Hypercalcemia of Malignancy

By Jean-Jacques Body

Less than 25 years ago tumor-induced hypercalcemia was often a lethal complication of cancer. Nowadays, it can be treated easily and successfully in at least 90% of cases by volume repletion in addition to the use of bisphosphonates that are potent anti-osteoclastic compounds. The standard therapy consists of the administration of 90 mg pamidronate or, more recently, 4 mg zoledronic acid, a more efficient bisphosphonate. When available, another alternative bisphosphonate is ibandronate. Recurrent hypercalcemia is nevertheless difficult to control and antibodies against parathyroid hormone–related protein could be useful for that matter in selected patients who are not in the terminal stage of their disease. Prevention of tumor-induced hypercalcemia is one of the objectives of long-term therapy with bisphosphonates in patients with tumor bone disease. The use of bisphosphonates in placebo-controlled trials has shown that the incidence of hypercalcemic episodes is reduced by more than one half.

THE CONCENTRATION of total extracellular calcium normally varies between 8.5 and 10.5 mg/dL (or 2.12-2.75 mmol/L). About half of it is ionized (as free calcium ion, Ca^{++}) whereas the other half is protein (mainly albumin) bound or complexed with anions. Only the ionized calcium is feedback regulated so that marked changes in serum albumin concentration can affect the total calcium concentration (every change of total serum albumin of 1 g/dL is roughly associated with a 0.8 mg/dL change in total calcium). This is essential to keep in mind in cancer patients because of the high prevalence of low protein levels.

The 2 main causes of hypercalcemia are tumor-induced hypercalcemia (TIH) and primary hyperparathyroidism. Hypercalcemia can be observed with any type of tumor, but breast and lung carcinomas are the 2 most frequently encountered causes.[1] TIH classically occurs in 10% to 15% of patients with advanced cancer, but the frequency is now decreasing because of an earlier and prolonged use of bisphosphonates in cancer patients with bone metastases.[2] Most often, TIH complicates advanced cancer and, depending on the series of studies reviewed, the median survival rate varies between 6 to 10 weeks.[1] However, breast cancer patients experience a somewhat longer median survival of 3 to 4.5 months.[3]

The diagnosis of TIH is not always clinically evident because of the lack of specificity of most symptoms.[1,2] Polyuria, polydypsia, arrhythmias, nausea and vomiting, constipation, obtundation, and, possibly, coma in severe cases all can be observed. The degree of the symptomatology is linked more to the rate of increase in serum Ca than to that of the absolute serum Ca level. A detailed analysis of the biochemical procedures allowing the correct diagnosis of hypercalcemia is beyond the scope of this review but a simple algorithm using ionized (or protein corrected) Ca, PTH, 25-OH vitamin D, and, if available, PTH-related protein (PTHrP) usually are sufficient.

Secretion of humoral and paracrine factors by the tumor cells stimulates osteoclast activity and proliferation, as exemplified by a marked increase in collagen cross-links excretion.[4] Several studies have established the essential role of PTHrP in most types of cancer hypercalcemia. Circulating PTHrP levels thus are increased in virtually all patients with humoral hypercalcemia of malignancy and in up to two thirds of patients with bone metastases.[5] Tubular reabsorption of calcium is enhanced by volume depletion in addition to the effect of PTHrP on the renal tubules. Moreover, osteoblast activity often is inhibited, leading to a characteristic uncoupling between bone resorption and bone formation.[6] All these factors explain why serum Ca levels often increase rapidly in cancer patients in contrast to the relatively stable levels in patients with primary hyperparathyroidism and why high doses of bisphosphonates are needed to normalize bone resorption and to overcome the possible contributory role of circulating PTHrP on the kidney.

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TREATMENT OF TUMOR-INDUCED HYPERCALCEMIA

Although an effective antitumor treatment is still the best means to obtain a long-term normalization of serum Ca level, a marked reduction of tumor burden often is not attainable because hypercalcemia generally complicates advanced and refractory cancer. Forced saline diuresis combined with large doses of furosemide is a risky and outdated procedure. However, volume repletion and rehydration with intravenous fluids should be part of the initial therapeutic approach, at least in patients with moderate or severe TIH. Rehydration and volume repletion have generally mild and transient effects on serum Ca levels, affecting a median decrease of only 1 mg/dL.[7] Yet, volume repletion improves the patient's clinical status and interrupts the vicious cycle of TIH by decreasing tubular reabsorption of calcium.

Besides volume repletion, bisphosphonates have supplanted all other drugs for the treatment of TIH, except corticosteroids for steroid-responsive tumors (ie, lymphoma and myeloma) for which recommended doses vary from 40 to 100 mg of prednisone daily. Intravenous administration of phosphate no longer has any place in the management of TIH because of the risks for extraskeletal calcium precipitation and renal insufficiency. Calcitonin is a natural anti-osteoclastic hormone whose main advantages in therapeutics are a rapid onset of action and a negligible toxicity. It generally is administered subcutaneously or intramuscularly. Calcitonin also exerts a calciuretic effect that contributes to its hypocalcemic activity.[8] Recommended doses vary and a dose-response relationship has not been shown. Unfortunately, the efficacy of calcitonin in TIH is variable, partial, and transient. Serum Ca levels usually increase again after a few days and there is no further response to an increase of the dose. It remains that salmon calcitonin still can be recommended during 2 to 4 days at 200 to 400 IU/d in cases of severe hypercalcemia because the Ca level–lowering effects of bisphosphonates generally only are evident after 1 or 2 days. Plicamycin (or mithramycin) is another anti-osteoclastic agent, but its use is limited by major potential toxicities, particularly when the administration is repeated, even at the recommended dose of 25 μg/kg intravenously, and this compound should no longer be part of our therapeutic armamentarium. The bisphosphonates most often used nowadays are clodronate, pamidronate, and, more recently, ibandronate and zoledronic acid. Other bisphosphonates are not reviewed here because they are not as efficacious in correcting hypercalcemia.[9,10] In addition, the studies of other bisphosphonates (alendronate, neridronate, olpadronate, risedronate) have been limited or nonexistent in the treatment of TIH.

Clodronate

A single-day, 1,500-mg infusion of clodronate is as efficient as daily 300-mg infusions for 5 days and this therapy achieves normocalcemia in 50% to 80% of the cases.[11,12] The superiority of pamidronate over clodronate has been shown in a randomized trial in a study including only 39 evaluable patients with TIH persisting after 48 hours of volume repletion. Pamidronate was more efficient in terms of success rate (100% versus 80%), but more importantly in the duration of normocalcemia with a median duration of action of 2 weeks for clodronate compared with 4 weeks for pamidronate ($P < .01$).[13] A more recent dose-response study suggests that there are actually no differences between clodronate doses going from 600 to 1,500 mg and that the overall response rate does not exceed 50%.[12]

Clodronate nevertheless has the advantage that it also can be administered by a subcutaneous infusion. At a dose of 1,500 mg over 4 to 30 hours, mild site toxicity has been observed in 29% of 45 infusions and a marked hypocalcemic activity was shown in 12 evaluable episodes. This mode of administration is particularly useful in the palliative setting and should be investigated further.[14] Oral clodronate often is prescribed after successful intravenous therapy but the efficacy of this strategy, compared with repeated intravenous treatment when hypercalcemia recurs, has actually not been examined systematically.[2]

Pamidronate

Pamidronate also is administered currently as a single infusion over 2 to 4 hours. Large studies indicate that a dose of 90 mg achieves normocalcemia in more than 90% of unselected patients.[15,16] At this dose, the effects of pamidronate on serum Ca level are not influenced greatly by the tumor type or by the presence of bone metastatic involvement. There is no need to adjust the dose of pam-

Table 1. Equivalent Doses of Intravenous Bisphosphonates in Patients with Moderate or Severe Hypercalcemia of Malignancy (Ca ≥ 12 mg/dl)

Drug	Commercial names	Dose (mg)	Success Rate (%)	Reference
Clodronate	Bonefos, Clastoban, Ostac	1500	50-70	11-12
Pamidronate	Aredia	90	70	26
Ibandronate	Bondronat	4	76	23
		6	77	23
Zoledronic acid	Zometa	4	87	26
		8	88	26

Data from reference 36.

idronate as a function of initial Ca levels and the response to lower doses of pamidronate will be less in patients with humoral hypercalcemia of malignancy as compared with patients with bone metastases because the contributory role of PTHrP on calcium reabsorption by the kidney will become less evident than when large doses of bisphosphonates are used.[17] The effect of circulating PTHrP on the response to bisphosphonate therapy has been a subject of controversy for a long time. It is indeed difficult to show when adequate doses of pamidronate are used or when more potent bisphosphonates are administered. In the largest published study (315 well rehydrated patients, 147 of whom had PTHrP measurement), kidney calcium reabsorption was increased in 65% of them but there was no correlation with PTHrP levels and PTHrP levels did not exert a significant effect on the response to ibandronate.[18] However, when hypercalcemia recurs and becomes refractory to therapy, the pathogenic and clinical importance of circulating PTHrP becomes essential.[19]

Volume repletion adjusted to clinical needs and a dose of 90 mg of pamidronate was the standard treatment of TIH until quite recently. The drug is well tolerated, with the only clinically detectable side effect being transient fever and/or a flu-like syndrome in about one fourth of cases.

Newer and more potent bisphosphonates, such as ibandronate and zoledronic acid,[20] have been evaluated recently and appear to be superior to pamidronate in moderate to severe cases (see Table 1). They are also more convenient to administer.

Ibandronate

In a randomized phase II trial in 174 hypercalcemic patients (corrected Ca level ≥ 2.70 mmol/L = 10.8 mg/dL) it was shown that infusions of 0.6, 1.1, and 2.0 mg of ibandronate normalized Ca levels in 44%, 52%, and 67% of the patients, respectively.[21] A further dose escalation trial with ibandronate then was conducted in 147 patients with Ca levels ≥ 3.0 mmol/L (12 mg/dL) after rehydration, 125 of whom were evaluable for response. The success rate was 50% in the 2-mg group, which was significantly lower than the response rates in the 4- and 6-mg dose groups, 76% and 77%, respectively. A logistic regression analysis indicated that the response rate also was dependent on the initial Ca level and on the tumor type because the group of patients with breast cancer or myeloma responded better than patients with other tumors. The drug was well tolerated, the only noticeable side effect was drug-induced fever in 13% of the cases.[22] These success rates appear to be less than for pamidronate, but this large-scale study with ibandronate only included patients with moderate or severe hypercalcemia and the results of a limited face-to-face comparative trial suggest that ibandronate actually could be more efficient than pamidronate in cases of severe hypercalcemia (Ca ≥ 3.5 mmol/L).[23]

Zoledronic Acid (Zoledronate)

A first phase I dose finding study in 30 evaluable hypercalcemic (corrected Ca level ≥ 2.75 mmol/L) cancer patients showed that very low doses of zoledronic acid (0.02 and 0.04 mg/kg; ie, 1.2 and 2.4 mg for a 60-kg individual) administered by a short-time infusion (30 min) were quite effective. Five of 5 patients became normocalcemic after 0.02 mg/kg, and 14 of 15 patients after 0.04 mg of zoledronic acid/kg. The success rate of the 0.04-mg/kg dose was thus 93% (95% confidence interval, 68% to 100%).[24] This trial provided the incen-

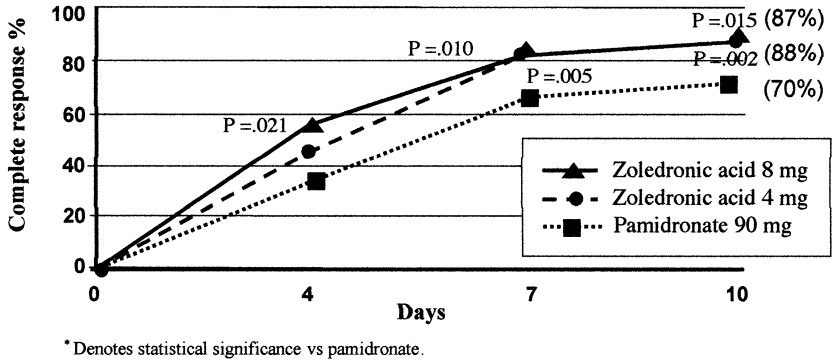

Fig 1. Comparative efficacy between zoledronic acid (4 or 8 mg) and pamidronate in 275 evaluable patients with moderate or severe TIH. Complete response rate was defined as normalization of corrected serum calcium levels of 10.8 mg/dL or less (≤2.7 mmol/L). P values denote statistical significance versus pamidronate. ▲, Zoledronic acid 8 mg; ●, zoledronic acid 4 mg; ■, pamidronate 90 mg. Adapted with permission from Major et al.[25]

tive to investigate further the clinical usefulness of this potent compound.

Two pooled, randomized, double-blind, double-dummy trials in 275 evaluable patients with moderate or severe TIH (corrected Ca level ≥ 12 mg/dL or 3 mmol/L) compared zoledronic acid, administered either as a 5-minute 4-mg infusion (n = 86) or as a 5-minute 8-mg infusion (n = 90), with pamidronate (90 mg over 2 h; n = 99). The groups were well balanced except that there were more patients with breast or hematologic tumors in the 4-mg zoledronic acid group than in the 2 other groups. As a whole, zoledronic acid was more efficient than pamidronate (Fig 1). At day 10, success rates (corrected Ca level ≤ 10.8 mg/dL) were 88%, 87%, and 70% for the 3 groups, respectively. The difference was less marked in patients with bone metastases (success rates of 90%, 84%, and 80%, respectively) but dramatic in patients without bone metastases (success rates of 87%, 90%, and 61%, respectively). There were more renal adverse events in the zoledronic acid groups than in the pamidronate group, although the incidence of increased creatinine levels was relatively low (5.2% in the 8-mg zoledronic acid group). Based on that study, the recommended dose of zoledronic acid for the treatment of TIH is 4 mg.[25] From further experience with repeated infusions for the long-term treatment of patients with tumor bone disease, the dose of 8 mg is not recommended for long-term therapy because of possible renal toxicity and the infusion time has been increased to 15 minutes for each monthly infusion to avoid renal toxicity.

Such newer compounds will simplify the current treatment for TIH because of their shorter infusion times and improvement in therapeutic results in patients with severe hypercalcemia, at least when hypercalcemia is of humoral origin.

The question often is asked if bisphosphonates can be administered safely in patients with renal failure. It is known that rapid injections can lead to renal failure, probably because of the formation of a solid phase of bisphosphonate, linked to calcium in the blood, which is then held back in the kidney. A direct tubular toxicity has not been shown convincingly. Recent reviews provide little or no recommendation for the treatment of patients with renal insufficiency that is nevertheless a classic complication of hypercalcemia.[1,26] It often is claimed that a full bisphosphonate dose can be administered safely in such patients but that repeated therapy for metastatic bone disease requires a larger interval between dosing or use of lower doses. There is no direct proof that bisphosphonates are indeed able to exert direct toxic effects on the renal tubular even if their potential renal toxicity appears to be variable from one compound to another. The safety of pamidronate administration in patients with underlying renal insufficiency was shown best in a retrospective review of 31 patients who received 33 courses of pamidronate in the usual doses of 60 to 90 mg. Eight courses were followed by a transient deterioration in renal function but a detailed analysis of these cases indicated that this deterioration did not appear to be related to pamidronate administration.[27] Based on pamidronate pharmacokinetics, it has been advised along

Table 2. Bisphosphonates for the Long-Term Treatment of Tumor Bone Disease: Some Practical Recommendations

Multiple myeloma:	-all patients with stage III disease
	-probably lifelong therapy (stop when complete remission?)
Breast cancer:	-start when metastatic bone disease is symptomatic *versus* start immediately at the diagnosis of bone metastases
	-lifelong therapy *versus* intermittent treatments (function of response to systemic antineoplastic therapy and symptoms of metastatic bone disease)
Prostate cancer:	-probably most patients with hormone-refractory prostate cancer and bone metastases
	-consider therapy in other patients with symptomatic bone disease

the same line that a reduction in the dose of pamidronate should not be necessary in patients with renal impairment.[28] Moreover, many investigators have reported an improvement in renal function in patients with severe hypercalcemia and secondary renal failure. Zoledronic acid could be somewhat more nephrotoxic than pamidronate but data are scanty. In the large comparative trial between both drugs, patients were excluded from the study if their baseline serum creatinine level was greater than 4.5 mg/dL (or 400 μmol/L) and kidney side effects appeared to be similar for both compounds.[25] Even if preclinical data were reassuring, doses higher than 4 mg nevertheless carry the risk for increased nephrotoxicity[29] and it would appear logical to be cautious in hypercalcemic patients with severe renal failure treated with zoledronic acid, especially if myeloma is the underlying neoplasm. Ibandronate is an attractive alternative because it is not nephrotoxic at the tested doses[22,30] and even quite intensive therapy appears not to have any deleterious effect on renal function.[31] Generally speaking, hypercalcemic patients with renal insufficiency thus can be treated at the recommended doses provided that particular attention is paid to the duration of the infusion.

PREVENTION OF TUMOR-INDUCED HYPERCALCEMIA

Bisphosphonates represent a major therapeutic advance for the supportive care of patients who present with a cancer that is metastatic in the skeleton. Trials controlled against placebo have established that, when administered over a prolonged period by the oral route (clodronate and ibandronate) or by the intravenous route (pamidronate, ibandronate, and zoledronic acid), bisphosphonates reduce the frequency of complications linked to bone metastases by 25% to 40% in patients who present with breast cancer, which is metastasized to the skeleton and significantly decrease the proportion of patients presenting with a severe bone complication.[2,32] In breast cancer, it currently is recommended to begin treatment with bisphosphonates as soon as osteolytic disease has been shown and, according to some experts, even as soon as the first bone metastasis has appeared, whether the patient is symptomatic or not. However, there is a risk for excessive therapy and cost effectiveness has to be taken into account as well.[33] When started very early in breast cancer, intermittent treatment probably has to be considered in patients who respond satisfactorily to their antineoplastic treatment and who do not have an aggressive metastatic bone disease.

Because osteolysis plays a key role in the progression of myelomatous disease, all experts now acknowledge that it is advisable to begin treatment with bisphosphonates as soon as stage III myeloma has been diagnosed and the treatment has to be maintained as long as the myelomatous disease is active. Zoledronic acid is the first bisphosphonate to have shown a clinically significant efficacy in a study controlled against placebo in patients with metastatic prostate cancer and in other solid tumors as well. These recent findings considerably expand the indications of bisphosphonates in metastatic bone disease although the timing to start bisphosphonates and the selection of patients currently remains a matter of debate. An algorithm is proposed in Table 2.

In a complete review of available trials using either clodronate or pamidronate, McCloskey et al[34] have estimated that the incidence of hypercalcemia was reduced by a weighted mean average of 63% in breast cancer and of 37% in myeloma. These figures are higher than the reduction in the frequency of other skeletal-related events[36] and

they are probably even higher with newer more potent bisphosphonates.

SPECULATIONS ON FUTURE OPTIONS

Several groups are working on new inhibitors of bone resorption. Interferences in the osteoprotegerin (OPG)/receptor activator of NF-KB(RANK)/receptor activator of NF-KB ligand (RANKL) system are likely to play a key role not only for the treatment of tumor-induced hypercalcemia but also for the treatment and the prevention of tumor-induced osteolysis in general. OPG recently was identified and shown to specifically inhibit osteoclast differentiation by acting as a decoy receptor for osteoprotegerin ligand (OPG-L or RANKL). A recombinant OPG construct recently has been shown in a phase I study to induce a rapid, sustained, and prolonged inhibition of bone resorption. The effects were at least as great as the ones of pamidronate. This was achieved by a single subcutaneous injection as compared with the classic 2-hour pamidronate infusion.[35] The drug was tolerated without evident side effects. Other ways currently evaluated to interfere with this key system include the administration of an anti-RANKL antiserum.

On the other hand, anti-PTHrP antibodies currently are undergoing testing to counteract the effects of PTHrP on bone resorption and, quite importantly for the pathogenesis of tumor-induced hypercalcemia, PTHrP-induced Ca renal reabsorption. Such antibodies could be particularly useful in patients with refractory tumor-induced hypercalcemia whose prognosis is currently extremely poor.[19]

In conclusion, there are several new drugs available for efficient treatment of TIH. Volume repletion remains part of a rational therapeutic approach but bisphosphonates have supplanted all other therapeutic compounds. They normalize serum Ca levels in more than 90% of patients with TIH but they are less efficient when hypercalcemia recurs. Quite importantly, much has been and will be learned from the understanding and the treatment of TIH for the prevention and the treatment of bone metastases and their complications.

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