Gloucestershire Hospitals
NHS Foundation Trust

Malignant Hypercalcaemia Management

Introduction

Malignant hypercalcaemia or tumour -induced hypercalcaemia (TIH) is a serum adjusted calcium (Adj. Ca2+) of 2.64mmols/L or greater in a patient with known or suspected malignancy. It is usually a complication of advanced malignant disease and can indicate a poor prognosis (median survival of a few months). Though it is commonest in non-small cell lung cancer, breast cancer, multiple myeloma, squamous cell cancers of head and neck and urothelial cancers it can occur in association with any malignancy. The commonest biological mechanisms are humoral i.e., excess PTH-related peptide secretion (typically few or no bone metastases) and local (osteolytic) from extensive bone metastases. Rarely it can be from excess 1,25 dihydroxyvitamin D or ectopic PTH production.

Presentation

Common symptoms	Malaise, weakness, anorexia, nausea, thirst, constipation, polyuria
Severe symptoms	Vomiting, ileus, mental changes (delirium, drowsiness), seizures, coma, arrhythmias
Other symptoms	Those of the underlying malignancy Pain can be precipitated/exacerbated by hypercalcaemia

Severity

Mild	Moderate	Severe
Adj. Ca2+ ≥ 2.64 - 2.99	**Adj. Ca2+ ≥ 3.0 - 3.49**	**Adj. Ca2+ ≥3.5**

Assessment

History and examination, including vital signs and fluid balance status
Investigations: FBC, urea & electrolytes, bone profile (includes Ca2+, albumin), liver function tests
Where appropriate Vitamin D, ECG (e.g., severe hyperCa2+), PTH

Pathway

Adjusted Ca2+ is 2.64mmols/L

Yes ↓	**No** ↓
Manage depending on severity, symptoms as in-patient or out-patient NB. In patients with very advanced ca and limited/no other treatment options consider if in best interests to treat d/w patient/carers/AOS team/medical team	Monitor Ca2+ if patient deemed to be at risk of hypercalcaemia (e.g., progressive ca/new diagnosis)

Author: Dr Marios Decatris, Laura Lockwood (cancer services pharmacist)
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Principles of treatment

1. Correct volume depletion (fluids, diuretics)
2. Inhibit bone resorption (bisphosphonates)
3. Treatment of underlying malignancy

<table>
<tr><th>Mild, no symptoms</th><th>Mild, symptoms</th><th>Moderate-Severe, symptoms</th></tr>
<tr><td>Adj. Ca2+ ≥ 2.64 - 2.99</td><td>Adj. Ca2+ ≥ 2.64 - 2.99</td><td>Adj. Ca2+ ≥ 3.0</td></tr>
<tr><td>TREAT AS DAYCASE
Treat as in-patient if day case treatment not practical (e.g., patient in hospital and long journey time to home)</td><td>TREAT AS DAYCASE/ ADMIT
If patient in hospital but no beds available, initiate treatment as day case and admit asap</td><td>ADMIT
Treatment of moderate-severe hyperCa2+ in symptomatic patient is a medical emergency
INFORM CONSULTANT IF Adj. Ca2+ >4.0mmols/L</td></tr>
<tr><td rowspan="4">HYDRATION
1-2litres N/S over 2-3hrs

BISPHOSPHONATES
Pamidronate 30mg in 500ml N/S over at least 30mins</td><td colspan="2">HYDRATION
Initial bolus of 1-2 litres N/S over 1-4hrs
Continuous iv N/S 250ml/hr next 24-48hrs
Frusemide 20-40mg po/iv (if nausea/vomiting), ONLY after initial rehydration or if at risk of fluid overload

BISPHOSPHONATES</td></tr>
<tr><td>Pamidronate 30mg in 500ml N/S over at least 30mins

Or

Zolendronic acid 4mg in 100ml N/S over 15mins

Zolendronic acid use in MILD hyperCa2+ is <u>not licensed</u> but can be considered if unavailability/shortage of or allergy to pamidronate</td><td>Zolendronic acid 4mg in 100ml N/S over 15mins

Or

Pamidronate 60-90mg in 500ml N/S over at least 30mins

Pamidronate can be used if zolendronic is unavailable

<u>Recommended doses of pamidronate</u>
<u>Initial Adj. Ca2+ Dose(mg)</u>
<3.0 15-30
3.0-3.5 30-60
3.5-4.0 60-90
>4.0 90</td></tr>
<tr><td colspan="2">No reduction in Ca2+ within 7days</td></tr>
<tr><td>Repeat Pamidronate, total dose over 2-4 days = 90mg</td><td>Repeat Zolendronic acid in 7days</td></tr>
<tr><td colspan="3">Other actions
STOP/HOLD other drugs which may contribute to hyperCa2+, e.g., Ca2+-Vit D supplements
STOP/HOLD drugs that can impair renal function e.g., NSAIDs, Lithium, Aminoglycosides
STOP/HOLD/ADJUST doses of drugs that are renally excreted if eGFR is reduced
WATCH for hypoCa2+ in patients with renal failure/hypovitaminosis D
RECHECK U&Es, Mg2+ and bone profile daily AND Ca2+ in 3-7days to ensure normalisation</td></tr>
</table>

Pamidronate	Zolendronic acid
Avoid in severe renal impairment (eGFR <30ml/min) if possible. If eGFR <30ml/min consider risk benefit before using Can repeat every 2-3wks Maximum total dose (single/multiple doses) over 2-4 days = 90mg	No dose reduction in TIH if creat. <400mmols/L Can repeat in 7 days if Ca2+ not lowered sufficiently and then every 3-4wks afterwards

Special situations

1. In refractory hyperCa2+ exclude non-malignant causes e.g., primary hyperparathyroidism (measure PTH), unless this has already been performed
2. If serum creat >400microls/L, hydrate and await improvement in creatine/eGFR before bisphosphonate
3. If need to treat hyperCa2+ with creat. >400, administer bisphosphonate at lower dose and or with longer infusion time
4. Consider **Calcitonin 100 iu tds-qds sc or im for hyperCa2+ >3.75 or if rapid Ca2+ reduction is needed** (e.g., because of reduced level of consciousness/seizures). **Dose can be increased after 24-48hrs to maximum 400 iu tds-qds**. Efficacy wears off after 48-72hrs because of tachyphylaxis. **FOR EMERGENCY TREATMENT use Calcitonin ivi 10 iu/kg in 500ml N/S over minimum of 6hrs**
5. Consider **Glucocorticoids e.g., PREDNISOLONE 60mg po od x10days** if hyperCa2+ secondary to high circulating 1,25 dihydroxyvitamin D
6. Consider dialysis in select patients, e.g., severe chronic kidney disease or acute life-threatening hyperCa2+ (calcium-free dialysate removes calcium transiently during dialysis, haemo/peritoneal)

References

1. Guise TA et al. Cancer-associated hypercalcaemia. N Engl J Med 2022; 386: 1443-51
2. Chakhtoura M and Fuleihan G E-H. Treatment of hypercalcaemia of malignancy. Endocrinol Metab Clin N Am 2021; 50: 781-792
3. Pamidronate SPC https://www.medicines.org.uk/emc/product/2277/smpc#gref (accessed 13.11.22)
4. Zolendronic acid SPC https://www.medicines.org.uk/emc/product/7205/smpc#gref (accessed 13.11.22)
5. Calccitonin SPC https://www.medicines.org.uk/emc/product/12867/smpc#gref (accessed 13.11.22)