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Serum Alkaline Phosphatase as a Predictive Marker for Bone Metastasis in Breast Cancer Patients Seen in a Tertiary Health Institution in Northern Nigeria.

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Abstract

Introduction: Early detection of bone metastases is helpful in the treatment of breast cancer. Change in serum levels of alkaline phosphatase could assist diagnosis and follow-up of metastatic breast cancer.

Aim: This study aimed to determine the clinical correlates of serum alkaline phosphatase (ALP) levels in breast cancer patients with bone metastases seen in the Department of Radiotherapy and Oncology, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria.

Material and Methods: All breast cancer patients' case note seen at the department of Radiotherapy and Oncology Usmanu Danfodiyo University Teaching Hospital, Sokoto from January 2012 to January 2017 were retrieved. The Information extracted include age, pre-treatment serum ALP, presence or absence of metastases, type and site of bone metastasis. Elevated serum level of ALP was defined as $\geq$ 110 IU/L. Only those with bone metastases and without metabolic bone, liver diseases and or other metastasis were included. Data was analysed using SPSS statistical software version 21.0 (SPSS Inc., Chicago, IL, USA) and presented in frequencies and percentages using tables.

Results: A total of 178 breast cancer patients were seen over the period studied. Thirty five (19.66%) had only bone metastases. Mean age was 43.5 (± 12.9) years. There was no difference in the proportion of those with elevated serum ALP in the various age groups. Patients with bone metastases had a higher proportion of those with elevated levels of serum ALP than those without bone metastases (54.3% vs 30.1%), similarly osteoblastic and mixed types had larger proportions with raised serum ALP (66.7% each) than those with osteolytic type (25.0%). Over 85% of those with multiple sites bone metastases had elevated serum ALP levels.

Conclusion: Our findings suggest that in poor resource settings serum ALP can be used to suspect bone metastases in breast cancer patients allowing early detection and prompt treatment.

Keywords: Alkaline phosphatase, Breast cancer, Bone metastases

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Introduction

The bone is the commonest site of distant metastases (1, 2). The cancers that commonly metastasize to the bone include breast, prostate and lung cancer (2). Breast cancer is also the most common cancer implicated in bone metastases in Nigeria (3). The commonest site of metastasis is the appendicular skeleton, especially the vertebral spine and the pelvis (4). Metastasis to these sites can cause serious complications if not identified and treated promptly.

Bone metastasis can be detected through radiological means using X-rays, Computed Tomography and Magnetic Resonance Imaging scans. Nuclear imaging like bone and Positron Emission Tomography scans can also identify bone metastasis.

Due to paucity of radiological imaging techniques in our environment (5, 6), other parameters can be used to point out bone metastases. Some authors also argue that the radiological investigations are not cost effective and carry the risk of radiation due to repeated use on the same set of patients (7,8). In addition, bone scan is not largely recommended as routine evaluation for evidence of bone metastasis at the time of diagnosis or during treatment except clearly indicated.

Tumour markers are used as parameters for diagnosis and monitoring of disease progress. Serum alkaline phosphate (ALP) increase occurs in the setting of bone metastasis and can be used in its early detection especially in places where the imaging modalities are either non existing or limited (9,10). This serum enzyme level in the body mirrors the activity of other isoenzymes found elsewhere in the body like gastrointestinal tract, liver and bones (11). An enormous amount of ALP is released by the osteoblast in the bones during bone repair and remodelling as well as in bone metastasis (11). Serum ALP is the most often used marker of bone formation due to the wide availability of inexpensive detection methods. Once liver disease is ruled out, serum ALP provides a good impression of osteoblast activity. Therefore, ALP is a good biomarker that can be used for early diagnosis, treatment and follow up of patients with bone metastasis.

The aim of this study is to determine the clinical correlates of ALP levels in breast cancer patients with bone metastases seen in the department of Radiotherapy and Oncology, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria.

Materials and Methods

Study area and design

The study was a retrospective study carried out at the department of Radiotherapy and Oncology Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria over a five year period (January 2012 to January 2017).

Patient selection

All breast cancer cases with bone metastasis seen within the study period were included. Elevated serum level of alkaline phosphatase was defined as value $\geq$ 110 IU/L. All patients with metabolic bone diseases, liver diseases or metastasis to the liver were excluded from the study.

Data collection

Clinical informations were retrieved from patients' records including histologic reports, radiologic and biochemical investigations. The Informations obtained include age, pre-treatment serum ALP, presence or absence of metastases, type of bone metastasis and site of metastasis. Radiologic imaging like plain x-rays, CT- scan, MRI with or without bone scan were retrieved to determine the patients that had bone metastasis and the site/region.

Ages of the patients were grouped in $\leq$39, 40-49, 50-59, 60-69 and $\geq$ 70 years. The types of bone metastasis were also grouped as osteolytic, osteoblastic or mixed and sites of metastases

grouped into regions; head and neck, cervical vertebra, thoracic vertebra, lumbar vertebra, sacro-cocygeal, upper limb, lower limb, pelvic and multiple sites. These were documented using a data extraction form.

Data analysis

The data were carefully entered, cleaned and analysed using SPSS statistical software version 21.0 (SPSS Inc., Chicago, IL, USA). Regular cleaning and editing were done to detect and correct errors. Mean (SD) was determined for age. Proportions of those with elevated and normal serum ALP according age group, presence, type and site of metastases were presented in frequencies and percentages using tables.

Results

One hundred and seventy eight breast cancer patients were seen during the period studied. A total of 35 patients (19.66%) with breast cancer had only bone metastases. The mean age of the patients seen was 43.5(± 12.9) years. Osteoblastic metastases was seen in 6, while 8 had osteolytic metastases and the remaining 21 had mixed lesions. In 17 of the patients they had metastases to multiple bone sites, 10 had metastases to the head and neck region, thoracic vertebrae (10), lumbar vertebrae (3), sacro-coccygeal (1), upper limb (2), lower limb (2) and pelvic bones (none).

Patients who had bone metastases had a higher proportion of those with elevated levels of serum ALP than those without bone metastases. The proportion of patients with elevated and normal serum ALP according various groups are shown in tables 1(age group), 2(presence of bone metastases), 3(type of bone metastases), and 4(site of bone metastases) below, respectively.

Table 1 below shows the distribution of serum levels of ALP and age groups. There is little or no difference in the proportion of those with elevated serum ALP and normal in the various age groups.

Table 1: Serum levels of ALP and age groups of the patients

	Serum ALP		
Age group	**Elevated (%)**	**Not Elevated (%)**	**Total (%)**
≤ 39	16(39.0)	25(61.0)	41(100.0)
40 – 49	21(36.8)	36(63.2)	57(100.0)
50 – 59	12(34.3)	23(65.7)	35(100.0)
60 – 69	5(18.5)	22(81.5)	27(100.0)
≥	8(44.5)	10(55.5)	18(100.0)
Total	**62(100.0)**	**116(100.0)**	**178(100.0)**

Table 2 below shows the proportion of elevated serum levels of ALP in the presence and absence of bone metastases. There is a larger proportion of those with elevated serum ALP and bone metastases (54.3%) than those without (30.1%).

Table 2: Serum levels of ALP and the presence of bone metastases

	Serum ALP		
Bone metastases	**Elevated (%)**	**Not Elevated (%)**	**Total (%)**
Present	19(54.3)	16(45.7)	35(100.0)
Absent	43(30.1)	100(69.9)	143(100.0)
Total	62(34.8)	116(65.2)	178(100.0)

Table 3 below shows the proportion of those with elevated serum level of ALP and type of bone metastases. Those with osteoblastic and mixed types had larger proportions with raised serum ALP (66.7% each) than those with osteolytic type (25.0%).

Table 3: Serum levels of ALP and the type of bone metastases

	Serum ALP level		
Type of Bone metastases	**Elevated (%)**	**Not Elevated (%)**	**Total (%)**
Osteolytic	2(25.0)	6(75.0)	8(100.0)
Osteoblastic	4(66.7)	2(33.3)	6(100.0)
Mixed	14(66.7)	7(33.3)	21(100.0)
Total	20(57.1)	15(42.9)	35(100.0)

Table 4 below shows the proportion of those with elevated serum level of ALP according to site of bone metastases. Over 85% of those with multiple

sites had raised serum ALP levels.

Table 4: Serum levels of ALP and Sites of bone metastases

	Serum ALP level			
Site	**Elevated (%)**	**Not Elevated (%)**	**Total (%)**	**P = 0.143**
Head and Neck region	7(70.0)	3(30.0)	10(100.0)	
Thoracic vertebrae	3(30.0)	7(70.0)	10(100.0)	
lumbar Vertebrae	1(33.3)	2(66.7)	3(100.0)	
Sacro-coccygeal	0(0.0)	1(100.0)	1(100.0)	
Upper limb bones	1(50.0)	1(50.0)	2(100.0)	
Lower limb bones	2(100.0)	0(0.0)	2(100.0)	
Pelvic	0(0.0)	0(0.0)	0(0.0)	
Multiple Sites	6(85.7)	11(4.3)	17(100.0)	
Total	20(57.1)	15(42.9)	35(100.0)	

Discussion

Breast cancer is a heterogeneous group of malignant tumours affecting the breast, with the potential to spread to distant sites like the bones, lungs and liver commonly (12). Bone metastasis is a serious problem in patients with advanced cancer and its presence often signifies serious morbidity prior to the patient's death. Therefore, when treating patients with breast cancer, early identification of bone metastasis is crucial. Skeletal metastases can lead to a number of related events which includes pain, pathological fractures and spinal cord compression (13).

Findings from post-mortem examination in breast cancer patients have demonstrated a very high incidence of bone metastasis of about 70 % (14). This is in contrast to our findings which was just over 19%. This may be explained our selection criteria and by the fact that some of the patients did not have higher imaging modalities like bone scan done to detect subtle metastasis as there is no bone scan facility in Sokoto, patients will have to travel far distances to other regions of the country. Except otherwise indicated and if patient can afford since they pay out of pocket bone scan was not routinely requested.

Bone metastases are often diagnosed using radiological investigations. Cost of radiologic investigations, paucity or absence of these services especially in sub Saharan Africa, necessitate the search for a simple bone biomarker in the serum with high sensitivity and specificity that can reliably detect the presence of bone metastasis once present. The advantage of biochemical bone markers over image studies are cost effectiveness (15), no fear of radiation side effects (16), differentiation of healing lesions from progressive lesions (17,18) increased sensitivity, relate to systemic changes rather than local, rapid response to treatment, and provides more information on the mechanisms and cellular dynamics of bone destruction (19).

Serum levels of alkaline phosphatase could be elevated in a number of diseases including bone metastases and can be used as a predictive marker for the early detection of bone metastases in cancer patients (9,10). This was seen in this study where a larger proportion of breast cancer patients with bone metastases had elevated levels of serum ALP compared to those without bone metastases. Similar findings were reported by Yazdani and colleagues who reported that serum ALP concentration was statistically significant in patients with and without bone metastases and the serum concentrations of ALP were significantly higher in patients with bone metastases compared with those without bone lesions (20).

In this study, we found no age group of the patients that have larger proportion of those with elevated serum than the other groups. The Danish Health 2006 5-year follow-up study on serum from 2308 participants which assessed the effects of age and sex on osteocalcin and bone-specific alkaline phosphatase, reported that levels of bone ALP increases with increasing age and sex had no effect (21). The participants did not have cancer. A study in Tehran Iran, also found increasing age and serum ALP to be independent prognostic factors for bone metastasis (20). In comparison to this study, no relationship observed between age groups may be due to our small sample size and this may also suggest that in the presence of bone metastases the effect of age on ALP as reported in

some studies may not be seen or is masked. More so total serum ALP was used in our study not bone ALP which may also account for such differences.

Increase in serum ALP levels is non-specific as it is also frequently associated with other diseases. ALP has many isoenzymes found in several organs in the body mainly liver and bones, and to some extent in placenta, kidney, intestines, and leucocytes (22). ALP isoenzyme has also been identified in various malignancies including those with bone metastasis (23). The increased level of this enzyme seen may be due to osteolytic bone metastases in breast cancer leading to increased osteoclastic activity and bone resorption.

From our findings, those with osteoblastic and mixed types had larger proportions with raised serum ALP (66.7% each) than those with osteolytic type (25.0%). A study comparing bone scintigraphy with bone markers in including total ALP in the diagnosis of bone metastasis in lung cancer patients reported that there was no significant difference in the marker levels between osteoblastic, osteolytic and mixed lesions (24).

Elevation of serum ALP to less than three times the normal level is usually not considered significant (25). On the basis of its biologic activity ALP has been shown to predict bone metastases in most studies, and to some extent liver metastases. Ritzke C. et al. (1998) reported that in addition to the high specificity of ALP in bone metastasis, the use of specific ALP isoenzymes should be considered (26).

We reported that over 85% of those with multiple sites had raised serum ALP levels which is more than the proportion of those with single site or region. This may suggest that due to the multiple sites the release of ALP is increased and is a sum effect of all the sites. A very high serum ALP has been used by some researchers to determine the burden of bone metastasis in breast cancer. Sarvari et al (2015) found that serum ALP is higher in breast cancer patients with extensive bone metastasis than normal subjects, breast cancer without bone metastasis and breast cancer with limited bone metastasis (14).

In a study conducted by the International (Ludwig) Breast Cancer Study Group (IBCSG) randomised clinical trials (1978 to 1985), ALP, aspartate transaminase (AST) and ?-glutamyltransferase (GGT) were analysed for their sensitivity in detecting recurrence in breast cancer. ALP was reported to be elevated significantly among breast cancer patients with bone metastases and /or liver metastasis as well as being more effective than AST and GGT in differentiating those with relapse from those without (27).

The use of ALP in combination with other markers in detecting bone metastasis was found to be more promising as shown by some studies. For highest predictive accuracy for bone metastases in breast cancer, a study showed usefulness of combination of axillary lymph node metastasis with CA15-3, ALP and haemoglobin concentration (28). According to the same study, the concentration of ALP identified as a risk factor for bone metastases in breast cancer patients has a cut-off value > 100.5 IU/l, our cut-off value was 110.0 IU/l. Ping Huang et al (2017) also demonstrated that for newly diagnosed patients with bladder cancer, the concentrations of ALP >116 U/L, Haemoglobin <37.5 g/L and calcium >2.54 mmol/L are risk factors for developing bone metastases (29). However, they noted that Combination of ALP, haemoglobin with calcium was more useful to diagnose the bone metastases than a single parameter. Even though this was reported in bladder cancer but we feel it can be extended to other tumours with bone metastases based on the findings in literatures discussed so far.

ALP can also be used to predict survival of breast cancer patients. The pre-treatment serum levels of

ALP is an independent prognostic factor that may help to predict survival in triple negative breast cancer (30). The aforementioned study also found that triple negative breast cancer patients with ALP >66.5 IU/L had statistically worst disease free and overall survival rates.

Our study used total serum ALP which may be impaired in the presence of other diseases. Some studies have opined that in certain situations, measurement of bone ALP rather than total ALP might provide a better index of bone formation, even though this will have to be subjected to further research (31).

Limitations of the study

This study is retrospective. Measurement of bone ALP rather than total ALP might provide a better index of bone formation. The study was hospital based. Not all patients did bone scan, therefore some patients with early bone metastases may have been missed.

Despite all the limitations, the study has highlighted an important information about serum levels of ALP in breast cancer patients with bone metastasis, which can generate questions for further research.

Conclusion

Conclusively, in a resource poor setting where some of the imaging modalities are luxuries, serum ALP can be used to suspect bone metastases in breast cancer allowing for early detection and prompt treatment of patients with metastatic bone disease in breast cancer.

Recommendation

A multi-centre randomise clinical controlled trial is required to ascertain the role of ALP in breast cancer patients with bone metastases.

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Conflict of interest

No conflict of interest in this study

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None

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