Onco-Nephrology: The Pathophysiology and Treatment of Malignancy-Associated Hypercalcemia

Mitchell H. Rosner* and Alan C. Dalkin†

Summary
Hypercalcemia complicates the course of 10%–30% of all patients with malignancies and can be a sign of very poor prognosis and advanced malignancy. Prompt recognition of the nonspecific signs and symptoms of hypercalcemia and institution of therapy can be lifesaving, affording the opportunity to address the underlying etiology. The mechanisms of malignancy-associated hypercalcemia generally fall into three categories: humoral hypercalcemia due to secreted factors (such as parathyroid-related hormone), local osteolysis due to tumor invasion of bone, and absorptive hypercalcemia due to excess vitamin D produced by malignancies. The mainstays of therapy for hypercalcemia are aggressive intravenous volume expansion with saline, bisphosphonate therapy, and perhaps loop diuretics. Adjunctive therapy may include calcitonin and corticosteroids. In refractory cases, gallium nitrate and perhaps denosumab are alternatives. In patients presenting with severe AKI, hemodialysis with a low-calcium bath can be effective. In most cases, therapy normalizes calcium levels and allows for palliation or curative therapy of the malignancy.

Introduction
Hypercalcemia (defined as a serum calcium level above the upper limit of the normal reference range of 10.5 mg/dl or 2.5 mmol/L, 40%–45% of which is ionized calcium) can complicate the course of 10%–30% of all patients with cancer (1–4). The incidence of hypercalcemia is low at the initial presentation of cancer (1%–5%) but increases dramatically in patients with advanced disease and a poor prognosis (5). In fact, the median duration of survival for patients with malignancy-associated hypercalcemia is only 2–6 months from the onset of hypercalcemia (3,5).

The symptoms of hypercalcemia are nonspecific, often develop gradually, and may resemble the symptoms of the underlying malignancy and its treatment. These nonspecific symptoms may lead to a delay in diagnosis, with increased morbidity and mortality. Clinical presentation is influenced by the rate of onset as well as the severity of hypercalcemia. Typical symptoms include nausea, vomiting, constipation, abdominal pain, anorexia, weight loss, bone pain, polyuria, fatigue, and weakness. In patients with more severe degrees of hypercalcemia (serum calcium > 14 mg/dl), neurologic symptoms such as confusion and even coma may become more apparent. These patients require hospitalization and urgent therapeutic intervention (6).

Given the presence of concomitant cachexia and malnutrition in this population, it is also critical to correct the serum calcium for a low albumin level or measure an ionized serum calcium level in order to assess the true degree of hypercalcemia (7). Although ionized calcium is more sensitive than albumin-corrected total calcium in the diagnosis of hypercalcemia of malignancy, the clinical usefulness of this measurement is unclear. In at least one study, slightly increased ionized calcium levels did not predict the development of frank hypercalcemia in patients with solid malignant tumors (8,9). Thus, evaluation of total calcium concentration in light of changes in bound versus ionized calcium is essential in order to obtain a complete patient assessment.

Mechanisms of Malignancy-Associated Hypercalcemia
Perturbations of calcium regulation in patients with hypercalcemia of malignancy fall into three general categories (Figure 1). First, most common are humoral factors secreted in a paracrine or endocrine fashion (humoral hypercalcemia of malignancy). Second, in patients with substantial tumor burden metastatic to bone, the local effects of tumor can directly facilitate bone dissolution and calcium mobilization (local osteolysis). Third, less commonly, absorptive hypercalcemia results from excess vitamin D activation by the neoplasm. The cellular basis for the former two mechanisms includes changes in the activity and balance at the level of the bone-remodeling unit.

Bone turnover involves the highly coordinated activity of two distinct types of cells (10). The osteoblast, or bone-forming cell, is derived from a mesenchymal stem cell and is closely related to adipocytes, chondrocyte, myocytes, and fibroblasts. In contrast, the osteoclast, or bone-removing cell, is derived from stems cells populating the monocyte and macrophage lineage. Although the specifics remain incompletely understood, communication between osteoblasts and osteoclasts primarily involves the
receptor activator of nuclear factor κ B (RANK) ligand (RANKL) signaling pathway (10–12). RANK is a receptor expressed on osteoclast precursor cells. The naturally occurring ligand, RANKL, is produced by osteoblasts and drives proliferation and differentiation of the osteoclasts into mature, multinucleated units. In addition, the osteoblast cell produces osteoprotegerin (OPG), a decoy receptor that binds to and inactivates RANKL.

The cellular regulation of RANK, RANKL, and OPG expression is incompletely understood, but the osteoblast is the focal point for the integration of endocrine and paracrine signals that alter bone remodeling. For example, osteoblast cells express estrogen receptors that when occupied with ligand can reduce RANKL and increase OPG (13). Directly related to the hypercalcemia of malignancy, osteoblasts also express the cell surface receptor for parathyroid hormone (PTH) and parathyroid hormone–related hormone (PTHrP), PTH1R (14). Both PTH and PTHrP stimulate PTH1R, which, in turn, increases osteoblast activity and RANKL signaling to the osteoclast. OPG expression may decline as well. In sum, PTH/PTHrP signaling results in an increased bone turnover with a greater increase in bone resorption than formation, resulting in a net efflux of calcium and hypercalcemia from the bone microenvironment.

Tumors that commonly produce PTHrP include squamous cell carcinomas of the lung, cervix, and esophagus; certain lymphomas; renal cell carcinoma; and adenocarcinoma of the breast, prostate, and ovary (15–17). In addition, several case reports have documented PTHrP secretion in other malignancies. Ectopic secretion of PTHrP is incompletely understood, but the osteoblast is the focal point for the integration of endocrine and paracrine signals that alter bone remodeling. For example, osteoblast cells express estrogen receptors that when occupied with ligand can reduce RANKL and increase OPG (13). Directly related to the hypercalcemia of malignancy, osteoblasts also express the cell surface receptor for parathyroid hormone (PTH) and parathyroid hormone–related hormone (PTHrP), PTH1R (14). Both PTH and PTHrP stimulate PTH1R, which, in turn, increases osteoblast activity and RANKL signaling to the osteoclast. OPG expression may decline as well. In sum, PTH/PTHrP signaling results in an increased bone turnover with a greater increase in bone resorption than formation, resulting in a net efflux of calcium and hypercalcemia from the bone microenvironment.

Laboratory Investigation

Given that the malignancy is usually advanced by the time hypercalcemia develops, a thorough history and physical examination can often lead to the correct diagnosis with limited laboratory evaluation. Measurement of intact PTH through an immunoradiometric or immunochemoluminescent assay will confirm a PTH-independent process.
In this case, the PTH levels will be suppressed (often <20 pg/ml) and should prompt further testing to distinguish among the multiple possible causes in patients with malignancy. This would include measurement of PTHrP, 1,25(OH)2D levels, serum and urine protein electrophoresis, assessment of serum free light chains, and possibly imaging studies (such as a skeletal survey). Less common causes of hypercalcemia in malignancy include drugs (e.g., retinoic acid [26]) and, rarely, parathyroid carcinomas producing excessive PTH.

**Therapy for Malignancy-Associated Hypercalcemia**

Patients presenting with acute and symptomatic hypercalcemia require prompt therapy that rapidly reduces the serum calcium level, restores the GFR, and leads to longer-term normalization of the serum calcium level. An algorithmic approach is shown in Figure 2.

**Intravenous Fluid and Diuretics**

Hypercalcemia leads to a decrease in the GFR through a combination of the natriuretic effects of high serum levels of calcium and renal vasoconstriction (27). In fact, polyuria is the most common renal manifestation of hypercalcemia, and it is thought that the impaired urinary concentrating ability is due to activation of the calcium-sensing receptor in the thick ascending limb of the loop of Henle (28). Activation of the calcium-sensing receptor leads to decreased resorption of sodium and chloride in the loop of Henle, resulting in decreased countercurrent multiplication and decreased ability to concentrate the urine. In addition, activation of the calcium-sensing receptor in the collecting duct blunts the response of this segment to the actions of arginine vasopressin (29). Thus, patients presenting with hypercalcemia are usually profoundly volume depleted. Furthermore, patients usually will present with poor oral intake and may have had nausea and vomiting that further worsen the volume depletion. The decrease in GFR leads to impaired calcium clearance and, thus, restoration of extracellular fluid volume, and GFR is a key goal of therapy.

Thus, initial therapy should begin with intravenous (IV) volume expansion with 0.9% saline at 200–500 ml per hour. Volume expansion will lead to an increase in GFR and an increase in urine calcium excretion. The goal should be establishing an adequate urine output (>75 ml per hour). In milder cases of hypercalcemia, this therapy can be sufficient to restore normal calcium levels (30). However, the effect of repleting the extracellular volume is transient, and other therapies are required. Careful monitoring of the patient’s vital signs and laboratory values must occur during the acute phase of volume repletion, along with vigilance for evidence of volume overload. Hypernatremia may be seen during this phase of therapy because of hypercalcemia-induced nephrogenic diabetes insipidus and may require changing from isotonic to hypotonic fluid therapy (31).

A common practice is to add a loop diuretic to saline therapy in an effort to increase urine calcium excretion (forced saline diuresis). LeGrand and colleagues reviewed the evidence-base for this approach (32). By inhibiting the sodium-potassium-chloride (NKCC2) transporter in the thick ascending limb of the loop of Henle, a loop diuretic decreases the lumen positive charge that normally drives calcium reabsorption; thus, a loop diuretic increases urine calcium excretion and theoretically should be useful in therapy for hypercalcemia (33,34). However, LeGrand et al. could find only nine articles that documented the use of furosemide in the treatment of hypercalcemia, the last of which was published in 1983. These studies comprised a total of 37 patients. The average dosage of furosemide was 1120 mg given over 24 hours, and serum calcium normalized in 14 of 39 episodes of hypercalcemia; however, normalization was rapid (<12 hours) in only two cases. Lower dosages of furosemide (40–60 mg/d) did not achieve normalization of the serum calcium. Most important, monitoring in these patients was intensive and included aggressive replacement of hourly urine output losses, and secondary electrolyte disorders, such as hypernatremia, hypophosphatemia, hypomagnesemia, and metabolic acidosis, were seen. Thus, the routine use of loop diuretics in the therapy for hypercalcemia cannot be recommended, and their use should be restricted to patients who develop fluid overload while receiving aggressive volume resuscitation.

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*Figure 2. | Treatment algorithm for malignancy-associated hypercalcemia.* IV, intravenous.
Bisphosphonates

High-potency IV bisphosphonates are effective agents for the treatment of malignancy-associated hypercalcemia. The three high-potency bisphosphonates are pamidronate, zoledronate, and ibandronate (dosing guidelines are shown in Table 1). Because the IV bisphosphonates are excreted unchanged by the kidneys through glomerular filtration, their dosing must be adjusted for impaired renal function to avoid toxicity (35,36). Mechanistically, bisphosphonates decrease bone resorption through extracellular and intracellular mechanisms (37–41). In the extracellular space, bisphosphonates bind to calcium phosphate and stabilize the bone matrix, while intracellularly these agents inhibit osteoclast activity, in part through inhibition of the mevalonate pathway (37–39). Furthermore, bisphosphonates impair cellular adenosine triphosphate-dependent metabolic pathways, disrupt the osteoclast cytoskeleton, and induce apoptosis (40,41).

Randomized clinical trials with pamidronate, zoledronate, and ibandronate have all shown efficacy in the treatment of hypercalcemia of malignancy (42–44). However, the three bisphosphonates differ in terms of their potency and risk for toxicity. Nussbaum et al. demonstrated a dose response using pamidronate, with 40%, 61%, and 100% of patients achieving normocalcemia with 30, 60, and 90 mg, respectively (45). Similar efficacy of pamidronate is seen over a dosing span ranging from 2 to 24 hours (46). Thus, a practical approach is to administer pamidronate, 60–90 mg, over 2–6 hours, with the longer dosing time reserved for patients with lower GFRs and the higher doses for patients with more severe hypercalcemia. The efficacy of pamidronate (and probably other bisphosphonates) is influenced by the mechanism of hypercalcemia (more effective in cases of hypercalcemia associated with bone metastases); the level of hypercalcemia (higher doses required to treat more severe hypercalcemia); and, in patients with humoral hypercalcemia, the level of PTHrP (higher levels of PTHrP are associated with a lower response rate) (47,48). The fact that patients with higher levels of PTHrP show less of a hypocalcemic response to bisphosphonates is probably due to the continued actions of PTHrP on the kidney to decrease calcium excretion, an effect that is not modulated by bisphosphonates.

Zoledronate is 100 times more potent than pamidronate, and two parallel randomized trials evaluated the efficacy of 4 or 8 mg of zoledronate versus 90 mg of pamidronate in restoring normocalcemia by day 10 after treatment (49). Both doses of zoledronate were superior to pamidronate, with serum calcium normalizing by day 10 in 88%, 87%, and 70% of patients receiving 4 and 8 mg of zoledronate and 90 mg of pamidronate, respectively (49). Moreover, the mean duration of complete response was 32, 43, and 18 days, respectively, in the three treatment groups (49).

Ibandronate is also effective in treating malignancy-associated hypercalcemia (44,50). Doses of 2, 4, and 6 mg had success rates of 50%, 76%, and 77%, respectively (44). Compared with pamidronate, the duration of response is longer with ibandronate (50). However, ibandronate is not approved by the Food and Drug Administration (FDA) to treat malignancy-associated hypercalcemia.

The most common side effect associated with these agents is infusion-related fever, which is usually mild (51). However, bisphosphonate-associated nephrotoxicity affecting both glomerular and tubular structures has been described in both case series and randomized clinical trials (35). In terms of glomerular toxicity, bisphosphonates (most commonly, pamidronate and, only rarely, zoledronate) have been associated with collapsing focal segmental glomerulosclerosis (FSGS), noncollapsing FSGS, and minimal-change disease in several case series (52–56). The most common lesion is collapsing FSGS, which is seen with high-dose IV pamidronate often in patients with underlying multiple

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<th>Table 1. Dosing guidelines for intravenous bisphosphonates in the treatment of acute hypercalcemia</th>
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<tr>
<td>Bisphosphonate per CrCl</td>
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<tr>
<td>CrCl &gt;60 ml/min</td>
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Data obtained from reference 61. CrCl, creatinine clearance; FDA, Food and Drug Administration.
myeloma and usually after repeated doses (35). In clinical trials, glomerular toxicity of the bisphosphonates was not reported (35). In some cases, the nephrotic syndrome resolves after cessation of the drug, but some patients may progress to ESRD, especially if the glomerular lesion is collapsing FSGS.

Tubular injury (nephrotoxic acute tubular necrosis) associated with bisphosphonates (mainly, zoledranate) has also been described in both case reports and clinical trials (57–59). In 2003, the FDA Adverse Event Reporting System experience with bisphosphonates and AKI revealed 72 cases associated with IV zoledronate (60). In this cohort, AKI developed approximately 2 months after initiation of therapy and after a mean of 2.4 doses of zoledronate. Risk factors for AKI included advanced cancer, previous bisphosphonate therapy, and use of nonsteroidal anti-inflammatory agents. Most patients did not fully recover to baseline renal function, and 37.5% of patients required dialysis (60).

On the basis of the renal toxicity of bisphosphonates, the American Society of Clinical Oncology developed dosing and monitoring guidelines (Table 1) and recommended that zoledranate be avoided in patients with a creatinine clearance <30 ml/min (61). Furthermore, serum creatinine should be monitored before each dose of bisphosphonate and the drug withheld in patients with worsening of renal function. Urine albumin excretion should be monitored at 3- to 6-month intervals, and the drug should be held if albuminuria develops (61).

Interestingly, ibandronate appears to have minimal to no renal toxicity, even in patients with underlying CKD (62–64). However, more experience with this drug for the treatment of malignancy-associated hypercalcemia is needed before firm conclusions on its renal safety can be made.

An increasingly recognized complication of bisphosphonate therapy is osteonecrosis of the jaw (ONJ) (65,66). The precise etiology is not known, and the most common precipitating factors include dental extraction, long-term sequential use of IV pamidronate or zoledranate, smoking, and poor dental health (67). The absolute risk for ONJ is unknown, although it is estimated to occur in <1:10,000 treated individuals and may be seen even less often in patients receiving shorter-term treatment. Diagnosis is based on clinical criteria that include pain and evidence of local infection. Management is largely supportive, with occasional need for surgical debridement. The condition can be prevented through good dental hygiene and avoidance of invasive dental procedures during bisphosphonate therapy (68).

**Gallium Nitrate**

Gallium nitrate is approved for the treatment of cancer-related hypercalcemia. The cellular basis for this action is unknown but appears to involve a reduction in osteoclast activity and bone remodeling (69–72). Clinically, gallium nitrate is administered by a continuous infusion at a dosage of 200 mg/m² per day over 5 consecutive days. Reports comparing gallium to bisphosphonates (73,74) and calcitonin (75) have shown equal or perhaps even superior efficacy in decreasing calcium levels. Adverse effects from treatment include hypocalcemia and hypophosphatemia, the latter being observed in nearly 80% of patients. In addition, renal impairment has been reported, and hence gallium nitrate is not recommended for use when the serum creatinine concentration exceeds 2.5 mg/dl. Adequate fluid resuscitation is essential before initiation of treatment with gallium, and BUN and creatinine must be followed closely during treatment. Patients receiving gallium have reported nausea, vomiting, lethargy, altered mental status, and both diarrhea and constipation.

**Calcitonin**

Calcitonin is a peptide hormone secreted by the parafollicular C cells of the thyroid gland. It inhibits osteoclast bone resorption and increases urinary calcium excretion. Synthetic calcitonin (derived from salmon) is administered as 4–8 U/kg intramuscularly or subcutaneously every 6–8 hours. Calcitonin has a rapid onset of effect, leading to reductions in serum calcium within 2–6 hours after dosing. The calcium-lowering effects of calcitonin are modest and transient, with a mean duration of effect of 2–4 days (76).

Furthermore, repeated administration of calcitonin results in downregulation of the calcitonin receptors on osteoclasts and diminution in effect (tachyphylaxis) (77). Overall, its efficacy is poor, inducing normocalcemia in just one third of patients (78). Calcitonin’s major role may be as an adjunctive agent with bisphosphonates in the treatment of severe, symptomatic hypercalcemia when calcium levels must be reduced rapidly (79). Side effects are minimal; nausea, vomiting, and injection site pain are the most common. Overall, there is little evidence that calcitonin use has better efficacy over volume repletion and bisphosphonate therapy alone.

**Corticosteroids**

Corticosteroids are effective agents in the treatment of hypercalcemia associated with malignancies that overproduce citriol. This is due to their effect in inhibiting 1α-hydroxylase conversion of 25-hydroxyvitamin D to calcitriol. Typically, these patients have underlying Hodgkin or non-Hodgkin lymphoma (80). The efficacy of corticosteroids is based on case reports and thus the dosing guidelines are uncertain; however, a reasonable regimen is IV hydrocortisone, 200–300 mg/d, for 3–5 days (79). Typically, calcium levels are slow to decrease with corticosteroid treatment alone. Patients who do respond with normalization of their serum calcium can be transitioned to maintenance oral prednisone, 10–30 mg/d (81).

**Hemodialysis**

For patients with acute hypercalcemia and significant AKI (especially in the setting of oliguria), saline-induced diuresis may not be feasible and may lead to volume overload. In these circumstances, hemodialysis using a very-low-calcium dialysate (≤1 mmol/L) is an option (82). For refractory cases of hypercalcemia, several case reports describe the use of citrate anticoagulation to chelate calcium along with continuous venovenous hemodiafiltration (83,84).

**Denosumab**

Given the important role RANKL in the pathogenesis of bone metastases and secondarily in leading to hypercalcemia, inhibition of this pathway is an attractive means of potentially treating forms of malignancy-associated hypercalcemia.
due to bone calcium release. Denosumab is a fully human monoclonal antibody that binds to RANKL and inhibits osteoclast maturation, activation, and function (85). It is FDA approved for preventing skeletal-related events in patients with solid malignancy, as well preventing bone fractures in postmenopausal women with osteoporosis. In clinical trials, denosumab has shown efficacy in preventing skeletal-related events (such as bone metastases) in patients with prostate, breast, and other solid-organ cancers, as well as multiple myeloma (85). Denosumab is well tolerated, with arthralgias as the most common side effect (86). Because RANKL is expressed on B and T cells, there was some concern that denosumab would increase the risk for serious infections. The FDA has reported only a slightly increased incidence of serious infections (4.1% for denosumab and 3.3% for placebo), with no increase in opportunistic infections seen (86). Of note, denosumab has been associated with a similar incidence of osteonecrosis of the jaw as zoledronic acid (87). Denosumab is not cleared through renal mechanisms and does not require dosing adjustments for renal impairment.

In clinical trials in patients with malignancies, the most common laboratory abnormality was hypocalcemia due to inhibition of bone resorption (88–90). This is not surprising given the mechanism of action of denosumab and leads to the obvious question of whether this drug can be used to treat malignancy-associated hypercalcemia. Hu et al. studied patients with bisphosphonate-refractory malignancy-associated hypercalcemia (91). These patients had solid malignancies or myeloma and elevated corrected serum calcium levels (>12.5 mg/dl) despite recent IV bisphosphate therapy. Patients received denosumab, 120 mg subcutaneously, every 4 weeks, with additional loading doses of 120 mg on days 8 and 15 of the first month. The primary end point was reaching a response defined as a corrected serum calcium level ≤11.5 mg/dl within the first 10 days after denosumab dosing. An interim analysis of this study (n=15) revealed that 80% of patients achieved a response by day 10, with a median response time of 8 days and a response duration of 28 days. Furthermore, an ad hoc pooled analysis of the clinical trials with denosumab (88–90) revealed that compared with zoledronic acid, denosumab significantly delayed the time to first on-study episodes of hypercalcemia (92). More work will be required to understand the role of denosumab in the treatment of malignancy-associated hypercalcemia, but it holds much promise as a safe, more convenient (subcutaneous versus IV) therapy.

Summary
Patients with underlying malignancy frequently encounter hypercalcemia. Indeed, hypercalcemia carries a poor prognosis. Multiple cellular mechanisms underlie the increase in calcium concentration, and a proper evaluation to elucidate the cause is essential to guide treatment. The mainstay of initial management is aggressive fluid resuscitation, with the addition of loop diuretics if volume overload is present. In addition, antiresorptive agents, primarily the bisphosphonates, can aid in the treatment of these patients. Although the physician must bear in mind potential pitfalls with the use of these medications, prompt and assertive treatment of hypercalcemia in patients with cancer can be successful and life-saving.

Disclosures
None.

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