

Evaluation of the Therapeutic Management of Hypercalcemia in Myeloma at the Nephrology Department of Louis Pasteur Hospital of Chartres: About 8 Cases

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Abstract

Introduction: Hypercalcemia is the most common metabolic complication in myeloma. The aim of this study was to evaluate the management strategy of hypercalcemia in myeloma at the nephrology department of Louis Pasteur hospital of Chartres. **Patients and Methods:** We carried a retrospective study of patients treated for myeloma-related hypercalcemia between January 1, 2019 to December 31, 2021. The clinical, paraclinical, therapeutic and evolutive characteristics were studied. **Results:** Eight patients were included in this study with a median age of 67 years [41 - 85] and a sex ratio (M/F) of 1. A quarter of patients were known with chronic kidney disease. Four patients (50%) had symptoms of hypercalcemia. Biologically, the mean hemoglobin was 9.8 ± 2.7 g/dl, all patients had an acute kidney injury with a mean creatinine level of 364.1 ± 173.3 mmol/l, a mean serum calcium of 3.42 ± 0.59 mmol/l and three quarter of patients had bone lesions. Five patients (62.5%) were rehydrated with a mean volume of saline of 2700 ± 836.7 ml/24h. Seven patients (87.5%) received biphosphonates and none received diuretics. The mean normalization time of the serum calcium was 5 days. **Conclusion:** Hypercalcemia is frequent in malignancy and represents a poor prognosis factor of the disease. A well-conducted therapeutic strategy allows rapid normalization.

Keywords

Hypercalcemia, Myeloma, Treatment, Malignancy, Neoplasia

1. Introduction

Calcium is essential for the proper functioning of many tissues and cells in the body. It is the most abundant cation in the body, it plays an essential role in neuronal transmission, enzyme activity, myocardial function, coagulation and other cellular functions. Almost all calcium is intraosseous and only a small percentage is found in cells and extracellular fluids. Serum calcium represents about 1% of the total calcium in the body and is divided into calcemia bound to proteins and ions and ionized calcium which represents the active form [1]. Hypercalcemia is an increase in serum calcium level above the upper limit of normal for a given reference value used in a laboratory [2]. Of all the causes of hypercalcemia, primary hyperparathyroidism and neoplastic processes are the most common, accounting for more than 90% of cases [3]. Its prevalence reported during neoplastic processes is 20% to 30% of cases and they represent the first cause of hypercalcemia in hospitalization [4]. Among all cancers, multiple myeloma has the highest prevalence of hypercalcemia [5]. Hypercalcemia is present in more than 10% of patients at diagnosis of myeloma [6]. Recently available data support the role of several cytokines such as RANKL, MIP-1 α , and DKK1 in the exaggerated osteoclastic bone resorption that characterizes myeloma bone disease, with compelling evidence that RANKL is the final common mediator [7]. While rehydration associated with corticosteroid therapy as part of the overall myeloma management protocol is effective in the majority of situations for mild to moderate hypercalcemia, inhibition of bone resorption by the addition of bisphosphonates more or less calcitonin is necessary in severe hypercalcemia [8] [9].

The aim of this work was to evaluate the therapeutic strategy of hypercalcemia during myeloma.

2. Patients and Methods

This was a retrospective, descriptive study carried out over a period of 3 years from January 1, 2019 to December 31, 2021 targeting all patients diagnosed with multiple myeloma during the study period. Were included, all patients with hypercalcemia at diagnosis or during follow-up of myeloma.

The definitions used for the diagnosis of hypercalcemia were [10]:

- Mild hypercalcemia: [2.6 à 3 mmol/l]
- Moderate hypercalcemia: [3 à 3.5 mmol/l]
- Severe hypercalcemia: serum calcium \geq 3.5 mmol/l

The definition of myeloma was that of the criteria of the International Myeloma Working Group (IMWG) of 2014 [11].

We studied the evolution of serum calcium on day 1, day 2, day 3 and day 6.

The data was collected using a clinical and paraclinical data collection sheet consisting of a questionnaire filled in from the patient files. Sociodemographic, clinical, biological and therapeutic data were collected retrospectively.

Data were entered with Excel 2019 software and SPSS software version 23.0.0 and analyzed using SPSS software version 23.0.0.

Descriptively, the quantitative data were presented in the form of means and standard deviations or median and extremes depending on the distribution of the variables. Qualitative data was presented as a proportion.

3. Results

Of the 18 patients diagnosed with myeloma, 8 patients were included (**Figure 1**).

The median age of the population was 67 years [41 - 85]. Of the 8 patients who presented with hypercalcemia, 4 (50%) were men. Two patients (25%) were carriers of known CKD and only one had heart failure (**Table 1**).

Clinically, 4 patients (50%) were dehydrated. At the paraclinic, five patients (62.5%) had anemia with an average hemoglobin level of 9.8 ± 2.7 g/dl. Acute renal failure was present in all patients with a mean serum creatinine of 364.1 ± 173.3 mmol/l. On imaging, 75% of patients had bone lesions. The characteristics of electrophoresis peaks, immunoglobulin chains and plasmacytosis are summarized in **Table 2**.

Among our patients, 44.44% had hypercalcemia during their follow-up, including 27.78% at the time of myeloma diagnosis. Mean serum calcium was 3.42 ± 0.59 mmol/l at diagnosis. The calcemia of patients during the first week following the diagnosis of hypercalcemia is shown in **Figure 2**. The average time to normalization of calcemia was 5.25 ± 2.19 days with extremes of [1; 8].

Therapeutically, five patients (62.5%) had been rehydrated with an average volume of 0.9% normal saline of 2700 ± 836.7 ml/24h. Seven patients (87.5%) received bisphosphonates (**Figure 3**). The time to normalization of serum calcium was identical for patients on pamidronate or on zoledronate with an average of 5 days.

No patient received diuretics.

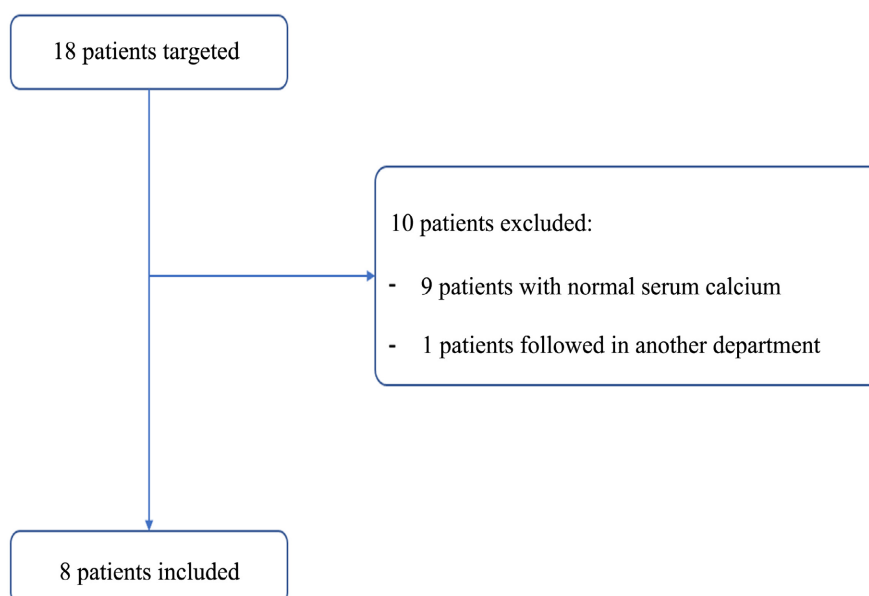


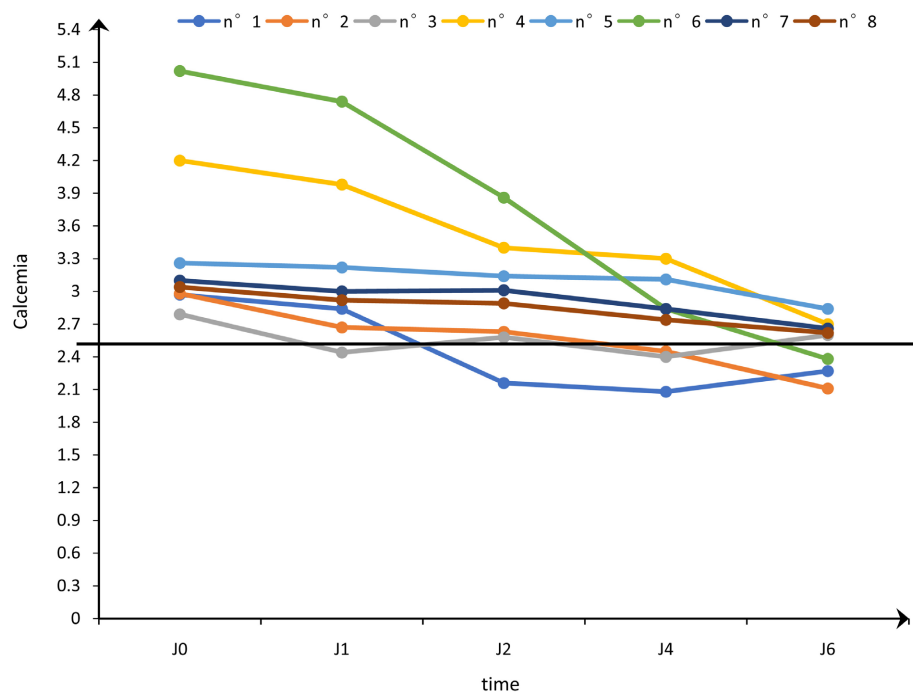
Figure 1. Flow diagram of 18 patients with myeloma.

Table 1. Patients medical history.

Antecedent	Effectif n = 8	
	Yes	No
Chronic kidney disease	2	6
Neoplasia (prostate)	1	7
Granulomatosis	0	8
Parathyroid pathology	0	8
Heart failure	1	7

Table 2. Immunological profile of patients. a = alpha, b = beta, g = gamma.

Patient	monoclonal peak		Heavy chain	Light chain k (g/l)	Light chain l (g/l)	Plasmacytosis (%)
	pic	Concentration (g/l)				
n° 1	a	10.3		12126.0	9.6	5
n° 2	g	45.3	IgA	240.0	15.6	
n° 3				35.0	5942.7	80
n° 4				10356.0	35.0	45
n° 5	b	41.4		3707.0	16.9	78
n° 6	g	49.3	IgG	651.0	11.6	30
n° 7	b	20.9	IgG	259.0	11.6	10
n° 8	g	26.4	IgA	2259.0	0.9	21

**Figure 2.** Evolution of patients' serum calcium during the first week following the diagnosis of hypercalcemia. Black line: normal serum calcium line.

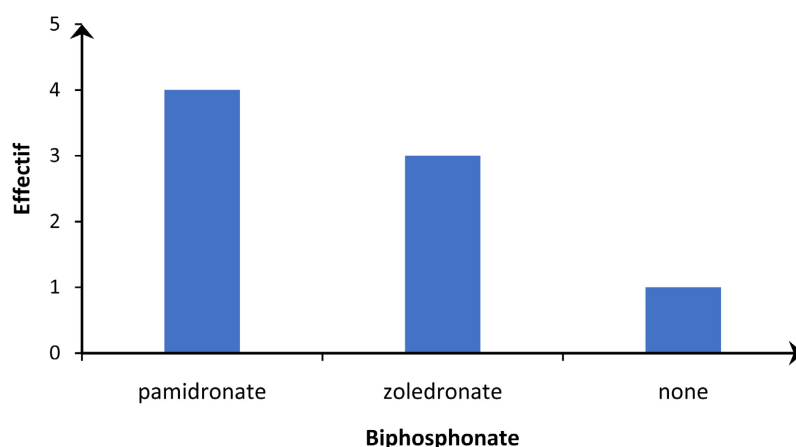


Figure 3. Bisphosphonate molecules used.

4. Discussion

Hypercalcemia is frequently observed in myeloma. A study of a large cohort of 2129 patients with newly diagnosed symptomatic myeloma reported a prevalence of 19.5% [12]. Most of the studies report a prevalence between 15% to 20% at the time of diagnosis [13] [14]. In our study, 44.4% of patients had hypercalcemia during the follow-up of their myeloma, including 27.8% at the time of diagnosis. This higher prevalence in our patients could be related to the fact that most of them had renal failure and were first referred to nephrology, on the contrary many of those without renal failure at presentation were probably referred to other services first. Although it has not been introduced into the International Prognostic Scoring System (ISS) and the revised ISS (R-ISS), hypercalcemia has been reported as a factor of poor prognosis in the course of the disease [12] [15].

Intravenous rehydration with isotonic saline is administered to restore the patient's volume, maintain adequate urine output. In our patients, the decision to hydrate was taken based on the volume of each patient and the volume of the infusion determined taking into account the underlying cardiovascular and renal status. The average rehydration was 2700 ± 836.7 ml/24h the first three days following the diagnosis of hypercalcemia. The use of diuretics in case of hypercalcemia is subject to discussion. A critical review of nine case series concluded that the routine use of loop diuretics in the treatment of cancer-associated hypercalcemia provided no additional benefit [16]. In our cohort, no patient received diuretics.

The use of bone resorption inhibitors is essential. Pamidronate and zoledronate are the main osteoclastic function blockers used in this indication. Two double-blind randomized trials comparing a single dose of zoledronate with a single dose of pamidronate showed superiority of zoledronate for the treatment of hypercalcemia. In our series, half of the patients were put on pamidronate. This is because all our patients had impaired renal function with the majority of them having a GFR < 30 ml/min contraindicating the use of zoledronate. In our

study, all the patients normalized their calcemia on the 8th day with an average of 5.25 days. The literature reports a normalization rate of 88.4% and 69.7% respectively under zoledronate and pamidronate on the 10th day [16]. One study showed good improvement in hypercalcemia within a week of the introduction of bisphosphonates and immunosuppression. This delay in normalization in our series could be explained by the fact that in our patients serum calcium at diagnosis was lower and blood volume better controlled. No adverse effects were noted in our patients related to the use of bisphosphonates.

Denosumab was not used in our patients. Normalization of serum calcium was obtained with rehydration alone or combined with bisphosphonates. This practice is consistent with the recommendations which reserve the use of these antibodies for severe hypercalcemia not responding to the use of bisphosphonates or in the event of contraindications to the latter [14] [17].

Limitations of the study

The limited number of cases of hypercalcemia during myeloma and more generally the number myeloma diagnosed in our service during the study period limited the possibility of carrying out an analytical study to try to highlight the effectiveness of each of the treatment components but also to be able to study the factors associated with the occurrence of hypercalcemia during myeloma pathology.

5. Conclusion

Hypercalcemia is the most common metabolic complication of multiple myeloma. It is associated with worse prognosis of the myeloma. The treatment tripod is based on the restoration of the patient's blood volume, the inhibition of bone resorption and the specific treatment of myeloma. The therapeutic practices in our center are in line with the various therapeutic recommendations.

Conflicts of Interest

All authors declare no conflicts of interest.

Consent

Informed consent from each patient was obtained.

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