

**FAST FACTS AND CONCEPTS #151**  
**HYPERCALCEMIA OF MALIGNANCY**

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**Background** Up to 30 percent of patients with cancer develop hypercalcemia. Approximately 50% of these patients will die within 30 days of a hypercalcemia diagnosis, even if the hypercalcemia is corrected, which suggests that hypercalcemia is a sign of hormonally advanced cancer. It is most commonly associated with squamous cell cancers of lung, head and neck, and esophagus, breast cancer, renal cell carcinoma, lymphomas and multiple myeloma.

**Pathophysiology**

- Local osteolytic hypercalcemia due to direct effect of bone metastases.
- Humoral Hypercalcemia of Malignancy – secretion of parathyroid hormone related protein (PTHrP) by malignant tumors.
- 1,25(OH)<sub>2</sub>D (vitamin D) secreting lymphomas.
- Ectopic secretion of authentic PTH (very rare).

**Symptoms/Signs** Symptoms roughly correlate with the degree of hypercalcemia (corrected) and the rapidity of rise: Mild (10.5-11.9 mg/dl); Moderate (12-13.9 mg/dl) Severe(>14 mg/dl).

- Cognitive: sedation, delirium, coma.
- Gastrointestinal: anorexia, nausea, vomiting.
- Renal: dehydration, polyuria, thirst/polydipsia.

**Diagnostics**

- Total serum calcium, corrected for albumin (*Formula: [(4 - albumin) x 0.8] + Ca<sup>++</sup>*).
- Ionized calcium.
- Renal function, phosphate, magnesium and potassium—monitor during treatment.

**Anti-Tumor Therapy** Treatment of the underlying malignancy with systemic therapy (e.g. chemotherapy) is essential for long-term management. In cases where further anti-neoplastic therapy is not feasible, the decision to treat or not treat hypercalcemia should be made by careful exploration of the patient's goals of care. In advanced untreatable cancer, the decision to not treat hypercalcemia may be very appropriate.

**Supportive measures**

- *Saline hydration and loop diuretics:* Normal saline 200-500 ml/hr increases GFR, increases filtered load of calcium, and is calciuretic. Loop diuretics (e.g. furosemide) blocks calcium resorption in the loop of Henle. *Note:* only use diuretics once dehydration has been corrected.
- *Discontinue medications* that can increase serum calcium (e.g. lithium, Vitamin D, supplements containing calcitriol, thiazides, calcium antacids); remove calcium from TPN.
- *Increase mobility* if possible.
- *Bisphosphonates* are the drug class of choice for most patients. They work via blocking osteoclastic bone resorption. Pamidronate and zoledronic acid are used in the US with full efficacy noted 2-4 days after administration; responses last 1-3 weeks. May lead to hypocalcemia or azotemia; use with caution in renal dysfunction. *Pamidronate* = 60-90 mg. Repeat only after 7 days have elapsed after 1<sup>st</sup> dose. Repeat infusions every 2-3 weeks or longer according to the degree and of severity of hypercalcemia. *Zoledronic acid* = 4 mg (maximum). Wait at least 7 days before considering retreatment.
- *Denosumab* is a human monoclonal antibody that is a potent inhibitor osteoclast mediated bone resorption. In repeated studies, it has led to durable responses in over 60% of patients with hypercalcemia refractory to bisphosphonates. Its cost may be prohibitive in hospice settings.
- *Other Agents:* *Glucocorticoids* are useful in lymphoid malignancies that secrete 1,25(OH)<sub>2</sub> Vitamin D. *Calcitonin* may lead to transient and reductions in serum calcium (12-24 hours). It is administered intramuscularly or subcutaneously; initially 4 units/kg every 12 hours; may increase up to 8 units/kg every 12 hours to a maximum of every 6 hours. *Mithramycin* was the standard agent prior to bisphosphonates; now it is used only rarely due to a higher side effect profile.

*Gallium nitrate* is usually impractical due to the need for a 5 day IV infusion. *Renal Dialysis* can be used in cases of acute/chronic renal failure.

**Summary** Hypercalcemia is a common oncologic complication that often portends a very short prognosis. The decision to attempt reversal should be made after first exploring the goals of care and assessing the feasibility of future systemic anti-cancer treatments. Vigorous hydration and bisphosphonates are the cornerstones of short-term hypercalcemia therapy.

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