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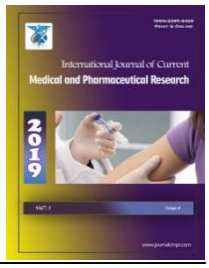

Research Article

STUDY OF SERUM BONE MARKERS IN PATIENTS OF CARCINOMA BREAST UNDERGOING CHEMOTHERAPY

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ABSTRACT

Background: Breast cancer is the most common cancer and the leading cause of cancer-related deaths among women worldwide. The annual global incidence of breast cancer is estimated to be >1.3 million cases and approximately 465,000 women die of this disease every year. Osteoporosis is a common chronic problem in postmenopausal women that increases the risk for spinal compression fractures and fractures of the femoral neck, causing life-threatening complications. Cancer-induced osteoporosis is a long-term complication associated with cancer therapy that can directly or indirectly affect bone metabolism. The change in rate of bone metabolism is reflected much earlier in biochemical markers than by bone mineral densitometry. **Objective:** To analyze the change in serum bone resorption marker, CTelopeptide (CTX) before and after the treatment in patients of carcinoma breast. Method: This prospective clinical study involves 27 histopathologically proven cases of carcinoma breast patients which was conducted during October 2017 to August 2018 to analyze the change in serum bone resorption marker, CTelopeptide (CTX) before and after the treatment in patients of carcinoma breast. In this study, frequency tables with counts and percentages are used to describe pre-treatment and treatment characteristics for each group .The categorical clinical characteristics between the two treatments are compared using chi-square test. **Result:** in this study the Majority of the patients had stage IIIB and IIB disease 12 out of 27(44.4%) patients presented with IIIB disease, 9 out of 27(33.3%) belongs to stage IIB, 4 out of 27 (14.8) were in IIIA, 3 patients out of 27(11.1%) had IIIC disease. The mean pre-treatment serum CTX level was 19.52±3.3 µg/ml and mean post-treatment serum CTX was 75.79±18.19 µg/ml ,highly significant difference was found between the mean pre and post-treatment serum CTX level in postmenopausal group (p=0.0001), it is statistically insignificant in pre-menopausal patients (p=0.460).**Conclusion:** Osteoporosis is a common chronic problem in postmenopausal women that increases the risk for spinal compression fractures and fractures of the femoral neck, causing life-threatening complications in older women. Women treated for cancer may be at risk for osteoporosis and fracture. Cancer-induced osteoporosis is a long-term complication associated with cancer therapy that can directly or indirectly affect bone metabolism. Serum biochemical bone turnover markers (BTM) are used in the management of bone diseases including postmenopausal osteoporosis (PMO). Among bone resorption markers, serum C-Telopeptide cross-link of type 1 collagen (CTX) is a highly sensitive indicator of bone resorption. By analysing the CTX before and after treatment can help cancer patients to know the grade of osteoporosis hence the appropriate treatment modality.

INTRODUCTION

Breast cancer is the most common cancer and the leading cause of cancer-related deaths among women worldwide. [1] The annual global incidence of breast cancer is estimated to be >1.3 million cases and approximately 465,000 women die of this disease every year. Advances in technologies for early diagnosis and therapies for breast cancer have substantially improved survival and clinical outcomes in recent years, especially in US and other developed countries. [2] Breast cancer significantly influences the women's health and is assuming greater importance in the developing countries due to the rising incidence, delay in presentation and dismal outcome. [3] Osteoporosis is a systemic disease with low bone mass and micro architectural changes that compromises bone strength leading to skeletal fragility and fracture. With increase in life expectancy, osteoporosis is one of the major and serious public health problems and common cause of morbidity and mortality in postmenopausal women and men above 60 years. [4] Osteoporosis is a common chronic problem in postmenopausal women that increases the risk for spinal compression fractures and fractures of the femoral neck, causing life-threatening complications. [5] Women treated for cancer may be at risk for osteoporosis and fracture. Cancer-

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induced osteoporosis is a long-term complication associated with cancer therapy that can directly or indirectly affect bone metabolism. Osteoporosis in women treated for cancer occurs more rapidly and tends to be more severe compared with the normal age-related bone loss. Cancer treatment induces bone loss, which causes bone fragility and an increased susceptibility to fractures. Bone loss was apparent in both spine and hip regions, suggesting that the effect of chemotherapy is systematic. Adjuvant chemotherapy could damage postmenopausal ovaries which may affect bone health in postmenopausal women. [6] Also suggested that adjuvant chemotherapy affected bone density adversely in postmenopausal women. The change in rate of bone metabolism is reflected much earlier in biochemical markers than by bone mineral densitometry. C-terminal cross-linked telopeptide of type I collagen (CTX) is the carboxyterminal peptide of mature type I collagen with the cross-links attached and are released during bone resorption. [7] Serum CTX provides a dynamic indicator of the current level of bone resorption, showing significantly earlier response to therapy (within 3-6 months).

Objective

To analyze the change in serum bone resorption marker, CTelopeptide (CTX) before and after the treatment in patients of carcinoma breast.

MATERIAL AND METHODS

The present prospective clinical study involving 27 patients of carcinoma breast was conducted during October 2017 to August 2018 in the Department of Radiotherapy, in collaboration with the Department of Community Medicine, Chhattisgarh Institute of Medical Sciences, CIMS Bilaspur, Chhattisgarh. The Departmental Research Committee has approved the study and the informed written consent of the subjects has been recorded individually.

Patient Inclusion criteria

The Patients taken up for the study were Required to meet the Following Criteria

a. Cytologically and histopathologically proven cases of carcinoma breast.
b. Premenopausal/postmenopausal women.
c. Age more than 25 years and less than 50 years.
d. ECOG performance score of 0 or 1.
e. Patient with normal liver function test, renal function test and haematological parameters.
f. Patient with normal electrocardiogram.

Investigation Done

Serum Carboxyterminal cross-linked Telopeptides of Collagen Type I (CTX) was done in every patient before start of treatment and was repeated in all the patients, during 3rd monthly follow up after completion of therapy.

Specimen Collection

Blood samples were collected by venepuncture taking care to avoid haemolysis. The serum was separated from the cells within 3 hours of blood collection. Then the serum samples were immediately frozen to <-18ºC and kept at the Department of Endocrinology. For monitoring the individual patient, follow up samples were collected under same conditions as that of baseline samples. Heparinised samples were used for analyzing plasma. Paired serum sample were collected both before starting therapy and during 3 months follow up, for the measurement of Serum CTX along with Serum Calcium, Serum Phosphorus and Serum Alkaline Phosphatase.

Materials Used

Streptaverdin coated microtitre plate.

Microwell strips (12×8 wells) pre-coated with streptaverdin.

Crosslaps Standard-0

One vial of ready for use PBS buffered solution with protein stabilizer and preservative.

Crosslaps Standard 1 to 5

Five vials of ready for use, Crosslaps standard in a PBS buffered solution with protein stabilizer and preservative. The exact value of each standard is printed on the Quality Control Report.

Control 1 and 2

Two vials of ready for use, desalted urinary antigen of human origin in a PBS buffered solution with protein stabilizer and preservative.

Biotinylated Antibody

One vial of concentrated solution of a biotinylated monoclonal murine antibody specific for degradation of C-terminal telopeptide of type-I collagen.

Peroxidase Conjugated Antibody

One vial of a concentrated solution of a peroxidase conjugated murine monoclonal antibody specific for degradation products of C-terminal telopeptide of type-I collagen.

Incubation Buffer

One vial of a ready for use of buffered solution eith protein stabilizer, detergent and preservative.

Substrate Solution

One vial of ready for use tetramethylbenzidine (TMB) substrate in acidic buffer.

Stopping Solution

One vial of ready for use 0.18 mol/L sulphuric acid.

Washing Buffer

One vial of a concentrated washing buffer with detergent and preservative.

Sealing Tape

Adhesive film for covering films during incubation.

Assay Procedure

All the reagents and samples were mixed before use, avoiding foam formation. In order to measure 40 paired samples, 80 strips were needed for the assay. All the samples were tested in duplicate. For each run, a total of 16 wells were used for standards and controls. Prior to use, all the solutions were equilibrated to room temperature (18-22ºC).

Steps of the assay

Preparation of the antibody solution

Antibody solution was prepared 30 minutes before starting the assay. Biotinylated Antibody, Peroxidase Conjugated Antibody and Incubation Buffer were mixed in the volumetric ratio of 1+1+100 in an empty container. It was carefully mixed and a fresh antibody solution was prepared.

One step incubation

50µl of standards, controls or unknown samples were pipetted into appropriate wells followed by 150µl of the antibody solution. The immunostrips were covered with sealing tape and incubated for 2 hours at room temperature on a microtitre plate mixing apparatus at 300rpm.

Washing

The immunostrips were washed 5 times with 300 µl diluted Washing Buffer, using an automated plate washer. It was made sure that the wells were completely emptied after each automated washing cycle.

Incubation with chromogenic substrate solution

100 µl of the Substrate Solution was pipetted into each well and incubated for 15 minutes at room temperature in the dark on the mixing apparatus (300rpm). Sealing tape was also used.

Stopping of the color reaction

100 µl of Stopping Solution was pipetted into each well.
A.*Absorbance* at 450 nm with 650 nm as reference was measured, within two hours. Osteomark CTX assay provides a quantitative measurement of the cross-linked Carboxy-telopeptides of the bone type I collagen (CTX). CTX is a specific biochemical indicator of bone resorption that is generated as result of osteoclast activity on bone.

CALCULATION OF RESULTS

The mean of the duplicate absorbance was calculated. A standard curve on graph paper was constructed by plotting the mean absorbances of the six standards 0-5 (ordinate) against the corresponding Crosslaps concentrations. The Crosslaps concentration of the controls and each patient sample was determined by interpolation.
Detection limit: 0.020 ng/ml Crosslaps.
The serum Crosslaps Elisa is linear in the range of 0.020 ng/ml to 3.380 ng/ml of Crosslaps.

Statistical Analysis

In this study, frequency tables with counts and percentages are used to describe pre-treatment and treatment characteristics for each group .The categorical clinical characteristics between the two treatments are compared using chi-square test. For continuous variables, mean and median values were compared between the groups using the t-test, Pearson Coefficient was used to derive the association between two variables. The comparison between treatment arms were done using log-rank test. A p -value of <0.05 was taken as significant. Data are analysed using the statistical software SPSS for windows (version 19.0).

Follow Up

After completion of treatment, patients were followed up on a monthly basis in the department of Radiotherapy. A minimum of 3 monthly follow up per patient was recorded. They were assessed for loco-regional recurrence and /or distant metastasis by clinical examination and/or by necessary investigations.

RESULTS

The present prospective study was carried out on 27 histopathologically proven cases of Carcinoma Breast during the period 0ctober 2017 to August 2018. All patients were evaluated with a detailed history, clinical examination, hematological and radiological investigations. In addition Serum C-Telopeptide measurement was done in all patients. The observations were recorded as per the proforma. 3 patients defaulted either before or during treatment and 3 patients expired during treatment. Hence, only 21 patients completed chemotherapy, and had investigations done during the follow up period. Patients completing chemotherapy had undergone C-terminal Telopeptide of Type I collagen (CTX) measurement during follow up.

Age

21 out of 27 patients (77.7%) among all patients completed chemotherapy and follow-up on time were in range of 34-50 yrs. And 3 out of 27 patients (11%) who expired after first measurement were in the range of 40-48 yrs. And 3 patients out of 27 (11%) who defaulted in follow-up were in range of 34-40 yrs. mean age were 44±4.9 yrs in all patients completing treatment. From among the 27 patients, the youngest patient was 34 years old and oldest was 50 years of age. (Table-1)

Table 1 Age wise Distribution of Patients

Age Groups (years)	All Patients Nos. (%)(n=27)	Patients Completing treatment Nos. (%) (n=21)
31-40	8 (29.6)	6 (28.5)
41-50	19 (70.3)	15 (71.4)
Mean ± S.D.	43.8±4.9	44±4.9
Minimum	34yrs	35yrs
Maximum	50yrs	50yrs

Menopausal Status

21 patients (77.7%) among all 27 patients were postmenopausal and rest 6 patients (22.2%) were premenopausal. In patients completing treatment and follow-up, 18 out of 21 patients (85.7%) were postmenopausal and the rest 3 patients (14.2%) were premenopausal. (Table-2)

Table 2 Menopausal Status of the patients

Menopausal Status	All Patients Nos. (%) (n=27)	Patients completing treatment Nos. (%) (n=21)
Premenopausal	6 (22.2)	3 (14.2)
Postmenopausal	21 (77.7)	18 (85.7)

TNM

Majority of the patients had stage IIIB and IIB disease. 12 patients out of 27(44.4%) presented with IIIB disease, 9 out of 27(33.3%) belongs to stage IIB, 4 out of 27 (14.8) were in IIIA, 3 patients out of 27(11.1%) had IIIC disease. (Table-3)

Table 3 Distribution of Patients according to TNM Stage

TNM Stage	All Patients Nos. (%)(n=27)	Patients completing treatment Nos. (%) (n=21)
IIIB	12 (44.4)	13 (61.9)
IIB	9 (33.3)	5(23.8)
IIIA	4 (14.8)	3 (14.2)
IIIC	3(11.1)	2 (9.5)

Body Mass Index (BMI)

Majority of the patients, i.e. 19/27 (70.3%) had a BMI in the normal range of 18.5 to 24.9kg/m². BMI <18.5 kg/m² was seen in 1 out of 27 patients (3.7%). None of the patients were obese (i.e. BMI>30 kg/m²). In patients completing treatment, 14 patients out of 21 (66.6%) had BMI in normal range (18.5-24.9 kg/m²) and in 1 patient (4.7%) it was less than 18.5 kg/m² (i.e. underweight). (Table-4)

Table 4 Distribution of patients according to Body Mass Index (BMI)

Body Mass Index (kg/m²)	All Patients Nos. (%) (n=27)	Patients completing treatment Nos. (%) (n=21)
<18.5	1 (3.7)	1 (4.7)
18.5-24.9	18 (66.6)	14 (66.6)
25.0-29.9	8 (29.6)	6 (28.5)
>30.0	0 (0)	0 (0)
Mean ± SD	23.48 ± 3.12	23.91±3.2
Minimum	17.8kg/m²	17.8kg/m²
Maximum	29.5kg/m²	29.5kg/m²

Change in Serum CTX level and Menopausal status

The mean pre-treatment serum CTX level was 19.52±3.3 µg/ml and mean post-treatment serum CTX was 75.79±18.19 µg/ml. The mean pre-treatment serum CTX level showed no significant difference between pre-menopausal and post-menopausal patients (p=0.741). Similarly, the mean post-treatment serum CTX level also had no statistically significant difference between premenopausal and postmenopausal patients (p=0.447). Whereas, highly significant difference was found between the mean pre and post-treatment serum CTX level in postmenopausal group (p=0.0001), it is statistically insignificant in pre-menopausal patients (p=0.460). (Table-5)

Table 5 Change in Serum CTX level after treatment according to Menopausal Status

Menopausal status (Nos.)	Pre-treatment(µg/ml)	Post-treatment(µg/ml)	P value (Between paired group)
Premenopausal (3)	22.50±1.3	90.45±20.09	0.460
Postmenopausal (18)	18.97±3.36	73.35±17.25	**0.0001**
Total (21)	19.47±3.37	75.79±18.19	**0.0001**
P value (Between above groups)	0.741	0.447	

DISCUSSION

Osteoporosis is a common chronic problem in postmenopausal women that increases the risk for spinal compression fractures and fractures of the femoral neck, causing life-threatening complications in older women. In a prospective study [8] the serum and urinary N-Telopeptide (NTx) levels, Bone Mineral Densitometry (BMD), serum concentrations of total and ionic Calcium, Phosphorus, and Total Alkaline Phosphatase in a group of 70 patients diagnosed to have osteoporosis were studied and were compared with 50 healthy subjects. The BMD value in the study group was 2.8 ± 1.2 SD below the mean value for young adults as compared to the control values, 1.6 ± 1 SD. The correlation coefficient of the urinary NTx and BMD was 0.98 and the correlation between serum NTx and BMD was 0.76, which is highly significant. They concluded that levels of serum total and ionic Calcium, serum Phosphorus and serum Total Alkaline Phosphatase showed no statistical significance in the two groups. Cancer-induced osteoporosis is common in women and men with breast cancer or men with prostate cancer who receive chemotherapy, hormone therapy, or surgical castration; these treatments are associated with hypogonadism and induce bone loss. In a study by [9] 49 premenopausal women with stage I or II breast cancer receiving adjuvant chemotherapy, 35 experienced ovarian failures, defined as more than 3 months of amenorrhea. In the present study 21 out of 27 patients (77.7%) who completed treatment were in range of age 34-50 yrs. 3 out of 27 patients (11%) who expired after first measurement were in the age range of 40-48 yrs. And 3 patients out of 27(11%) who defaulted in follow-up were in the range of 34-40 yrs mean age was 44±4.9 yrs in patients completing treatment. From among the 27 patients, the youngest patient was 34 years old and oldest was 50 years of age. 21 patients (77.7%) among all 27 patients were postmenopausal and rest 6 patients (22.2%) were premenopausal. In patients completing treatment, 19 out of 21 patients (90.4%) were postmenopausal and the rest 2 patients (9.5%) were premenopausal. Majority of the patients had stage IIIB and IIB. 12 patients out of 27(44.4%) presented with IIIB disease, 9 out of 27(33.3%) had stage IIB, 4 out of 27 (14.8) were in IIIA, 3 patients out of 27(11.1%) were at the time of presentation had IIIC. Majority of the patients, i.e. 19/27 (70.3%) had a BMI in the normal range of 18.5 to 24.9kg/m². BMI <18.5 kg/m² was seen in 1 out of 27 patients (3.7%). None of the patients were obese (i.e. BMI>30 kg/m²). In patients completing treatment, 14 patients out of 21 (66.6%) had BMI in normal range (18.5-24.9 kg/m²) and in 1 patient (4.7%) it was less than 18.5 kg/m² (i.e. underweight). In the present study, Serum CTX values were significantly raised in these patients suggesting increased demineralization and worsening of osteoporosis as a result of chemoradiotherapy. In 95.2% cases, serum CTX was raised more than two times the pretreatment level indicating extensive bone loss. Biochemical markers of bone metabolism provide valuable information for the detection of bone loss. Monitoring of bone turnover markers might be useful for the identification of patients at high risk for skeletal complications and guide the frequency of treatment. [10] studied early breast cancer patients receiving adjuvant Letrozole who were randomly assigned to receive either upfront or delayed-start Zoledronic acid (4 mg intravenously every 6 months). The delayed group received Zoledronic acid when lumbar spine (LS) or total hip (TH) T score decreased to less than −2.0 or when a nontraumatic fracture occurred. The primary end point of this study was to compare the change in Lumbar Spine BMD at month 12 between the groups. Secondary end points included change in Total Hip BMD and changes in serum bone turnover markers at 12 months. Serum NTx and BSAP concentrations were measured in a subset of 212 patients with baseline characteristics similar to the entire study population. Both serum NTx and BSAP concentrations significantly decreased in the upfront group and significantly increased in the delayed group by month 12. Upfront treatment with Zoledronic acid induced relatively rapid decreases in the rate of bone turnover. 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. Levels of the urinary bone resorption marker N-telopeptide and the serum bone formation marker bone-specific Alkaline Phosphatase were assessed by [11] every 3 months for patients with prostate cancer (203) and NSCLC or other solid tumors (238) and were categorized as low or high. Patients were monitored for skeletal-related events, bone disease progression, and death. Patients with high N-Telopeptide levels had an increased relative risk of skeletal-related events (prostate cancer, RR =3.25, 95% CI = 2.26 to 4.68, *P*<.001; NSCLC and other solid tumors, RR = 1.79, 95% CI = 1.15 to

2.79, *P* = .010), disease progression (prostate cancer, RR = 2.02, 95% CI = 1.48 to 2.74, *P*<.001; NSCLC and other solid tumors, RR = 1.91, 95% CI = 1.16 to 3.15, *P* = .011), and death (prostate cancer, RR = 4.59, 95% CI = 2.82 to 7.46, *P*<.001; NSCLC and other solid tumors, RR = 2.67, 95% CI = 1.85 to 3.85, *P*<.001) compared with patients with low N-Telopeptide levels.The study of bone markers by [12] documented values of biochemical markers of bone remodeling in 106 patients of breast cancer with bone metastasis. Based on scintigraphic and radiological findings, patients were divided into 3 groups: 19 patients with bone metastases, 65 patients without bone metastases and normal bone scintigrams, and 22 patients with pathological, non-malignant findings on scintigraphy without proof of bone metastases. Urinary cross-linked type I collagen N-telopeptides (NTx) and serum cross-linked type I collagen C-telopeptides (CTX) were assessed as markers of bone resorption. Bone Alkaline Phosphatase (BAP) was assessed as a marker of bone formation. All three markers were significantly higher in patients with bone metastases compared to both patients without skeletal recurrence and those with pathological, non-malignant scintigraphic findings ($p < 0.01$). There were no statistically significant differences between the latter two groups. The clinical sensitivity for diagnosing bone metastases was 44% for NTx, 65% for CTX, and 26% for BAP, respectively.

In the 21 patients completing treatment, the serum CTX levels were measured both before and after treatment. The mean pre-treatment and post-treatment serum CTX level were 19.52 ± 3.3µg/ml and 75.79 ± 18.19µg/ml respectively. There was a highly significant increase (p=0.0001) in mean serum CTX among paired samples of patients completing treatment. Whereas, highly significant difference was found between the mean pre and post-treatment serum CTX level in postmenopausal group (p=0.0001), it was statistically insignificant in pre-menopausal patients (p=0.460).

CONCLUSIONS

In patients completing chemo-radiotherapy, majority of the premenopausal patients were osteopenic, whereas majority of the postmenopausal patients were osteoporotic. The serum CTX values after completion of treatment were significantly raised, indicating increase in bone resorption as a result of chemo-radiotherapy. Rapidly progressing bone resorption results in worsening of osteoporosis which causes bone fragility and an increased susceptibility to fractures at Lumbar spine and Hip region. The post-menopausal patients were having the most significant increase in serum CTX level as compared to premenopausal patients. Patients with advanced stage disease had more significant increase in serum CTX as compared to early stage disease.Clinicians should be aware of the risk of bone loss, so that such predisposed patients can be screened and treated appropriately to prevent the long-term morbidity and mortality of osteoporosis in these patients.

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