Therapeutic approach to hypercalcemia in solid neoplasms: retrospective analysis in an Internal Medicine service.

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Abstract

The authors present a retrospective study on the therapeutic approach to hypercalcemia in patients with solid neoplasms, hospitalized in the Medical Service II of the HUC. The study group included 171 patients, 45 (26.3%) of which had hypercalcemia (serum calcium ≥ 10.4 mg/dL, after correction for albuminemia). In these patients, analyses were performed of the therapies used, the criteria for choice of therapy (calcemic levels, symptomatology, and bone metastization), response obtained, and relationship with the basic therapeutic approach.

The following facts merit special emphasis: A) The therapies used were: hydration, either in isolation (n = 27) or in association with drugs (n = 18), always including furosemide), {corticoids (n = 6), calcitonin (n = 9), biphosphonates (n = 12)}. B) All 10 patients with severe hypercalcemia (≥ 13 mg/dL) and only 6 of the 29 with slight hypercalcemia (≥ 10.4 – 11.5 mg/dL) underwent therapeutic associations. Of the 14 patients with severe symptoms attributed to hypercalcemia, drugs were only used in 7. In the patients with documented bone metastization (n = 15) the use of calcitonin or bisphosphonates was prevalent. C) There was temporary control of calcemias in the patients that underwent therapy, which is more relevant when various drugs are associated. Regression of the symptoms was more significant in the group that used bisphosphonates. In a third of the patients who used bisphosphonates or calcitonin, there was an improvement in pain. D) Mortality in hospitalization and average delay were about double that of the total group of inpatients.

Conclusions: 1) Significant prevalence of this metabolic disorder (26%) in the solid neoplasms. 2) Hypercalcemia was attributed greater value, with the use of therapeutic measures in addition to hydration in 40% of the patients. 3) The therapeutic option was based more specifically on the levels of calcemia than on the symptoms, and bone metastization influenced the use of calcitonin and bisphosphonates. 4) The improvement of symptoms in a significant number of patients, and the temporary control of calcium levels, are factors that could improve the quality of life of these patients, counterbalancing them until basic measures are adopted, which occurred in a third of the cases.

Key words: therapeutic approach to hypercalcemia; solid neoplasms.

Introduction

Malignant neoplasms are the most prevalent cause of hypercalcemia in hospitalization; this being the metabolic disorder that most frequently leads to clinical deterioration and it is life-threatening to the oncological patient.[1,2] Among the malignant diseases, they differ from those of the hematological type, especially myeloma, which has different incidence, physiopathological implications and approach.[3]

In solid neoplasms, the subject of this study, the prevalence of hypercalcemia is difficult to assess, depending on the type of neoplasms included in the series studied.[1] Its prevalence is high in breast and lung neoplasms, and low in colon and prostate tumors1.[4,5,6] Although the physiopathology of hypercalcemia of malignant diseases is not uniform (attributed to osteolytic metastases in one group and to the production of humoral factors (PTH-r) in the remainder) the increase of bone resorption by the osteoclasts is a determining parameter, with implications on the proposed therapeutic approaches.[1,2,4,5] The presence of symptoms and complications attributable to hypercalcemia makes the compensation of this disorder interesting in the attempt to improve the quality of life of these patients, although the presence of an episode of hypercalcemia is an indicator of poor prognosis.[4,7] The clinical symptoms are significant in moderate and severe hypercalcemia, although there is

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no linear relation between calcemia and symptoms, which also depends on the speed of onset, age, functional state, and other organic dysfunctions.[1,4] The symptom of pain and pathologic fractures associated with intense bone resorption are another parameter that should be given greater value in the therapeutic approach.[8]

In the absence of therapeutic measures targeting the underlying neoplasm, the hypercalcemia therapy merely achieves transitory corrections, its efficacy diminishing over time. Therefore, therapeutic measures to reduce calcemia are indicated mainly in patients in which neoplasm-oriented approaches are likely, and in those with debilitating symptoms, although in the latter, the indication should be carefully weighed where there is a very short life expectancy or deterioration of the patient's general condition.[2,4]

Although hydration is important as an initial therapy, the main point of the hypercalcemia therapy is the inhibition of bone resorption, and in some cases, physicians have to resort to drugs. Of these, special emphasis is given to second-generation biphosphonates (clodronate, pamidronate) that constitute the best combination of potency in the inhibition of osteoclastic activity, efficacy in the control of hypercalcemia, prolonged effect, ease of administration, and low toxicity. It also has the additional benefit that it can reduce the complications of osteolysis.[2,4,7,8,9,10]. The usefulness of Calcitonin, another bone resorption inhibitor, is limited by its lower potency and the development of tachyphylaxis, and its role is restricted to association with biphosphonates, particularly when a rapid effect is needed, as the latter are slower to start acting.[2,4,9]

Other approaches are the use of forced diuresis with furosemide and corticotherapy. The first promotes effective kaliuresis, an effect that is lost when the therapy is terminated, and maintaining the therapy leads to the depletion of other electrolytes, requiring close monitoring and previous water replacement.[2,4,11] The role of corticoids in these cases is debatable, although some studies point to an increase in therapeutic efficacy when associated with calcitonin, offsetting tachyphylaxis,[4,10] or with diuretics.[12] Their role appears to be limited to hypercalcemia of hematological neoplasms, and they are not indicated here as routine.[2,11] Drugs with which we have no experience, such as mithramycin or gallium nitrate, appear not to present any advantages over bisphosphonates in relation to toxicity, price, convenience or efficacy. In the future, the development of PTH-r antagonists may bring benefits in these pathological situations 4. In view of the abovementioned aspects, the authors decided to retrospectively analyze the approaches used in this area, in their Internal Medicine Service.

Material and methods

The population studied consisted of 171 patients diagnosed with solid neoplasm, admitted to the Medical Service II of the Coimbra University Hospitals between January 1989 and September 1993.

Patients with serum calcium values ≥ 10.4 mg/dL (2.6 mmol/L), after correction in relation to albuminemia (corrected calcium (mg/dL) = measured calcium (mg/dL) – albumin (g/l) + 4)[1,13] were considered as having hypercalcemia.

Mild hypercalcemia was classified as ≥ 10.4 and < 11.5 mg/dL; moderate as ≥ 11.5 and < 13 mg/dL and severe as ≥ 13 mg/dL.[11]

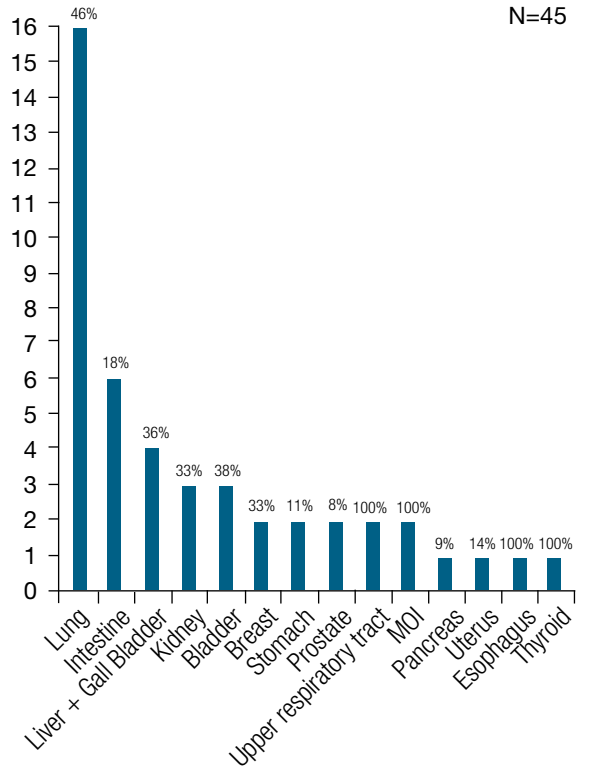
Severe clinical symptoms attributable to hypercalcemia included: stupor, state of confusion, convulsions, coma, pancreatitis, arrhythmias and kidney failure, and other symptoms included anorexia, vomiting, obstipation, polyuria, polydipsia, fatigue, irritability, depression, mood changes and drowsiness.[1,6,8]

The presence of bone metastases was considered only in the patients in whom these were documented by supplementary exams (radiography and/or scintigraphy).

All the patients that took a given drug, in association with hydration or other drugs, were included in the therapeutic groups "association with....". For this reason, some of patients are accounted for in more than one of these groups. It was not possible to document the effect of each drug separately, as they were often used together. It was only possible to analyze the groups of patients that took a given drug, regardless of the associations.

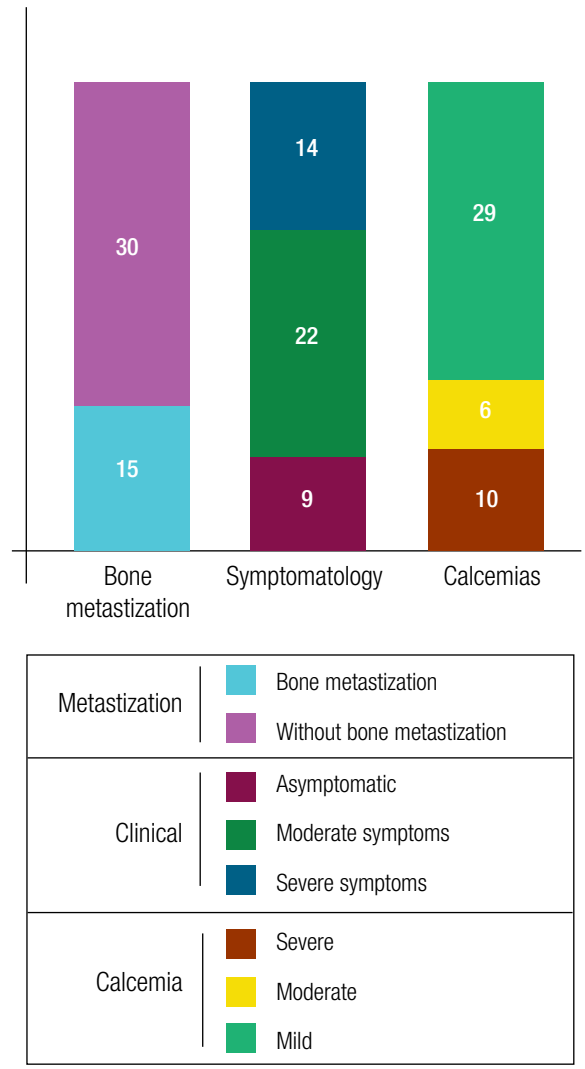
The decrease of calcemia presented relates to the difference between the serum calcium value before the start of therapy and the lowest value obtained, when controlled, or, in the patients who have suffered a relapse, the value before this one. The mean value of the differences was calculated for each group.

The patients included in the group that received therapy for the underlying disease were those sub-



Number and percentage of hypercalcemia in the different types of tumor.

FIG. 1



Characteristics of the population of hypercalcemic patients (serum levels, symptomatology, bone metastization).

FIG. 2

mitted to surgical intervention, chemotherapy or radiotherapy.

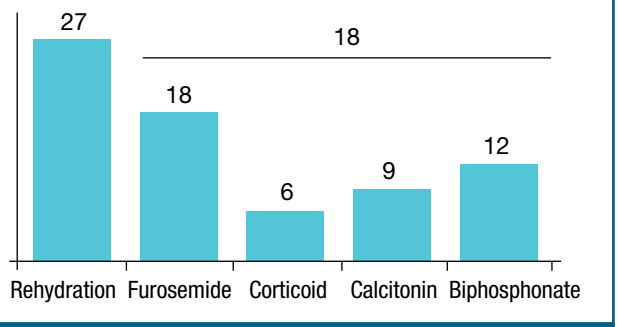
The parameters mortality in hospitalization and average delay were compared with those for all the patients hospitalized in the same Service during the same period of time.

The main goals of this study were to analyze, in this group of patients, the therapies used in hypercalcemia, the criteria for choice of therapy, the response obtained, their benefits, and the interest of the measures applied in this group of patients.

Results

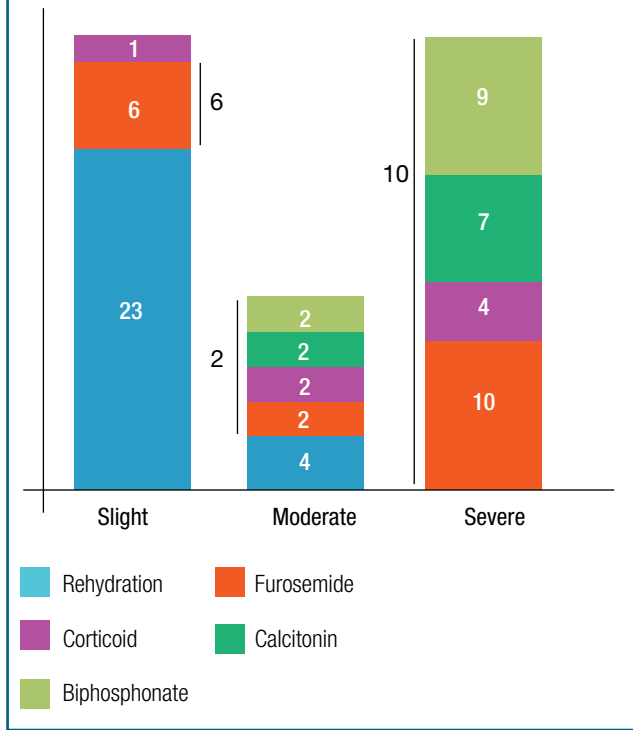
Hypercalcemia occurred, at some stage of the hospitalization in 45 (26.3%) of the 171 patients diagnosed with solid neoplasm, whereas its distribution by tumors (percentage in relation to the total number of this type of tumor in the series observed) is as follows: lung – 16 (46%), intestine – 6 (18%), liver and bile duct– 4 (36%), kidney – 3 (33%), bladder – 3 (38%), breast – 2 (33%), stomach – 2 (11%), prostate – 2 (8%), upper respiratory tract – 2 (100%), metastases of undetermined origin – 2 (100%), pancreas – 1 (9%), uterus – 1 (14%), esophagus – 1 (100%) and thyroid – 1 (100%) (*Fig. 1*). Primary hyperparathyroidism was associated in one case.

The hypercalcemia was severe (≥ 13 mg/dL) in 10 cases, moderate (≥ 11.5 and < 13 mg/dL) in 6, and mild (≥ 10.4 and < 11.5 mg/dL) in 29. 80% (36 patients) reported symptoms compatible with hypercalcemia, which were severe in 14 cases and moderate



Therapies used in patients with hypercalcemia.

FIG. 3



Therapeutic option in relation to the serum calcium levels.

FIG. 4

in the remaining 22 patients. 9 (20%) patients were asymptomatic. The presence of bone metastization was documented in 15 patients (33%) (*Fig. 2*).

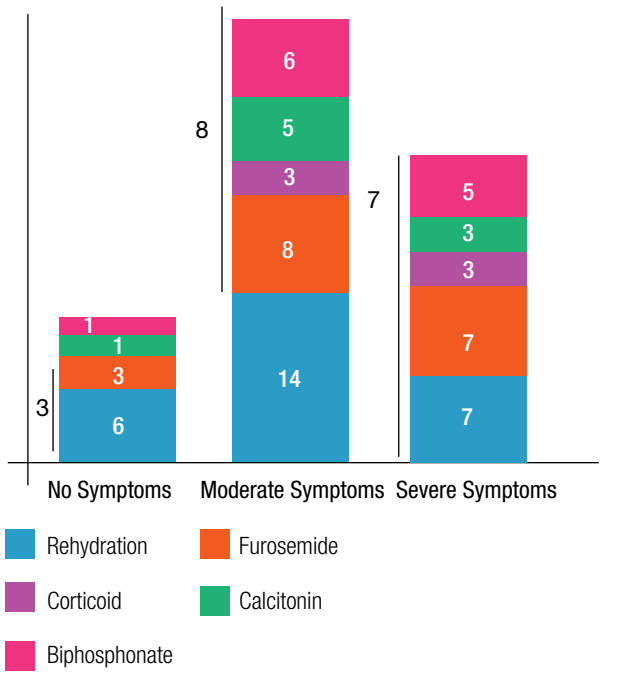
The therapies used with the aim of correcting the hypercalcemia were as follows: hydration alone in 27 patients (60%); - association of drugs with hydration in 18 patients (40%), all with furosemide, with the addition of corticosteroids in 6 (13%), calcitonin in 9 (20%) bisphosphonates in 12 (27%) (clodronate in + 6 and pamidronate in 6) (*Fig. 3*).

Analyzing the criteria for choice of therapy, we observed that of the patients with mild hypercalcemia (n = 29) 23 (79%) had hydration only, and drugs were administered in 6 (21%) (furosemide in 6, associated biphosphonate in 1). In the patients with moderate hypercalcemia, (n = 6) hydration only was used in 4 while drugs were used in association in the other 2 (33%) (all received furosemide, corticoids, calcitonin and biphosphonate). In the patients with severe hypercalcemia (n = 10), all received associations of drugs (100%) (furosemide in 10 patients, biphosphonates in 9, calcitonin in 7 and corticosteroids in 4) (*Fig.4*). In terms of the symptomatology present, the therapies used were as follows: of the asymptomatic patients (n = 9), 6 received hydration (67%), with the use of drugs in the remaining 3 (33%) (furosemide in 3, calcitonin in 1, biphosphonate in 1); in the patients with moderate symptoms (n = 22), hydration was the therapy used in isolation in 14 (64%), and drug associations in the remaining 8 (36%) (furosemide in 8, corticosteroids in 3, calcitonin in 5 and biphosphonates in 6); of the patients with severe symptoms (n = 14), 7 received isolated hydration (50%) and the remaining 50% were medicated with drugs (furosemide in 7, corticoids and calcitonin in 3, biphosphonates in 5) (*Fig. 5*). In the 15 patients with bone metastization, resorption inhibitors were administered in 9 (60%), 8 used biphosphonates and 5 used calcitonin (56% and 67% of those that received these drugs, respectively).

Of the 36 patients with symptoms attributable to hypercalcemia, 15 were submitted to other measures besides simple hydration. Of the 36 patients, 8 (22%) reported symptomatic improvement. In the 21 that received hydration, this improvement was restricted to 3 patients (14%). After therapy with drugs, an improvement was recorded in 5 of the 15 patients (33%). It was more significant in those that used bone resorption inhibitors – calcitonin 3 out of 8 (38%), biphosphonates 5 out of 11 (46%) (*Fig. 6*).

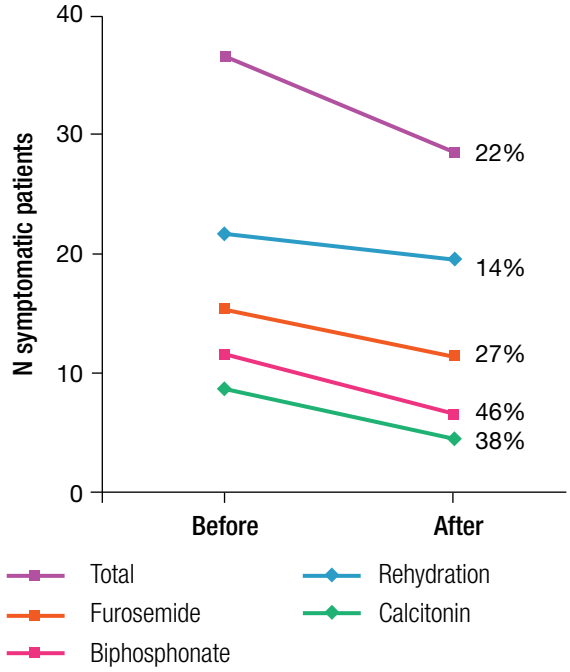
Of this set of 45 patients, 16 reported painful bone symptomatology. Of these, 8 reported an improvement during hospitalization, and it was observed that 7 of these were included in the group that took calcitonin or biphosphonates.

After evaluating the reduction of calcemia with



Therapeutic option in relation to the symptomatology.

FIG. 5



Symptomatic response to therapy.

FIG. 6

the various therapeutic measures, we were able, using the abovementioned methods, to verify the following results (*Fig.* 7): 1) isolated hydration – mean decrease 0.4 mg/dl (0.1 mmol/L), ranging between 0 and 2.1 mg/dL; 2) association including furosemide – 2.0 mg/dL (0.5 mmol/L), from 0 to 5.7 mg/dL; 3) furosemide only + hydration – 1.18 mg/dL (0.3 mmol/L), from 0 to 2.8 mg/dL; 3) association including calcitonin – 2.46 mg/dL (0.62 mmol/L), from 0.3 to 5.6 mg/dL; 4) association including bisphosphonate – 2.65 mg/dL (0.66 mmol/L), from 0.3 to 5.7 mg/dL; 5) association including corticosteroid – 2.71 mg/dL (0.68 mmol/L), from 0.3 to 5.6 mg/dL; 6) patients who received all the drugs (furosemide + calcitonin + corticoid + biphosphonate) – 3.1 mg/dL (0.78 mmol/L), from 0.3 to 5.6 mg/dL.

Therapeutic approaches to treat the underlying neoplasm (surgery, radiotherapy, chemotherapy) were used in 17 of the 45 patients. In this group, the use of a therapeutic approach to hypercalcemia with drug associations was more frequent than in the set of 45 patients, as was therapy with biphosphonates (*Fig.* 8).

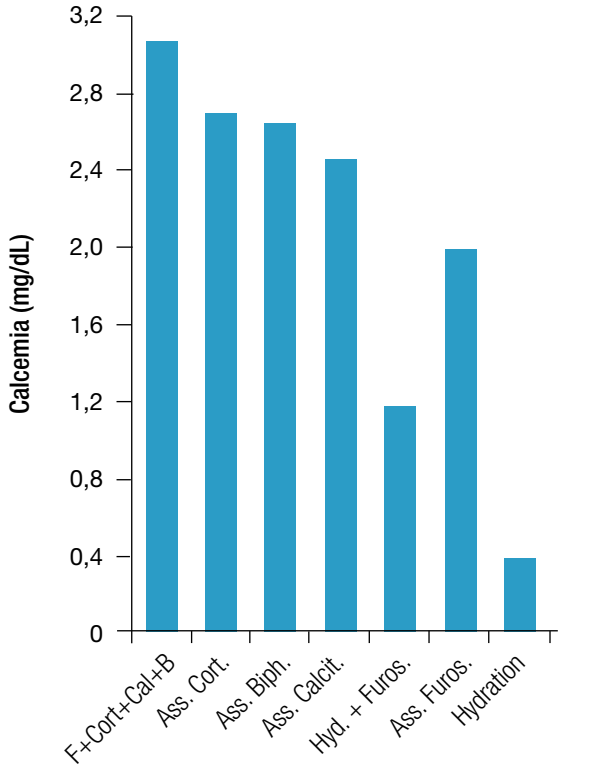
In these patients with hypercalcemia caused by solid neoplasm, the mortality during hospitalization was 17.7% and the mean delay was 25.4 days, in contrast with the mean mortality and delay of hospitalization in general, in the same period of time, which were 4.6% and 12.5 days, respectively.

Discussion

Commenting on the results of this retrospective analysis, the authors emphasize:

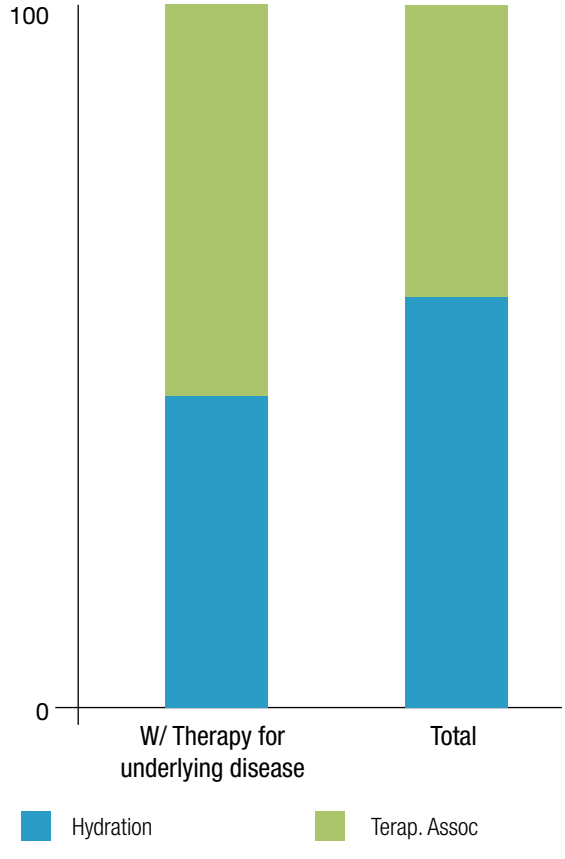
1) The significant prevalence of hypercalcemia (26.3%) in the group of patients with solid neoplasms that was studied. This result is due to the predominance of lung neoplasm, with 16 of the 45 cases of hypercalcemia, a tumor habitually linked to this metabolic disorder, although in percentages slightly lower than the 46% of our series.[1,4,5,6] Furthermore, the fact that this study was conducted with inpatients may account for this increased prevalence.[1]

2) The presence in this group of a high number of patients with symptoms (80%) attributable to hypercalcemia, and with calcemia above 13 mg/dL in 22% of the cases, reinforces the interest of the therapeutic approach to this disease.



Mean reduction of calcemia obtained by the therapy.

FIG. 7



Relationship between the use of hypocalcemiant drugs and therapy for the underlying disease

FIG. 8

3) The attribution of greater value to hypercalcemia, in this series, translated by the number of patients in whom pharmacological therapy was performed. Measures targeted beyond hydration were used in 40% of the patients, involving biphosphonates in 27% of the cases. It should be mentioned that although the study relates to the beginning of 1989, biphosphonates were only introduced in our Service around 1990, therefore this figure is lower than it is now.

4) The therapeutic option based more on the serum calcium level (all the patients with calcemia ≥ 13 mg/dL received associations of drugs) than on the severity of the symptomatology attributable to hypercalcemia, although this also influenced the decision (pharmacological therapy in 50% of the patients with severe symptoms, 33% in the asymptomatic patients). This approach is justified by the fact that the symptoms considered are not specific, and can be attributed to the underlying neoplasm or to another disorder, such as anemia, or the use of narcotics.[2,10,13] Therefore, they were attributed greater value when accompanied by higher calcemia. The use of calcitonin and/or biphosphates was more prevalent in the patients with documented bone metastization, and it appears to be in this group that the therapy for hypercalcemia with bone resorption inhibitors is most effective.[4,14]

5) Improvement with the pharmacological therapy in one third of the patients with symptoms attributable to hypercalcemia, which is more significant in those submitted to therapy with biphosphonates. We also recorded an improvement in symptoms of bone pain in some patients, predominantly in the group of those that received calcitonin and/or biphosphonates, as these can prevent the pain-related complications associated with osteolysis,[8,14] an effect that enables an improvement in walking, which in itself also decreases calcemia.[4]

6) The control of hypercalcemia by the therapies used, with special emphasis on the results obtained with the association of several drugs (calcitonin, corticoids, biphosphonates), which were superior to those achieved in using hydration alone, or hydration in association with furosemide. These results were transitory in the absence of therapy for the underlying disease.
7) The poor prognosis of these patients, documented by the high rate of mortality in hospitalization, although therapy targeting the underlying neoplasm (surgery, radiotherapy, chemotherapy) was used in around one third of the patients. Associations of drugs were used more frequently in these patients than in the group in general.

In spite of the limitations originating from a retrospective analysis, we can conclude as to the interest of targeted therapy in the attempt to lower calcemia in patients with neoplasms, even though its effects are transitory. This approach contributes to the stabilization of the clinical situation in those in which therapies targeting the underlying tumor are planned, and in others, it enables an improvement in symptoms and consequently, quality of life, and can reduce the length of hospitalization, which is prolonged in this group.[4,7] For this purpose, and although simple measures such as rehydration are useful and should be applied in all patients, in some, due to the severity of the hypercalcemia or the symptoms, it is necessary to resort to other drugs, with emphasis on bone resorption inhibitors (for example, calcitonin and biphosphonates),[10] as demonstrated by the results of this series. ■

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