# Hypercalcaemia of Malignancy

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# Hypercalcaemia of Malignancy

- Hypercalcaemia of malignancy (HCM) is a condition which occurs in cancer patients and can be defined when the serum calcium level (corrected for albumin) is greater than 2.6 mmol/L or greater than the upper limit of normal (ULN) for a given reference value used in a lab.

- Hypercalcaemia is a frequent metabolic complication of both solid cancers and haematological malignancies, with a reported incidence of 20%–30%.
- breast cancer, multiple myeloma, small cell lung cancer and renal cell carcinoma.
- Bone destruction by osteolytic metastasis
- primarily by osteoclast activation as a result of tumoural secretion of parathyroid hormone-related protein (PTHrP).
- Secretion of PTH by tumour cells other than parathyroid carcinoma is extremely rare. Reports have been published on ovarian carcinoma, small cell and squamous cell lung carcinoma.
- PTHrP causes hypercalcaemia through an increase in expression of receptor activator of nuclear factor kappa-B ligand (RANKL) in bone, which consequently causes osteoclast activation by binding to RANK, present on their surface

- Renal
- GI
- Musculoskeletal
- Neurologic
- Cardiovascular

“bones, stones, groans, abdominal moans

- no formal classification schemes for defining severity of hypercalcaemia, some consider:
  - **mild** hypercalcaemia to be a total adjusted serum calcium of 2.6 to 2.9 mmol/L
  - **moderate** hypercalcaemia a level of 3.0 to 3.4 mmol/L, and
  - **severe** hypercalcaemia a level of > 3.4 mmol/L.

As hypercalcaemia can affect several organ systems, initially it may be asymptomatic or present with non-specific symptoms which may be similar to that of advanced malignancy or the side-effects of chemotherapy or analgesia.

- Common symptoms include polydipsia, polyuria, confusion, muscle weakness, fatigue, anorexia, constipation.
- In severe cases, there may be nausea, vomiting, abdominal pain, lethargy and altered level of consciousness.
- Cardiac arrhythmias may develop but are rare.
- Severe hypercalcaemia can result in coma and death.

# Investigations

Abnormalities of parathyroid function, bone resorption, renal calcium reabsorption or dihydroxylation of vitamin D may cause regulatory mechanisms to fail and serum calcium may rise.

confirm a diagnosis of hypercalcaemia:

- Check calcium level, corrected for serum albumin (as serum calcium is bound to albumin), which gives an indication of the amount of ionised (active) calcium.

Additional laboratory evaluations include:

- serum creatinine
- urea and electrolytes
- phosphate and magnesium level
- parathyroid hormone (PTH) to rule out primary hyperparathyroidism
- PTHrP to rule out humoral hypercalcaemia of malignancy
- 25-hydroxy vitamin D (25(OH)D) to rule out vitamin D intoxication
- ECG to look for shortened QT interval or other conduction abnormalities

# When symptoms are present, they are related not only to the absolute calcium level but also to how fast the rise in serum calcium occurred.

| Severity | Symptoms and approach |
|---|---|
| **Grade 1 (> ULN to 2.9 mmol/ L)** | - |
| **Grade 2 (> 2.9 to 3.0 mmol/L)** | Often asymptomatic and **does not usually require urgent correction.** |
| **Grade 3 (> 3.0 to 3.4 mmol/L)** | May be well tolerated if has occurred slowly, whilst an acute rise may cause marked symptoms, including polyuria, polydipsia, dehydration, anorexia, nausea, muscle weakness, and cognitive changes **prompt treatment is usually indicated.** |
| **Grade 4 (> 3.4 mmol/L)** | Requires urgent correction, regardless of symptoms due to the risk of dysrhythmia and coma. |

*UKONS Acute Oncology Initial Management Guidelines v.3., accessed November 2022.*

# Management

- The aim of treatment is to improve symptoms and reduce corrected calcium level to within the normal range and, if possible, treating the underlying disease.
- Effective treatments reduce serum calcium by inhibiting bone resorption, increasing urinary calcium excretion, or decreasing intestinal calcium absorption.
- The timing and type of treatment are dependent on the severity of the hypercalcaemia and associated symptoms.

- It is also important to review the patient's other medications and consider discontinuing or dose reducing (if appropriate) any medications that may be contributing to hypercalcaemia (e.g., thiazide diuretics, calcitriol, calcium supplementation, antacids, lithium)

# Fluid replacement

- Correct volume depleted as a result of impaired renal concentrating ability and decreased oral intake. 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. Rehydration reverses this situation and is a critical component of therapy.
- Intravenous sodium chloride 0.9% is recommended, with the rate and duration dependent on the patient's volume, cardiovascular and renal status. For acute severe hypercalcaemia a reasonable infusion rate for an adult is:
- sodium chloride 0.9% 4 to 6 litres by intravenous infusion over 24 hours.

Practice points

Monitor for fluid overload if renal impairment or elderly.

Loop diuretics rarely used and only if fluid overload develops; not effective for reducing serum calcium. If loop diuretics are used, other electrolytes e.g. potassium and phosphate need to be monitored and replaced.

Monitor serum calcium response – with nadir reached at 2 to 4 days.

May need to consider dialysis if severe renal failure.

# Bisphosphonate therapy

- Intravenous bisphosphonates are used because they have a faster onset of action and the burden of treatment is more favourable than with oral bisphosphonates.
- The choice of bisphosphonate may be determined by local policy i.e. either zoledronic acid or pamidronate. However, zoledronic acid may be more favourable as it is more potent than pamidronate and can be administered over a shorter time period (15 minutes compared with two to four hours).
- Practice points
  - Bisphosphonates can cause nephrotoxicity, adequate hydration can enhance renal protection.
  - In patients with renal impairment, bisphosphonates may be contraindicated or dose adjustments may be required. Refer to product information for detail.
  - Monitor serum calcium response – maximum effect occurs at 2 to 4 days. For pamidronate, if plasma calcium does not decrease within 48 hours, further treatments may be given.
  - For zoledronic acid, dose may be repeated after at least 7 days in patients who are refractory to initial treatment or who subsequently relapse.11
  - Can cause hypocalcaemia if vitamin D deficiency or suppressed PTH
  - Pamidronate 90mg IV in 500 ml sodium chloride 0.9%over 4 hours
  - Zoledronic acid 4 mg IV in 100mg sodium chloride 0.9% over at least 15 minutes

# Denosumab

- Denosumab is a RANKL monoclonal antibody which inhibits osteoclast activation and function.
- It may be an option for patients with hypercalcemia that is refractory to zoledronic acid or in whom bisphosphonates are contraindicated due to severe renal impairment.
- Regular monitoring of calcium is important as the risk of hypocalcaemia is high, particularly in patients with reduced renal function.
- May be used in renal impairment, CrCl <30ml/min
- Note increased risk of hypocalcaemia
- Dose 120 mg subcut
- Nonformulary – requires an IPU

# Calcitonin

- Calcitonin blocks osteoclast activity and also renal tubular reabsorption of calcium.
- Calcitonin effect is rapid, usually within a few hours of first administration.
- Clinical use is limited by the transient effect and development of tolerance within days of use.
- Because of its limited duration of effect, calcitonin is most beneficial in symptomatic patients with severe hypercalcemia i.e. serum calcium > 3.5 mmol/L, when combined with hydration and bisphosphonates.
- Calcitonin and hydration provide a rapid reduction in serum calcium concentration, while a bisphosphonate provides a more sustained effect.

No dose adjustments are required in patients with renal insufficiency. In Australia, calcitonin is available as salcatonin

# Glucocorticoids

- Corticosteroids can be given
- may only be useful where hypercalcaemia is due to sarcoidosis, lymphoma or vitamin D intoxication or multiple myeloma.
- Additionally they often take several days (~ 2-4 days) to achieve the desired effect.

# Summary

- HCM is relatively common
- Most common cause of hyperCa2+ in the inpatient setting
- Patients with HCM have a poor prognosis
- Treatment is aimed at lowering the serum Ca2+ & treating the underlying disease

- Oncological emergencies can be life threatening and may result in significant morbidity and mortality.
- Requires high degree of suspicion
- Likely to need specialist input oncology/surgeons/radiation oncology

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