

# Management of Malignant Hypercalcaemia

This guideline has been produced in line with the national Scottish Palliative Care Guideline: Hypercalcaemia<sup>1</sup> and the NICE guidelines: Hypercalcaemia – known malignancy<sup>2</sup>.

## Background

Hypercalcaemia is defined as elevated adjusted calcium levels as per locally agreed limits. In NHS Lanarkshire this relates to adjusted calcium  $>2.6\text{mmol/l}$  (adjusted Ca = measured Ca +  $(0.015 \times (47.4 - \text{ALB}))$ ).

Hypercalcaemia is the most common metabolic disorder in people with cancer and although it may be seen with any tumour type it is most common in lung cancer, breast cancer and multiple myeloma<sup>3</sup>. Hypercalcaemia occurs due to several different factors in malignancy:

- Release of parathyroid hormone-related peptide
- Osteolytic metastases resulting in the release of mineralised calcium
- Ectopic activity of 1-alpha-hydroxylase
- Ectopic production of parathyroid related hormone<sup>4</sup>.

## Presentation

Symptoms of hypercalcaemia are varied and can often be subtle. They are more commonly seen in cases of moderate / severe hypercalcaemia (defined as  $>3.0\text{mmol/l}$ ) however, it is important to be vigilant as symptoms can occur at any level.

Common symptoms include malaise, thirst, anorexia, nausea, constipation and polyuria. Severe symptoms include vomiting, ileus, delirium, seizures, drowsiness and coma<sup>1,5</sup>. Hypercalcaemia has also been known to reduce the pain threshold<sup>6</sup>. Furthermore, it has been recognised that hypercalcaemia is a predictor for poor prognosis<sup>7</sup>.

## Management

### Who to treat

The aim of treatment should be to improve symptoms and reduce corrected calcium to within the normal range.

It may not be appropriate to treat all people with malignant hypercalcaemia. In those who are in the last days of life, it may be decided by an experienced clinician that invasive investigations and treatments may not be beneficial.

Prepared by: Dr Sarah Bowers, Dr Kerry McWilliams and Linda Johnstone (Macmillan Pharmacist)

Approved by: Specialist Palliative Care Drugs and Therapeutics Group and NHSL ADTC

Date active: September 2022

Version 1.1

Review date: December 2023

People with symptoms or with moderate /severe hypercalcaemia (>3.0mmol/L) should be admitted to hospital for management as detailed below.

Asymptomatic people with mild hypercalcaemia (3.0mmol/L or less) should be assessed on a case by case basis. Advice may be sought from specialists and patients should be involved in discussions regarding the appropriateness of treatment. In some circumstances it may be appropriate to advise increased oral intake of fluid, avoid exacerbating drugs or diet and vigilance regarding symptoms<sup>1,2</sup>.

Patients with myeloma or suspected myeloma should be discussed with haematology.

### Discontinuation of other drugs

A full medicines reconciliation should be undertaken to identify any drugs that may be exacerbating hypercalcaemia. These commonly include calcium-containing vitamin supplements and drugs which affect renal blood flow such as non-steroidal anti-inflammatories and thiazide diuretics<sup>8</sup>.

### Pre-hydration

Pre-hydration should be undertaken prior to definitive bisphosphonate therapy. This has a number of benefits including: replacing lost sodium, increasing glomerular filtration rate and circulating volume and promoting urinary calcium excretion.

Sodium chloride 0.9% is the IV fluid of choice and ideally patients should receive 1-3 litres prior to calcium levels and renal function being rechecked the following day. In patients with symptomatic hypercalcaemia, hydration is unlikely to be a definitive treatment, even if there is an improvement in calcium levels it will likely increase again when fluids are discontinued. Bisphosphonates will most likely be required for longer term control of calcium levels.

### Bisphosphonate Therapy

The NHS Lanarkshire bisphosphonate therapy of choice is Zoledronic acid (Zoledronate). Other options of Pamidronate (an alternative bisphosphonate) and Denosumab (a human monoclonal antibody) can be considered in special circumstances under the advice of palliative care, oncology or haematology.

Zoledronic acid is delivered as an infusion of 4mg of zoledronic acid in 100ml NaCl 0.9% over at least 15 minutes. Zoledronic acid has been shown to be superior to Pamidronate with regards to: longer duration of effect, shorter infusion duration, simpler dosing and similar safety data<sup>1,8</sup>.

Patients should be counselled regarding potential adverse events including atypical femoral fractures, osteonecrosis of the jaw and osteonecrosis of the external auditory canal. Common side effects may include hypocalcaemia, influenza like illness, nausea and vomiting and renal impairment.

### Dose Adjustments in Renal Impairment

Zoledronate requires dose adjustment in the event of renal impairment. Refer to SPC for further information. Zoledronate should be avoided if serum creatinine is >400 micromol/litre or eGFR <30ml/min<sup>9,10</sup>. Advice from palliative care, oncology or haematology should be sought in these circumstances.

## Follow Up

Following bisphosphonate administration, IV fluids should be continued until patients are deemed to have adequate hydration by an experienced clinician. Renal function should be monitored.

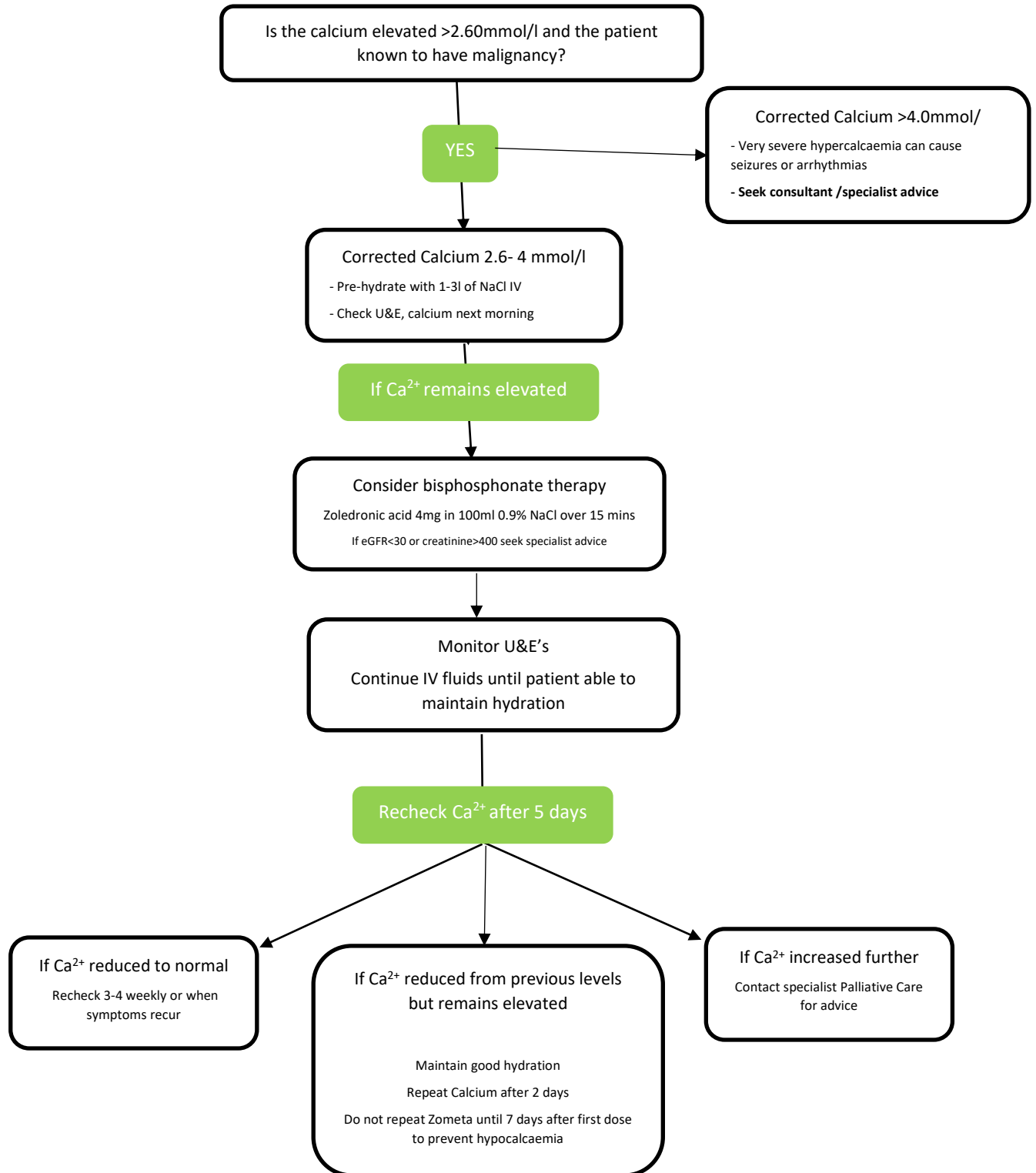
Calcium levels should be rechecked after 5 days. It is rarely helpful to check the calcium levels before this, and in fact can cause unnecessary concern, as calcium levels will take a few days to fall. In the event of increased post-treatment calcium levels, specialist advice should be sought on next steps.

If calcium has returned to normal and patients are no longer symptomatic, calcium levels should be monitored every 3-4 weeks or when symptoms of hypercalcaemia occur<sup>1,5,7</sup>.

Monitor renal function in patients at risk, such as those with pre-existing renal impairment, those of advanced age, those taking concomitant nephrotoxic drugs or diuretics, or those who are dehydrated.

## Management of Malignant Hypercalcaemia

Advice can always be sought via the on-call Specialist Palliative Care Team



1. NHS Scotland. Scottish Palliative Care Guidelines. Hypercalcaemia. Available from: <https://www.palliativecareguidelines.scot.nhs.uk/guidelines/palliative-emergencies/hypercalcaemia.aspx> [Accessed 2<sup>nd</sup> November 2020]
2. NICE Guidelines. Hypercalcaemia – known malignancy. Available from: <https://cks.nice.org.uk/hypercalcaemia#!scenario:2> [Accessed 2<sup>nd</sup> November 2020]
3. Jick S, Li L, Gastanaga VM, Liede A. Prevalence of hypercalcaemia of malignancy among cancer patients in the UK: analysis of the Clinical Practice Research Datalink database. *Cancer Epidemiol* 2015;39(6):901-7. Available from: doi:10.1016/j.canep.2015.10.012
4. Mirrakhimov AE. Hypercalcaemia of Malignancy: An Update on Pathogenesis and Management. *N AM J Med Sci*. 2015;7(11):483-493. Available from: doi:10.4103/1947-2714.170600
5. Bower M, Cox S. Endocrine and metabolic complications of advanced cancer. In: Doyle D, Hanks G, Cherny N, Calman K (eds). *Oxford Textbook of Palliative Medicine*. 3rd edition. 2005 Oxford. Oxford University Press. p. 687-702
6. Goldner W. Cancer Related Hypercalcaemia. *J Oncol Pract* 2016;12(5):426-32. Available from: doi:10.1200/JOP.2016.011155
7. NHS North West Clinical Senates. Guidelines for the treatment of cancer associated hypercalcaemia. Available from: [https://nwcscsenate.nhs.uk/files/7315/3313/1158/Guideline\\_for\\_the\\_Clinical\\_Management\\_of\\_Cancer-related\\_Hypercalcaemia\\_FINAL\\_July\\_2018.pdf](https://nwcscsenate.nhs.uk/files/7315/3313/1158/Guideline_for_the_Clinical_Management_of_Cancer-related_Hypercalcaemia_FINAL_July_2018.pdf) [accessed 19<sup>th</sup> June 2019]
8. Major P et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcaemia of malignancy: a pooled analysis of two randomized controlled clinical trials. *J Clin Oncol*. 2001;19(2):558-67. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/11208851>
9. NICE. British National Formulary. Zoledronic Acid. Available from: <https://bnf.nice.org.uk/drug/zoledronic-acid.html> [accessed 2<sup>nd</sup> November 2020]
10. SPC for Zometa 4mg/5ml Concentrate for Solution for Infusion. Available from: <http://www.medicines.org.uk/EMC/medicine/14062/SPC/Zometa+4mg+5ml+Concentrate+for+Solution+for+Infusion/> [accessed 9<sup>th</sup> December 2020]