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Prognostic significance of the serum phosphorus level and its relationship with other prognostic factors in multiple myeloma

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Abstract We studied the serum phosphorus (P) level of 110 patients with multiple myeloma (MM) (age range 42–83 years, median 62 years) and evaluated the relationship between that and other prognostic factors. Serum P level significantly correlated with the prognostic factors that are relevant to renal dysfunction: serum creatinine (P<0.00000001), serum β2-microglobulin (P=0.00000088), serum uric acid (P=0.0000014), and corrected serum calcium (cCa P=0.000067). Although it also correlated with the percentage of plasma cells in bone marrow nucleated cells (BMPC%) and the hemoglobin (Hb) and leukocyte counts, the significance was less than for the other four prognostic factors. Serum creatinine, BMPC%, leukocyte count, serum uric acid, bone lesions, β2-microglobulin, and serum cCa were all significantly higher and Hb significantly was lower in the MM patients with hyperphosphatemia (serum P>3.8 mg/dl). The survival time was significantly shorter in these patients (P=0.000087). Multivariate analysis (Cox's proportional hazards regression model) showed that the serum P level is a significant negative prognostic factor in MM patients.

Keywords Hyperphosphatemia · Multiple myeloma · Prognostic factor · Renal failure · Serum phosphorus level

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Introduction

Phosphorus (P) is one of the most abundant constituents of tissues, and approximately 85% of the total amount of P in the normal adult is in the skeleton [1]. Most of the P in the plasma is present as inorganic orthophosphate and only about 12% is bound to protein. In multiple myeloma (MM), hyperphosphatemia may result either from inadequate clearance during severe renal failure or from osteolytic bone destruction.

There are several case reports of MM in which pseudohyperphosphatemia caused by hypergammaglobulinemia had been found [2, 3]. In those patients, there was a correlation between the serum level of P and myeloma protein (M-protein), and the pseudohyperphosphatemia resulted from an increase in optic density caused by interference between the M-protein and the molybdic reagent used to determine P in serum [4–8].

The prognostic significance of the serum P level in MM has not been evaluated. In the present study, we measured the serum inorganic phosphorus (iP) level by a method that is not based on the reaction between ammonium molybdate and inorganic phosphorus and also examined the prognostic significance of the baseline serum P levels.

Materials and methods

Patients and treatment

The study group was comprised of 110 patients with MM who underwent treatment in hospital between 1988 and 2003 [57 males, 53 females; median age 63 years (range 42–83)]. The diagnosis of MM was based on the diagnostic criteria of the Leukemia–Myeloma Taskforce (NCI 1973, [9]). The types of MM were IgG type in 62 patients (IgGκ in 45 and IgGλ in 17), IgA type in 32 (IgAκ in 21 and IgAλ in 11), Bence–Jones (BJ) type in 14 (BJκ in 11 and BJλ in three), and IgDκ in one patient. One patient had a non-secretory myeloma (BJλ). The clinical stage of the disease,

Table 1 Correlation between serum phosphorus levels and other prognostic factors in multiple myeloma (Pearson's correlation test)

Prognostic factors	Correlation coefficient	*T*-value	Significance	Number of patients
Serum creatinine	0.636	8.565	*P*<0.00000001	110
Serum β2-microgrobulin	0.545	5.241	*P*=0.00000088	67
Serum uric acid	0.429	4.936	*P*=0.0000014	110
Corrected serum Ca	0.356	3.959	*P*=0.000067	110

according to Durie and Salmon's criteria [10], was stage IA in five, stage IIA in 28, stage IIB in one, stage IIIA in 58, and stage IIIB in 18.

The survival time from the initiation of therapy was known in 97 cases and was used for the evaluation of the significance of prognostic factors. The initial chemotherapy regimen in 49 patients was VCAP [11], comprising of vincristine (2 mg/person, intravenously, day 1), cyclophosphamide (100 mg/m^2/day, orally, days 1–4), adriamycin (25 mg/m^2/day, intravenously, day 1), and prednisolone (60 mg/m^2/day, orally, days 1–4); VCAP with interferon-α (IFN-α) in 21; VCAP/MVMP [MCNU (ranimustine), vincristine, melphalan and prednisolone] chemotherapy (alternating VCAP and MVMP regimens) in 13; and VCAP/MVMP chemotherapy plus IFN-α in nine. The MVMP regimen comprises MCNU (30 mg/m^2, intravenous infusion, day 1), vincristine (2 mg, intravenously, day 1), melphalan (4 mg/m^2/day, orally, days 1–4), and prednisolone (60 mg/m^2/day, orally, days 1–4). The VCMP, VCP, and MP regimens were used in one patient each [VCMP regimen: vincristine (2 mg/person, intravenously, day 1), cyclophosphamide (100 mg/m^2/day, orally, days 1–4), melphalan (4 mg/m^2/day, orally, days 1–4), and prednisolone (60 mg/m^2/day, orally, days 1–4); MP regimen: melphalan (4 mg/m^2/day, orally, days 1–4), and prednisolone (60 mg/m^2/day, orally, days 1–4)]. No patients underwent stem cell transplantation.

Blood chemistry

The serum P level at the time of diagnosis of MM was evaluated for its prognostic importance, and other clinical parameters determined as significant prognostic factors by univariate analysis (log-rank method) [12] [i.e., corrected serum calcium (serum cCa), serum creatinine, serum uric acid, serum albumin, total cholesterol, serum lactate dehydrogenase (serum LDH), serum β2-microglobulin, percentage of plasma cells in bone marrow nucleated cells (BMPC%), hemoglobin (Hb), leukocyte count, serum immunoglobulin M (IgM), grade of bone lesions (Durie–Salmon scale) [10], and age (years)] were evaluated for their prognostic importance.

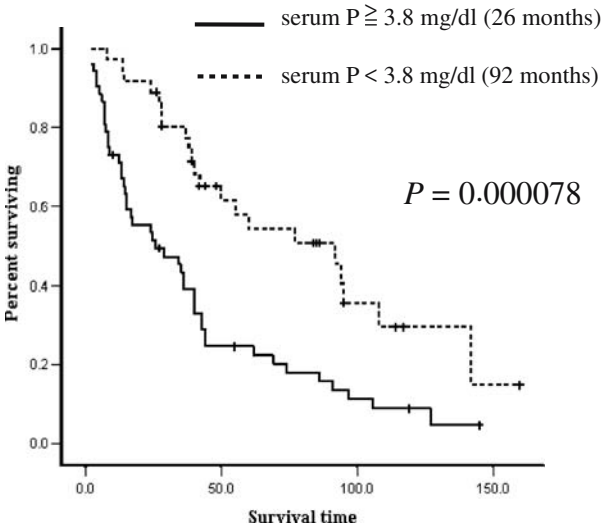

Fig. 1 Survival curves according to serum phosphorus level in multiple myeloma (cut-off value 3.8 mg/dl)

The iP level was measured by IatroLQ IP diagnostic kit (Mitsubishi Chemistry Iatron, Tokyo) because it uses purine nucleoside phosphorylase, xanthine peroxidase, and peroxidase in an enzymatic method so is not based on the reaction between ammonium molybdate and iP. The normal level of serum iP measured in a Hitachi autoanalyzer by this method ranges between 2.5 and 3.8 mg/dl.

The serum concentration of Ca was corrected using serum albumin according to the formula of Payne et al. [13]:

$$\begin{aligned} Serum\ cCa\ (mg/dl) = {} & measured\ serum\ Ca\ (mg/dl) \\ & -(g/dl\ of\ serum\ albumin)(mg/dl) \\ & +4mg/dl \end{aligned}$$

The grade of bone lesion was evaluated by the Durie–Salmon scale [10]. Correlations between the serum P level and other prognostic factors were examined by Pearson's

Table 2 Difference of laboratory data betwen patients with hyperphosphatemia and those without hyperphosphatemia

Prognostic factors	Serum P ≧ 3.8 mg/dl	Serum P <3.8 mg/dl	*N*	T-value	Significance
Serum creatinine	2.08±1.99 mg/dl	1.04±0.692 mg/dl	109	−3.792	*P*=0.00012
Bone marrow plasma cell	41.8±24.8%	30.5±18.4%	108	−2.719	*P*=0.0038
Leukocyte count	6,380±4,370 cells/μl	4,820±1,720 cells/μl	108	−2.547	*P*=0.0061
Serum uric acid	7.48±3.02 mg/dl	6.24±2.17 mg/dl	108	−2.503	*P*=0.0068

All data are expressed as mean±SD.

Table 3 Univariate analysis of serum phosphorus level and other prognostic factors in MM patients (log-rank method)

Prognostic factors	Cut-off value	Statistic (χ^2)	Significance (P value)	Median survival (months, number of patients) Favorable group/unfavorable group
Serum phosphorus	3.8 mg/dl	12.39	0.000432	92 months (52)/26 months (36)
Bone marrow plasma cell	40%	12.06	0.000515	50 months (53)/22 months (33)
Serum cCa	12 mg/dl	11.30	0.000775	43 months (73)/ 8 months (15)
Serum β2-microglobulin	3 mg/dl	8.82	0.00298	97 months (42)/ 16.5 months (45)
Serum LDH	400 mg/dl	8.09	0.00445	50 months (64)/ 4.5 months (24)
Hemoglobin	10 g/dl	7.81	0.00520	44 months (57)/ 24 months (31)
Age	65 years	7.49	0.00619	60 months (60)/ 24 months (32)
Serum creatinine	2 mg/dl	7.35	0.00671	42 months (73)/ 16.5 months (15)
CRP	0.4 mg/dl	6.17	0.0129	40 months (67)/ 19 months (29)
Serum IgM	40 mg/dl	5.09	0.0240	77 months (22)/ 39 months (64)
Serum uric acid	9 mg/dl	4.88	0.0272	43 months (70)/24 months (17)
Total cholesterol	120 mg/dl	4.61	0.0312	44 months (55)/35.7 months (31)
Urine BJ-protein	−/+	4.06	0.0438	42 months (55)/28 months(35)
Serum albumin	3.5 mg/dl	3.89	0.0485	44 months (40)/35.7 months (48)

correlation test. The relationship between the serum levels of P and M-protein (serum IgG concentration in IgG type MM patients and serum IgA concentration in IgA type MM patients) was also evaluated.

The difference in the average of the laboratory data between the patients with MM complicated by hyperphosphatemia (serum P >3.8 mg/dl) at first hospitalization and those without hyperphosphatemia was evaluated by Student's t test, and the median survival time was calculated by Kaplan–Meier's method [14]. The significance of difference of the survival curves was estimated by log-rank test [12].

Multivariate analysis to define independent prognostic factors used Cox's proportional hazards regression model [15].

Results

Of the 110 patients with MM, 36 (32.7%) had hyperphosphatemia (serum P >3.8 mg/dl) and 12 (11%) had a serum P level greater than 5 mg/dl. One patient had profound hypophosphatemia (serum P 1.1 mg/dl), hypercalcemia, moderately increased serum Ig (6,621 mg/dl of IgGκ) and positive urine Bence–Jones protein, but the serum creatinine level was almost normal (1.1 mg/dl).

According to Pearson's correlation test, the serum P level significantly correlated with the prognostic factors related to renal dysfunction; that is, serum creatinine (r=0.636, P<0.00000001), serum β2-microglobulin (r=0.545, P=0.00000088), serum uric acid (r=0.429, P=0.0000014), and serum cCa (r=0.356, P=0.000067) (Table 1). Although it also correlated with BMPC% (P=0.0011), Hb (P=0.0028), and the leukocyte count (P=0.0032), these correlations were less than for the other four prognostic factors. Serum P did not correlate with age, albumin, serum LDH, or total cholesterol.

Table 4 Multivariate analysis of prognostic factors using Cox's proportional hazards model

Prognostic factors	Statistic (χ^2)	Significance (P)
Age	16.46	0.0000496
Serum cCa	14.04	0.000179
Serum phosphorus	6.552	0.0105
BMPC%	6.080	0.0136

Because of the concern that high M-protein levels might result in pseudohyperphosphatemia, we investigated whether there was any relationship between the M-protein and serum P levels. No significant correlation between the serum P levels and serum IgG levels in IgG-type MM patients or with the serum IgA levels in IgA type MM patients was observed.

The difference in the average of the laboratory data between the MM patients complicated with hyperphosphatemia (serum P ≥3.8 mg/dl) at first hospitalization and those without hyperphosphatemia (serum P <3.8 mg/dl) was examined (Table 2). The average of serum creatinine in the hyperphosphatemic group (2.08±1.99 mg/dl) was significantly higher than that in the non-hyperphosphatemic group (1.04±0.692 mg/dl) (P=0.00012). Furthermore, the BMPC% (P=0.0038), leukocyte count (P=0.0061), serum uric acid (P=0.0068), bone lesions (P=0.011), serum β2-microglobulin (P=0.017), Hb (P=0.031), and serum cCa (P=0.037) were also significantly different between the two groups.

As to the prognostic significance of the serum P level, the survival time was significantly shorter in MM patients with hyperphosphatemia (median survival 26 months) than in those without (92 months) (P=0.000432) (Fig. 1, Table 3). Of the other prognostic factors, BMPC% (P=0.000515), serum cCa (P=0.000775), serum β2-microglobulin (P=0.00298), serum LDH (P=0.00445), Hb (P=0.00520), age (P=0.00619), and serum creatinine (P=0.00671) were significant prognostic factors for MM.

CRP (P=0.0129), IgM (P=0.0240), serum uric acid (P=0.0272), total cholesterol (P=0.0312), urine BJ-protein (P=0.0438), and albumin (P=0.0485) were slightly significant prognostic factors (Table 3). Overall, the serum P level was the most significant of the prognostic factors we examined by univariate analysis.

Multivariate analysis using BMPC%, serum cCa, serum P, serum β2-microglobulin, serum LDH, Hb, age, creatinine, CRP, IgM, serum uric acid, total cholesterol, urine BJ-protein, and albumin revealed that age (χ^2=16.46, P=0.0000496) was the most significant factor, followed by serum cCa level (χ^2=14.04, P=0.000179), serum P level (χ^2=6.552, P=0.0105), and percentage of plasma cells in bone marrow (χ^2=6.080, P=0.0136) (Table 4).

Discussion

Hyperphosphatemia is caused by decreased filtration by the kidney, hyperparathyroidism, hyperthyroidism, increased loading of P, anti-acid drug, diet, and acute destruction of any tissue. There are no symptoms related directly to hyperphosphatemia, unless high levels are maintained for long periods. The serum P level significantly correlates with serum creatinine (P<0.00000001), serum β2-microglobulin (P=0.00000088), serum uric acid (P=0.0000014), and serum cCa (P=0.000067), and these prognostic factors may be strongly influenced by disturbed renal function. The serum creatinine level increases with renal dysfunction, and an increase in the serum levels of β2-microglobulin and uric acid is related to both renal dysfunction and the volume of the myeloma. Serum cCa may be influenced by renal dysfunction and bone lesions, and serum P level also correlates with BMPC%, Hb, and bone lesions, which are factors that may also reflect the volume of tumor. However, in the present study, the correlations between serum P level and the three latter prognostic factors were less than with the four prognostic factors that are related to renal dysfunction. The patients with hyperphosphatemia also had higher values for serum creatinine, serum uric acid, serum cCa level and BMPC% than those without hyperphosphatemia, as well as having anemia and thrombocytopenia. Therefore, the serum P level is influenced mainly not only by renal dysfunction but also by the grade of tumor burden and disease progression.

Several cases of MM with hyperphosphatemia have been reported, but in most those cases, it was spurious.[4, 6, 7, 16–18] Busse et al. [4] reported two cases of IgG type MM complicated with pseudohyperphosphatemia, which was caused by interference of the monoclonal gammaglobulins with the phosphomolybdate colorimetric assay. Subsequent ultrafiltration of the serum samples resulted in normalization of the P values. Oren et al. [7] reported that in three patients with MM and pseudohyperphosphatemia, there was a correlation between the serum P level and the amount of M-protein and that pseudohyperphosphatemia resulted from an increase in optic density caused by interference between the M-protein and the molybdic reagent used to determine P in serum. In all cases, the M-protein was IgG. The mechanism underlying this spurious result may be turbidity in the reaction mixture caused by acid precipitation of the monoclonal IgG protein in the new generation of simplified kits or in some automated systems. Another explanation is possible binding of a large amount of P by the M-protein [2, 3]. Spurious hyperphosphatemia might be considered in newly diagnosed MM patients with increased serum P level but normal renal function and minimal skeletal disease. Most of the present patients with hyperphosphatemia had increased serum creatinine, hypercalcemia, and an advanced stage of MM, which suggests that most of the cases of hyperphosphatemia in these patients were induced by renal failure or lytic bone lesions.

One of the MM patients had profound hypophosphatemia, hypercalcemia, moderately increased serum immunoglobulin level, subnormal serum creatinine, and positive Bence–Jones protein. Several cases of spurious hypophosphatemia caused by the presence of M-protein have been reported [19–23]. Dash et al. [21] reported profound hypophosphatemia and isolated hypersphosphaturia, and Engle and Wallis [23] reported renal tubular defects when there is Fanconi's syndrome in MM. The mechanism of tubular dysfunction is unknown but may be related to the deposition of monoclonal light chains as crystalline inclusions within proximal tubular cells [24].

A number of prognostic factors for MM have been found and several prognostic systems have been proposed since 1973. Among the prognostic factors identified are bone lesion scale [10], monoclonal protein [10, 25], serum cCa [10, 25, 26], hemoglobin [10, 25, 26, 29, 30], serum creatinine [10, 25, 26, 29, 30], performance state [27, 29], albumin [27, 28, 31–33], blood urea nitrogen [28], BMPC % [26], paraprotein index [29], platelet count [30], Durie–Salmon clinical stage [30], lytic bone lesions [30], age [30], serum β2-microglobulin [31–33], morphology of the myeloma cells [31], and serum LDH. However, to date, the prognostic significance of the serum P level in MM has not been previously reported and, in the present study population, it was a significant negative prognostic factor.

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