Hypercalcaemia of Malignancy

Hypercalcaemia is a common complication of many cancers (breast, lung, myeloma). It often occurs in patients with bone metastases, but it can also occur in the absence of such metastases probably due to the production of cytokines such as parathormone related peptide (PTHrP).

Symptoms and signs

Nausea, vomiting, thirst, polyuria, constipation, headache and impaired consciousness.
Examination may reveal the patient to be severely dehydrated.
Biochemistry may show renal failure.

Management

1. Rehydration

Mild hypercalcaemia = Corrected serum calcium <3 mmol/L
In asymptomatic patients who are about to start anticancer treatment, hydration followed by observation is an option.
In symptomatic patients who may respond slower or are less likely to respond to anticancer treatment then treat the hypercalcaemia to improve symptoms.

Moderate to severe hypercalcaemia = corrected calcium 3.0-3.5 mmol/L
Urgent rehydration with normal saline; may require 3-6 litres in the first 24 hours as tolerated. This should improve symptoms in 24 hours.

2. Bisphosphonate

Once the patient has been rehydrated, administer a bisphosphonate: pamidronate. These drugs inhibit osteoclast activity and thus treat the bone resorptive component of hypercalcaemia. The dose of pamidronate depends on initial calcium level as follows:

Serum corrected Ca (mmol/L)	Dose	Duration	Minimum vol. N.Saline
2.5 – 3.0	30 mg	1 hour	125 ml
3.1 – 3.5	60 – 90 mg	3 hours	250 ml
>3.5	90 mg	4 hours	500 ml

Renal failure is a relative contraindication to the use of bisphosphonates, therefore, check electrolytes, urea and creatinine prior to administration.
In patients with creatinine clearance/GFR >40ml/min, pamidronate should be infused at a maximum rate of 1mg/minute. In patients with creatinine clearance/GFR <40ml/min the maximum rate of administration is 22.5mg/hour.

The rate of fall of calcium levels is dose dependent and begins within 24 - 48 hours of the infusion. Maximum effect can be expected within 3 to 7 days. If normocalcaemia is not achieved within this time a further dose may be given (or consider zoledronic acid).

Ideally hypercalcaemia should then be controlled by appropriate systemic treatment (chemotherapy). If this is not appropriate the patient may be maintained with oral bisphosphonates such as sodium clodronate 1.6-3.2gms daily in divided doses or repeat pamidronate 4 weekly infusions.

3. Role of diuretics

Do not use loop diuretics whilst rehydrating patient as this may exacerbate dehydration. However can be used once hydrated if there are problems with fluid overload or to enhance renal calcium excretion (20 – 40 mg/12 hourly).
Avoid thiazide diuretics as they reduce calcium excretion.

4. General measures

Stop drugs that increase calcium levels:
Thiazide diuretics
Lithium
Calcium and vitamin D supplements
Cimetidine/ranitidine
Mobilise the patient.

5. Resistant hypercalcaemia

Hypercalcaemia not responding to pamidronate or recurring frequently can be treated in the first instance with zoledronic acid. Zoledronic acid is a much more potent inhibitor of osteoclast activity.

Creatinine clearance (mls/min)	Dose zoledronic acid (given over 15 minutes
>60	4 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 - 39	3.0 mg

Also consider steroids in haematological malignancies.

6. Salmon calcitonin

In severe hypercalcaemia or severe symptoms, calcitonin can be used. It is only effective with a bisphosphonate so is started at the same time as pamidronate and can lower serum calcium level rapidly within hours. The effect lasts for hours only and wears off after a few days.
Dose: 4 units/kg SC/IM 6 -12 hourly increasing to 8 units/kg 6 hourly for 2 days