THE PROGNOSTIC AND PREDICTIVE VALUE OF SERUM BONE BIOMARKER (CTX) IN PATIENTS WITH BREAST CANCER METASTATIC TO BONE RECEIVING ZOLEDRONIC ACID

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ABSTRACT

Background: *Bone metastasis in breast cancer patients can lead to the development of skeletal related events such as pathological fractures, cord compression, bone marrow infiltration, hypercalcemia of malignancy and the need of radiotherapy or surgery to bone. Each of these complications may substantially reduce quality of life and, in some cases, may affect the overall survival. The use of bone targeted agents had led to decrease of the skeletal related events, however, prognostic and predictive markers are needed to identify patients who are at greater risk of bone disease progression and development of SRE despite using bone modifying agents.*

Aim of the Work: *The aim of this study was assessment of the prognostic and predictive role of serum bone biomarker CTX in breast cancer patients with bone metastasis.*

Patients and methods*: Sixty five consecutive patients who have received any type of systemic treatment (chemotherapy, hormonal therapy or targeted therapy) and zoledronic acid i.v. every 4 weeks were enrolled in this prospective non randomized study. Serumβ CTX was measured at 6 month intervals and it was correlated with the clinical outcomes*

Results*: Between March 2017 and December 2018, 65 patients with breast cancer and bone metastases were included in the study, 31 patients with bone only disease and 34 with bone and visceral metastasis. Patients with baseline serum β CTX above 122 pg/ml (the median value) had statistically significantly lower mean PFS compared to patients who had baseline β CTX equal or below 122pg /ml (9 months versus 10.5 months). Also patients with increasing β CTX during the follow up period had significantly lower PFS compared to patients with decreasing serum βCTX (7.7 months versus 11.2 months), patients who developed at least one SRE during the study period had statistically significant higher baseline serum βCTX, however the median values at 6 months and 12 months did not correlate with the occurrence of SRE.*

Conclusion: *Baseline serum βCTX is a promising tool that can be used as a potential prognostic marker for bone disease outcome and a predictive marker for occurrence of skeletal related events in breast cancer patients with bone metastasis.*

Key words: *Breast cancer, Tumor marker, Bone marker, Bone metastases. Beta-crosslaps, Collagen degradation products.*

INTRODUCTION:

Breast cancer is the most common malignancy and the leading cause of cancer related death among women worldwide. In EGYPT it is the most commonly diagnosed cancer among women representing 32.04% of the newly diagnosed cases[(1)].

Metastatic breast cancer (MBC), is not curable, but it is considered treatable, with a 5-year average survival of 23.4%, so, therapeutic decisions should be realistic, individualized and should primarily focuses on prolonging survival, maintaining quality of life, and delaying disease progression. Bone is the most common organ affected by distant relapse of breast cancer. Around 70% of metastatic patients will have lesions at bone and the most commonly affected sites are throughout the axial skeleton. Across all tumor types, patients with breast cancer have the highest incidence of skeletal complications[(2)].

Even though, breast carcinoma with metastases confined to bone is generally regarded as an indolent disease, bone secondaries usually present with bone pain and, whether lytic or blastic in appearance, often lead to skeletal complications typically referred to as skeletal related events (SREs) such as pathological fractures, cord compression, bone marrow infiltration, hypercalcemia of malignancy and the need of radiotherapy or surgery to bone. Each of these complications may substantially reduce quality of life and, in some cases, may affect the overall survival[(3)].

Bisphosphonates can reduce skeletal complications from malignant bone disease. In the absence of bone-targeted treatments, 68% of breast cancer patients with bone metastasis will develop one or more skeletal related events in two years[(2)].

Evidence suggests that bone markers may help to identify patients at high risk of developing bone metastasis complications or bone lesion progression, allowing improved follow-up. Many trials concluded that they can be used as a quantitative method of response evaluation, prediction of the occurrence of skeletal related events and a as prognostic tool for bone metastasis patients[(4)]

Bone formation markers include osteoblastic enzymes or by-products of active osteoblasts during osteoblastogenesis as bone-specific alkaline phosphatase (BALP) and serum procollagen type I N-terminal and C-terminal peptides (PINP and PICP)[(5)].

The majority of bone resorption markers are by-products of type I collagen degradation which is present in more than 90% of organic bone matrix as Serum levels of the carboxy [C]-terminal cross-linked telopeptides of type I collagen CTX and urinary concentration of amino [N]- terminal cross-linked telopeptides of type I collagen (NTX). Also non collagenous bone matrix proteins, osteoclastic enzymes in addition to several regulators of bone cells' activity[(5)].

Measurement of C-terminal telopeptide of type 1collagen (CTx-I) is one of the most reliable methods to monitor the process of bone turnover as it is a sensitive marker of bone resorption that is released into the circulation during the bone remodeling process. Therefore, the rate of bone loss can be monitored by frequent measurement of CTX levels[(6)].

CTX can be measured in the serum and the urine with manual and automated tests. CTX peptides occur in heterogeneous forms; they occur as native, non-isomerized α CTX and isomerized β CTX form. β CTX reflect the dynamics of relatively old bone and has a significantly circadian rhythm being highest in the early morning and lowest in the afternoon. Also, its level decreases with eating, for these reasons, blood tests for determination of β CTX should be withdrawn in the early morning after overnight fasting[(7)].

Zoledronic acid produces significant declines from baseline in serum and urinary levels of beta CTX, and this response

appears to be associated with a favorable clinical outcome[8].

Assuming that bone metastasis requires a modification of bone formation and resorption, it seems likely that measurement of bone markers like CTX during palliative therapy in metastatic breast cancer patients could be useful as a prognostic marker and for prediction of therapeutic response to zoledronic acid if applied and interpreted correctly. In contrast to imaging techniques, bone marker measurements are easy to perform, minimally invasive and relatively inexpensive.

AIM OF THE WORK:

The aim of this study was assessment of the prognostic and predictive role of serum bone biomarker CTX in breast cancer patients with bone metastasis.

PATIENTS AND METHODS:

This study was a prospective single arm non-randomized study including consecutive breast cancer patients with bone metastasis treated at the department of clinical oncology Ain Shams University hospitals.

Patient population: Sixty-five pathologically confirmed breast cancer metastatic bone patients who have received any type of systemic treatment (chemotherapy, hormonal therapy or targeted therapy) and zoledronic acid i.v. every 4 weeks were recruited in this study.

Eligibility criteria: Patients >18 years. Histologically confirmed breast cancer. Bone metastasis with or without visceral metastasis. Eligible for receiving zoledronic acid treatment.

Exclusion criteria: Metabolic bone disease. The presence of any contraindication to zoledronic acid as renal failure or hyper sensitivity or non-correctable hypocalcemia. Second malignancy.

Pretreatment evaluation and sample collection: All eligible patients had a written consent before the study entry, followed by baseline clinical evaluation including assessment of the ECOG performance status and the RTOG numerical pain score with full examination of breast, chest, abdomen and skeletal system. Also a review of the analgesics used by the patient, available labs and available imaging was done. Baseline imaging including CT chest and pelvi-abdomen with contrast and bone scan were requested. Blood sample (5 ml) was collected on the next morning before 9 o'clock in the fasting state (overnight fasting) for the analysis of beta CTX serum level using ELISA technique. The samples were processed immediately and the serum was stored at -20°C until further examination.

All patients in the study received treatment with zoledronic acid as a 15-minute intravenous infusion every 3-4 weeks, before starting treatment with zoledronic acid the patients underwent dental assessment so as to do any intervention 14 days before starting treatment. Also renal function test, serum calcium level and creatinine clearance were done.

During follow-up, clinical assessment was performed at monthly intervals, evaluation of extra skeletal disease by CT scans was performed every 2-3 months. Bone evaluation was repeated every 6 months or on bone disease progression and it included bone scintigraphy with Tc-99m, as well as CT scans or MRI when necessary. Blood samples for CTX determination was obtained approximately every 6 months. The patients were followed up for 12 months. Skeletal-related events, including pathological fractures, hypercalcemia of malignancy, neurologic abnormalities due to spinal cord compression, the need of surgical fixation and need for bone

irradiation, were recorded. Assessment of bone response was done using the MD Anderson criteria (MDA).

The ability of serum beta CTX to predict the clinical outcome (prognostic marker) and to predict the treatment effect of zoledronic acid (predictive marker), was tested in multiple ways. Patients were divided into two groups for comparison with clinical outcomes: group with high baseline CTX (above median value) and other with low baseline CTX (below median value). Another comparison was done between the groups with declined CTX during 12 months of treatment versus increasing CTX during 12 months of treatment. According to clinical response patients were divided to responders (CR, PR, and SD) or non-responders (PD).

Progression free survival was defined as the time from randomization till progression or death.

Statistical analysis: The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for social science (SPSS15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data were presented as mean and standard deviation for parametric quantitative data and median with interquartile range for quantitative non parametric data. Frequency and percentage used for presenting the qualitative data.

RESULTS

Demographics characteristics

Between March 2017 and December 2018, 65 patients with breast cancer and bone metastases were included in the study, 31 patients with bone only disease and 34 with bone and visceral metastasis. Baseline patient characteristics and CTX expression are shown in Table 1

Serum CTX in the study groups

There was a correlation between serum CTX and the type and extent of bone disease. More specifically it was higher in patients with bone lesions more than 3 versus equal or less than three lesions and it was also higher in patients with predominantly lytic lesions.

Table (1): Comparison of baseline expression of serum CTX protein in bone metastatic cancer breast patients according to the age and menopausal status

Groups	**Number (%)**	**Basal Serum CTX level(pg./ml)Median (range)**	**Statistics**
Age subgroups			□2=0.08
≤53	35 (54)	90 (10 – 220)	p=0.77 [NS]
>53	30 (46)	91 (12 – 255)	
Menopausal status			F=0.311
Pre-menopausal	24 (37)	83 (10 – 220)	p=0.73[NS]
Post-menopausal	41 (64)	92 (12 – 255)	

□^{2}= Kruskal Wallis test value, F: ANOVA test value, NS: non-significant statistical difference.

Table (2): The baseline expression of serum CTX protein in bone metastatic cancer breast patients according to stage at diagnosis and different histopathological features.

Groups	Number (%)	Basal Serum CTX level(pg./ml)	Statistics
Histopathology			□2=0.232
Invasive ductal	55 (85)	90 (10 – 225)	p=0.63 [NS]
Invasive Lobular	10 (15)	96 (40 – 252)	
Tumor Grade			□2=0.118
II	51 (79)	86 (10 – 255)	p=0.73 [NS]
III	14 (21)	97 (35 – 155)	
Molecular			F= 0.585
Luminal A	55 (85)	92 (10 – 255)	p=0.63 [NS]
Luminal B	5 (8)	69 (35 – 133)	
HER2 enriched	1 (1)	NA	
Triple negative	4 (6)	71 (63 – 155)	
Stage at diagnosis			□2=0.005
I/II/III	38 (59)	91 (12 – 255)	p=0.94 [NS]
IV "metastatic"	27 (41)	90 (10 – 220)	

Luminal A: [ER^+/PR^+, $HER2^-$], Luminal B: Triple positive, NA: not available "only one case in this group"

Table (3): The baseline expression of serum CTX protein in bone metastatic cancer breast patients according to number, site and predominant type of bone metastases at diagnosis

Groups	Number (%)	Basal Serum CTX level(pg./ml)	Statistics
Number of bone metastases at diagnosis			≠:=5.079
≤3	21 (32)	46 (35-69)	p=0.00٧ [HS]
>3	44 (68)	109.5(84–138)	
Site of bone metastases			F= 0.77
Axial	28 (43)	90 (12 – 252)	p=0.46 [NS]
Extra axial	3 (5)	139 (95 – 156)	
Both	34 (52)	84 (10 – 252)	
Predominant type of bone metastases			□2=13.019
Lytic	42 (65)	93.5(69–139)	p=0.001 [HS]
Sclerotic	8 (12)	63.5(47.5–95)	
Mixed	15 (23)	69(41–126)	

≠:Mann-Whitney test, □2: Kruskal-wallis test

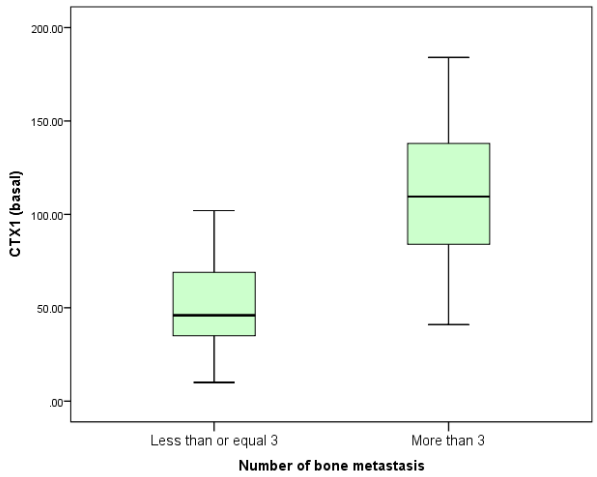
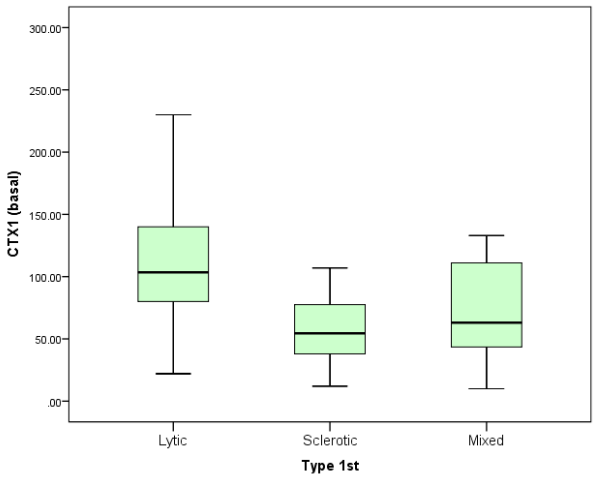


Figure (1): Correlation between CTX and number of bone metastasis.



Figure(2):Correlation between CTX and type of bone metastasis.

Serum CTX as a prognostic factor:

During the study period 57 out of 64 patients had the 3rd sample, of them, 36 patients showed reduction in the serum CTX level.

Patients with baseline serum CTX above 122 pg/ml (the median value) had statistically significantly lower mean PFS compared to patients who had baseline CTX equal or below 122pg /ml (9 months versus 10.5 months). Also patients with increasing CTX during the follow up period had significantly lower PFS compared to patients with decreasing serum CTX(7.7 months versus 11.2 months as shown in table (4) and figure(3,4).

Table (4): Comparative analysis between the different values of baseline CTX (above versus below median) and change of CTX level from basal to 12 month, and patients PFS (Kaplan Meier survival analysis).

		Total N	PFS (months)		95% CI		Log rank Test	
			Mean	SE	Lower	Upper	X^2	P-value
Basal CTX	Below or equal median(≤122pg/ ml)	31	9.128	0.664	7.827	10.43	8.872	0.003(S)
	Above median (>122pg/ ml)	34	10.56	0.528	9.524	11.595		
CTX change	Increased	24	7.750	0.768	6.245	9.255	26.217	0.000(HS)
	Decreased	33	11.226	0.404	10.434	12.017		

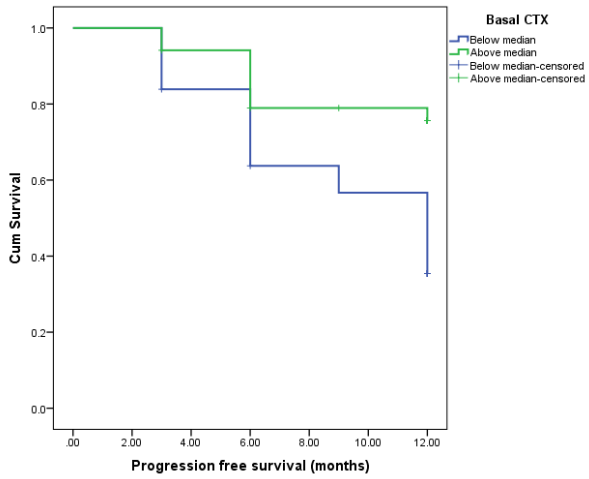


Figure (3): Kaplan Meier graph illustrating the difference in PFS between the group of patients who had above median baseline serum CTX and those with baseline lower than median value.

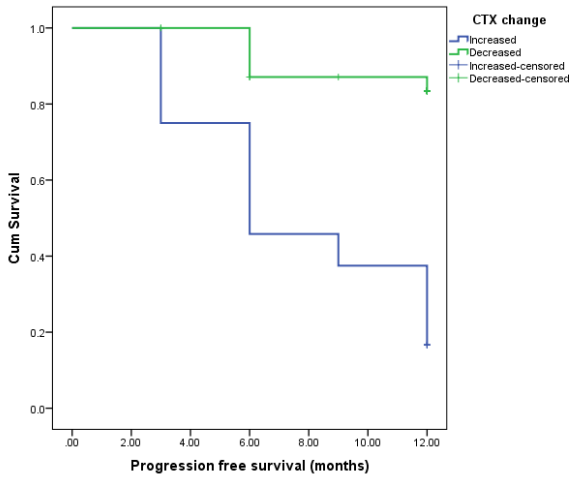


Figure (4): Kaplan Meier graph illustrating the difference in PFS between the group of patients with increasing serum CTX versus those with decreasing CTX during the study period.

There were 33 patients in the clinical benefit group who had any degree of clinical response (stable disease or regression) and 24 patients with clinical progression. Serum CTX showed significant decrease in 85% of the responders group and significant increase in 79% of non-responders as seen in table (5) and figure(5).

Table (5): Correlation between the CTX level change during the study period and the imaging response

		CTX change				Test value	P-value	Sig.
		Increased		Decreased				
		No.	%	No.	%			
Imaging response	Non responder	19	79.2%	5	15.2%	23.358	0.000	HS
	Responder	5	20.8%	28	84.8%			

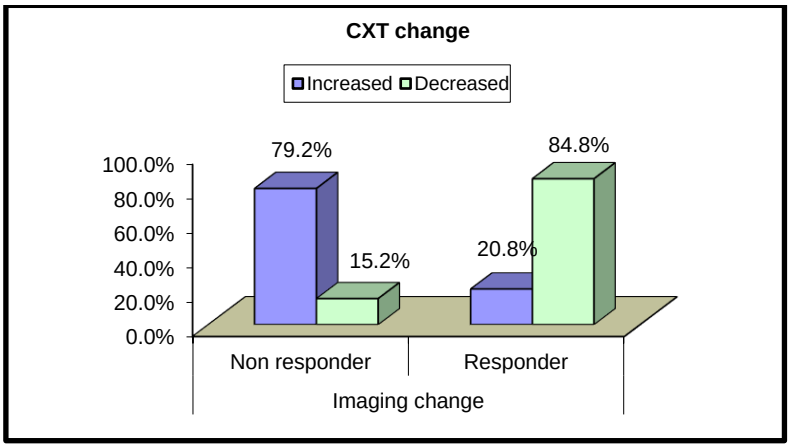


Figure (5): Correlation between imaging response and the change in CTX level during the study period.

CTX as a predictive factor:

Correlation between serum CTX level and occurrence of SRE:

When a Correlation between serum CTX level and occurrence of SRE was done, patients who developed at least one SRE during the study period had statistically significant higher baseline serum CTX, however the median values at 6 months and 12 months did not correlate with the occurrence of SRE as shown in table (6)

Table (6): Correlation between median CTX levels at different time points with the occurrence of SRE.

	Skeletal related events		Test value	P-value	Sig.
	No	Yes			
	Median(IQR)	Median(IQR)			
CTX1 (basal)	76(56 –90)	103.5(60.5 –139.5)	-2.041	0.041	S
CTX2 (at 6months)	81(40 –105.5)	89(64 –130.5)	-1.688	0.091	NS
CTX3 (at 12 months)	90(46 –155)	95(55 –130)	-0.042	0.966	NS

Also, patients who had baseline serum level above 122 pg/ml (the median level) showed higher rate of skeletal related events during the study time. However there was no significant correlation between increasing CTX during the study and the rate of SRE as shown in tables (7,8) and figures(6).

Table (7): Correlation between the median baseline level of CTX and the frequency of skeletal related events during the study period.

		Skeletal related events				Test value	P-value	Sig.
		No		Yes				
		No.	%	No.	%			
Basal CTX	Below median	14	66.7%	17	38.6%	4.477	0.034	S
	Above median	7	33.3%	27	61.4%			

Table (8): Correlation between the change in level of CTX and the frequency of skeletal related events during the study period.

		Skeletal related events				**Test value**	**P-value**	**Sig.**
		No		**Yes**				
		No.	**%**	**No.**	**%**			
CTX change groups	Increased	9	47.4%	15	39.5%	0.324	0.569	NS
	Decreased	10	52.6%	23	60.5%			

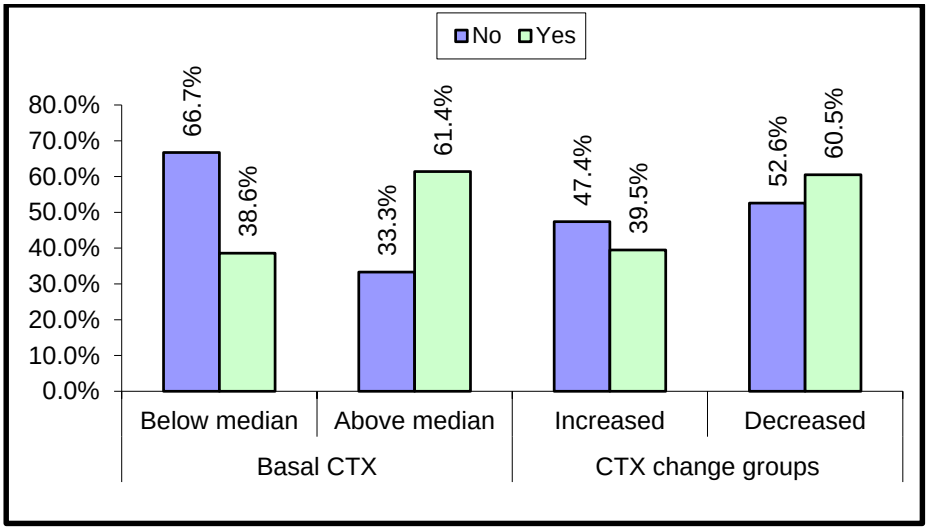


Figure (6): Bar chart showing the relation between serum CTX level difference at baseline and changes over the study and the occurrence of SRE.

DISCUSSION:

Breast cancer is the most common malignancy in women, with approximately 1.7million new cases of breast cancer occurring worldwide each year. Bone is one of the most common sites of distant metastases in breast cancer and usually associated with the development of skeletal related events that may affect the patient`s quality of life.

Bone metabolism involves a continuous and dynamic process, known as the bone remodeling cycle. The presence of the breast cancer cells in the bone microenvironment alters the remodeling balance in many circumstances in favor of bone resorption[(9)].

Bone targeted agents as bispho-sphonates are recommended as a standard therapy in breast cancer patients with bone metastases, whether they are symptomatic or not as it can reduce skeletal complications from malignant bone disease.

Bone markers in serum or urine may be useful tools for diagnosis, prognosis and monitoring of bone metastasis as well as prediction of efficacy of bisphosphonates in prevention of skeletal-related events. It can reflect both the formation and resorption of bone and can be used as a quantitative method of response evaluation if applied and interpreted correctly.

In the current study baseline serum CTX was significantly higher in patients with more than 3 bone metastasis and patients with predominantly lytic metastasis. The ZOTECT study assesses the effect of zoledronic acid on bone-marker levels and potential correlations with disease outcomes in breast and prostate cancer patients. They have also reported that greater extent of bone disease was associated with elevated bone turnover marker levels (≤6 metastasis versus 6-20 metastasis versus superscan)[(10)].

This was addressed in other types of cancers as well. In a study conducted in China to assess the diagnostic and prognostic role of formation and resorption bone markers in lung cancer patients, Wang et al found that the levels of BALP, PINP and β-CTX were significantly higher in patients with multiple bone site involvement but, no statistically significant difference among patients with lytic, blastic or mixed bone lesions. Their interpretation to the nonsignificant difference between the osteoblastic and osteolytic metastasis was that both the occurrence of lytic or blastic metastasis are characterized by

simultaneous resorptive and osteoblastic processes [11].

There was a statistically significant reduction in serum CTX level after zoledronic acid treatment in the whole study population. Our results were consistent with the results of the study conducted by Mountzios G et al which had evaluated the effect of treatment with zoledronic acid on biochemical markers of bone remodeling including CTX in patients with solid tumors and osseous metastases including breast cancer patients, as he had found that among all markers of bone resorption, only CTX was found to be significantly reduced in the whole study population after zoledronic acid therapy [12].

Also, a study conducted in Spain by Lopez et al. to evaluate serum CTX as a predictive markers for disease progression in cancer patients with bone metastases, who are being treated with zoledronic acid, had a similar results. The study enrolled 26 patients of different tumor types including 8 patients who had breast cancer and it showed that serum CTX had decreased significantly at 6 months and remained low at 12 months compared to baseline among patients with different tumor types.

During follow-up, serum CTX levels declined significantly following the administration of zoledronic acid. Following the initial decline, serum CTX levels remained suppressed as long as patients responded to the antiresorptive treatment. When bone disease progressed, in contrast, 79% of patients who had imaging progression had increase in the CTX observed, indicating that the serum CTX concentration closely follows the evolution of bone disease.

These results were similar to those which were reported by Song et al., in their study conducted in China to investigate the application of the bone turnover markers PICP and β-CTX in the diagnosis and treatment of breast cancer with bone metastases. Their results have shown that as there was a statistically significant increase in the serum level of CTX in patients who had clinical progression, also, there was a statistically significant decrease in serum CTX in the clinical benefit group (SD or regression of bone disease), however, his samples was withdrawn after 3 months only [13].

The study conducted in Spain by Lopez et al reported that, patients who had disease progression had significantly higher serum CTX levels at baseline and after 18 months of zoledronic acid therapy.

As regard the progression free survival, in our study, patients in whom serum CTX level increased during the study period had a statistically significant shorter progression free survival as compared to patients with decreased serum CTX. Also patients with baseline serum CTX above median level (≥122pg/dl) had statistically significant shorter PFS.

This outcome was not addressed in breast cancer before, however, it has been addressed in patients with other types cancers, for example, in the TUGAMO study, patients with renal cell carcinoma, higher b-CTX levels at baseline were related with shorter PFS and OS time [14].

The relation between serum CTX and SRE is an area of debate and there is discrepancy in the results of literature. In our study, patients who had baseline serum level above median level showed higher rate of skeletal related events during the study time. However there was no significant correlation between increasing CTX during the study and the rate of SRE.

In their study, Lopez el al. reported that there was statistically significant correlation between increasing serum level of CTX and the development of SRE during the study period.

In a phase II multicenter trial conducted by Addison C. L. et al., it was found that

baseline CTX or BSAP were not prognostic for having a SRE in their study evaluating the effects of switching from 3–4 to 12 weekly intravenous pamidronate therapy in patients with biochemically defined low-risk bone metastases[(15)].

In their observational, prospective, multicenter trial, Barnadas et al found no significant correlation between the levels of alfa CTX, NTX, BALP and the occurrence of SREs in breast cancer patients with bone metastasis treated with zoledronic acid. This may be explained by that they measured alfa CTX that reflects the new bone turnover only not beta CTX and they measured CTX and NTX in urine not serum. Also, the low number of SREs observed in their patients (~20%) caused the study to be not powered enough to obtain statistical significance [(16)].

Several limitations of our study must be noted. First of all our study was a non-randomized prospective study with a relatively small number of patients. Second, bone metastases in breast cancer are mixed bone metastases that mainly consist of osteolytic metastases and bone formation and resorption coexist when bone metastases occur. Therefore, combining biochemical indicators reflecting bone resorption and formation can have better sensitivity and specificity in detection of abnormal bone remodeling.

Conclusion:

In conclusion, serum beta CTX level measured at baseline evaluation before starting zoledronic acid is a promising tool that can be used as a potential prognostic marker for bone disease outcome and a predictive marker for occurrence of skeletal related events in breast cancer patients with bone metastasis. Also serial measures of serum CTX can be used a prognostic tool as increasing CTX during treatment is related to shorter bone progression free survival time.

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القيمة التنبؤية و المنذرة للمعامل CTX فى الدم فى مرضى سرطان الثدى و ثانويات العظام اللاتى يتليقين عقار حمض الزوليدرونيك

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المقدمة: ثانويات العظام المصاحبة لسرطان الثدى يمكن ان تسبب زيادة فى معدل مضاعفات العظام كزيادة معدل الكسور و الضغط على اعصاب العمود الفقرى و زيادة نسبة الكالسيوم فى الدم مع الاحتياج الى تلقى العلاج الاشعاعى . و قد اثبتت الابحاث ان زيادة معدل هذة المضاعفات يؤثر سلبا على حياة المرضى. استخدام العلاج الموجة للعظام مثل عقار حمض الزوليدرونيك يساعد على انقاص معدل المضاعفات و مع ذلك مازلنا بحاجة الى استعمال عوامل تنبؤية و عوامل منذرة لتحديد المرضى اللذين غالبا ما سوف يصابون بمضاعفات العظام و تدهور ثانويات العظام حتى مع استعمال حمض الزوليدرونيك.

الهدف من الدراسة: تقيم القدرة التنبؤية و المنذرة للمعامل CTXفى الدم فى مرضى سرطان الثدى و ثانويات العظام .

الحالات و طريقة البحث: تم ادراج ٦٥ مريضة سرطان ثدى و ثانويات بالعظام و اللاتى يتليقين العقار حمض الزولدرونيك فى مستشفيات جامعة عين شمس فى هذة الدراسة المستقبلية الغير عشوائية على ان لا يكون لدي اى مريضة اى موانع مرضية تعيق استخدامها هذا العقار.

النتائج:ارتفاع المعامل CTXعن القيمة المتوسطة ١٢٢ بيكوجرام لكل ميللى فى القياس الاول و زيادتة على مدار الدراسة كان مصاحبا لسرعة تدهور ثانويات العظام. ايضا ارتفاعة فى القياس الاول كان مصاحبا لزيادة معدل مضاعفات العظام.

الاستنتاج: المعامل CTXفى الدم يمكن ان يستخدم للتنبوء بارتفاع معدل المضاعفات و سرعة تدهور ثانويات العظام فى مرضى سرطان الثدى و ثانويات العظام