Guidelines for the Management of Adult Patients with Malignant Hypercalcaemia

This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. Health care professionals must be prepared to justify any deviation from this guidance.

Introduction

Hypercalcaemia is a common presentation in solid and haematological cancers, in addition to being a common complaint in patients who have skeletal metastases. This guideline will outline the management for adult patients who presents with hypercalcaemia due to malignancy.

This guideline is for use by the following staff groups :

All qualified healthcare professionals involved in prescribing or administering treatment for malignant hypercalcaemia in adult patients.

Lead Clinician(s)

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Approved by Oncology Directorate Governance Meeting on:	28th January 2022
Approved by Medicines Safety Committee on:	11th May 2022
Review Date: This is the most current document and should be used until a revised version is in place	2nd Dec 2025

Key amendments to this guideline

Date	Amendment	Approved by:
May 2018	Update of Guideline	
September 2018	Denosumab information prescribing information added to guideline.	
November 2018	New document approved at Medicines Safety Committee	MSC
October 2020	Document extended for 3 months whilst document is review and approved	MSC
September 2021	Full review of content – document approved for 3 years	Oncology Directorate/ MSC
July 2025	6 month extension to review date	

Guidelines for the Management of Adult Patients with Malignant Hypercalcaemia

Introduction

Hypercalcaemia can be a presenting feature in solid and haematological cancers, in addition to being a common complaint in patients who have skeletal metastases. Hypercalcaemia in malignancy is usually due to production of PTHrP (PTH-related protein), and does not have to relate to the presence of bone metastases. It is most commonly associated in breast cancer, lung cancer and multiple myeloma but has been seen in a variety of other malignancies. It is associated with a poor prognosis in metastatic disease[1-5].

Signs and symptoms of hypercalcaemia are varied, and may reflect both the degree of hypercalcaemia and the speed of onset. Acute, rapid changes and hypercalcaemia in elderly patients are more often associated with symptoms, while a slower, more chronic course can often be asymptomatic. Symptoms include fatigue, myalgia or increased bone pain, gastrointestinal disturbances (abdominal pain, nausea, vomiting and diarrhoea), polyuria, polydipsia, confusion, reduced renal function, renal stones, psychosis, stupor, and coma[1-5].

Bisphosphonates are the drug class used to treat hypercalcaemia of malignancy. The mechanism of action is via induction of apoptosis in osteoclasts[6-10]. The management of hypercalcaemia in patients with malignancy is described below. Zoledronic acid is felt to be more effective for treating malignant hypercalcaemia and has a shorter infusion time (15 minutes versus 2 hours) when compared to pamidronate[1-10, 13].

Definitions

Abbreviation	Definition
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related protein
CKD	Chronic kidney disease
CrCl	Creatinine clearance

Classification of Hypercalcaemia (adjusted calcium concentration)	
Normal	2.2 -2.59 mmol/L
Mild	2.6 - 3.0 mmol/L
Moderate	> 3.0 - 3.4 mmol/L
Severe	> 3.4 mmol/L

Investigations for patient with known malignancy to include

- Renal profile
- Bone profile (to include calcium and phosphate)
- Vitamin D
- PTH if not known to have bone metastases (prior to treatment with bisphosphonates)

Investigations for patient not known to have malignancy

- Perform the above investigations and discuss with endocrinology

Treatment[1-10]

If adjusted Ca^{2+} is 2.6 - 3.0 mmol/L and asymptomatic:

1. Encourage oral fluids / give IV fluids (Sodium chloride 0.9%) according to the fluid balance assessment to ensure rehydration and promote renal excretion of calcium.

2. Review the medication list for drugs which could exacerbate hypercalcaemia and withhold if safe to do so: those that inhibit urinary calcium elimination and those that reduce renal blood flow (e.g. thiazide diuretics, calcium supplements, Vitamin A and Vitamin D supplements, Lithium, Antacids, NSAIDs, Cimetidine).

3. Recheck corrected calcium levels within a week and regularly with GP.

If adjusted Ca^{2+} is 2.6 - 3.0 mmol/L AND symptomatic OR > 3.0 mmol/L:

1. Admit for IV infusion of 2-4 litres sodium chloride 0.9% over 24hrs to ensure adequate urine output 100ml-150ml/hr. Accurate input/ output fluid monitoring is required e.g. patients with heart failure or CKD still need fluid resuscitation, but must be carefully monitored: consider a slower infusion rate).

2. Review the medication list for drugs - see point 2 above

3. Inform the acute oncology team of the patient

4. After the 24 hours of fluids, administer Zoledronic acid as per dosing see table below[11-13].

   NB. Renal function may be impaired due to the effects of hypercalcaemia and may improve after fluid resuscitation, however dosage of Zoledronic acid is based on the most recent CrCl.

To calculate CrCl use the Cockcroft and Gault Formula:

$$\frac{[140\text{-Age(years)}] \times \text{Weight(Kilograms)} \times \text{Factor (1.23 for Male OR 1.04 for Female)}}{\text{Creatinine (in mmol)}}$$

CrCl (ml/min)	Zoledronic acid dose (mg)	Route	Diluent and rate
Greater than 60	4.0	Intravenous infusion	100ml Sodium Chloride 0.9% over 15 minutes.
50 - 60	3.5		
40 - 49	3.3		
30 - 39	3.0		
< 30	**Use *Ibandronic acid*: 2mg in 500ml 0.9% sodium chloride intravenous infusion over 2 hours[14]**		

5. Recheck renal profile, phosphate and magnesium at least the day after treatment and monitor for any reductions in CrCl particularly if given with other nephrotoxic drugs.

6. Recheck serum adjusted calcium levels no sooner than 3 days after bisphosphonate infusion. There may be an additive effect of lowering the calcium for more prolonged periods if zoledronic acid is used with aminogylcosides, calcitonin or loop diuretics[13]. Occasionally short term calcium supplements may be required if profound hypocalcaemia results.

7. If calcium levels are still raised 5-7 days post-bisphosphonate treatment, consider prescribing another dose of bisphosphonate. A repeat dose of Zoledronic acid within this timeframe is not licensed and requires consultant approval. It should be noted that following a single dose of Zolendronic acid, 45.3% of patients responded by day 4, 82.6% of patients responded by day 7 and 88.4% responded by day 10[10]. Dose as per up to date renal function and recheck calcium levels no sooner than 3 days after the repeated dose.

8. Once the acute episode has resolved, recheck serum calcium in 3 weeks, or earlier if symptoms return (often via GP if appropriate).

9. If the calcium levels are resistant to the measures in point 7, see below for management of refractory hypercalcaemia.

Cautions

If the patient has had a previous adverse event with bisphosphonates consider using the monoclonal antibody, Denosumab (discuss with Oncology Consultant, see below).

Osteonecrosis of the jaw is a recognised, but rare side effect of the newer bisphosphonates and denosumab. Patients should be advised of this and encouraged to see a dentist for review but in the emergency situation of symptomatic hypercalcaemia this should not delay the initiation of therapy[1].

Refractory hypercalcaemia

This is defined as persistent hypercalcaemia not responding to initial treatment as above. If appropriate consult oncology/ endocrine consultant for consideration of denosumab (not currently licensed for this indication therefore use would be off label). Prescribing information and dosing individualised based on current evidence. Other options may include calcitonin or dialysis.

No intravenous access

In the unlikely event of being unable to gain intravenous access sub cutaneous calcitonin may be considered in severe life threatening hypercalcaemia e.g. adjusted calcium level >4.0.

Ensure patients are referred to the palliative care team.

Monitoring Tool

This should include realistic goals, timeframes and measurable outcomes.

How will monitoring be carried out?

Who will monitor compliance with the guideline?

Page/ Section of Key Document	Key control:	Checks to be carried out to confirm compliance with the policy:	How often the check will be carried out:	Responsible for carrying out the check:	Results of check reported to: *(Responsible for also ensuring actions are developed to address any areas of non-compliance)*	Frequency of reporting:
	WHAT?	**HOW?**	**WHEN?**	**WHO?**	**WHERE?**	**WHEN?**
	These are the 'key' parts of the process that we are relying on to manage risk. We may not be able to monitor every part of the process, but we MUST monitor the key elements, otherwise we won't know whether we are keeping patients, visitors and/or staff safe.	What are we going to do to make sure the key parts of the process we have identified are being followed? (Some techniques to consider are; audits, spot-checks, analysis of incident trends, monitoring of attendance at training.)	Be realistic. Set achievable frequencies. Use terms such as '10 times a year' instead of 'monthly'.	Who is responsible for the check? Is it listed in the 'duties' section of the policy? Is it in the job description?	Who will receive the monitoring results? Where this is a committee the committee's specific responsibility for monitoring the process must be described within its terms of reference.	Use terms such as '10 times a year' instead of 'monthly'.
	Treatment of Malignant Hypercalcaemia is as per guideline	Audit the use of Bisphophonates in Malignant hypercalcaemia	Annually	Rotational doctor in Haematology/Oncology as a selected audit during rotation	Clinical Governance Group	Annually

References

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3.	Walsh, Jennifer et al. SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: Emergency Management of Acute Hypercalcaemia in Adult Patients. *Endocrine Connections* 5.5 (2016): G9–G11. *PMC*. Web. 8 Apr. 2018.
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13.	Medicines.org.uk. (2017). *Zolendronic acid Summary of Product Characteristics*. [Online.] Available at: https://www.medicines.org.uk/emc/product/44 [accessed 8 April. 2018].
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16.	https://www.xgeva.com/hcp/other-indications/ [accessed 20 September. 2018].

Contribution List

This key document has been circulated to the following individuals for consultation;

Designation
All WAHT oncology, haematology and palliative care consultants
Dr X - Consultant Endocrinologist
Stephanie Cook – Countywide lead pharmacist cancer and aseptic services
Amanda Moore - Divisional Director of Nursing
Sarah Wallace, Divisional Quality Governance Lead - SCSD

This key document has been circulated to the chair(s) of the following committee's / groups for comments;

Committee
Alison Smith - Principal Pharmacist Medicines Safety
Medicines Safety Committee

Supporting Document 1 - Equality Impact Assessment Tool

To be completed by the key document author and included as an appendix to key document when submitted to the appropriate committee for consideration and approval.

Please complete assessment form on next page;

Herefordshire & Worcestershire STP - Equality Impact Assessment (EIA) Form
Please read EIA guidelines when completing this form

Section 1 - Name of Organisation (please tick)

Herefordshire & Worcestershire STP		Herefordshire Council		Herefordshire CCG	
Worcestershire Acute Hospitals NHS Trust	x	Worcestershire County Council		Worcestershire CCGs	
Worcestershire Health and Care NHS Trust		Wye Valley NHS Trust		Other (please state)	

Name of Lead for Activity	

Details of individuals completing this assessment	**Name**	**Job title**	**e-mail contact**
Date assessment completed			

Section 2

Activity being assessed (e.g. policy/procedure, document, service redesign, policy, strategy etc.)	**Title:** Guidelines for the Management of Adult Patients with Malignant Hypercalcaemia			
What is the aim, purpose and/or intended outcomes of this Activity?	See body of document			
Who will be affected by the development & implementation of this activity?	❑ Service User ❑ Patient ❑ Carers ❑ Visitors		❑ Staff ❑ Communities ❑ Other _____	
Is this:	❑ xReview of an existing activity ❑ New activity ❑ Planning to withdraw or reduce a service, activity or presence?			
What information and evidence have you reviewed to help inform this assessment? (Please name sources, eg demographic information for patients / services / staff groups affected, complaints etc.	See body of document			
Summary of engagement or consultation undertaken (e.g. who and how have you engaged with, or why do you believe this is not required)	See body of document			

Summary of relevant findings	See body of document

Section 3

Please consider the potential impact of this activity (during development & implementation) on each of the equality groups outlined below. **Please tick one or more impact box below for each Equality Group and explain your rationale**. Please note it is possible for the potential impact to be both positive and negative within the same equality group and this should be recorded. Remember to consider the impact on e.g. staff, public, patients, carers etc. in these equality groups.

Equality Group	Potential positive impact	Potential neutral impact	Potential negative impact	Please explain your reasons for any potential positive, neutral or negative impact identified
Age		x		
Disability		x		
Gender Reassignment		x		
Marriage & Civil Partnerships		x		
Pregnancy & Maternity		x		
Race including Traveling Communities		x		
Religion & Belief		x		
Sex		x		
Sexual Orientation		x		
Other Vulnerable and Disadvantaged Groups (e.g. carers; care leavers; homeless; Social/Economic deprivation, travelling communities etc.)		x		
Health Inequalities (any preventable, unfair & unjust differences in health status between groups, populations or individuals that arise from the unequal distribution of social, environmental & economic conditions within societies)		x		

Section 4

What actions will you take to mitigate any potential negative impacts?	Risk identified	Actions required to reduce / eliminate negative impact	Who will lead on the action?	Timeframe
	N/A	.		

How will you monitor these actions?	See body of document			
When will you review this EIA? (e.g in a service redesign, this EIA should be revisited regularly throughout the design & implementation)	See body of document			

Section 5 - Please read and agree to the following Equality Statement

1. Equality Statement

1.1. All public bodies have a statutory duty under the Equality Act 2010 to set out arrangements to assess and consult on how their policies and functions impact on the 9 protected characteristics: Age; Disability; Gender Reassignment; Marriage & Civil Partnership; Pregnancy & Maternity; Race; Religion & Belief; Sex; Sexual Orientation
1.2. Our Organisations will challenge discrimination, promote equality, respect human rights, and aims to design and implement services, policies and measures that meet the diverse needs of our service, and population, ensuring that none are placed at a disadvantage over others.
1.3. All staff are expected to deliver services and provide services and care in a manner which respects the individuality of service users, patients, carer's etc, and as such treat them and members of the workforce respectfully, paying due regard to the 9 protected characteristics.

Signature of person completing EIA	Completed on behalf of owner
Date signed	May 2022
Comments:	
Signature of person the Leader Person for this activity	
Date signed	
Comments:	

Supporting Document 2 – Financial Impact Assessment

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

	Title of document:	Yes/No
1.	Does the implementation of this document require any additional Capital resources	No
2.	Does the implementation of this document require additional revenue	No
3.	Does the implementation of this document require additional manpower	No
4.	Does the implementation of this document release any manpower costs through a change in practice	No
5.	Are there additional staff training costs associated with implementing this document which cannot be delivered through current training programmes or allocated training times for staff	No
	Other comments: This guideline formalises current accepted practice	

If the response to any of the above is yes, please complete a business case and which is signed by your Finance Manager and Directorate Manager for consideration by the Accountable Director before progressing to the relevant committee for approval