

## CLINICAL PRACTICE

## Hypercalcemia Associated with Cancer

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*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 author's clinical recommendations.*

**A 47-year-old woman with a history of breast cancer presents with confusion and dehydration. The serum calcium level is 18.0 mg per deciliter (4.5 mmol per liter). She has postural hypotension and low central venous pressure on examination of the jugular veins. The serum phosphorus level is 5.0 mg per deciliter (1.6 mmol per liter), the blood urea nitrogen level is 80.0 mg per deciliter (28.6 mmol per liter), the serum creatinine level is 2.0 mg per deciliter (177  $\mu$ mol per liter), and the albumin level is 3.3 g per deciliter. A bone scintigraphic scan reveals no evidence of skeletal involvement by the tumor. How should she be treated?**

## THE CLINICAL PROBLEM

Hypercalcemia has been reported to occur in up to 20 to 30 percent of patients with cancer at some time during the course of their disease.<sup>1-4</sup> This incidence may be falling owing to the wide use of bisphosphonates in patients with either multiple myeloma or breast cancer, although data are lacking. Hypercalcemia leads to progressive mental impairment, including coma, as well as renal failure. These complications are particularly common terminal events among patients with cancer. The detection of hypercalcemia in a patient with cancer signifies a very poor prognosis; approximately 50 percent of such patients die within 30 days.<sup>5</sup>

Hypercalcemia associated with cancer can be classified into four types (Table 1).<sup>1-4</sup> In patients with local osteolytic hypercalcemia, the hypercalcemia results from the marked increase in osteoclastic bone resorption in areas surrounding the malignant cells within the marrow space.<sup>3,4,6</sup> The condition known as humoral hypercalcemia of malignancy (HHM) is caused by systemic secretion of parathyroid hormone (PTH)-related protein (PTHrP) by malignant tumors.<sup>1,2,7,8</sup> PTHrP causes increased bone resorption<sup>1,2,7,8</sup> and enhances renal retention of calcium.<sup>9,10</sup> The tumors that most commonly cause HHM are listed in Table 1, but essentially any tumor may cause this syndrome. Some lymphomas secrete the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), causing hypercalcemia as a result of the combination of enhanced osteoclastic bone resorption and enhanced intestinal absorption of calcium.<sup>1,2,11</sup> Finally, ectopic secretion of authentic PTH is a rare cause of hypercalcemia, having been well documented in only eight patients to date.<sup>1,2,12</sup>

## STRATEGIES AND EVIDENCE

## DIAGNOSIS

Although clinical laboratories generally measure the total serum calcium level, it is occasionally valuable to measure the serum level of ionized calcium, because increases or decreases in the albumin level may cause misleading increases or decreases, respectively, in the total serum calcium level. In addition, in rare patients with myeloma in whom cal-

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**Table 1. Types of Hypercalcemia Associated with Cancer.\***

Type	Frequency (%)	Bone Metastases	Causal Agent	Typical Tumors
Local osteolytic hypercalcemia	20	Common, extensive	Cytokines, chemokines, PTHrP	Breast cancer, multiple myeloma, lymphoma
Humoral hypercalcemia of malignancy	80	Minimal or absent	PTHrP	Squamous-cell cancer, (e.g., of head and neck, esophagus, cervix, or lung), renal cancer, ovarian cancer, endometrial cancer, HTLV-associated lymphoma, breast cancer
1,25(OH) <sub>2</sub> D-secreting lymphomas	<1	Variable	1,25(OH) <sub>2</sub> D	Lymphoma (all types)
Ectopic hyperparathyroidism	<1	Variable	PTH	Variable

\* PTH denotes parathyroid hormone, PTHrP PTH-related protein, 1,25(OH)<sub>2</sub>D 1,25-dihydroxyvitamin D, and HTLV human T-cell lymphotropic virus.

cium-binding immunoglobulins are produced,<sup>13</sup> measurement of total serum calcium may substantially overestimate the serum ionized calcium level. There are formulas with which to calculate the serum ionized calcium level or to “correct” the total calcium level (e.g., add 0.8 mg per deciliter to the total calcium level for every 1.0 g per deciliter of serum albumin below the level of 3.5 g per deciliter), but they are not precise or always reliable.<sup>14</sup> Thus, measurement of serum ionized calcium should be considered whenever there is doubt about the validity of the measurement of total calcium. The test can be performed rapidly in most hospital laboratories or neonatal intensive care units.

If the calcium level is elevated, a further evaluation should consider not only the mechanisms that are potentially related to the cancer but also causes of the elevation of the calcium level that are unrelated to the cancer (e.g., primary hyperparathyroidism, the use of thiazide diuretics, and granulomatous disease, among other causes).<sup>15–18</sup> The tumors present in hypercalcemia associated with malignant disease are generally large and readily apparent<sup>1–4</sup>; notable exceptions are small neuroendocrine tumors (such as islet tumors and pheochromocytomas). The levels of intact PTH should be measured routinely. Although ectopic hyperparathyroidism is extremely rare in hypercalcemia associated with cancer, concomitant primary hyperparathyroidism is not (we found that in 8 of 133 patients with cancer and hypercalcemia, primary hyperparathyroidism was the cause).<sup>18</sup> Although most patients with typical HHM (Table 1) have increased levels of circulating PTHrP, the diagnosis is usually obvious on

clinical grounds; PTHrP should therefore be measured in the occasional cases in which the diagnosis of HHM cannot be made on clinical grounds or when the cause of hypercalcemia is obscure. Plasma 1,25(OH)<sub>2</sub>D should be measured when sarcoidosis, other granulomatous disorders, or the 1,25(OH)<sub>2</sub>D lymphoma syndrome is considered in the differential diagnosis. A bone scan (or a skeletal survey, in the case of myeloma) is useful to assess the skeletal tumor burden in patients with cancer and hypercalcemia, if the test was not previously performed for tumor staging.

#### THERAPEUTIC CONSIDERATIONS

In planning therapy for patients with hypercalcemia associated with malignant disease, antihypercalcemic therapy should be considered an interim measure, one with no ultimate effect on survival.<sup>5</sup> Thus, it is imperative that antitumor therapy be implemented promptly: control of the serum calcium level merely buys time in which such therapy can work. Another critical point is that when all the available therapies have failed, withholding antihypercalcemic therapy (which will eventually result in coma and death) may be an appropriate and humane approach. In cases in which treatment is considered appropriate, an assessment of the severity of the hypercalcemia is needed to guide therapy.

Although there are no formal guidelines, I consider mild hypercalcemia to be a serum calcium level of 10.5 to 11.9 mg per deciliter (2.6 to 2.9 mmol per liter), moderate hypercalcemia a level of 12.0 to 13.9 mg per deciliter (3.0 to 3.4 mmol per liter), and severe hypercalcemia a level of 14.0 mg per deciliter

(3.5 mmol per liter) or greater. In general, the neurologic and renal complications of hypercalcemia worsen with increasing severity of hypercalcemia, but other factors also influence the response to hypercalcemia. For example, the rate of the ascent of the serum calcium level is important — a rapid increase to moderate hypercalcemia frequently results in marked neurologic dysfunction, whereas chronic severe hypercalcemia may cause only minimal neurologic symptoms. Similarly, older patients with preexisting neurologic or cognitive dysfunction may become severely obtunded in the presence of mild hypercalcemia, whereas younger patients with moderate-to-severe hypercalcemia may remain alert. Finally, the concomitant administration of sedatives or narcotics may worsen the neurologic response to hypercalcemia.

The optimal therapy for hypercalcemia associated with cancer is one that is tailored both to the degree of hypercalcemia and to its underlying cause. True hypercalcemia (i.e., an elevated serum level of ionized calcium) occurs through three basic mechanisms: enhanced osteoclastic bone resorption (in local osteolytic hypercalcemia, HHM, 1,25(OH)<sub>2</sub>D-secreting lymphomas, and the rare case of ectopic hyperparathyroidism); enhanced renal tubular reabsorption of calcium (in HHM and ectopic hyperparathyroidism); and enhanced intestinal absorption of calcium (in 1,25(OH)<sub>2</sub>D-secreting lymphomas and possibly ectopic hyperparathyroidism). Therapy should be targeted accordingly.

#### GENERAL SUPPORTIVE MEASURES

The important general supportive measures include the removal of calcium from parenteral feeding solutions (a measure often overlooked); discontinuation of the use of oral calcium supplements in enteral feeding solutions or as calcium tablets; discontinuation of medications that may independently lead to hypercalcemia (e.g., lithium, calcitriol, vitamin D, and thiazides); an increase in the weight-bearing mobility of the patient, if possible; and discontinuation of the use of sedative drugs, including analgesic drugs, if possible, to enhance the patient's mental clarity and promote weight-bearing ambulation.

Hypophosphatemia develops in most patients with hypercalcemia associated with cancer at some point during the course of the disease, regardless of the underlying cause, because of decreased food intake, saline diuresis, the use of loop diuretics, the phosphaturic effects of PTHrP, the hypercalcemia

itself, and treatment with calcitonin or antacids. In general, the presence of hypophosphatemia increases the difficulty of treating the hypercalcemia, and in animal models hypophosphatemia has been shown to cause hypercalcemia.<sup>19</sup> Phosphorus should be replaced orally or administered through a nasogastric tube as neutral phosphate.<sup>20</sup> The serum phosphorus and creatinine levels should be followed closely, in an effort to keep the phosphorus level in the range of 2.5 to 3.0 mg per deciliter (0.98 to 1.0 mmol per liter), the serum creatinine level in the normal range, and the calcium-phosphorus product below 40, ideally in the range of 30 (when both are expressed in milligrams per deciliter). Intravenous phosphorus replacement should not be given except in dire circumstances, when oral or nasogastric administration is impossible, because its use can result in severe hypocalcemia, seizures, and acute renal failure.<sup>21</sup> These general support measures alone may be sufficient to treat patients with mild hypercalcemia.

#### SALINE HYDRATION AND CALCIURESIS

Patients with hypercalcemia associated with cancer are substantially dehydrated as a result of a renal water-concentrating defect (nephrogenic diabetes insipidus) induced by hypercalcemia and by decreased oral hydration resulting from anorexia and nausea, vomiting, or both. The dehydration leads to a reduction in the glomerular filtration rate that further reduces the ability of the kidney to excrete the excess serum calcium. First, therefore, parenteral volume expansion should be initiated, with the administration of normal saline. Although there are no randomized clinical trials to guide this therapy, in general practice normal saline is administered at a rate of 200 to 500 ml per hour, depending on the baseline level of dehydration and renal function, the patient's cardiovascular status, the degree of mental impairment, and the severity of the hypercalcemia. These factors must be assessed with the use of careful clinical monitoring for physical findings that are consistent with fluid overload. The goals of treatment are to increase the glomerular filtration rate, thus increasing the filtered load of calcium that passes through the glomerulus into the tubular lumen, and to inhibit calcium reabsorption in the proximal nephron (because saline itself is calciuretic). Increasing the glomerular filtration rate to or above the normal range (within safe limits) also permits the use of loop diuretics (Table 2) to increase the renal excretion of calcium (loop di-

**Table 2. Pharmacologic Therapy for Hypercalcemia Associated with Cancer.\***

Intervention	Dose	Adverse Effect
Hydration or calciuresis		
Intravenous saline	200–500 ml/hr, depending on the cardiovascular and renal status of the patient	Congestive heart failure
Furosemide	20–40 mg intravenously, after rehydration has been achieved	Dehydration, hypokalemia
Phosphate repletion		
Oral phosphorus (if serum phosphorus $\leq 3.0$ mg/dl)†	For example, 250 mg Neutraphos orally, four times daily until serum phosphorus level $>3.0$ mg/dl or until serum creatinine level increases	Renal failure, hypocalcemia, seizures, abnormalities of cardiac conduction, diarrhea
First-line medications		
Intravenous bisphosphonates‡		
Pamidronate	60–90 mg intravenously over a 2-hr period in a solution of 50–200 ml of saline or 5% dextrose in water§	Renal failure, transient flu-like syndrome with aches, chills, and fever
Zoledronate	4 mg intravenously over a 15-min period in a solution of 50 ml of saline or 5% dextrose in water	Renal failure, transient flu-like syndrome with aches, chills, and fever
Second-line medications		
Glucocorticoids¶	For example, prednisone, 60 mg orally daily for 10 days	Potential interference with chemotherapy; hypokalemia, hyperglycemia, hypertension, Cushing's syndrome, immunosuppression
Mithramycin	A single dose of 25 $\mu$ g/kg of body weight over a 4-to-6-hour period in saline	Thrombocytopenia, platelet-aggregation defect, anemia, leukopenia, hepatitis, renal failure
Calcitonin	4–8 IU per kilogram subcutaneously or intramuscularly every 12 hr	Flushing, nausea
Gallium nitrate	100–200 mg/m <sup>2</sup> of body-surface area intravenously given continuously over a 24-hr period for five days	Renal failure

\* Many of the recommendations in this table are based on historical precedent and common practice rather than on randomized clinical trials. There are data from randomized trials comparing bisphosphonates to the other agents listed and to one another.

† The use of intravenous phosphorus should be avoided except in the presence of severe hypophosphatemia (serum phosphorus level  $<1.5$  mg per deciliter [0.48 mmol per liter]) and when oral phosphorus cannot be administered. If intravenous phosphorus is used, it should be used with extreme caution and with careful observation of the levels of serum phosphorus and creatinine.<sup>20,21</sup> To convert values for phosphorus to millimoles per liter, multiply by 0.3229.

‡ Pamidronate and zoledronate are approved by the Food and Drug Administration. Ibandronate and clodronate are available in continental Europe, the United Kingdom, and elsewhere. Bisphosphonates should be used with caution if at all when the serum creatinine level exceeds 2.5 to 3.0 mg per deciliter (221.0 to 265.2  $\mu$ mol per liter).

§ Pamidronate is generally used at a dose of 90 mg, but the 60-mg dose may be used to treat patients of small stature or those with renal impairment or mild hypercalcemia.

¶ These drugs have a slow onset of action, as compared with the bisphosphonates; approximately 4 to 10 days are required for a response.

|| These effects have been reported in association with higher-dose regimens used to treat testicular cancer (50  $\mu$ g per kilogram of body weight per day over a period of five days) and in patients receiving multiple doses of 25  $\mu$ g per kilogram; they are not expected to occur with a single dose of 25  $\mu$ g per kilogram unless preexisting liver, kidney, or hematologic disease is present.

uretics block calcium reabsorption in the loop of Henle and make possible increased administration of saline, which induces further calcium excretion). Loop diuretics should not be administered until after full hydration has been achieved, because these agents can cause or worsen dehydration, leading to a decline in the glomerular filtration rate and the filtered load of calcium. In contrast to loop diuretics,

thiazide diuretics should not be administered, since they stimulate, rather than inhibit, renal calcium reabsorption.

#### MEDICATIONS

Intravenous bisphosphonates are by far the best studied, safest, and most effective agents for use in patients with hypercalcemia associated with cancer.

These drugs work by blocking osteoclastic bone resorption.<sup>22-33</sup> Because they are poorly absorbed when given orally (approximately 1 to 2 percent of an oral dose is absorbed), only intravenously administered bisphosphonates are used for this indication. In the United States, the two drugs that are approved by the Food and Drug Administration (FDA) and are currently considered the agents of choice in the treatment of mild-to-severe hypercalcemia associated with cancer are pamidronate<sup>22,24,25</sup> and zoledronate.<sup>22,23,26,27</sup> In continental Europe, the United Kingdom, and other countries, ibandronate<sup>22,28,29</sup> and clodronate<sup>22,30-32</sup> are also widely used. Etidronate, which was the first to be used for this indication,<sup>22</sup> has been replaced by these more potent bisphosphonates. A number of randomized clinical trials comparing bisphosphonates to saline and diuretics alone, to other bisphosphonates, and to other antiresorptive agents such as calcitonin have confirmed the superiority of bisphosphonates.<sup>22,27,28,33</sup>

Bisphosphonate therapy should be initiated as soon as hypercalcemia is discovered, because a response requires two to four days, and the nadir in serum calcium generally occurs within four to seven days after therapy is initiated.<sup>22-33</sup> Approximately 60 to 90 percent of patients have normal serum calcium levels within four to seven days, and responses last for one to three weeks.<sup>22-33</sup> As compared with pamidronate, zoledronate has the advantage of rapid and simpler administration (15 minutes vs. 2 hours for infusion), whereas pamidronate is less expensive. Although a direct comparison of the two drugs in a randomized clinical trial showed a statistically significant increase in the efficacy of zoledronate,<sup>27</sup> the difference in control of calcemia was small (mean nadir serum calcium level, 9.8 mg per deciliter [2.4 mmol per liter] with zoledronate and 10.5 mg per deciliter [2.6 mmol per liter] with pamidronate; the proportion of patients in whom a corrected serum calcium level of 10.8 mg per deciliter [2.7 mmol per liter] was achieved by day 10 was 88 percent and 70 percent, respectively). Thus, the differences are of arguable clinical importance, and the choice is largely one between convenience and cost. Either pamidronate or zoledronate is acceptable therapy.

In animal models, bisphosphonates have been associated with azotemia<sup>22,23</sup> and thus, their use in patients with renal failure is a potential concern. However, because hypercalcemia is a frequent cause of renal dysfunction in patients with hypercalcemia

associated with cancer, effective treatment of the hypercalcemia associated with cancer often improves renal function.<sup>25,34</sup> The manufacturer and the American Society of Clinical Oncology<sup>35</sup> do not recommend the use of a reduced dose of pamidronate or zoledronate for patients with serum creatinine values of less than 3.0 mg per deciliter (265.2  $\mu$ mol per liter), but they do advise that the recommended duration of the infusion not be shortened. Pamidronate and zoledronate have been reported to cause or exacerbate renal failure, but this effect has generally occurred in patients receiving multiple doses.<sup>36</sup> In patients whose condition fails to respond to a low initial dose of bisphosphonates, the use of a second, larger dose (an approach that has not been approved by the FDA) or a second-line agent may be considered.

#### OTHER PHARMACOLOGIC AGENTS

Several agents commonly used before the advent of bisphosphonates are now used infrequently, usually when bisphosphonates are ineffective or contraindicated (Table 2). Glucocorticoids<sup>37,38</sup> may still have a role in the treatment of some patients, such as those with lymphomas resulting in elevated levels of 1,25(OH)<sub>2</sub> vitamin D. Calcitonin may result in a more rapid reduction in serum calcium levels than do other agents (the maximal response occurs within 12 to 24 hours), but its value is questionable because the reductions are small (approximately 1.0 mg per deciliter [0.25 mmol per liter]) and transient.<sup>37,39</sup> Mithramycin, which was the mainstay of therapy for hypercalcemia associated with cancer before the bisphosphonates became available,<sup>40</sup> remains effective, but its use is limited by potential adverse effects (Table 2). Gallium nitrate is also approved for treatment,<sup>41</sup> but the need for continuous intravenous administration over a period of five days limits its use.

#### DIALYSIS

In patients who have cancers that are likely to respond to therapy but in whom acute or chronic renal failure is present, aggressive saline infusion is not possible, and other therapies such as bisphosphonates should be used with caution, if at all. In these circumstances, dialysis against a dialysate containing little or no calcium is a reasonable and highly effective option for selected patients.<sup>42,43</sup> There are no specific guidelines with regard to how low the glomerular filtration rate must be for dialysis to be a rational choice in treating hypercalcemia,

but in general, when the rate falls below 10 to 20 ml per minute, or when the presence of congestive heart failure contraindicates an adequate administration of saline, or both, dialysis should be considered.

#### AREAS OF UNCERTAINTY

The receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) system is the molecular pathway that leads to osteoclast recruitment and differentiation and bone resorption in hypercalcemia associated with cancer. Agents that interfere with the system, such as recombinant osteoprotegerin (a decoy receptor for RANKL) or monoclonal antibodies directed against RANKL, have been proposed as novel treatments for hypercalcemia associated with malignant disease, as have monoclonal antibodies, which neutralize PTHrP. Preliminary data from studies in animals or small studies involving women with osteoporosis indicate reductions in bone resorption with these approaches.<sup>44-46</sup> Whether these agents will prove to be safe and effective in humans with hypercalcemia associated with cancer, whether they can be produced commercially at a cost competitive with that of bisphosphonates, and whether they can reverse hypercalcemia more effectively than the potent bisphosphonates remain unknown.

#### GUIDELINES

No guidelines are available from the major professional societies for the treatment of hypercalcemia associated with cancer.

#### RECOMMENDATIONS

The patient described in the vignette, who has breast cancer and a large, obvious tumor burden, is typical of patients with hypercalcemia associated with can-

cer in general and with HHM in particular. As in all cases of hypercalcemia in patients with cancer, other causes of the hypercalcemia need to be carefully considered. Coexisting primary hyperparathyroidism should routinely be ruled out by measurement of the level of immunoreactive parathyroid hormone. In the patient described, HHM is the most likely cause of the hypercalcemia; thus, immunoreactive parathyroid hormone would be suppressed and circulating PTHrP would be elevated (however, I do not routinely measure PTHrP unless the diagnosis is uncertain).

When a patient presents with hypercalcemia associated with cancer, the physician should first consider whether treatment is appropriate according to an assessment of the overall prognosis. The cornerstones of successful antihypercalcemic therapy are vigorous rehydration (with the use of normal saline at 200 to 500 ml per hour, depending on the patient's cardiovascular status and renal function); aggressive calciuresis with the use of loop diuretics, after normovolemia has been restored; and inhibition of bone resorption with the use of intravenous bisphosphonates (in the United States, the administration of either pamidronate [an infusion of 60 to 90 mg over a 2-hour period] or zoledronate [4 mg over a 15-minute period]). Pamidronate is at present less expensive, whereas zoledronate is more convenient to use and results in slightly greater mean reductions in the serum calcium level, although the differences are small. The expectation with the use of either regimen is that the serum calcium level will begin to fall within 12 hours after the therapy is initiated and will reach the nadir within approximately four to seven days. The serum calcium level generally will remain in the normal or near-normal range for one to three weeks, allowing time to institute other treatments for the malignant disease responsible for the hypercalcemia.

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