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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Hypercalcaemia of Malignancy

Introduction

Hypercalcaemia of malignancy is estimated to occur in 20-30% patients with cancer. This incidence varies depending on the underlying tumour type and is more common in myeloma, lung and breast cancer.

There are several mechanisms by which malignancy can cause hypercalcaemia including:

- secondary to bone metastasis
- secretion of Parathyroid Hormone related peptide (PTHrP) by the malignant cells
- secretion of calcitriol by the malignant cells (rare but if occurs usually occurs secondary to lymphomas)

Parathyroid hormone is an endogenous protein which is secreted in response to low serum calcium. It causes an increase in serum calcium by increasing:

- bone resorption (via increased osteoclast activity)
- calcium absorption from the GI tract (by increasing calcitriol secretion from the kidney)
- calcium reabsorption from the kidneys.

Parathyroid secretion is tightly controlled via a negative feedback mechanism. PTHrP is structurally related to parathyroid hormone and has similar effects however this process is not regulated via any feedback mechanism which leads to hypercalcaemia.

Symptoms

Patients with hypercalcaemia may be asymptomatic (especially if calcium has increased gradually). If symptoms are present they may include:

- Bone pain, muscle weakness
- Nausea, vomiting, constipation
- Thirst, polyuria
- Renal impairment
- Nephrolithiasis, nephrocalcinosis
- Mood disturbance, cognitive function, confusion, coma
- Shortened QT interval and dysrhythmias
- Hypertension, cardiomyopathy

Diagnosis

Check patient's **adjusted calcium** level. Any value above 2.60 mmol/L indicates hypercalcaemia.

Alternative causes of hypercalcaemia include:

- Primary Hyperparathyroidism
- Granulomatous conditions
- Drug induced (such as excessive alfacalcidol / calcium / vitamin D / lithium / thiazide diuretics)

For further information on non-malignant causes of hypercalcaemia, please refer to the Management of Hypercalcaemia of Unknown Origin MIL.

Treatment
Treat all patients with an adjusted calcium greater than or equal to 3.0 mmol/L with IV fluids and zoledronic acid (see below) unless contra-indicated or if patients are thought to be in last days of life.

In hypercalcaemia of malignancy, calcium will continue to rise unless treated so asymptomatic patients should be treated with the same criteria (as they may become symptomatic quickly).

For patients with a new diagnosis of lymphoma, discuss with the haematology team. A short course of steroids may be indicated (prednisolone 1mg/kg daily) and will reduce serum calcium concentrations by decreasing calcitriol production by the malignant cells.

As above, if patients are thought to be in last days of life, they may not benefit from treatment of hypercalcaemia and IV rehydration needs to be more carefully considered. Discuss with palliative medicine team if unsure.

For symptoms of hypercalcaemia, consider pharmacological management e.g. haloperidol 0.5-1mg daily to manage nausea or confusion, and analgesia to manage bone pain. Obtain further advice from palliative care if required.

1. **Hydration and Bisphosphonates**

All patients should be adequately hydrated prior to receiving bisphosphonates.

1A. IV Hydration
Hydrate with intravenous 0.9% sodium chloride solution. This helps correct hypovolemia secondary to vomiting or fluid loss caused by polyuria. The infusion rate depends on several factors including patient age, co-morbidities (e.g. renal impairment and heart failure) and severity of hypercalcaemia but as an estimate in patients with no co-morbidities an initial rate of 200 to 300 mL/hour would be recommended. Re-assess fluid status after 1L given. This can then be adjusted to maintain the urine output at 100 to 150mL/hour.

Caution is advised if patients are clinically euvolaemic or at risk of fluid overload. In this situation, IV hydration may be omitted or kept to a minimum (i.e. 1L before giving zoledronic acid).

Mode of Action: Restoration of intravascular volume and promotion of urinary calcium excretion

Onset of Action: Hours

Duration of Action: During Infusion

1B. Bisphosphonates
The first line bisphosphonate for hypercalcaemia caused by malignancy is zoledronic acid. Pamidronate is an alternative option when zoledronic acid is not suitable or available; however zoledronic acid is preferred as it is more potent than pamidronate and can be administered over a shorter time period (15 minutes vs 2 hours). 90% of patients with hypercalcaemia of malignancy are estimated to respond to zoledronic acid compared to 75% of patients treated with pamidronate.

Zoledronic Acid
FIRST DOSE ONLY: A single dose of zoledronic acid of 4mg in 100ml given over 15 minutes is recommended. No dose adjustment is usually advised in patients in serum creatinine less than 400 µmol/L; however caution should be exercised in patients with low muscle mass/BMI in whom serum creatinine alone may not be representative of their renal function. In this situation, consider reducing the first dose on the basis of creatinine clearance (table 1).

IF SUBSEQUENT DOSES ARE REQUIRED: In case of renal impairment, clinicians should consider dose reduction (table 1).

Table 1: Dose adjustments in renal impairment for second dose onwards

Estimated Cockcroft and Gault CrCl (mL/min)	Recommended zoledronic acid dose	Infusion Rate
60 or greater	4mg	15mins
50-59	3.5mg	15mins
40-49	3.3mg	15mins
30-39	3mg	15mins

For patients with an estimated CrCl of less than 30mL/min the repeated use of zoledronic is **unlicensed** and any use would be a clinical decision weighing up benefits vs increased risk of adverse events.

The recommended interval between doses, taking into account the pharmacokinetics of zoledronic acid, is 7 days.

If a patient is likely to require zoledronic acid every 4 weeks then consideration should be given to osteonecrosis of the jaw. The SPC states: "The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations. A dental examination with appropriate preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with bisphosphonates in patients with concomitant risk factors".

Adverse effects of zoledronic acid

Acute phase reaction occurs within 3 days of treatment and usually resolves spontaneously – symptoms include bone pain, fever, fatigue, arthralgia, myalgia, rigors and arthritis with subsequent joint swelling.

Other common side effects include: renal impairment, hypocalcaemia, hypophosphatemia, nausea, vomiting, and conjunctivitis. Some uncommon side effects include osteonecrosis of the jaw (ONJ), hypertension & atrial fibrillation.

Mode of Action: Inhibition of bone resorption via direct interference with osteoclast function

Onset of Action: 24-48 hours, maximum effect seen at 5-7 days

Duration of Action: 2-4 weeks

2. Denosumab (unlicensed indication)

Denosumab should be considered for hypercalcaemia resistant to bisphosphonates or where bisphosphonate use is not indicated due to poor renal function. Patients treated with denosumab should not be treated concomitantly with bisphosphonates.

Denosumab is a fully human monoclonal antibody which binds to receptor activator of nuclear factor kappa-B ligand (RANKL) and prevents ligand interaction with RANK receptors on precursor osteoclasts. It interferes with osteoclast maturation, function and survival, reducing bone resorption and subsequent hypercalcemia. Denosumab (XGEVA®) is recommended for hypercalcaemia refractory to bisphosphonates or where use of bisphosphonates is not indicated due to renal impairment. It is not licensed for this indication in the UK, so ensure trust unlicensed processes are followed.

Dose:

- The recommended dosing schedule is: 120mg SC injection on day 1, 8, 15 and 29 then every 4 weeks thereafter.
- Ensure repeat adjusted calcium level has been re-checked prior to giving following dose. If level is within normal range, omit dose.

- If appropriate, patients/carer may be taught to self-administer subsequent doses following training by the oncology or haematology teams; however bloods should still be checked as above.

No dose adjustment is required in renal impairment. Denosumab can lead to hypocalcaemia, especially with presence of vitamin D deficiency, renal impairment or history of hypoparathyroidism. Monitor calcium levels for the first 1-2 weeks of initiating treatment, and more frequently if indicated (e.g poor renal function, symptomatic of hypercalcaemia).

Adverse effects of denosumab

Common side effects include: gastrointestinal disorders (nausea, vomiting, diarrhoea or constipation), peripheral oedema, dyspnoea and anaemia. Atypical femoral fractures and osteonecrosis of the jaw (ONJ) have been reported. If this occurs, interruption of treatment should be considered. To reduce the risk of ONJ, patients should be informed of maintaining good oral hygiene and receiving routine dental check-ups, and to inform their doctor or dentist that they have had denosumab prior to undergoing any dental treatment or surgery.

Mode of Action: Inhibition of bone resorption via inhibition of RANKL

Onset of Action: 2-4 days

Duration of Action: 4-15 weeks

3. Renal replacement therapy

Haemodialysis with little or no calcium in dialysis fluid and peritoneal dialysis is recommended in hypercalcaemia as a last solution. It may be indicated in cases of tumour induced hypercalcaemia and renal impairment or heart failure where hydration cannot be administered safely. Cases of haemodialysis in patient with normal renal function have been reported as beneficial. Advice from the renal dialysis team is required to avoid exacerbations or induction of other metabolic abnormalities.

Follow Up

Ensure the patient has follow-up arranged with the oncology, haematology and/or palliative care team as appropriate. In patients with hypercalcacemia of malignancy, the progression of disease is often associated with progressive hypercalcaemia. Therefore, the underlying disease should be treated if at all possible.

Local protocols are available for the management of metastatic bone disease, which aim to prevent recurrence of hypercalcaemia.

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References

1. Stewart AF (2005). Hypercalcemia associated with cancer. *N Engl J Med*; 52(4):373-379.
2. Mirrakhimov AE (2015). Hypercalcemia of Malignancy: An Update on Pathogenesis and Management. *N Am J Med Sci;*7(11):483-493. doi:10.4103/1947-2714.170600
3. Horwitz MJ. Hypercalcemia of malignancy. UpToDate. Last updated: 28/05/2020. Accessed on 22/9/2021
4. Shane E and Berenson J. Treatment of hypercalcemia. UpToDate. Last updated: 6/8/2020. Accessed on 22/9/2021
5. Walsh J, et al (2016). Emergency management of acute hypercalcaemia in adult patients. Endocrine connections vol. 5,5: G9-G11.
6. Palliative Care Formulary (online). Accessed on 10/11/2021 via www.medicinescomplete.com
7. Feldenzer KL, Sarno J. (2018) Hypercalcemia of Malignancy. J Adv Pract Oncol;9(5):496-504.