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 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 SCSD Clinical Governance on:	28th April 2018
Approved by Medicines Safety Committee on:	5th November 2018
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Key amendments to this guideline

Date	Amendment	Approved by:
November 2018	New document approved at Medicines Safety Committee	MSC

Guidelines for the Management of Adult Patients with Malignant Hypercalcaemia

Introduction

Hypercalcaemia is a common presentation 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 seen 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 myalgia, gastrointestinal disturbances (nausea, vomiting, 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

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

Classification of Hypercalcaemia **(adjusted calcium concentration)**	
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

- Renal profile
- Bone profile (to include calcium and phosphate)
- 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]

- Inform the acute oncology team of the patient

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

1. Encourage oral fluids / give IV fluids 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: those that inhibit urinary calcium elimination and those that reduce renal blood flow (e.g. withhold thiazide diuretics, Vitamin A and Vitamin D supplements, lithium, calcium supplements, NSAIDs, cimetidine).

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

4. Patients may already be on a bisphosphonate, this will need to be withheld and changed or restarted after management of acute episode.

If Ca^{2+} > 3.0 mmol/L or 2.6 - 3.0 mmol/L AND symptomatic initiate therapy:

1. IV infusion of 2–3 litres of sodium chloride 0.9% over 24hrs (based on fluid assessment; patients with heart failure or CKD still need fluid resuscitation, but must be carefully monitored: consider a slower infusion rate). Aim for urine output of at least 100ml/hour.

2. Review the medication list for drugs which could exacerbate hypercalcaemia, those that inhibit urinary calcium elimination and those that reduce renal blood flow (e.g. withhold thiazide diuretics, Vitamin A and Vitamin D supplements, lithium, calcium supplements).

3. After the 24 hours of fluids, give Zoledronic acid 4mg in 100ml 0.9% sodium chloride IV over 15 minutes **if** renal function CrCl >60 ml/min[11-13]. Dose to be adjusted as below if CrCl <60ml/min.

   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 renal profile.

To calculate renal function use the Cockcroft and Gault Formula:

$$\frac{[140\text{-Age(in years)}] \times \text{Weight(in Kilograms)} \times \text{Factor (1.23 for Male OR 1.05 for Female)}}{\text{Creatinine (in mmol)}}$$

If renal function is between **30 - 60ml/min**, dose reduce *zoledronic acid* as follows[11,13]:
-CrCl 50 - 60ml/min: 3.5mg in 100ml 0.9% Normal Saline IV over 15 minutes
-CrCl 40 - 49ml/min: 3.3mg in 100ml 0.9% Normal Saline IV over 15 minutes
-CrCl 30 - 39ml/min: 3.0mg in 100ml 0.9% Normal Saline IV over 15 minutes

If renal function is **less than 30ml/min**, use *ibandronic acid*: 2mg in 500ml 0.9% sodium chloride over 2 hours[14].

4. Recheck renal profile after treatment.

5. Recheck serum corrected calcium levels 3 days after bisphosphonate infusion.

6. 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 renal function and recheck calcium levels not sooner than 3 days after the repeated dose.

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

8. Patients may already be on a bisphosphonate, this will need to be withheld and changed or restarted after management of acute episode.

Cautions

If the patient is **allergic** to bisphosphonates or has had a previous adverse effect to bisphosphonates, consider using Denosumab (discuss with Oncology Consultant, see below).

Osteonecrosis of the jaw is a recognised, but rare side effect of the newer bisphosphonates. 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. In such cases discuss with the Oncology Consultant to consider the use of denosumab (Xgeva)[1,4-6,9]. Denosumab is currently approved for use following NICE TA265[11]: Treatment of bone metastases from solid tumours in patients ineligible for intravenous bisphosphonate therapy: either significant renal impairment; intolerance to bisphosphonates: or documented poor venous access. Denosumab[16] is not NICE approved for treating malignant hypercalaemia, and funding approval must be obtained before proceeding with therapy. Check current prescribing information with pharmacy before proceeding. This must be initiated by an oncology consultant.

Recurrent severe hypercalcaemia can cause rapid onset delirium so ensure that the patient is already known to the palliative care team as advanced care planning may be appropriate.

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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Contribution List

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

Designation
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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
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Supporting Document 1 - Equality Impact Assessment Tool

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

		Yes/No	Comments
1.	**Does the policy/guidance affect one group less or more favourably than another on the basis of:**		
	• Race	No	
	• Ethnic origins (including gypsies and travellers)	No	
	• Nationality	No	
	• Gender	No	
	• Culture	No	
	• Religion or belief	No	
	• Sexual orientation including lesbian, gay and bisexual people	No	
	• Age	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	N/A	
4.	**Is the impact of the policy/guidance likely to be negative?**	No	
5.	**If so can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the policy/guidance without the impact?**	N/A	
7.	**Can we reduce the impact by taking different action?**	N/A	

If you have identified a potential discriminatory impact of this key document, please refer it to Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.

For advice in respect of answering the above questions, please contact Human Resources.

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