Disclosures

- Paid consulting for: Teva, Amgen, Merck, Ipsen
- Research funding: Novartis
Objectives

- Prevalence
- Cancers
- Calcium regulation
- Hypercalcaemia in cancer
- Clinical manifestations
- Diagnosis
- Management
Prevalence

- Most common metabolic complication of cancer
- 10-20% of all cancer patients per year will be diagnosed with hypercalcemia
Associated Malignancies

- Lung - 35% (NSCLC) - 15%
- Breast - 40-50%
- Multiple Myeloma - 20-40%
- Head and Neck - 6%
- Genitourinary - 6%
- Other/Unknown primary - 15%
Thyroid releases **CALCITONIN**

- Increase $\text{Ca}^{2+}$ deposition in bones
- Decrease $\text{Ca}^{2+}$ uptake in intestines
- Decrease $\text{Ca}^{2+}$ reabsorption from urine

If $\text{Ca}^{2+}$ levels too high

Parathyroid releases **PTH**

- Increase $\text{Ca}^{2+}$ release from bones
- Increase $\text{Ca}^{2+}$ uptake in intestines
- Increase $\text{Ca}^{2+}$ reabsorption from urine

If $\text{Ca}^{2+}$ levels too low

**Homeostasis** (normal calcium levels in blood)

- Calcium levels fall
  - Increase $\text{Ca}^{2+}$ deposition in bones
  - Decrease $\text{Ca}^{2+}$ uptake in intestines
  - Decrease $\text{Ca}^{2+}$ reabsorption from urine

- Calcium levels rise
  - Increase $\text{Ca}^{2+}$ release from bones
  - Increase $\text{Ca}^{2+}$ uptake in intestines
  - Increase $\text{Ca}^{2+}$ reabsorption from urine
Hypercalcemia in Cancer

Due to increased bone resorption and release of calcium from bone

Three mechanisms

– Osteolytic metastases with local release of cytokines
– Tumor secretion of parathyroid hormone-related protein (PTrP)
– Tumor production of calcitriol
PTHRP and hypercalcemia

- PTHrP 60% homology with PTH
- Activates osteoclastic bone resorption
- Loop of Henle/ distal convoluted tubule
- Îrenal 1,25-(OH)2D
Osteolytic metastases

- Tumor cells produce growth factors that stimulate bone destruction
  - i.e. RANK ligand
- Osteoclasts are activated and break down bone
- Osteoblasts cannot build bone back fast enough
- Decreased bone density and strength; high risk for fracture

Clinical manifestations

- Stones, bones, groans and psychiatric moans…
- Stones → Kidney stones
- Bones → Bone pain
- Groans → Abdominal Pain
- Psychiatric moans → Depression, anxiety, confusion
Clinical manifestations

- Constipation
- Anorexia
- Nausea
- Weakness
- Lethargy
- Dehydration
- No physical signs
Clinical Manifestations

Cardiovascular
- Hypertension
- Bradycardia
- Cardiac arrhythmias
- Cardiac arrest
- Heart block
Diagnosis

Laboratory tests

- Ionized calcium or free calcium is the physiologically active form of calcium circulating in the blood
- 50% of serum calcium is ionized
Medical Management

Mild hypercalcemia
- Calcium 2.7-3 mmol/l
- Asymptomatic
- Does not need urgent correction
Medical Management

- Moderate to severe hypercalcemia
  - Moderate 3-3.5mmol/l
  - Severe >3.5mmol/l Urgent correction

Therapy

- Rehydration
- Discontinue thiazide diuretics
Medical Management

Antiresorptive therapy
Bisphosphonates

- Pamidronate- Aredia
- Zoledronic acid- Zometa
Bisphosphonates MOA

inhibit osteoclast formation, migration and osteolytic activity, promote apoptosis

modulate signalling from osteoblasts to osteoclasts

local release during bone resorption

concentrated in newly mineralizing bone and under osteoclasts
52♀ known met RCC (lungs)
C/o confusion and dehydration
Ca 2+ 3.2mmol/l no bone mets
High parathyroid hormone-related protein
Admitted
Zometa given- Ca minimally responsive
Denosumab given- Ca2+↓
Denosumab

- Now approved for The Treatment Of Hypercalcemia Of Malignancy Refractory To Bisphosphonate Therapy
- Single arm study
- Achieved primary endpoint: response rate at d.10 of 63.6% in the 33 patients evaluated. The overall complete response rate was 63.6%. The median time to response was 9d, and median duration of response was 104 days
Denosumab MOA

![Diagram showing the mechanism of action (MOA) of Denosumab](image)

- **Tumor cells** release PTHrP, which stimulates mature osteoblasts to produce OPG and RANKL.
- OPG binds to RANKL, inhibiting its binding to RANK on osteoclasts.
- This prevents the activation of osteoclasts, reducing bone resorption.
- Bone-derived growth factors are also shown to be involved in the process.

**HHM** (Height-Herb Month) scale is used to indicate the timeline.
Other options

- Calcitonin
- Corticosteroids
- Haemodialysis
Summary

- Hypercalcaemia common in Cancer
- Symptoms to look for
- Treatment depends on concentration of Ca²⁺ and rate of change
- Management using bisphosphonates
- Consider RANK ligand inhibitors in resistant hypercalcemia.