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Hypercalcemia of Malignancy

Introduction

1. Hypercalcemia of Malignancy (HCM) is an oncologic emergency typically seen in patients with advanced stage cancers
2. HCM is more common in patients with tumors that are associated with bone metastases (breast, lung, multiple myeloma, renal cell carcinoma and colorectal cancer)
3. Hypercalcemia is defined as a corrected calcium level > 10.5 mg/dL
4. Symptoms occur slowly (or may be absent) and can include nephrolithiasis, polyuria, polydipsia, gout, ventricular tachyarrhythmias, fatigue, anorexia, cognitive dysfunction, etc.
5. Management of hypercalcemia is traditionally with aggressive IV fluids, calcitonin, and bisphosphonates. Loop diuretics and steroids have a limited role in treatment for most patients.

Pharmacology

	Calcitonin	Bisphosphonates
Role in Therapy	• Used to provide a transient decrease in serum calcium levels • Used with aggressive fluid hydration and IV bisphosphonates	• Should be administered ASAP after diagnosis
Mechanism	• Inhibits osteoclastic bone resorption and promotes renal excretion of calcium	• Deposits into bone and lowers calcium levels by inhibiting osteoclastic bone resorption
Dose	• 4 IU/kg IM/SQ Q12 hours x48 hours	**Zoledronic Acid (Zometa)** • 4mg IV over 15-30 minutes (NO dose adjustments needed for HCM indication) • SCr must be < 4.5 mg/dL **Pamidronate** • 90 mg IV over 4 hours May use if SCr > 4.5 mg/dL
PK/PD	• Onset of action: 4-6 hours • Efficacy limited to 48 hours due to tachyphylaxis	• Onset of action: 48 hours (maximal effect: 2-4 days) • Duration of action: 3-4 weeks
Adverse Effects	• Hypersensitivity reactions (including anaphylaxis), hypocalcemia, flushing, headache, nausea/vomiting	• Renal dysfunction, osteonecrosis of the jaw, bone and joint pain
Comments	• Consider administering if corrected Ca ≥ 14 mg/dL and/or neurologic or cardiac symptoms • Must administer IVF x4-6 hours and recheck Ca PRIOR to ordering	• Zoledronic is more efficacious with regards to time to normalization of calcium and duration of complete response • May repeat bisphosphonate dose in 7 days if needed

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Literature			
Author, year	**Design**	**Purpose**	**Outcome**
Kammerman, 1970	Case Series (n=8)	Report the efficacy **of porcine calcitonin** in patients with hypercalcemia	In the 7 patients given a uniform dose of 4 MRC U/kg body weight, a mean change in serum calcium concentration of −1.97 mg/dL The calcium-lowering effect was measurable at 2 hr and maximal at 6–9 hr; by 20–24 hr the serum calcium had begun to rise.
Thiébaud, 1990	RCT (n=34)	To assess whether a combined **calcitonin and pamidronate lead** to earlier normalization of the plasma calcium level than does pamidronate alone	In the group receiving calcitonin, the mean plasma calcium level decreased from 3.22 ±0.09 mmol/L to 2.29 ±0.03 mmol/L by day 9 (P<.001) and was normalized by day 3. **There was a significant difference the groups in the plasma calcium level from day 2 to day 4, reflecting the earlier drop in calcium level in the group receiving calcitonin.**
Major, 2001	RCT (n= 287)	Compare the efficacy and safety of **zoledronic acid and pamidronate** for treating hypercalcemia of malignancy	Zoledronic acid **is superior to pamidronate with a complete response rate by day 10 (88.4% vs**. 69.7%) and longer median duration of complete response (32 days vs. 18 days)
Hu. 2014	Open-label, single arm (n= 33)	Evaluate the efficacy of **denosumab** in patients with bisphosphonaterefractory HCM	Denosumab lowered calcium in 64% of patients within 10 days, with an estimated median time to response of 9 days. • FDA-approved denosumab for HCM
Sabry, 2010	Observational, (n=80)	Evaluate the difference in efficacy and safety of **zoledronic acid and clodronate** in malignant hypercalcemia secondary to bone metastases.	**The calcium level significantly decreased in both groups.** At least one skeletal-related event occurred in 15 (37.5%) patients receiving zoledronic acid and 32 (80%) patients receiving clodronate.
Hosking, 1981	Observational (n=16)	Evaluate the efficacy of rehydration (NS) in patients with hypercalcemia	A substantial fall in serum calcium (mean decrease 0.6 mmol/l) was achieved in thirteen patients.
Sleeboom, 1983	Observational (n=30)	Evaluate the effects of tumor-induced hypercalcemia management with volume repletion and intravenous pamidronate	**Volume repletion was only partially effective in lowering serum calcium** and raising glomerular filtration rate and it increased the tendency towards hypomagnesaemia. In **twenty-nine of the patient's serum calcium, serum magnesium, and glomerular filtration rate were rapidly restored to normal** by intravenous **pamidronate**, in doses of 1.75-30 mg/day.

Conclusions

- Reported in 20 – 30% of cancer patients and is a poor prognostic indicator
- Primarily associated with lung and breast cancer, as well as myeloma and lymphoma
- Presentation can range from asymptomatic to progressive mental impairment, arrhythmias, and renal failure
- Cornerstones of therapy include aggressive hydration, calcitonin, and IV bisphosphonates

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