CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Cancer-Associated Hypercalcemia

Theresa A. Guise, M.D., and John J. Wysolmerski, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 60-year-old woman presents to the emergency department with somnolence and poor appetite. Five months earlier, she received a diagnosis of invasive, high-grade, urothelial carcinoma and underwent four cycles of neoadjuvant chemotherapy, and 1 month earlier, she underwent open radical cystectomy. She has no other significant medical history. The serum calcium level is 16.1 mg per deciliter (4.02 mmol per liter; reference range, 8.8 to 10.2 mg per deciliter [2.2 to 2.5 mmol per liter]); previous serum calcium levels were normal. The albumin level is 4 g per deciliter , blood urea nitrogen 27 mg per deciliter (9.6 mmol per liter), creatinine 1.2 mg per deciliter (106.1 μmol per liter), and phosphorus 2.1 mg per deciliter (0.7 mmol per liter). The parathyroid hormone (PTH) level is 10 pg per milliliter (reference range, 15 to 65), parathyroid hormone–related protein (PTHrP) 187 pg per milliliter (reference range, 14 to 27), 25-hydroxyvitamin D 28 ng per milliliter (70 nmol per liter; reference range, 20 to 50 ng per milliliter [50 to 125 nmol per liter]), and 1,25-dihydroxyvitamin D 77 pg per milliliter (200 nmol per liter; reference range, 25 to 66 pg per milliliter [65 to 172 nmol per liter]). A whole-body bone scan shows no skeletal metastases. How should this patient be treated?

From the Section of Bone and Mineral Disorders, Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas M.D. Anderson Cancer Center, and the Lawrence Bone Disease Program of Texas, Houston, and the Cancer Prevention Research Institute of Texas, Austin (T.A.G.); and the Section of Endocrinology and Metabolism, Department of Medicine, Yale School of Medicine, New Haven, CT (J.J.W.).

N Engl J Med 2022;386:1443-51.
DOI: 10.1056/NEJMcp2113128

CME at NEJM.org

THE CLINICAL PROBLEM

Hypercalcemia frequently complicates the care of patients with cancer, occurring in up to 30% of such patients during the course of their disease.[1] Hypercalcemia has been reported in association with most cancers, but it is most common in patients with non–small-cell lung cancer, breast cancer, multiple myeloma, squamous-cell cancers of the head and neck, urothelial carcinomas, or ovarian cancers.[1-4] The prevalence of cancer-associated hypercalcemia appears to be declining owing to the prophylactic use of bisphosphonates or denosumab in patients with bone metastases.[5-7] In retrospective studies conducted in the United States with the use of data from electronic medical records, a prevalence of 2 to 3% has been reported in patients with cancer and a 1-percentage-point decline in prevalence was documented between 2009 and 2013.[8,9]

Cancer-associated hypercalcemia is a complication of advanced cancers and portends a poor prognosis. Older studies showed a median survival of 30 days after the onset of hypercalcemia.[4] Despite the current availability of more effective treatments, outcomes remain poor, with a median survival of 25 to 52 days after the onset of hypercalcemia.[2,10,11] In case series involving patients with hypercalcemia, improved survival was more likely among those with hematologic cancers or breast cancer than among those with other tumor types. Patients who had normalization of calcium levels and received chemotherapy also had longer survival.[2,11,12]

An audio version of this article is available at NEJM.org

DIFFERENTIAL DIAGNOSIS AND PATHOPHYSIOLOGY

Historically, cancer-associated hypercalcemia has been classified into four subtypes: humoral, local osteolytic, 1,25-dihydroxyvitamin D–mediated, and ectopic hyper-

KEY CLINICAL POINTS

CANCER-ASSOCIATED HYPERCALCEMIA

- Hypercalcemia complicates the course of a variety of cancers when tumor factors overwhelm normal calcium and bone homeostasis.
- Cancer-associated hypercalcemia often occurs late in the course of solid-tumor development and portends a poor prognosis.
- Hypercalcemia in the context of cancer may have nonmalignant causes, such as primary hyperparathyroidism; this possibility should be ruled out with the use of appropriate clinical assessment and laboratory testing.
- Because patients with cancer-associated hypercalcemia typically present with profound dehydration, the initial treatment should involve the administration of intravenous fluids.
- Increased osteoclastic bone resorption is almost always responsible for hypercalcemia, regardless of tumor type or mediator; after hydration, the use of bone-resorption inhibitors (most commonly intravenous bisphosphonates) to lower calcium levels is the mainstay of treatment.
- Successful treatment of cancer-associated hypercalcemia ultimately depends on treatment of the underlying cancer.

parathyroidism (see Fig. 1). The condition known as humoral hypercalcemia of malignancy is usually caused by tumor secretion of PTHrP.[13] Normally, PTHrP is a locally produced growth factor, but its dysregulated, systemic secretion by tumors increases osteoclastic bone resorption and renal tubular reabsorption of calcium by binding the PTH–PTHrP type 1 receptor in the bones and kidneys.[14] Humoral hypercalcemia of malignancy is typically associated with squamous tumors of the lung and the head and neck, urothelial carcinomas, and breast cancers, although almost any tumor type may produce PTHrP.[2,10] Patients with humoral hypercalcemia of malignancy typically have few or no bone metastases.

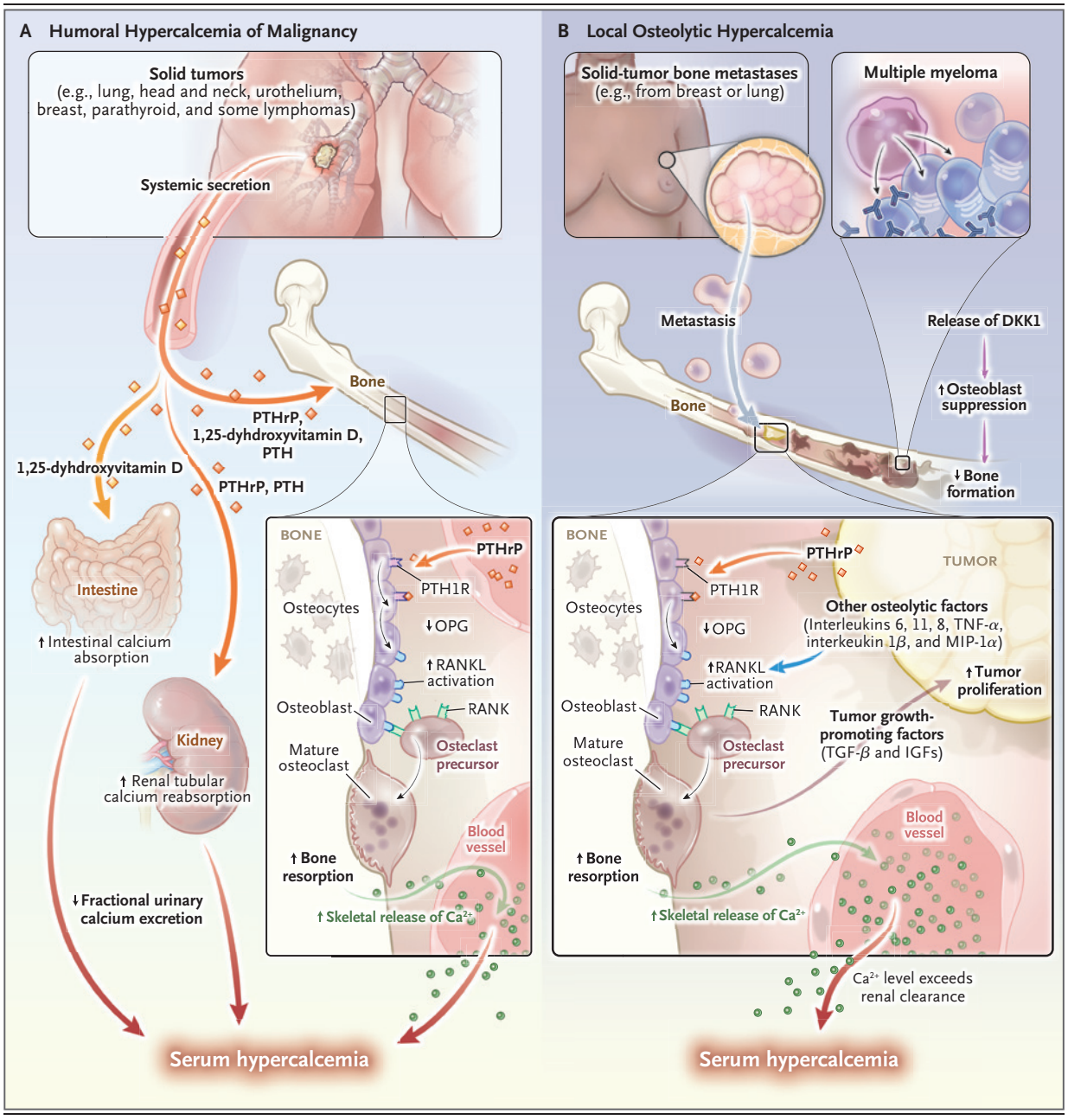
Patients with local osteolytic hypercalcemia have extensive bone metastases, most often resulting from breast cancer or multiple myeloma. Tumor cells in bone produce cytokines that act locally to increase osteoclastic bone resorption and suppress osteoblastic bone formation.[15] Given a large enough skeletal tumor burden, the calcium outflow from bone exceeds renal calcium clearance, causing hypercalcemia.

The remaining categories are also humoral in nature and are caused by the production by tumors of hormones involved in bone remodeling. Some tumors up-regulate the expression of *Cyp27B1*, which encodes 1-alpha-hydoxylase, the enzyme responsible for converting 25-hydroxyvitamin D to the active hormone 1,25-dihydroxyvitamin D. Excess 1,25-dihydroxyvitamin D increases intestinal calcium absorption as well as bone resorption, leading to hypercalcemia.[16,17] Ectopic hyperparathyroidism is caused by rare tumors that produce PTH instead of PTHrP[18]; parathyroid cancers also cause hypercalcemia by secreting PTH.[19,20]

Although initial studies from the 1980s suggested that a humoral cause represented 75 to

Figure 1 (facing page). Pathophysiology of Humoral Hypercalcemia of Malignancy.

Humoral hypercalcemia of malignancy (Panel A) involves tumor-cell secretion of systemically acting factors that act on bone, kidney, and intestine to disrupt normal calcium homeostasis. A variety of tumor types are responsible and include solid tumors arising in the lung, head and neck, kidneys and bladder, breast, and parathyroid gland, as well as some lymphomas. Patients with hypercalcemia of malignancy typically have few or no bone metastases. Most commonly, the humoral factor involved is parathyroid hormone–related protein (PTHrP), but some tumors may produce 1,25-dihydroxyvitamin D, parathyroid hormone (PTH), or other cytokines, and these factors can act alone or in combination with PTHrP to stimulate bone resorption by increasing levels of anti–receptor activator of nuclear factor κB ligand (RANKL) and reducing the levels of its inhibitory decoy receptor, osteoprotegerin (OPG). Parathyroid cancers secrete PTH and not PTHrP. Increases in RANKL and decreases in OPG cause activation of the receptor activator of NFκB (RANKL–RANK) causing increased osteoclastic bone resorption. PTHrP and PTH also act on the kidney to increase renal tubular reabsorption of calcium, whereas 1,25-dihydroxyvitamin D acts on the intestine to increase dietary calcium absorption. Local osteolytic hypercalcemia (Panel B) is caused by the induction of local bone resorption around metastatic tumor deposits in bone. In this type of hypercalcemia, tumor cells in the bone marrow secrete cytokines activating RANKL–RANK signaling in the vicinity of the tumor metastases, causing an increase in the number and activity of osteoclasts and the destruction of peritumoral bone. Increased bone resorption leads to the release of factors from the bone matrix that stimulate further tumor growth, resulting in a vicious cycle of osteolysis and tumor-cell proliferation. Systemic hypercalcemia ensues when osteolytic metastases release enough skeletal calcium to overwhelm renal calcium excretion. Tumors (typically multiple myelomas) can also produce factors such as DKK1 (dickkopf1), a Wnt signaling pathway inhibitor that suppresses osteoblast activity and differentiation. Iinterleukins 6, 11, 8, and 1β denote different members of the interleukin family of cytokines, MIP-1α macrophage inflammatory protein-1α, TGF-β transforming growth factor β, and TNFα tumor necrosis factor α.



80% of all cases of cancer-associated hypercalcemia,[1,13] two retrospective studies showed that serum PTHrP levels were elevated in only 32 to 38% of these patients.[21,22] Another study classified 57% of cases of cancer-associated hypercalcemia as humoral on the basis of the absence of bone metastases.[23] These disparate estimates probably reflect differences in the definition of humoral hypercalcemia of malignancy, a lack of sensitivity in commercial immunoassays for the detection of biologically active fragments of PTHrP, the lability of PTHrP in clinical specimens, or an evolution of the patient population with hypercalcemia.[24] Nevertheless, humoral hypercalcemia of malignancy and local osteolytic hypercalcemia represent a spectrum that includes the vast majority of patients; cases of hypercalcemia mediated by 1,25-dihydroxyvitamin D or PTH account for less than 1% of cases.[1,3]

The pathophysiological characteristics of cancer-associated hypercalcemia are probably more complex than the historical categorizations suggest-

ed. For example, one report indicated that up to 30% of patients may have simultaneous elevations in both PTHrP and 1,25-dihydroxyvitamin D.[25] Furthermore, if humoral hypercalcemia of malignancy is defined as the absence of bone metastases, rather than simply as an increase in circulating levels of PTHrP, then tumors that produce other humoral mediators, such as PTH, macrophage inflammatory protein-1α, and 1,25-dihydroxyvitamin D, can be included under the classification of humoral hypercalcemia of malignancy.[16-18,26] Table 1 reviews suggested classifications and clinical features.

Given the grave prognosis associated with cancer-associated hypercalcemia, it is important to rule out other causes. Two studies showed that 6 to 21% of patients with cancer who had hypercalcemia had concomitant, benign hyperparathyroidism.[27,28] Hypercalcemia may also be caused by increased osteoclast activity resulting from withdrawal of denosumab, the anti–receptor activator of nuclear factor κB ligand (RANKL) antibody used to treat bone metastases and osteoporosis.[29]

STRATEGIES AND EVIDENCE

PRINCIPLES OF TREATMENT

The treatment of hypercalcemia in patients with cancer encompasses three basic principles: correcting volume depletion, inhibiting bone resorption, and instituting effective treatment to address the underlying cancer. Treatment decisions are informed by the absolute value as well as the rate of increase in calcium levels and by the presence or absence of neurologic symptoms such as confusion. If albumin levels are low, the calcium level should be corrected with the use of the standard formula: corrected calcium level (in milligrams per deciliter) = measured total calcium level (in milligrams per deciliter) + 0.8 × (4.0 − serum albumin level [in grams per deciliter]).[30] Alternatively, one can measure ionized calcium, but this approach requires specific phlebotomy and sample-handling techniques in order to achieve accurate results[30] and is rarely needed in therapeutic decision making. If the corrected calcium level exceeds 13 mg per deciliter, if calcium levels are increasing rapidly (e.g., at a rate of more than 1 mg per deciliter per 24 hours), or if the patient has altered mental status, treatment should be started without delay. Treatment options are outlined in Table 2 and discussed below.

HYDRATION AND SALINE NATRIURESIS

Hypercalcemia is associated with anorexia, nausea, vomiting, and nephrogenic diabetes insipidus.[31] These factors often produce extreme dehydration and lead to a reduced glomerular filtration rate, which limits the ability of the kidney to excrete calcium.[32] Thus, the first goal of therapy is to correct volume depletion. The initial rate and duration of fluid administration should be determined on the basis of clinical signs of dehydration, the duration and severity of hypercalcemia, and underlying medical conditions, especially cardiovascular disease. Sodium delivery to the distal tubule promotes urinary calcium excretion and increases calcium clearance by the kidneys.[1,32] Therefore, it has become common practice to add loop diuretics, such as furosemide, after rehydration has been achieved. However, no controlled studies have been conducted to determine whether the addition of loop diuretics lowers calcium levels more rapidly than hydration alone, and the authors of a critical review of nine case series concluded that the routine use of loop diuretics in the treatment of cancer-associated hypercalcemia was not helpful.[33] The administration of diuretics before the achievement of adequate volume repletion may prolong dehydration and impair calcium excretion, worsening hypercalcemia. Therefore, if used, diuretics should be administered only after volume status has been fully restored or during the care of patients with hypercalcemia who are at high risk for the development of fluid overload after aggressive fluid resuscitation.[33] In older patients or in those with a history of cardiac dysfunction, monitoring of central venous pressures may be helpful. Aggressive hydration and the use of loop diuretics can cause electrolyte disturbances (especially hypokalemia), and careful monitoring of both electrolyte levels and calcium levels is required. The administration of intravenous saline with or without loop diuretics can typically lower serum calcium levels by 1 to 2 mg per deciliter, but the effect is transient unless additional treatments directed against bone resorption and the cancer are provided.

INHIBITION OF BONE RESORPTION

In most instances, cancer-associated hypercalcemia occurs as a result of excessive bone resorption (Table 1). Therefore, the mainstay of therapy is the administration of powerful antiresorptive agents — primarily bisphosphonates or denosumab — and, in some instances, calcitonin.

Table 1. Classification of Types of Cancer-Associated Hypercalcemia.*

Feature	Humoral Hypercalcemia			Local Osteolytic Hypocalemia	
Mediator	PTHrP	1,25 dihydroxy-vitamin D	Parathyroid hormone	TNF, interleukin-6, interleukin-1, macrophage inhibitory protein, and others	PTHrP, TNF, interleukin-6, interleukin-1, and others
Tumor type	Lung, breast, renal, and many others	Hematologic cancer, T-cell lymphoma	Parathyroid cancer, neuroendocrine, ovarian, and others	Myeloma or lymphoma in bone	Breast, lung, kidney
Bone metastases, tumor in bone	None or few	None or few	None or few	Extensive	Extensive
Parathyroid hormone	Low	Low	High	Low	Low
PTHrP	High or normal	Low	High	Low	Variable
1,25-dihydroxyvitamin D	Variable	High	High	Variable	Low
Phosphorus	Low	High	Low	Variable	Variable
Osteoclast activity	High	High	High	High	High

* PTHrP denotes parathyroid hormone–related protein, and TNF tumor necrosis factor.

Bisphosphonates

Pamidronate, zoledronate, and ibandronate interfere with protein prenylation and inhibit osteoclast function by inducing apoptosis.[38] Intravenous administration of each of these drugs has been shown to transiently normalize calcium levels in 60 to 90% of patients with cancer-associated hypercalcemia, although ibandronate is used for this indication principally in Europe. Pooled analyses from two randomized, double-blind, parallel-group trials in which a single dose of zoledronate (4 mg or 8 mg) was compared with a single dose of pamidronate (90 mg)[39,40] showed that zolendronate was superior for the treatment of hypercalcemia. Calcium levels normalized by day 10 in 88.4% of those receiving the 4-mg dose of zoledronate and 86.7% of those receiving the 8-mg dose of zoledronate, whereas calcium levels normalized in only 69.7% of those receiving pamidronate.[40] Furthermore, calcium levels normalized by day 4 in 50.0% of the patients receiving zoledronate but in only 33.3% of those receiving pamidronate. The median duration of complete response was 32 days in those receiving the 4-mg dose of zoledronic acid, 43 days in those receiving the 8-mg dose of zoledronic acid, and 18 days in those receiving pamidronate.[40] Given these data, the 4-mg dose of zoledronate is the preferred regimen and is typically administered every 3 to 4 weeks as needed for recurrence of hypercalcemia. Higher circulating PTHrP levels and tumors of the lung and upper respiratory tract may predict resistance to bisphosophonates and more rapid recurrence of hypercalcemia.[41,42] Because intravenous bisphosphonates may worsen renal insufficiency, their use is not recommended in patients with severe volume depletion or a creatinine clearance of less than 35 ml per minute.[43]

Denosumab

Denosumab is a fully human monoclonal antibody that binds to RANKL and prevents it from binding to the receptor activator of nuclear factor κB on osteoclast precursors and mature osteoclasts. In doing so, denosumab inhibits the formation, differentiation, activation, and functioning of osteoclasts, greatly reducing bone resorption.[44] Denosumab is not cleared by the kidney and has no renal toxicity, making it useful in patients with impaired renal function who cannot take bisphosphonates.

Among patients with advanced cancers, denosumab has been documented to prevent skeletal-associated events, a composite end point consisting of hypercalcemia, pathologic fracture, spinal cord compression, and radiation or surgery for the treatment of bone metastases.[5,6,45,46] In one small study, denosumab normalized serum calcium levels in 70% of patients with cancer-associated hypercalcemia,[47] and in a post hoc analysis of pooled data from two phase 3 trials involving patients with bone metastases from multiple myeloma, it significantly delayed the time to first hypercalcemic event and reduced the risk of recurrent hypercalcemia as compared with zoledronate.[48] Furthermore, in a small open-label trial involving 15 patients with disease that

Table 2. Treatment Options for Cancer-Associated Hypercalcemia.

Treatment	Mechanism	Dose	Expected Effect	Adverse Events	Comments
Intravenous fluids	Corrects volume deficit and induces calciuresis	Sodium chloride solution (0.9%) in initial bolus of 1–2 liters, followed by continuous intravenous infusion at 200–500 ml/hr intravenously	Lowers calcium by 1–1.5 mg/dl over first 24 hr	Volume overload	Adjust to urinary output of 100–150 ml/hr. Carefully assess for volume overload.
Furosemide	Acts through natriuresis-induced calciuresis	20–40 mg	Lowers calcium by 0.5–1.0 mg/dl after resolution of volume depletion	Potential volume depletion and worsening of hypercalcemia if volume not replete when initiated	Administer only after volume status restored. Particular benefit in patients at risk for volume overload.
Salmon calcitonin	Inhibits osteoclast activity	Subcutaneous or intramuscular infusion of 4–8 IU per kg of body weight, subcutaneous or intramuscular, every 8–12 hr for 48–72 hr	Rapidly lowers calcium by 1–2 mg/dl		Consider in patients with calcium level >15 mg/dl or altered consciousness. Tachyphylaxis may occur after 48–72 hr.
Pamidronate	Inhibits osteoclast activity, causes osteoclast apoptosis	Intravenous infusion of 60–90 mg over 2 hr in 50–200 ml of saline or 5% dextrose in water	Normalizes calcium in 60–70% of patients over 48–72 hr; median treatment duration of 11–14 days	Acute-phase response relatively common, with hypocalcemia especially likely if vitamin D deficiency present; renal insufficiency possible if administered in presence of decreased GFR or volume depletion or if administered too quickly; osteonecrosis of jaw and atypical femoral fractures possible but rare	Can be repeated every 2–3 wk. May cause kidney damage, especially if GFR <30–35 ml/min.
Zoledronate	Inhibits osteoclast activity, causes osteoclast apoptosis	Intravenous infusion of 4 mg over 15 min in 50 ml of saline or 5% dextrose in water	Normalizes calcium in 80–90% of patients over 48–72 hr, with median treatment duration of 30–40 days	Same as pamidronate; dose adjustment required if GFR <60 ml/min (see package insert)	Rehydrate before administration. Do not administer loop diuretics until patient is adequately rehydrated and use with caution in combination with zoledronate to avoid hypocalcemia (refer to package insert). Treatment can be repeated in 7 days if sufficient lowering of calcium level not achieved and every 3–4 weeks thereafter. May cause kidney damage, especially in patients with GFR <30–35 ml per minute.
Denosumab	Inhibits osteoclast formation, differentiation, and activity	Subcutaneous administration of 120 mg	Normalizes calcium in at least 70% of patients; median duration of response, 104 days	Acute-phase response less common than with bisphosphonates; osteonecrosis of jaw and atypical fractures rare. Rebound osteoclastogenesis may occur when denosumab discontinued without initiation of other therapy (e.g., bisphosphonate).	Not as well studied as bisphosphonates in cancer-associated hypercalcemia. Patients with GFR <30 have a higher risk of hypocalcemia, and a lower dose should be considered (see package insert). Can be given weekly for 4 wk, then monthly for maintenance.

Glucorticoid	Inhibits 1-alpha hydroxylase and lowers 1,25-dihydroxyvitamin D levels	Oral administration of 60 mg of prednisone per day for 10 days†	Has variable effects. Normalization of calcium levels possible if 1,25-dihydroxyvitamin D levels are significantly reduced. Response typically transient unless tumors are treated.	Hyperglycemia, altered mental status, hypertension, increased risk of infection and thromboembolism	Most commonly used in patients with lymphoma. Consider adding to bisphosphonate or denosumab in patients with humoral hypercalcemia and elevated circulating levels of 1,25-dihydroxyvitamin D.
Cinacalcet	Binds calcium-sensing receptor and inhibits secretion of parathyroid hormone in patients with parathyroid carcinoma and may increase renal calcium absorption through renal calcium-sensing receptor in nonparathyroid hypercalcemia	Oral administration of 30 mg per day initially. Can increase to 90 mg four times daily as needed to control hypercalcemia	Reduced calcium by at least 1 mg/dl in approximately 60% of patients with inoperable parathyroid carcinoma. Case reports of normalization of calcium in some nonparathyroid cancers in combination with other treatments.	Nausea, vomiting, headache, fractures	Approved for treatment of hypercalcemia related to parathyroid cancer. Case reports indicate reduction of calcium levels in patients with refractory hypercalcemia related to non–small-cell lung, neuroendocrine, breast, or renal cancer.
Dialysis	Removes excess calcium directly	Administration of low-calcium or calcium-free dialysate through peritoneal dialysis or hemodialysis	Transient reduction of calcium during dialysis		Can be useful initially in patients with severe chronic kidney disease or acute, life-threatening hypercalcemia

* GFR denotes glomerular filtration rate.
† Other glucocorticoids may be used alternatively.

was refractory to treatment with bisphosphonates, denosumab administered at a dose of 120 mg on days 1, 8, 15, and 29 and then every 4 weeks reduced calcium to levels below 11.5 mg per deciliter in 80% of patients within 10 days; the median duration of response was 26 days.[49]

Both bisphosphonates and denosumab are associated with rare adverse events, such as osteonecrosis of the jaw and atypical femoral fractures.[38] Most cases of cancer-associated hypercalcemia are life-threatening, and the benefits of treatment far outweigh these small risks. Hypocalcemia can occur in patients with renal insufficiency or vitamin D deficiency. Patients may have transient acute-phase responses, characterized by fever, musculoskeletal pain, and flu-like symptoms, all of which may be blunted through pretreatment with acetaminophen.

Calcitonin

Calcitonin is a peptide hormone secreted by the parafollicular cells of the thyroid gland that inhibits osteoclast activity and promotes renal calcium excretion.[32,34-36] When administered, calcitonin lowers serum calcium levels rapidly, within 12 to 24 hours. However, the reductions are small (approximately 1 mg per deciliter), and the effects are lost within 48 to 96 hours owing to the down-regulation of calcitonin receptors.[37] Calcitonin is primarily useful in the initial lowering of very high calcium levels while waiting for the more prolonged onset of action of other antiresorptive agents.[32,34-36]

Other Treatments

Glucocorticoids can reduce the hypercalcemia associated with an overproduction of 1,25-dihydroxyvitamin D, typically in patients with lymphoma,[32] but related randomized trials comparing glucocorticoids with other treatments are lacking. Patients with simultaneous elevations of PTHrP and 1,25-dihydroxyvitamin D are more likely to have an incomplete response to antiresorptive therapy and may benefit from the addition of glucocorticoids.[25] The presence of hypercalcemia and acute kidney injury with oliguria may warrant hemodialysis or peritoneal dialysis in which a dialysate low in calcium is used.[32] Such treatment can result in a rapid though transient decrease in total serum calcium levels.[50]

The oral calcimimetic agent cinacalcet reduces PTH secretion and blocks renal tubular reabsorp-

tion of calcium by binding to the calcium-sensing receptors on the parathyroid glands and kidneys.[19,20] In two studies, cinacalcet was reported to reduce calcium levels by at least 1 mg per deciliter, but not PTH levels, in approximately 60% of patients with parathyroid carcinoma, with greatest benefit seen in those with the highest calcium levels.[19,20] Case reports have described reductions in calcium levels with cinacalcet in patients with refractory, non–PTH-mediated hypercalcemia associated with non–small-cell lung, renal, breast, or neuroendocrine cancer.[51,52]

GUIDELINES

We are not aware of any professional guidelines focused on the treatment of cancer-associated hypercalcemia.

AREAS OF UNCERTAINTY

New approaches are needed for patients with disease that is refractory to treatment with currently available antiresorptive agents. In animal models, targeting PTHrP or the PTH receptor effectively reduces calcium levels,[53,54] but there are no known currently available drugs for humans that target PTHrP or its receptor. It remains unclear whether the direct inhibition of PTHrP or the effects of other cytokines on bone and kidney would be effective in the treatment of cancer-associated hypercalcemia. Larger trials are needed to determine whether calcimimetics such as cinacalcet should be used routinely in patients with cancer-associated hypercalcemia.[51,52] Given frequent reports of solid tumors that produce both PTHrP and 1,25-dihydroxyvitamin D,[25] formal study of the addition of glucocorticoids to antiresorptive therapy in such cases is also warranted. In addition, medications used in cancer treatment may contribute to hypercalcemia; data are needed to inform whether emerging cancer therapies that inhibit fibroblast growth factor receptors, currently being reviewed in clinical trials for many tumor types, could lead to hypercalcemia by increasing 1α-hydroxylase activity and thus circulating 1,25-dihydroxyvitamin D levels.[55]

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has a known cancer and presents with severe hypercalcemia and associated somnolence and anorexia; her elevated levels of PTHrP and 1,25-dihydroxyvitamin D indicate that the cancer has a humoral cause. Because she has no history of cardiac disease, we would start treatment with aggressive intravenous hydration (200 to 250 ml per hour of normal saline), paying careful attention to her volume status and electrolyte levels. Once volume has been repleted, we would add a loop diuretic and calcitonin in an effort to rapidly lower her calcium level by 1 to 2 mg per deciliter within the first 24 hours of therapy. We would also administer a single 4-mg dose of intravenous zoledronic acid, with the expectation that this treatment will begin to lower her calcium levels substantially within 36 to 48 hours. If her calcium levels did not fall below 12 mg per deciliter within 5 to 7 days, we would consider starting treatment with denosumab, adding glucocorticoids to lower her 1,25-dihydroxyvitamin D level, or both, although the use of glucocorticoids has not been supported in the findings of any clinical trial. The goal is to stabilize her condition such that further cancer treatment can be started as the ultimate means of controlling the hypercalcemia.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Stewart AF. Hypercalcemia associated with cancer. N Engl J Med 2005;352:373-9.
2. Donovan PJ, Achong N, Griffin K, Galligan J, Pretorius CJ, McLeod DSA. PTHrP-mediated hypercalcemia: causes and survival in 138 patients. J Clin Endocrinol Metab 2015;100:2024-9.
3. Grill V, Martin TJ. Hypercalcemia of malignancy. Rev Endocr Metab Disord 2000;1:253-63.
4. Ralston SH, Gallacher SJ, Patel U, Campbell J, Boyle IT. Cancer-associated hypercalcemia: morbidity and mortality: clinical experience in 126 treated patients. Ann Intern Med 1990;112:499-504.
5. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377:813-22.
6. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011;29:1125-32.
7. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial. J Clin Oncol 2003;21:3150-7.
8. Bhandari S, Kumar R, Tripathi P, Chan A, Mudra S, Redman R. Outcomes of hypercalcemia of malignancy in patients with solid cancer: a national inpatient analysis. Med Oncol 2019;36:90.
9. Gastanaga VM, Schwartzberg LS, Jain RK, et al. Prevalence of hypercalcemia

among cancer patients in the United States. Cancer Med 2016;5:2091-100.
10. Jin J, Chung JO, Chung MY, Cho DH, Chung DJ. Clinical characteristics, causes and survival in 115 cancer patients with parathyroid hormone related protein-mediated hypercalcemia. J Bone Metab 2017;24:249-55.
11. Ramos REO, Perez Mak M, Alves MFS, et al. Malignancy-related hypercalcemia in advanced solid tumors: survival outcomes. J Glob Oncol 2017;3:728-33.
12. Zagouri F, Kastritis E, Zomas A, et al. Hypercalcemia remains an adverse prognostic factor for newly diagnosed multiple myeloma patients in the era of novel antimyeloma therapies. Eur J Haematol 2017;99:409-14.
13. Burtis WJ, Brady TG, Orloff JJ, et al. Immunochemical characterization of circulating parathyroid hormone-related protein in patients with humoral hypercalcemia of cancer. N Engl J Med 1990;322:1106-12.
14. Wysolmerski JJ. Parathyroid hormone-related protein: an update. J Clin Endocrinol Metab 2012;97:2947-56.
15. Coleman RE, Croucher PI, Padhani AR, et al. Bone metastases. Nat Rev Dis Primers 2020;6:83.
16. Adams JS. Vitamin D metabolite-mediated hypercalcemia. Endocrinol Metab Clin North Am 1989;18:765-78.
17. Breslau NA, McGuire JL, Zerwekh JE, Frenkel EP, Pak CY. Hypercalcemia associated with increased serum calcitriol levels in three patients with lymphoma. Ann Intern Med 1984;100:1-6.
18. VanHouten JN, Yu N, Rimm D, et al. Hypercalcemia of malignancy due to ectopic transactivation of the parathyroid hormone gene. J Clin Endocrinol Metab 2006;91:580-3.
19. Silverberg SJ, Rubin MR, Faiman C, et al. Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. J Clin Endocrinol Metab 2007;92:3803-8.
20. Takeuchi Y, Takahashi S, Miura D, et al. Cinacalcet hydrochloride relieves hypercalcemia in Japanese patients with parathyroid cancer and intractable primary hyperparathyroidism. J Bone Miner Metab 2017;35:616-22.
21. Fritchie K, Zedek D, Grenache DG. The clinical utility of parathyroid hormone-related peptide in the assessment of hypercalcemia. Clin Chim Acta 2009;402:146-9.
22. Szymanski JJ, Otrock ZK, Patel KK, Scott MG. Incidence of humoral hypercalcemia of malignancy among hypercalcemic patients with cancer. Clin Chim Acta 2016;453:190-3.
23. Wright JD, Tergas AI, Ananth CV, et al. Quality and outcomes of treatment of hypercalcemia of malignancy. Cancer Invest 2015;33:331-9.
24. Grill V, Rankin W, Martin TJ. Parathyroid hormone-related protein (PTHrP) and hypercalcaemia. Eur J Cancer 1998;34:222-9.
25. Chukir T, Liu Y, Hoffman K, Bilezikian JP, Farooki A. Calcitriol elevation is associated with a higher risk of refractory hypercalcemia of malignancy in solid tumors. J Clin Endocrinol Metab 2020;105(4):e1115-e1123.
26. Okada Y, Tsukada J, Nakano K, Tonai S, Mine S, Tanaka Y. Macrophage inflammatory protein-1alpha induces hypercalcemia in adult T-cell leukemia. J Bone Miner Res 2004;19:1105-11.
27. Hutchesson AC, Bundred NJ, Ratcliffe WA. Survival in hypercalcaemic patients with cancer and co-existing primary hyperparathyroidism. Postgrad Med J 1995;71:28-31.
28. Strodel WE, Thompson NW, Eckhauser FE, Knol JA. Malignancy and concomitant primary hyperparathyroidism. J Surg Oncol 1988;37:10-2.
29. Horiuchi K, Kobayashi E, Mizuno T, Susa M, Chiba K. Hypercalcemia following discontinuation of denosumab therapy: a systematic review. Bone Rep 2021;15:101148.
30. Baird GS. Ionized calcium. Clin Chim Acta 2011;412:696-701.
31. Wysolmerski J, Insogna K. The parathyroid glands, hypercalcemia, and hypocalcemia. In: Goldman L, Schafer AI, eds. Goldman's Cecil medicine. 24th ed. Philadelphia: Elsevier Saunders, 2011:1591-601.
32. Rosner MH, Dalkin AC. Onco-nephrology: the pathophysiology and treatment of malignancy-associated hypercalcemia. Clin J Am Soc Nephrol 2012;7:1722-9.
33. LeGrand SB, Leskuski D, Zama I. Narrative review: furosemide for hypercalcemia: an unproven yet common practice. Ann Intern Med 2008;149:259-63.
34. Carroll R, Matfin G. Endocrine and metabolic emergencies: hypercalcaemia. Ther Adv Endocrinol Metab 2010;1:225-34.
35. Clines GA. Mechanisms and treatment of hypercalcemia of malignancy. Curr Opin Endocrinol Diabetes Obes 2011;18:339-46.
36. Dellay B, Groth M. Emergency management of malignancy-associated hypercalcemia. Adv Emerg Nurs J 2016;38:15-25, E1.
37. Binstock ML, Mundy GR. Effect of calcitonin and glutocorticoids in combination on the hypercalcemia of malignancy. Ann Intern Med 1980;93:269-72.
38. Zaidi M, Blair HC, Moonga BS, Abe E, Huang CLH. Osteoclastogenesis, bone resorption, and osteoclast-based therapeutics. J Bone Miner Res 2003;18:599-609.
39. Cheer SM, Noble S. Zoledronic acid. Drugs 2001;61:799-806.
40. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001;19:558-67.
41. Gurney H, Grill V, Martin TJ. Parathyroid hormone-related protein and response to pamidronate in tumour-induced hypercalcaemia. Lancet 1993;341:1611-3.
42. Rizzoli R, Thiébaud D, Bundred N, et al. Serum parathyroid hormone-related protein levels and response to bisphosphonate treatment in hypercalcemia of malignancy. J Clin Endocrinol Metab 1999;84:3545-50.
43. Miller PD. The kidney and bisphosphonates. Bone 2011;49:77-81.
44. Baron R, Ferrari S, Russell RGR. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011;48:677-92.
45. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer 2012;48:3082-92.
46. Stopeck AT, Lipton A, Body J-J, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010;28:5132-9.
47. Dietzek A, Connelly K, Cotugno M, Bartel S, McDonnell AM. Denosumab in hypercalcemia of malignancy: a case series. J Oncol Pharm Pract 2015;21:143-7.
48. Diel IJ, Body J-J, Stopeck AT, et al. The role of denosumab in the prevention of hypercalcaemia of malignancy in cancer patients with metastatic bone disease. Eur J Cancer 2015;51:1467-75.
49. Hu MI, Glezerman IG, Leboulleux S, et al. Denosumab for treatment of hypercalcemia of malignancy. J Clin Endocrinol Metab 2014;99:3144-52.
50. Camus C, Charasse C, Jouannic-Montier I, et al. Calcium free hemodialysis: experience in the treatment of 33 patients with severe hypercalcemia. Intensive Care Med 1996;22:116-21.
51. O'Callaghan S, Yau H. Treatment of malignancy-associated hypercalcemia with cinacalcet: a paradigm shift. Endocr Connect 2021;10:R13-R24.
52. Sheehan MT, Wermers RA, Jatoi A, Loprinzi CL, Onitilo AA. Oral cinacalcet responsiveness in non-parathyroid hormone mediated hypercalcemia of malignancy. Med Hypotheses 2020;143:110149.
53. Kir S, Komaba H, Garcia AP, et al. PTH/PTHrP receptor mediates cachexia in models of kidney failure and cancer. Cell Metab 2016;23:315-23.
54. Sato K, Onuma E, Yocum RC, Ogata E. Treatment of malignancy-associated hypercalcemia and cachexia with humanized anti-parathyroid hormone-related protein antibody. Semin Oncol 2003;30:Suppl 16:167-73.
55. Roskoski R Jr The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. Pharmacol Res 2020;151:104567.