		cT1	3 (2.8)
		cT2	33 (30.3)
		cT3	37 (33.9)
		cT4	35 (32.1)
8	Stage	Early	34 (31.2)
		Locally advanced	75 (68.8)
9	Histological grade	1	17 (15.6)
		2	70 (64.2)
		3	18 (16.5)
		Unknown	4 (3.7)
10	Performance status	0–1	108 (99.1)
		2	1 (0.9)
11	Hormone receptors status	HR positive, Her 2 neu negative	49 (45.0)
		HR positive, Her 2 neu positive	16 (14.7)
		Her 2 neu positive	17 (15.6)
		Triple-negative	15 (13.8)
		Her 2 unknown	12 (11.0)
12	Ki -67	<14	8 (7.3)
		>14	73 (67.0)
		Unknown	28 (25.7)
13	Node	cN0	20 (18.3)
		cN1	58 (53.2)
		cN2	27 (24.8)
		cN3	4 (3.7)

at baseline × 100% at LS, FN, and TH. Baseline BMD at all three sites was checked for normality using the NS test and found to be normally distributed. Paired *t*-test and repeated measures of ANOVA were used to compare the continuous variables. McNemar–Bowker's chi-square test was used to compare the VF before and after chemotherapy.

Univariate linear regression (general linear model) was used to test the association between percentage change in BMD of LS by various factors hypothesized to impact BMD either in a positive (e.g., BMI) or negative (e.g., cumulative dose of dexamethasone, hormonal receptors, and age) direction. We used linear regression to compute the mean percentage change and 95% confidence intervals (95% CI) for LS BMD. A *P*-value of < 0.05 was considered significant. The statistical analysis was done using IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, N.Y., USA).

Result

Study population

A total of 689 postmenopausal women with non-metastatic BC patients were screened for eligibility between June 2018 and December 2021, of which 541 were excluded. Out of 541, 236 (43.6%) patients received an alternative chemotherapy regime, 100 (18.5%) patients were aged more than 65 years, and 86 (15.9%) patients were osteoporosis at baseline. A total of 148 patients were enrolled in the study. Furthermore, 23 patients were lost to follow-up, 3 had progressive disease, 6 died due to chemotoxicity, and chemotherapy modifications were done in 7 patients due to COVID-19. One hundred nine patients completed two BMD time points (baseline and end of chemotherapy). A subset of patients (*n*=76) had an additional BMD (third) at 6 months post-chemotherapy to study the long-term effects of chemotherapy on bone health, as shown in Fig. 1.

The baseline characteristics of the study population are shown in Table 1 and supplementary table 1. The median age of the study population was 53 (45–65) years. The median duration of menopause among the women was 5 (1–22) years. The baseline BMI was 27.0 ± 4.82 kg/m^2.

Thirty-four (31.2%) of women had diabetes, and none of the subjects were treated with thiazolidinediones (TZDs) or sodium-glucose cotransporter-2 (SGLT2) inhibitors. There were 34 (31.2%) early and 75 (68.8%) locally advanced BC patients. The majority of our patients had Grade II 70 (64.2%), followed by grade III 18(16.5%) and grade I 17(15.6%) tumors.

Out of the 109 patients, 38 (34.9%) patients received adjuvant chemotherapy, and 71(65.1%) received neoadjuvant chemotherapy (NACT). Only 4 (3.7%) patients had undergone breast-conserving surgery, 98 (89.9%) patients were treated with modified radical mastectomy, and 7 (6.4%) patients had never undergone surgery. Out of 7 patients, one patient defaulted, three patients had progressive diseases, and three never underwent surgery.

Hormone receptor-positive breast cancer was seen in 71 (65.14%) patients, and 59 received hormonal therapy as maintenance after chemotherapy. All biochemical parameters at baseline were normal except serum total alkaline phosphatase. Sixteen (14.7%) patients had high serum ALP at baseline. None of the patients in our study population was vitamin D deficient at baseline, as shown in supplementary table 2.

Bone mineral density

Overall data

Baseline and end of chemotherapy (*N* = 109) Twenty-nine patients with normal BMD and 80 patients with osteopenia at baseline were included in the study. The mean BMD level

Table 2 Changes in mean BMD and FRAX score before and after chemotherapy in postmenopausal women with non-metastatic breast cancer

S.No	Parameter	Baseline (*N*=109)	End of chemotherapy (*N*=109)	% Change in BMD	*P*-value
I	Bone mineral density				
1	Lumbar Spine (gm/sq.cm)	0.922 ± 0.096	0.900 ± 0.094	-2.36 ± 2.90	0.0001
	T score (SD)	-1.14 ± 0.87	-1.33 ± 0.85		
2	Neck of the femur (gm/sq.cm)	0.745 ± 0.088	0.726 ± 0.096	-2.63 ± 3.79	0.0001
	T score (SD)	-0.93 ± 0.79	-1.10 ± 0.86		
3	Total hip (gm/sq.cm)	0.876 ± 0.098	0.857 ± 0.099	-2.08 ± 2.80	0.0001
	T score (SD)	-0.55 ± 0.81	-0.69 ± 0.83		
II	FRAX score				
1	Major osteoporotic fracture risk (%) (median, IQR)	1.7 (1.4)	2.7 (2.4)		0.0001
2	Hip fracture (%) (median, IQR)	0.2 (0.2)	0.4 (0.6)		0.0001

a: Change in BMD in Lumbar spine on treatment
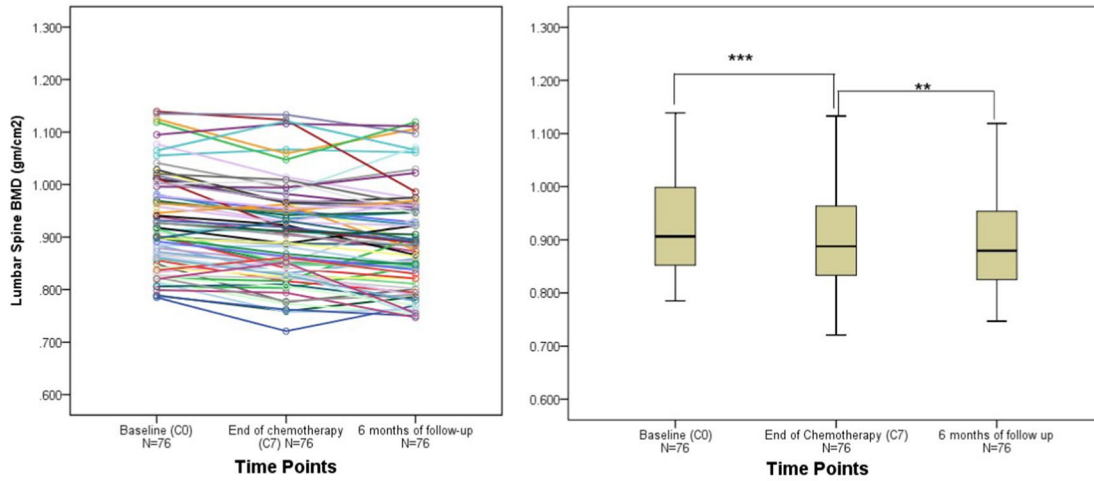
b: Change in BMD at the Femoral Neck on treatment
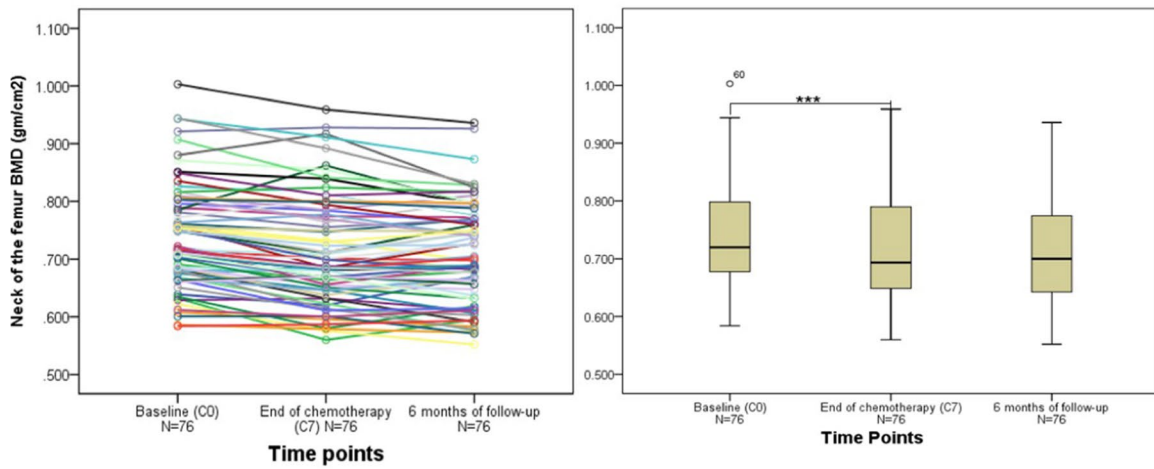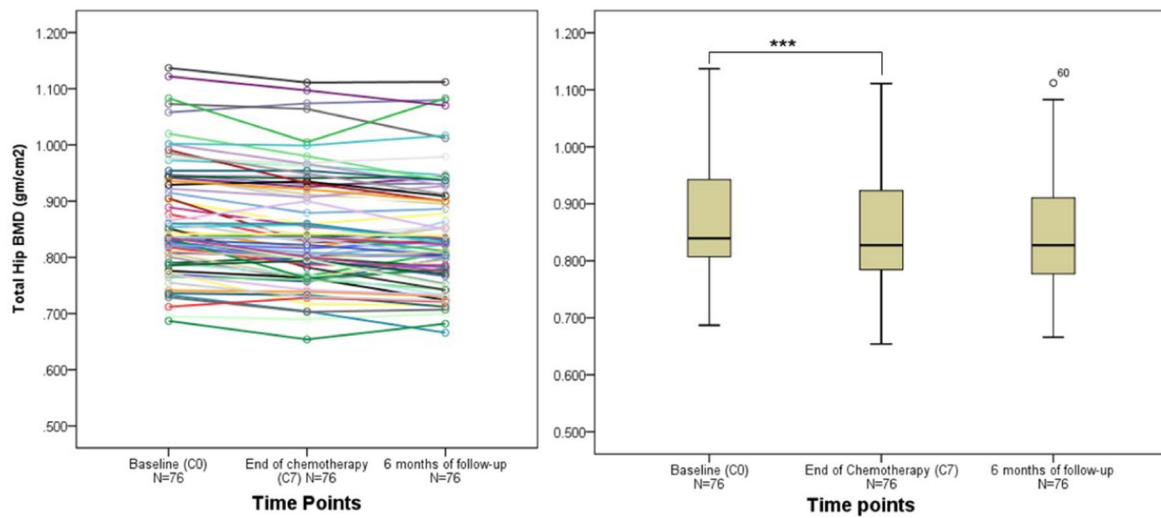

c: Change in BMD at the total hip on treatment

◄**Fig. 2** Changes in BMD levels at three sites during chemotherapy and after six months of follow-up ($n = 76$) in postmenopausal women with non-metastatic breast cancer. **P value < 0.05; ***P value < 0.0001

at baseline was 0.922 ± 0.096 gm/sq.cm at LS, 0.745 ± 0.088 gm/sq.cm at FN, and 0.876 ± 0.098 gm/sq.cm at TH. Mean BMD was decreased, at all skeletal sites, after the completion of 7 cycles of chemotherapy as compared with baseline. Significant decrease in the BMD level at LS from 0.922 ± 0.096 gm/sq.cm to 0.900 ± 0.094 gm/sq.cm, FN from 0.745 ± 0.088 gm/sq.cm to 0.726 ± 0.096 gm/sq.cm, and TH from 0.876 ± 0.098 gm/sq.cm to 0.857 ± 0.099 gm/sq.cm (P-value $= 0.0001$). The percentage decreased in BMD levels at LS, FN, and TH were -2.36 ± 2.90, -2.63 ± 3.79, and -2.08 ± 2.80, respectively, as shown in Table 2.

Follow-up BMD data ($N = 76$) Out of 109 patients, follow-up data was available only for 76 patients to assess BMD. Figure 2 shows a significant decrease in BMD level at LS after completion of chemotherapy as compared with baseline (P-value $= 0.001$) and after 6 months of follow-up as compared with the end of chemotherapy BMD (P-value $= 0.02$). However, a statistically significant decrease in BMD level was found in FN and TH after completion of chemotherapy as compared with baseline (P-value < 0.05). There was no significant difference in BMD levels at the FN and TH between the end of chemotherapy and 6 months later.

Hormone positive versus hormone-negative group

BMI and age-matched subgroup analysis ($n = 76$) was performed based on hormone receptor status. Significant worsening of % BMD at all three sites was observed in both the hormone-positive and hormone-negative groups during chemotherapy. Worsening of BMD (-1%) at all three sites continues even after the stoppage of chemotherapy over the next 6 months in the hormone negative group. There was a significant decrease in mean % BMD change at LS of -5.1% from baseline in the hormone-negative group compared with the hormone-positive group of -2.8% ($P = 0.02$), as shown in Fig. 3.

FRAX scores

The median risk of major osteoporotic fracture at 10 years during chemotherapy increased from 1.7 (1.4) to 2.7% (2.4) (P value $= 0.0001$), and for hip fracture increased from 0.2 (0.2) to 0.4% (0.6) (P-value $= 0.0001$) as shown in Table 2. The median risk of major osteoporotic fracture at 10 years ($n = 76$) increased from 1.9 (1.6) to 2.2% (1.9) (P value $= 0.0001$), and for hip fracture increased from 0.2 (0.3) to 0.3% (0.5) (P-value $= 0.0001$) during follow up.

Vertebral fracture

Assessment of VF was done by using Genant's classification. Out of 66 patients, 5 (7.6%) patients had asymptomatic VF with moderate and severe deformity at baseline. Seven have developed new-onset fractures after completion of chemotherapy (P-value $= 0.016$), as shown in Table 3. There is a worsening in the fracture grade and type of deformity compared with the baseline as shown in Table 4 and supplementary table 3. The mean percentage change in BMD in a patient with and without a fracture at LS was -2.50 ± 2.74 and -1.84 ± 2.83, respectively ($P = 0.33$).

Univariate analysis

In univariate analyses, no significant associations were found between covariates (age at menopause, BMI, time since menopause, baseline vitamin D level, stage, surgery, subtypes, chemotherapy, baseline DXA, fracture) and percentage BMD change at LS post-chemotherapy, as shown in supplementary table 4a.

In the univariate analysis during follow-up, the patients with hormone-negative had a substantial BMD loss of 5.1%. This was significantly higher than the loss seen in patients with the hormone-positive group ($P = 0.02$). BMD levels are decreased substantially in non-obese patients as compared with obese as shown in supplementary table 4b.

Discussion

There is insufficient evidence to recommend bone-modifying agents and monitoring BMD in women with BC on chemotherapy. According to the literature, various international guidelines such as ASCO, SIOG, St. Gallen, and Belgian Bone Club recommend screening and managing bone health in women with BC during hormonal therapy. Serial monitoring of BMD is recommended in patients with non-metastatic BC with high-risk factors for osteoporosis and increased fracture risk on hormonal treatment [12–15]. On reviewing the guidelines, we found that only ESMO guidelines suggest zoledronate, typically initiated along with GnRH analogues during neoadjuvant chemotherapy for women with early BC irrespective of their menopausal status deemed at significant risk for recurrence [16]. The grade of recommendation is low as the evidence is limited. This was the reason for prospectively studying bone health during cytotoxic chemotherapy in a well-selected population of early and locally advanced breast cancer.

The significant decrease in BMD (2%) at the lumbar spine, femoral neck, and total hip during cytotoxic chemotherapy translates into a considerably increased risk of clinical and subclinical fractures if not treated with

Fig. 3 Percentage changes in BMD levels at three sites in postmenopausal women with non-metastatic breast cancer based on hormonal status (*n* = 76)

Percentage changes in BMD levels at three sites

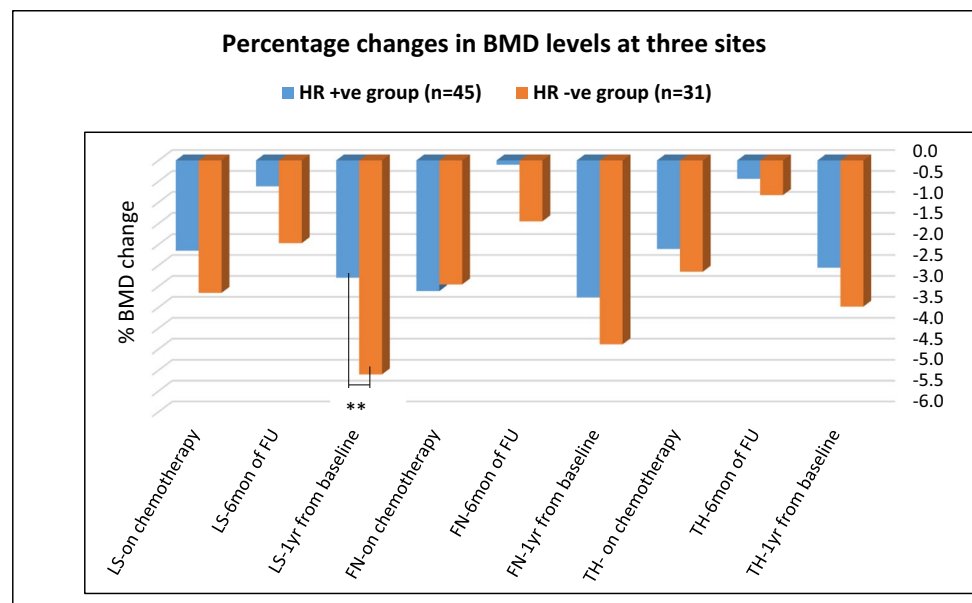■ HR +ve group (n=45)   ■ HR -ve group (n=31)

Table 3 Assessment of vertebral fracture in postmenopausal women with non-metastatic breast cancer on chemotherapy

S.No	Baseline (*N*=66)	End of chemotherapy (*N*=66)				*P*-value
1	Fracture	Yes (*n*=12)			No (*n*=54)	
	Yes (*n*=5)	5 (41.7)			0(0.0)	0.016
	No (*n*=61)	7 (58.3)			54 (100.0)	
2	Site of fracture					
		No (*n*=0)	L1 (*n*=2)	L2 (*n*=2)	L5 (*n*=8)	
	No (*n*=7)	0	0	1	6	
	L1 (*n*=2)	0	2	0	0	
	L2 (*n*=1)	0	0	1	0	
	L5 (*n*=2)	0	0	0	2	

Table 4 Assessment of fracture grade in postmenopausal women with non-metastatic breast cancer on chemotherapy

Baseline (*n*=66)		End of chemotherapy—grade (*n*=66))			
		Normal	Mild deformity	Moderate deformity	Severe deformity
		(*N*=54)	(*N*=6)	(*N*=5)	(*N*=1)
Grade	Normal (*n*=61)	54	6	1	0
	Moderate deformity (*n*=4)	0	0	4	0
	Severe deformity (*n*=1)	0	0	0	1

bone-modifying drugs. A bone loss of approximately 0.1 g/cm^2 at LS increases the risk of VF by a factor of 2.3 [17, 18].

Other studies on women with BC on chemotherapy showed a significant decrease in BMD levels. These studies include a mixed population of pre and postmenopausal women with BC and non-uniform chemotherapy regimens [7]. BMD loss of 0.018 ± 0.025 g/cm^2/5 months in the hip region was observed in our study population after chemotherapy, which corresponds to a 2% loss in BMD. We believe that a loss of 2% in 5 months within a short interval is as significant as a loss of 10% over 2 to 24 years. Studies have shown that a decrease in total hip BMD level of 0.01 g/cm^2/year was associated with a 1.2-fold increase in fracture risk [19]. Our study shows that BMD changes could be demonstrated within a short interval of 5 months which may not be attributed to the aging process, which is usually seen over a longer time period. A 5% decrease in BMD at the lumbar spine after 6 months of completion of chemotherapy has

been observed in hormone-negative patients. This suggests that worsening of bone matrix continues even after stoppage of chemotherapy. This effect was more prominent in the hormone negative compared to hormone positive group. The possible reason for this could be due to treatment with bisphosphonates during hormone therapy at follow up after completion of chemotherapy in the hormone positive group.

Anthracyclines, taxanes, and steroids (dexamethasone) as antiemetics affect bone mineral density during chemotherapy. Several chemotherapy agents, including cyclophosphamide and methotrexate, may directly affect bone metabolism independent of their impact on the gonadal state [9]. Studies have shown that 5-FU induces severe trabecular bone loss due to enhanced resorption. It also causes significant suppression of hematopoietic cell proliferation and promotes apoptosis of chondrocytes and osteoblasts. Epirubicin has genotoxic effects on mouse bone marrow cells. Cyclophosphamide inhibits bone remodeling and promotes low bone mass [20].

The vertebral fracture rate was seen in 12 (18.2%), of which 9.1% had moderate-to-severe grade VF. The characterization of the type of VF showed that the biconcave fracture was the most common type, followed by the wedge fracture and the crush fracture. The VF grade is concordant with the study by Rajan et al., who reported that 29.2% of postmenopausal women over 60 had moderate to severe VF [21]. Patients with VF have a 2- to fourfold higher mortality than subjects without VF [22]. New onset fractures during chemotherapy were seen in 7 (11.5%), again suggesting the clinical relevance of falls in the BMD during cytotoxic chemotherapy.

The median risk of Major Osteoporosis Fracture at 10 years and hip fracture (FRAX score) after completion of chemotherapy in our study population was 2.7% (2.4) and 0.4% (0.6), respectively. Rajan et al. proposed a FRAX Score cut-off for MOF cut-off of $\geq 9\%$ and a hip fracture cut-off of $\geq 2.5\%$ for predicting VF in non-cancerous populations [21]. This tool is not validated in women with BC on chemotherapy. There seems to be a significant increase in the FRAX score during chemotherapy, although not reaching the cut-off as proposed by Rajan et al. This may be due to short follow-up, and over the years, during the follow-up, it could increase the risk.

We were not able to demonstrate any factor that could possibly be associated with bone health, like age, tumor biology, chemotherapy regimens such as neoadjuvant and adjuvant chemotherapy, and hormonal therapy.

Strength of the study

The strength of this study is robust inclusion and exclusion criteria with a uniform population (postmenopausal with ages between 45 and 65 years and antineoplastic therapy and exclusion of metabolic disorders).

Limitations of the study

The enrolment of healthy individuals as control would have provided more information regarding the age-related decrease in BMD. We had a shorter follow-up to study the clinical risk of fracture. The inclusion of biochemical parameters for bone metabolism corroborates with the BMD findings.

Conclusion

This study prospectively suggests and confirms a significant worsening of bone health associated with cytotoxic chemotherapy as evidenced by BMD in a uniform population, which continues to worsen during follow-up even after completion of chemotherapy. A causal effect cannot be inferred from this study due to a lack of control. The need for bone-modifying agents like bisphosphonates, denosumab, and calcium/vitamin D supplements should be considered during the time of chemotherapy initiation, irrespective of the baseline bone health status.

Data Availability Data will be available on request.

Declarations

Conflict of interest None.

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