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ORIGINAL ARTICLE

Alkaline Phosphatase as Serum Tumor Marker in Osteosarcoma

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ABSTRACT

Aim: To reassess the high specificity of alkaline phosphatase as a serum tumor marker in patients with osteosarcoma
Study type: Retrospective cohort study
Study place and duration: Department of Orthopedics, DHQ Hospital Gujranwala from January 2013 to June 2021
Methods: The medical record of 140 osteosarcoma patients were reviewed retrospectively, who received treatment for osteosarcoma during January 2015 and June 2021. According to clinical factors at diagnosis, the difference in prevalence of increased ALP was assessed using Fisher`s extract test and χ2 test. In the groups with normal and high level of serum ALP at presentation, the disease-free survival (DFS) and overall survival (OS) were compared using The Kaplan–Meier estimate. At presentation the prognostic ability of increased ALP was examined using Cox regression analyses. For determination of therapeutic steps and survival related changes in levels of ALP during therapy and survival related response of ALP to therapy, Linear Mixed model (fixed model) was used.
Results: Sensitivity, specificity , Positive predictive value, negative predictive value, PLR, NLR and DOR of ALP in Metastatic osteosarcoma at 15 months follow up was 55.4%, 80.3%, 62.1%, 74.2%, 3.14, 0.864 and 5.241 respectively. Similarly, Sensitivity, specificity , Positive predictive value, negative predictive value, PLR, NLR and DOR of ALP in Metastatic osteosarcoma at 3 years follow up was 56.4%, 92.5%, 83.1%, 70.1%, 6.321, 0.632 and 8.543 respectively.
Conclusion: ALP has been found to be a very important tumor marker having high specificity in patients with osteosarcoma.
MeSH words: Osteosarcoma, Tumor, Biomarker, Alkaline Phosphatase, Metastasis, Sensitivity, Specificity

INTRODUCTION

For managing different types of cancers, serum tumor markers can be used. The serum tumor markers can also be used for diagnosing, screening of early malignancy, determining prognosis, monitoring response to treatment, and post- operative surveillance[1,2]. For sarcomas such as osteosarcoma, Ewing`s sarcoma, and rhabdomyosarcoma alkaline phosphatase (ALP) and lactate dehydrogenase (LDH), LDH, and myoglobin have been reported to be used respectively, as prognostic serum markers[3-8]. But, the tumor marker role of these serum markers for sarcoma has not been recognized. The ubiquitous enzyme, ALP, as it is present in higher amount in kidneys, liver, bones, and placenta but is also found in all other tissues too[9]. ALP is abundantly found in the osteoblasts in the musculoskeletal system and plays an important role in mineralization of bones that are formed recently[10,11] and has been considered in monitoring the primary bone lesions. In primary bone lesions, the elevation of ALP levels have been reported that lead to recognition of role of ALP as a tumor marker for osteosarcoma[3-5,12-14]. But, there are no valid values reported for ALP levels in these diseases. Sensitivity and specificity to a tumor, direct reflection of tumor severity, comparable to the outcomes of treatment, and useful for postoperative surveillance, are the entire clinical requirement an ideal tumor marker should meet[15].

For practicing a new tumor marker clinically the marker's properties must be validated for determination whether it meets the clinical requirements. The serum ALP levels were examined at each step of treatment and during each follow-up from diagnosis to postoperative surveillance, measured according to other clinical factors, and reanalyzed ALP as a marker for osteosarcoma using standard for clinical requirements mentioned above.

MATERIAL AND METHOD

The medical record of 140 osteosarcoma patients were reviewed retrospectively, who received treatment for osteosarcoma during January 2013 and June 2021 in District Head Quarters Hospital Gujranwala in Department of Orthopedics after permission from IRB. The serum AP levels was assessed at the time of diagnosis, during each step of treatment i.e. surgery, adjuvant chemotherapy, and neo-adjuvant chemotherapy, metastasis and each follow-up and examined according to oncologic results and other clinical features. Institutional review board of District Head Quarters Hospital Gujranwala approved the protocols of this study. This study included patients who received chemotherapy and surgery. Adjuvant, neo-adjuvant, and palliative chemotherapy were done in all patients in whom surgery was not done. Intra-arterial doxorubicin and cisplatin were given as double regimen, while intra-arterial cisplatin, ifosfamide, and doxorubicin were given as triplet and other regimens were used for osteosarcoma patients. For neo-adjuvant chemotherapy, the oncologic and histological outcomes were also recorded.

International units (IU) were used for quantification of level of serum ALP and p-nitro phenyl phosphate method was used for measuring the enzyme activity[16]. As there is increased velocity of skeletal growth and fast rate of bone turnover the levels of serum ALP in children are considerably high[17]. Hence, for patients below 15 years the range of serum ALP is 60.0–300.0 IU/L and for patient of age 15 or high the range 38.0–115.5 IU/L of serum ALP is considered normal. Levels of serum ALP were not considered as only bone isoenzyme but as total enzyme.

According to clinical factors at diagnosis, the difference in prevalence of increased ALP was assessed using Fisher`s extract test and χ2 test. In the groups with normal and high level of serum ALP at presentation, the disease-free survival (DFS) and overall survival (OS) were compared using The Kaplan–Meier estimate. At presentation the prognostic ability of increased ALP was examined using Cox regression analyses. For determination of therapeutic steps and survival related changes in levels of ALP during therapy and survival related response of ALP to therapy, Linear Mixed model (fixed model) was used. The relation of tumor burden and levels of Alp at presentation was evaluated using Spearman correlation analysis. During diagnosis and metastasis the ALP's diagnostic performance was validated using two-way contingency table analysis. The value of $p < 0.05$ was considered significant and all the data for serum ALP was assessed separately in patients.

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RESULTS

Table I

Variable	Normal n=60 (42.9%)	Elevation n=80 (57.1%)	P-value
Metastasis rate			
Positive	n=22 (36.7%)	n=57 (71.3%)	0.000
Free	n=38 (63.3%)	n=23 (28.8%)	
Stage			
Localized	n=40 (66.7%)	n=43 (53.8%)	0.124
Metastatic	n=20 (33.3%)	n=37 (46.2%)	
Age			
≥15	n=26 (43.3%)	n=42 (52.5%)	0.283
<15	n=34 (56.7%)	n=38 (47.5%)	
Gender			
Male	n=29 (48.3%)	n=56 (70.0%)	0.009
Female	n=31 (51.7%)	n=24 (30.0%)	
Size			
≥ 8 cm	n=25 (41.7%)	n=48 (60.0%)	0.032
<8 cm	n=35 (58.3%)	n=32 (40.0%)	
Location			
Extremity	n=22 (36.7%)	n=44 (55.0%)	0.032
Axial and proximal femur	n=38 (63.3%)	n=36 (45.0%)	
Histologic grade			
Low	n=52 (86.7%)	n=14 (17.5%)	0.000
High	n=8 (13.3%)	n=66 (82.5%)	
Histology (High grade)			
Osteoblastic	n=38 (63.3%)	n=41 (51.3%)	0.033
Chondroblastic	n=8 (13.3%)	n=9 (11.3%)	
Fibroblastic	n=5 (8.3%)	n=2 (2.5%)	
Mixed	n=5 (8.3%)	n=23 (28.8%)	
Nonconventional	n=4 (6.7%)	n=5 (6.3%)	
Huvos grade			
I and II	n=25 (41.7%)	n=56 (70.0%)	0.001
III and IV	n=35 (58.3%)	n=24 (30.0%)	
(Operability)			
Operable	n=29 (48.3%)	n=38 (47.5%)	0.922
Inoperable	n=31 (51.7%)	n=42 (52.5%)	
Resection margin			
R0	n=37 (61.7%)	n=44 (55.0%)	0.429
R1 and R2	n=23 (38.3%)	n=36 (45.0%)	
Pathologic fracture			
Yes	n=38 (63.3%)	n=27 (33.8%)	0.001
No	n=22 (36.7%)	n=53 (66.3%)	
Intracapsular extension			
Yes	n=37 (61.7%)	n=36 (45.0%)	0.051
No	n=23 (38.3%)	n=44 (55.0%)	
ALP At diagnosis	n=29 (48.3%)	n=48 (60.0%)	0.170
ALP at 1st metastasis			
Elevation	n=12 (20.0%)	n=57 (71.3%)	0.000
Normal	n=48 (80.0%)	n=23 (28.8%)	

In table I clinical and baseline characteristics of the patients included in this study have been shown. Value of ALP in patients will overall survival (60.7%) was 3.01 (2.85-4.28) (P value 0.000) while in patients with disease free survival (n=55) was 2.20 (1.54-3.68) (P value 0.005). univariate cox regression for prediction of survival and involved factors have been shown in Table II. When linear model analysis for serum levels of ALP during treatment were performed the results obtained have been shown in Table III. The relationship between levels of ALP in patients younger than 15 years of age and the total volume of the tumor, volume of the tumor in the bone and volume of the tumor extended into the soft tissue is shown in the table IV. Similarly the relationship of ALP levels in patients older than 15 years with tumor volumes is also shown in table IV.

Sensitivity, specificity , Positive predictive value, negative predictive value, PLR, NLR and DOR of ALP in Metastatic osteosarcoma at 15 months follow up was 55.4%, 80.3%, 62.1%, 74.2%, 3.14, 0.864 and 5.241 respectively. Similarly, Sensitivity, specificity , Positive predictive value, negative predictive value, PLR, NLR and DOR of ALP in Metastatic osteosarcoma at 3 years follow up was 56.4%, 92.5%, 83.1%, 70.1%, 6.321, 0.632 and 8.543 respectively.

Table II: Uni-variate cox regression for predicting factors

	Overall survival n=85 (60.7%) HR (95% C.I)	P-value	Disease free survival n=55 (39.3%) HR (95% C.I)	P-value
Metastasis at diagnosis	6.12 (4.24-7.35)	0.000	-	-
Age	1.23 (0.89-1.52)	0.001	2.01 (1.68-3.24)	0.365
Size	1.84 (0.98-1.98)	0.000	1.56 (0.68-2.58)	0.000
Location	3.58 (3.21-4.65)	0.000	2.36 (1.36-3.69)	0.000
Histologic grade	7.32 (6.87-8.35)	0.007	6.35 (5.68-7.95)	0.241
Huvos grade	1.65 (1.24-2.38)	0.658	1.05 (0.58-3.54)	0.000
Resection margin	3.69 (3.47-4.01)	0.000	2.54 (1.54-3.69)	0.001
ALP	3.01 (2.85-4.28)	0.000	2.20 (1.54-3.68)	0.005

Table III: Linear mixed model analysis for serum levels of ALP during treatment

	≥15 years				< 15 years			
	Normal β±S.E	P-value	Elevation β±S.E	P-value	Normal β±S.E	P-value	Elevation β±S.E	P-value
Intercept	102.21±14.52	0.000	155.32±32.51	0.000	236.24±25.6	0.000	145.51±14.5	0.000
Treatment	-32.25±3.65	0.000	-3.54±6.54	0.365	-106.11±23.6	0.000	-13.24±6.98	0.051
Survival	85.62±2.35	0.000	23.47±6.58	0.000	241.21±25.4	0.001	60.25±36.5	0.000
Treatment+Survival	-10.25±16.54	0.000	-10.25±5.89	0.095	-103.14±36.9	0.054	-28.65±89.8	0.000

Table IV

ALP	Total tumor volume		Bone tumor volume		Extended soft tissue tumor volume	
	Pearson correlation	P-value	Pearson correlation	P-value	Pearson correlation	P-value
≥15 years	0.452	0.021	0.471	0.014	0.325	0.014
<15 years	-0.124	0.254	-0.321	0.521	-0.014	0.652

Table V

ALP at Metastasis	15 months postoperative		3 years postoperative	
	Metastasis positive	Metastasis free	Metastasis positive	Metastasis free
Elevation	n=12 (20.0%)	n=57 (71.3%)	n=38 (63.3%)	n=27 (33.8%)
Normal	n=48 (80.0%)	n=23 (28.8%)	n=22 (36.7%)	n=53 (66.3%)
Accuracy	75.2%		76.3%	
Sensitivity	55.4%		56.4%	
Specificity	80.3%		92.5%	
PPV	62.1%		83.1%	
NPV	74.2%		70.1%	
PLR	3.14		6.321	
NLR	0.864		0.632	
DOR	5.241		8.543	

DISCUSSION

At diagnosis, our cohort was 60.0% for the prevalence of increased serum levels of ALP in osteosarcoma (Table 1). In patients with osteosarcoma, sex was the only factor that affected the level of ALP unlike any other factor related to tumor (P=0.009). Many large scaled studies showed disagreement to the outcomes that sex and the prevalence of increased ALP at presentation are related to each other. In Southern China, the cohort of 177 patients with osteosarcoma in the study of Han et al. showed that there is no

correlation between sex and the prevalence of increased ALP[18]. Two studies done by Rizzoli group on showed contrary outcomes. In one study on 741 patients with osteosarcoma during March 1972 - December 1989 showed no association between sex and the prevalence of increased ALP[4] while in other study during March 1983 - June 1955 on 560 patients with osteosarcoma the male gender was reported to be associated with the prevalence of increased ALP[19]. The range of prevalence of increased ALP at presentation was 31.5%-66.3%[4,20–24]. The division of metastatic stages in every cohort study was reported to be the main cause of change in these outcomes.

In fact, in the metastatic stage the prevalence of the increased ALP at diagnosis in a previous study was reported to be 91.5%[4] and in this study was 71.3% (Table 1). However, the studies in which the metastatic stage was not included the prevalence was low i.e. 37.2% and 47%[22,23] as compared to those in which metastatic stage was included i.e. 51.2%, 58.5%, and 66.3%[4,20,24]. The sensitivity of ALP at diagnosis in our cohort was 55.4%, which can be generalized according to these findings.

During postoperative surveillance on metastasis, the specificity and sensitivity of the ALP is another critical factor of a tumor marker. When ALP levels were analyzed at first metastasis its sensitivity was 55.4% and specificity was 80.3% at the time of early stage of metastasis but in later stages its specificity was higher i.e. 92.5%. In comparison to the other tumor related markers in other type of cancers sensitivity of ALP in osteosarcoma was similar to that of alpha fetoprotein in liver cancer (hepatocellular carcinoma)[25,26] and to that of cytokeratin 19 (CYFRA-21) fragment and carcinoembryonic antigen (CEA) in the lung cancer[27-29], as in these cases the sensitivity ranged from 39% to 68%. On the other hand however, ALP sensitivity at diagnosis was not better than that of prostate specific antigen i.e. tumor marker for prostate cancer, CA-125 i.e. tumor marker for ovarian cancer and tumor marker of pancreatic cancer i.e. CA19-9 as in these cases the sensitivity ranged from 71.9% to 89.3% [30-36] but ALP sensitivity was higher than the sensitivity of CEA and CA-19-9 in colorectal cancer[37] and that of CA-15-3 in breast cancer [38, 39] where it ranged from 15.4% to 31.7%. The sensitivity and specificity of alkaline phosphatase in metastasis at the time of postoperative follow-up were quite similar to the sensitivity and specificity of CA 19-9 in colorectal cancer[37].

Some of the limitations of this study included it being a retrospective study over a long period of time. Moreover, ALP levels were measured as total levels of the enzyme instead of bone isoenzyme which in theoretical perspective is more specific to the bone, but it is not clear whether bone isoenzyme is superior to total enzyme value for representing the bone formation activity in common clinical setups[10].

CONCLUSION

Clinical value of a certain tumor marker is based on its sensitivity, specificity, responsiveness to therapy and correlation of the tumor marker to the actual tumor burden and on the basis of these criteria ALP has been found to be a very important tumor marker having high specificity in patients with osteosarcoma.

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