Cancer-related hypercalcemia

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Mr H. is a 54-year-old man with non–small cell lung cancer. Six months ago he had surgery and recovered fairly well, requiring no chemotherapy or radiation therapy. He presents to the office with a 4-week history of progressive fatigue, poor appetite, nausea, constipation, and occasional confusion. Two days ago he went for routine scans (ie, computed tomography scans of thorax, abdomen, and pelvis). In 4 days he will meet with his oncologist for his quarterly review and will discuss the results of the scans. Unfortunately, he looks unwell. The results of the physical examination are remarkable for weight loss, dehydration, and mild cognitive impairment.

You are concerned that this might be related to his cancer (metastases), but it might also be a combination of a virus and side effects from medications such as opioids. You tell Mr H. and his wife that this could be many things and that you would like to do some blood tests to help understand what is happening. Mr H. agrees, as he was going to have blood work before seeing his oncologist anyway.

The results demonstrate a calcium level of 2.98 mmol/L and an albumin level of 30 g/L. The high level of calcium makes you suspicious of hypercalcemia associated with malignancy. You discuss the results with the oncologist, who checks the results of the recent computed tomography scans and reports that unfortunately Mr H. has metastatic disease in the lungs, mediastinum, and liver. You are surprised that there were no bone metastases identified, given the hypercalcemia.

Hypercalcemia affects up to 10% to 30% of cancer patients, and cancer-related hypercalcemia is the leading cause of hypercalcemia in hospitalized patients.[1,2] Patients with breast cancer, lung cancer, and myeloma are most commonly affected, but hypercalcemia can also occur with other malignancies, including renal, gynecologic, and head and neck cancers.[3,4] Unfortunately, cancer-related hypercalcemia has a poor prognosis, as it is most often associated with disseminated disease. Eighty percent of patients will die within a year, and there is a median survival of 3 to 4 months.

The main pathogenesis of hypercalcemia in malignancy is increased osteoclastic bone resorption, which can occur with or without bone metastases. The enhanced bone resorption is mainly secondary to different humoural factors that alter calcium regulation and are released by tumour cells locally (at the site of metastatic bone lesions) or systemically. The main humoural factor associated with cancer-related hypercalcemia is parathyroid hormone–related protein, which is produced by many solid tumours. Parathyroid hormone–related protein increases calcium by activating parathyroid hormone receptors in tissue, which results in osteoclastic bone resorption; it also increases renal tubular resorption of calcium.[1-5]

There are a number of clinical features that can accompany hypercalcemia and many of them are nonspecific (eg, fatigue, nausea, constipation, and confusion). The rapidity of onset is more likely to correlate with the severity of the symptoms rather than the degree of hypercalcemia.[3] Untreated severe hypercalcemia can be fatal, but treatment can bring relief of many symptoms and positively affect quality of life. Common clinical features can be general (eg, dehydration, polyuria, polydipsia), gastrointestinal (eg, nausea, vomiting, constipation, anorexia), or neurologic (eg, fatigue, delirium, myopathy). In very severe cases, patients can experience seizures, coma, or cardiovascular collapse.[1,4]

Calcium levels

Because such a variety of symptoms exist, symptomatic cancer patients should always have their plasma calcium measured. In most centres, total plasma calcium is measured, including protein-bound and ionized calcium. As the measured plasma calcium is affected by the albumin level, the measured calcium needs to be corrected according to the serum albumin. The formula for this is as follows: corrected calcium (mmol/L) level = measured calcium (mmol/L) + ([40 - albumin (g/L)] 0.02).

With respect to Mr H., his measured calcium level is 2.98 mmol/L and his albumin level is 30 g/L. The calculation for Mr H. is as follows: corrected calcium = 2.98 + ([40 - 30] 0.02) = 2.98 + (10 0.02) = 3.18. Although laboratory values vary, a normal calcium level is approximately 2.65 mmol/L.

You call Mr H. immediately after seeing the result of his calcium level test and speaking with his oncologist. You ask him to meet you at the emergency department where you can review the test results and treatment options. Mr H. arrives with his wife and son. They understandably have many questions and concerns. You take this opportunity to review the test results and explain that unfortunately the cancer has recurred and progressed, resulting in his high calcium level. The discussion is also a natural segue into discussing goals of care and advance directives. Although this is

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very upsetting and sad for Mr H. and his family, they appreciate knowing what is happening so that they can make plans. They take some comfort in the fact that the medication you have ordered will likely lower his calcium level and make him feel better.

Management

The mainstay of treatment for cancer-related hypercalcemia is hydration with normal saline and intravenous (IV) bisphosphonates.[1-5] Hydration alone is not sufficient to achieve and maintain normocalcemia in cancer patients. Many centres will give 2 to 3 L of normal saline per 24 hours until the patient is drinking well, but this might overwhelm frail patients. The amount of fluid varies depending on the volume status and cardiovascular status of the patient. It was once standard practice to prescribe loop diuretics (eg, furosemide) to promote calciuresis, but given the effectiveness of bisphosphonates and the lack of evidence for furosemide, loop diuretics are no longer recommended except if there is evidence of fluid overload.[6]

Intravenous bisphosphonates should be given as soon as hypercalcemia is diagnosed. They work by blocking osteoclast activity and subsequently decreasing bone resorption. The additional benefits of bisphosphonates are possibly reducing malignant bone pain and delaying the onset of progressive bone disease in various cancers, including breast, multiple myeloma, and lung.[7,8] Two commonly used IV bisphosphonates are pamidronate and zoledronate. In a study comparing the 2 agents, zoledronate was proven to be superior at achieving normocalcemia faster, for longer, and for more patients[9]; however, the clinical significance of the differences is uncertain.[3] Another advantage of zoledronate is that it only requires a 15-minute infusion versus a 2- to 4-hour infusion for pamidronate; however, zoledronate is more expensive. Either drug is a reasonable choice in treating cancer-related hypercalcemia. The dose of pamidronate is typically 90 mg in 500 mL of normal saline infused intravenously over 2 to 4 hours. The dose of zoledronate is 4 mg intravenously over 15 minutes. The dose of bisphosphonates might need to be adjusted for renal dysfunction.

You check Mr H.'s calcium level 1 week after treatment with 90 mg of pamidronate. His corrected calcium level is now 2.48 mmol/L. His nausea and constipation have abated and he is feeling less fatigued. He has met with his oncologist and is scheduled for palliative chemotherapy within a week. The family has decided they will try 1 course of chemotherapy, but if it compromises his quality of life they will stop.

Using a bisphosphonate will start to decrease the serum calcium in approximately 12 hours, with the nadir being reached in 4 to 7 days. Calcium levels can be checked approximately 1 week after bisphosphonate infusion. If there is an incomplete response, the infusion can be repeated. The use of bisphosphonates will result in a normocalcemic state for most patients. Without anticancer treatment, however, the hypercalcemia will likely recur within 2 to 4 weeks and the bisphosphonate treatment will need to be repeated.

There were many other treatments used in hypercalcemia before the advent of bisphosphonates, including corticosteroids, calcitonin, plicamycin, and gallium nitrate. Steroids might still play a role for those rare lymphomas that secrete active vitamin D. Calcitonin is rarely used, despite the fact that it works rapidly, because its effect is short lived (2 to 3 days); repeated doses of calcitonin are less effective because patients develop tolerance to the calcium-lowering effect due to the down-regulation of calcitonin receptors in osteoclasts. Calcitonin can be used initially with bisphosphonates in cases of severe symptoms and very high calcium levels to incur a rapid response and allow time for the bisphosphonates to work. The usual dose of calcitonin is 100 units subcutaneously 3 times a day for 1 to 2 days. Gallium nitrate is rarely used because it inconveniently has to be infused continuously for 5 days and it has nephrotoxicity.

BOTTOM LINE

- Cancer-related hypercalcemia is not always associated with bone metastases.
- Always correct for serum calcium with the following formula: corrected calcium (mmol/L) level = measured calcium (mmol/L) + ([40 - albumin (g/L)] 0.02).
- Cancer-related hypercalcemia has a poor prognosis, as it is most often associated with disseminated disease; therefore, whenever it is diagnosed, physicians should discuss goals of care and advance directives with the patient and the family.

POINTS SAILLANTS

- L'hypercalcémie reliée au cancer n'est pas toujours associée à des métastases osseuses.
- Il faut toujours corriger le calcium sérique en fonction de la formule suivante: taux de calcium corrigé (mmol/l) = calcium mesuré (mmol/l) + ([40 - albumine (g/l)] 0,02).
- Le pronostic d'une hypercalcémie reliée au cancer n'est pas favorable, parce qu'elle est le plus souvent associée à une propagation de la maladie; par conséquent, quand elle est diagnostiquée, les médecins devraient discuter des objectifs des soins et des directives préalables avec le patient et la famille.

Conclusion

Unfortunately, despite chemotherapy, Mr H.'s disease continues to progress. His hypercalcemia returns and

causes a delirium. The IV pamidronate steadily decreases his calcium level and improves the delirium; however, he continues to deteriorate overall and is eventually bedbound. The IV pamidronate is discontinued as is all blood work. Comfort measures are instituted with only subcutaneous medications, including haloperidol for the delirium and hydromorphone for the pain. Mr H. passes away comfortably.

It is important to remember that just because we *can* treat hypercalcemia, it does not mean that we *should*. Always keep the goals of care and prognosis in mind.

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Competing interests
None declared

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