



Research Paper

Alkaline phosphatase (alp) levels in multiple myeloma and solid cancers with bone lesions: Is there any difference?



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ABSTRACT

Introduction: Bone involvement in Multiple Myeloma results from increased osteoclast formation and activity that occurs in proximity to myeloma cells. The role of Alkaline Phosphatase (ALP) in this process and the diagnostic significance of plasma levels in patients with MM are unclear.

Aim: To compare plasma ALP levels in patients with MM and solid cancers and metastatic lesions to the bone.

Results: In this observational retrospective study we enrolled 901 patients were enrolled: 440 patients (49%) with Multiple Myeloma, 461 (51%) with solid cancers. All 901 patients had bone lesions. Among patients with Multiple Myeloma, ALP values were mainly in the range of normality than those observed in patients with solid cancers and bone lesions. This difference is independent of stage, number and type of bone lesions.

Conclusion: This study suggests that plasma ALP has a different clinical significance in MM than in other neoplasms and could be used as a discriminating marker in presence of bone lesions. In particular, lower or normal values, should suggest further investigations such as urinary and serum electrophoresis, associated with bone marrow aspirate in case of the presence of a monoclonal component, in order to confirm or exclude a MM diagnosis.

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1. Background

Multiple myeloma (MM) is a B-cell neoplasm characterized by the proliferation of monoclonal plasma cells in the bone marrow. Lytic bone lesions are a very common in patients with MM and they increase with the progression of the disease [1].

MM cells induce a significant alteration of the bone remodeling process due to the increased formation and activation of osteoclasts and the suppression of osteoblast. Therefore, biochemical markers of bone turnover could be predictive of the bone status in patients with MM patients [2–4]. Among these, Alkaline Phosphatase (ALP) is an enzyme that is expressed in different tissues

but is particularly concentrated in the liver, kidneys, placenta and bone. In the bone, it is expressed on the surface of osteoblasts and is involved in the mineralization process of removing phosphate groups from many types of molecules, including nucleotides, proteins and alkaloids. ALP plasma levels are often increased in presence of tumor bone lesions [5]. The role of ALP as a marker of skeletal involvement has been studied in several solid cancers, especially in prostate cancer. Bone involvement in MM results from increased osteoclast formation and activity that occurs in proximity to myelomatous cells associated to the suppression of osteoblasts differentiation leading to the development of lytic lesions. The role of ALP in this process and the diagnostic significance of its plasma levels are unclear in patients with MM.

In this study we investigated the role of ALP by comparing ALP plasma levels in patients with MM and with solid cancers who had bone lesions.

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2. Material and methods

Observational retrospective study was conducted on 901 patients affected from MM or solid tumors in the period between 1991 and 2015: 440 patients with MM derived from the Italian Group of the Hematologic Disease of the Adults (GIMEMA), and 461 patients with solid tumors followed at the Oncology Unit of the University Campus Bio-Medico in Rome. All living patients have joined the study by written informed consent. All patients were over the age of 18 at the time of diagnosis and did not suffer from any other bone or liver diseases responsible for the increased plasma ALP levels. Patients were considered eligible if they were affected by MM or other malignancy with bone lesions detected with only of the following radiological procedures: X-ray, computed tomography scan (CT-scan), magnetic resonance imaging (MRI), or bone scintigraphy. MM was diagnosed according to International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma [6]. Patients with MM were classified according to International Staging System classification system (ISS) and Durie-Salmon Staging System [7,8]. MM and patients with solid Tumors were grouped according to the number of bone lesions (one lesion, two or three and more than 3 lesions), type of lesions (osteolytic, osteoblastic and mixed), number and type of bone lesion. Moreover, solid tumors were also grouped according to primary cancer (breast, prostate, lung, colorectal, kidney, stomach and other kind cancer -uterus, ovary, adrenal glands and bladder). Plasma ALP levels were collected at the time of diagnosis of malignant skeletal disease. Laboratory range of ALP between 20 and 140 U/L was considered as normal.

Statistical analysis: Demographic data were analyzed using descriptive statistics. ALP values were compared for each group using ANOVA test and Tukey's post hoc test. Two tailored P-values < 0.05 were considered statistically significant. Data were analyzed using GraphPad Prism 3.0.

3. Results

Table 1 summarizes clinical and pathological characteristics of the 901 patients entered in the Among patients with MM, 105 patients had only one osteolytic bone lesion (23.9%), 118 patients had 2–3 lesions (26.8%), the majority had more than three osteolytic lesions at the time of diagnosis (217 patients, 49.3%) with a mean ALP value of respectively 117.2U/L, 145.0U/L and 115.4U/L. Most patients were classified as first MM stage according to ISS classification (168 patients, 43.8%) and third stage according to DS staging (277 patients, 63%), of 57 patients ISS classification was not retrieved. Further detail of mean levels of ALP are reported in **Table 1**. Most patients with MM had a number of osteolytic lesions >3 (217 patients, 49.3%), first ISS stage (168 patients, 48.3%) and third stage according to the D&S stage (277 patients, 63.7%).

As for solid tumors, in our population, the bone lesions were more frequently observed: lung cancers (200 patients, 43.4%), followed by breast cancer (132 patients, 28.6%), colorectal cancer (8.7%) and prostate cancer (8.0%). Less common are kidney (3.9%), stomach (3.5%) and, eventually, urothelial and gynecological cancers which account for a total of 3.9%. Regardless of the primary tumor, bone lesions were mainly multiple (82.4%, 380 patients) while osteolytic lesions were more frequent than osteoblastic lesions (193 vs 150 patients) and only 118 had mixed bone lesions. Demographics and characteristics are shown in **Table 1**.

3.1. Statistical analysis

In patients with Multiple Myeloma no difference can be found among gender, number of osteolytic lesions, ISS and D&S stage. Moreover, in these patients, the values of ALP are normal and commonly lower than those observed in solid tumors. This difference is evident in each group and seems independent of the stage (D&S and ISS), the number and type of bone lesions. Patients with solid cancer and bone lesions have a higher mean level of ALP (187.1 U/L) compared with MM (123.8 U/L) while the lowest levels of ALP can be found in patients with bone metastatic kidney cancer (that shows a mean level of ALP of 83.9U/L).

Statistically significant differences are observed when comparing MM with prostate cancer (ALP of 328.7 U/L), particularly when this cancer shows more than 3 lesions and when these lesion are osteoblastic (mean ALP level of 365.9 and 384.0 respectively) **Table 2**.

Patients with solid tumors and more than 3 bone osteoblastic lesions (mean ALP of 216.2 U/L) have statistically and significantly different values of ALP when compared to lung cancer (ALP mean 142.8U/L, $P = 0.002$), lung cancer and osteolytic lesions (ALP mean of 115.4, $P = 0.001$), and solid tumors with lytic lesions (ALP mean 135.1 U/L, $P = 0.001$).

Patients affected by prostate cancer presenting more than 3 bone lesions (mean ALP of 365.9 U/L) and patients with prostate cancer that showed more than 3 osteoblastic lesions (mean ALP of 384.0U/L) have significantly different values of ALP when compared to solid cancers and osteolytic lesions (mean ALP of 135.1U/L, $P = 0.015$ and $P = 0.027$ respectively), lung cancer (mean ALP of 142.8U/L, $P = 0.030$ and $P = 0.047$, respectively) and lung cancer with osteolytic lesions (mean ALP of 115.4 U/L, $P = 0.10$ and $P = 0.15$, respectively).

4. Discussion

In solid Tumors, bone is the third most frequent site of metastasis, behind lung and liver. Bone metastatic disease develops as a result of multiple interactions between tumor cells and bone cells that cause alteration of normal bone metabolism [9]. ALP as bone turnover marker activity, in particular the bone-specific alkaline phosphatase isoform, is a sensitive and reliable measure of osteoblastic activity [10]. High levels are found in multiple malignancies and appear to be associated with risk of negative clinical outcomes [11]. However, lack of specificity and controversial data in the literature make this test not validated as standard in clinical practice. Its role as diagnostic marker or prognostic predictor for bone metastases is still potential and under study for several solid tumors.

Data about prostate cancer show a good sensitivity and specificity of bone alkaline phosphatase enzyme for the prediction of bone metastases and progression of disease. The vast majority of patients with metastatic prostatic cancer to bone have the higher ALP levels. Furthermore, according to some studies, higher pre-treatment ALP levels are associated with a lower response to therapy and a poorer prognosis. These data suggest that ALP is a biological marker that could be used in the evaluation of patients with metastatic prostate carcinoma to predict bone metastases and monitor the response to treatment. Therefore, in addition to the PSA, plasma ALP should also be dosed in patients affected by prostate cancer, and not only in the suspect of skeletal involvement but also during treatment [5,12–15]. Although the role of ALP has been primarily studied in prostate cancer, there is mild evidence that it

Table 1
Demographics and characteristics.

MULTIPLE MYELOMA		N	%	MEAN ALP	SD ALP
GENDER	Total	440	100.0	123.8	79.8
	M	223	50.7	122.4	77.3
	F	217	49.3	125.1	82.3
NUMBER OF OSTEOLYTIC LESIONS	1	105	23.9	117.2	79.8
	2-3	118	26.8	145.0	90.4
	>3	217	49.3	115.4	71.5
ISS STAGGE	1	168	43.8	123.6	78.6
	2	114	29.8	114.7	74.0
	3	101	26.4	128.7	86.4
DURIE AND SALMON STAGE	1	50	11.3	96.15	68.9
	2	113	25.7	119.1	74.7
	3	277	63.0	129.3	82.0
OSTEOBLASTIC LESIONS					
GENDER	Total				
	M	238	51.6	187.1	218.3
	F	223	48.4	172.3	343.3
NUMBER OF LESIONS	1	81	17.6	139.3	126.1
	2-3	115	24.9	125.2	99.4
	>3	265	57.5	216.2	360.2
TYPE OF LESIONS	Total	461	100.0	180.0	285.5
NUMBER AND TYPE OF LESION	OSTEOLYTIC	193	41.9	135.1	109.0
	OSTEOBLASTIC	150	32.5	236.8	450.0
	MIXED	118	25.6	181.2	186.4
HISTOTYPE	1 OSTEOLYTIC	38	8.2	113.3	94.3
	1 OSTEOLYTIC	29	6.3	183.6	168.5
	1 MIXED	14	3.0	117.9	67.2
	2-3 OSTEOLYTIC	54	11.7	117.1	86.4
	2-3 OSTEOLYTIC	37	8.0	120.6	94.7
	2-3 MIXED	24	5.2	150.8	129.9
	>3 OSTEOLYTIC	101	21.9	152.9	122.0
	>3 OSTEOLYTIC	84	18.2	306.3	582.5
	>3 MIXED	80	17.5	201.3	210.7
LUNG	200	43.4	142.8	424.7	
BREAST	132	28.6	176.3	152.8	
PROSTATE	37	8.0	328.6	366.4	
COLORECTAL	40	8.7	196.1	151.1	
KIDNEY	18	3.9	83.9	28.37	
STOMACH	16	3.5	321.7	205.2	
OTHERS	18	3.9	248.6	261.4	

is a predictive marker of bone metastases for other solid tumors. In breast cancer, serum ALP levels increase significantly as the stage of the cancer progresses and might indicate that the disease metastasizes to bone [16]. A study carried out on patients with renal cell carcinoma shows that high levels of ALP is associated with the presence of bone metastases and little prognostic capability [17]. Even in patients with lung cancer, a study confirms the potential role of ALP serum in detecting bone metastases [18]. According to a recent study, bone alkaline phosphatase is a possible surrogate marker of bone metastasis also in gastric cancer patients [19].

By reviewing the literature, high levels of ALP appear to be a credible predictive marker of bone metastasis from solid tumors. Conversely, data about multiple myeloma are lacking. Our study confirms the potential role of high plasma ALP value as a predictor of bone metastasis in solid tumors, especially in prostate cancer and in the case of multiple osteoblastic lesions. On the contrary, in MM the plasma levels of ALP are generally normal or slightly altered, regardless of the stage (ISS or D&S) and the number of osteolytic lesions. The differences between MM and solid tumors,

especially compared to prostate cancer, are significant. These results confirm that the process of bone involvement in multiple myeloma is different from that occurring in solid tumors because there is a lower bone turnover and/or osteoblastic associated to a lower expression of plasmatic ALP with is greatly related to the osteoblastic activity.

Limitations of the study are the retrospective design and heterogeneity of the sample. However, this is the first study investigating the role of baseline plasma ALP in multiple myeloma on such a large number of patients, comparing it with the most prevalent tumors with bone metastases.

Our study suggests that plasma ALP has a different clinical significance in MM than other cancers and it could be used as a discriminating marker in presence of bone lesions. ALP plasma dosage is a simple and cheap test that could be performed preliminarily in patients with malignant bone lesions. In case of lower or normal range values, it should suggest further simple investigations such as: urinary and serum electrophoresis, associated with bone marrow aspirate in case of the presence of monoclonal component, in order to confirm or exclude MM diagnosis.

Table 2
The correlation of Alkaline phosphatase in Prostate cancer and Multiple Myeloma.

	Multiple Myeloma	Mean ALP (SD)	P-values
Alkaline phosphatase in osteoblastic tumor with more than 3 osteosclerotic lesions (mean: 306.3; SD:582.5)	Total values from patients with multiple myeloma	123.8 (79.8)	0.0079
	1 osteolytic lesion	117.2 (79.8)	0.0011
	2–3 osteolytic lesions	145.0 (90.4)	0.0263
	>3 osteolytic lesions	115.4 (71.5)	0.0001
	1 ISS stage	123.6 (78.6)	0.0002
	2 ISS stage	114.7 (74.0)	0.0004
	3 ISS stage	128.7 (86.4)	0.0068
	1 D&S stage	96.15 (68.9)	0.0171
	2 D&S stage	119.1 (74.7)	0.001
	3 D&S stage	129.3 (82.0)	0.0001
Alkaline phosphatase in Prostate cancer (mean: 328.7; SD: 366.4)	Total values from patients with multiple myeloma	123.8 (79.8)	0.0076
	1 osteolytic lesion	117.2 (79.8)	0.0394
	2–3 osteolytic lesions	145.0 (90.4)	0.2576 (n.s)
	>3 osteolytic lesions	115.4 (71.5)	0.0073
	1 ISS stage	123.6 (78.6)	0.0265
	2 ISS stage	114.7 (74.0)	0.0257
	3 ISS stage	128.7 (86.4)	0.1091 (n.s.)
	1 D&S stage	96.15 (68.9)	0.0843 (n.s.)
	2 D&S stage	119.1 (74.7)	0.0407
	3 D&S stage	129.3 (82.0)	0.0223
Alkaline phosphatase in Prostate cancer with>3 bone lesions(mean: 365.9, SD: 399.6)	Total values from patients with multiple myeloma	123.8 (79.8)	0.0020
	1 osteolytic lesion	117.2 (79.8)	0.0095
	2–3 osteolytic lesions	145.0 (90.4)	0.0751 (n.s.)
	>3 osteolytic lesions	115.4 (71.5)	0.0018
	1 ISS stage	123.6 (78.6)	0.0065
	2 ISS stage	114.7 (74.0)	0.0061
	3 ISS stage	128.7 (86.4)	0.0281
	1 D&S stage	96.15 (68.9)	0.0210
	2 D&S stage	119.1 (74.7)	0.0099
	3 D&S stage	129.3 (82.0)	0.0056
Alkaline phosphatase in Prostate cancer with more than 3 bone osteosclerotic lesions (mean: 384.0, SD: 435.8)	Total values from patients with multiple myeloma	123.8 (79.8)	0.0052
	1 osteolytic lesion	117.2 (79.8)	0.0156
	2–3 osteolytic lesions	145.0 (90.4)	0.0973
	>3 osteolytic lesions	115.4 (71.5)	0.0044
	1 ISS stage	123.6 (78.6)	0.0124
	2 ISS stage	114.7 (74.0)	0.0109
	3 ISS stage	128.7 (86.4)	0.0401
	1 D&S stage	96.15 (68.9)	0.0256
	2 D&S stage	119.1 (74.7)	0.0164
	3 D&S stage	129.3 (82.0)	0.0118

Legend: ISS: international Staging System, SD: standard Deviation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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