

Specialist Palliative Care
Audit and Guidelines Group

SPAGG

Coversheet for Specialist Palliative Audit and Guideline Group Agreed Documentation

This sheet is to accompany all documentation agreed by SPAGG. This will assist maintenance of the guidelines as well as demonstrating the governance process undertaken prior to members seeking local approval in their areas of work.

Document Title	Management of Hypercalcaemia of Malignancy	
Document Date	January 2023	
Document Purpose and Intended Audience	To support specialist palliative care clinicians in hospices and hospital trusts to manage and treat hypercalcaemia related to malignancy.	
Authors	Radka Klezlova, Consultant in Palliative Medicine, Walsall Healthcare NHS Trust Chantal Meystre, Consultant in Palliative Medicine, HEFT NHS Trust	
References	Palliative Care Formulary 8 th Edition 2022 Twycross, R. Symptom Management in Advanced Cancer British National Formulary 71 st Edition 2016 NHS Scotland – Scottish Palliative Care Guidelines – accessed via www.palliativecareguidelines.scot.nhs.uk www.medicines.org.uk	
Consultation Process	Circulated to SPAGG group for comments and approval	
Monitoring	This guideline will be audited by members of the group every 3 years.	
Review Date (must be within three years)	January 2026 Michelle Aslett Nik Sanyal Warwickshire Laura Dewhirst Alice Gray	Pharmacist, Marie Curie Consultant in Palliative Medicine, Coventry and Palliative Care Registrar Palliative Care Registrar
Approval Signatures	SPAGG Chair: SPAGG Secretary:	Jon Tomas Emma Wooldridge
Date Approved by SPAGG: 10 / 7 / 2019		
Date submitted to Area Prescribing Committee:		

Guidance Name

Version History

Version	Date	Summary of change/ process
0.1	Sept 2015	Guidelines written by Dr Chantal Meystre and Dr Radka Klezlova amalgamated into SPAGG format. For circulation to SPAGG.
0.2	April 2016	Guidelines reviewed by Michelle Aslett and Jo Bartlett and changes made based on comments from the group. For presentation at SPAGG on 20/4/16.
0.3	May 2019	Guidelines were reviewed by Brenda Ward and Radka Klezlova. Paragraphs about aetiology of hypercalcaemia of malignancy and other treatment options - Calcitonin and Denosumab were added.
0.4	Jan 2023	Guidelines reviewed by Laura Dewhirst and Alice Gray changes made based on comments from the group. Emphasis placed on reviewing the need for treating hypercalcaemia and flow chart updated

Contents

1. SCOPE OF THE GUIDELINE	3
2. GUIDELINE BACKGROUND	3
3. PRESENTATION	4
4. TREATMENT	5
5. TREATMENT IN RENAL IMPAIRMENT	6
6. MANAGEMENT OF TREATMENT RESISTANT AND/OR RECURRENT HYPERCALCAEMIA	6
7. ROLE OF OTHER AGENTS IN THE TREATMENT OF MALIGNANT HYPERCALCAEMIA	6
8. SUBCUTANEOUS ADMINISTRATION OF BISPHOSPHONATES.....	7
9. REFERENCES.....	8
10. APPENDICES	9

1. Scope of the Guideline

This guideline has been produced to support the care of palliative patients with hypercalcaemia related to malignancy. These guidelines set out the diagnosis, assessment and management of hypercalcaemia.

2. Guideline Background

2.1. Hypercalcaemia of malignancy (HM) is one of the most common metabolic emergencies in patients with cancer. It can be highly symptomatic and it is fatal, if left untreated. HM occurs mostly in patients with advanced disease and it usually indicates poor prognosis, although does not always equate to the extent of disease.

2.2. Hypercalcaemia is defined as: “A corrected plasma calcium concentration above the upper limit of normal”

Calcium ions are involved in neuromuscular transmission and cell function. Serum calcium is tightly controlled between 2.15 - 2.6mmol/l (HEFT reference range). The majority is protein bound, with the active ionised portion available for metabolic function. In cancer patients blood proteins are frequently low and hypercalcaemia will be missed without the serum level being corrected for concomitant hypoalbuminaemia.

2.3. Most labs quote the corrected calcium, where this is not available the following formula may be used.

$\text{Measured serum calcium mmol/l} + 0.02 \times (40 - [\text{albumin g/l}]) = \text{corrected calcium mmol/l}$
--

2.4. HM has a prevalence of up to 20-30% in cancer patients, with squamous cell lung cancer, breast cancer, and myeloma being the most common (see table below).

Common	Uncommon
Lung – squamous cell	Lung – small cell
Breast	Large bowel
Myeloma	Stomach
Head and neck	Prostate
Kidney	
Cervix	
Lymphoma	

2.5. HM can complicate any cancer type but is less common with adenocarcinomas and small cell lung cancer. Other causes of hypercalcaemia should be considered as Primary Hyperparathyroidism (PHPT) and cancer coexist in 15%. Particularly in colon and breast cancer, associated with MEN type 1 and lymphoma. Rarely ionising radiation may cause hyperparathyroidism.

2.6. There are generally two main mechanisms of HM. The majority of cases are caused by secretion of a humoral substance, usually PTH related protein (PTHrP), directly by the cancer cells. This results in hypercalcaemia in patients even without bone metastases. Only approximately 20% cases are caused by excessive bone metastatic disease. Therefore, the diagnosis of hypercalcaemia should be considered in all cancer patients including those without bone metastases.

2.7. It is important to differentiate hypercalcaemia of malignancy from a benign hypercalcaemia in a patient with cancer.

The prognosis of hypercalcaemia in a cancer patient with coexistent hyperparathyroidism is years, but a true HM has a median survival of 2 months. Treatment resistant hypercalcaemia is associated with a very poor prognosis. The appropriateness of treatment should always be considered, with involvement of Oncology or Specialist Palliative Care teams as needed. Good communication with the patient and family is essential. Involvement of the Specialist Palliative Care Team will help support the patient, family and responsible medical team.

- 2.8 There are many other causes of hypercalcaemia and if the patient is **not** known to have active malignant disease, they should be investigated for underlying disease. Investigations should include Full Blood Count, Urea and Electrolytes, Glucose, ESR, Liver Function Tests, Thyroid Function Tests, plasma Cortisol, Synacthen test, Vitamin D level, Parathyroid Hormone (PTH) level and myeloma screen. Oral calcium therapy, thiazide diuretics, vitamins A and D promote hypercalcaemia and should be stopped.

3. Presentation

- 3.1 Symptoms are determined mainly by the speed of rising calcium, not its actual level. The classic presentation of 'Stones, Bones, Abdominal Groans and Psychic Moans' describes the patient with a slowly rising calcium. The presentation of a patient with a rapid rise in serum calcium is more acute as homeostatic mechanisms attempt to excrete calcium causing polyuria and loss of sodium, potassium and magnesium in the proximal renal tubule. Loss of concentrating ability by the nephron leads to worsening dehydration. Further direct damage to the renal tubule itself is possible when the serum calcium exceeds 3mmol/l.
- 3.2 Patients usually complain of anorexia, nausea, vomiting, constipation, thirst and mental changes early in the course of the HM, leading on to a presentation with dehydration, renal insufficiency, obtundation, twitching, fitting, coma, and cardiac arrest, as the calcium rises above 4mmol/l. Severity of symptoms does not always correlate with degree of hypercalcaemia.

Mild symptoms	Moderate symptoms	Severe symptoms
Fatigue / Lethargy Weakness Thirst Cognitive dysfunction Anorexia, nausea, Constipation Pain more difficult to control	Polyuria, Dehydration Renal failure, Nausea and vomiting Drowsiness Mental dullness, confusion Worsening of pain	Patient incapacitated Delirium Coma Fits Myoclonus Cardiac arrest due to arrhythmia

- 3.3 Despite the acute presentation and poor prognosis, treatment is often rapidly effective and worth and good symptom control is frequently achievable. HM is a rare instance where one can misdiagnose dying in a patient with an advanced malignancy.

4. Treatment

There are times where HM can be recognised to be part of a terminal decline and the burdens of treatment outweigh the benefits. **It is important to assess the stage of disease, and discuss with the patient, and if not competent with the relatives or advocate, the context of the current exacerbation and if treatment would be acceptable and appropriate.** It is important to,

‘Stop and think! Is it appropriate to treat? Or is the patient in the final days of life?’

Points to consider prior to treatment:

- First episode or long interval since previous episode
- Patient reports good quality of life prior to episode
- Multi-disciplinary team expectation is that treatment will have durable effect
- Patient is willing and able to have intravenous treatment and blood tests

4.1 Rehydration & discontinuation of other drugs

The patient will have lost fluid and electrolytes and the immediate treatment is rehydration with saline and potassium depending on the laboratory measurements. Intravenous fluids reverse the dehydration cycle, improve the glomerular filtration rate and increase sodium linked calcium diuresis via the kidney, such that the serum calcium falls by up to 0.5mmol/l. The patient improves at this point and a common error is to declare them better and take the drip down. The process that caused the hypercalcaemia is however unresolved and the condition rapidly recurs. After initial rehydration maintenance fluids should continue until the patient is euvolaemic. Medications which reduce renal blood flow or renal calcium excretion should be discontinued/avoided where appropriate e.g. NSAIDS, thiazide diuretics. Stop Vitamin A, D and calcium supplements which can all increase calcium levels.

4.2 Bisphosphonates

Bisphosphonates are the drugs of choice to treat HM. They are analogues of inorganic pyrophosphate that bind to hydroxyapatite crystals in bone and are released by bone resorption. Once taken up by the osteoclast they are cytotoxic and inhibit signalling pathways. When given for HM bisphosphonates stop the release of calcium from the bones allowing the rehydrated patient to normalise their serum calcium by excretion of excess calcium in the urine.

4.3 Disodium Pamidronate has been used for many years. The manufacturer gives a schedule of dosing for Pamidronate dependent upon the serum calcium but systematic review evidence suggests 90mg should be given whatever the serum calcium level to effectively combat the ongoing HM process.

4.4 Zoledronic acid belongs to the third generation. Studies have revealed rapid onset of action and longer duration when compared to Disodium Pamidronate, and so therefore Zoledronic acid is usually the preferred bisphosphonate in treatment of HM. Ibandronate is also the third generation bisphosphonate with better renal profile. Other bisphosphonates are Clodronate, Etidronate and Alendronate although these are difficult to obtain in the UK.

The actual selection of bisphosphonate is usually dictated by local policies.

4.5 Potency

Zoledronic acid 100 to 850 times more potent than pamidronate
Ibandronic acid 50 times more potent than pamidronate

4.7 Side effects

Bisphosphonates are well tolerated such that even a seriously ill patient has the option of a trial of therapy. The main side effects are mild pyrexia and flu like symptoms for 24-48 hours; fatigue, headache, myalgia, bone pain and hypocalcaemia which occasionally requires calcium

replacement if the patient has excreted large amounts of calcium whilst serum levels were high. A very rare but challenging side effect is osteonecrosis of the jaw but this usually develops only in patients on long term bisphosphonate treatment.

Bisphosphonates can affect renal function that's why administration in moderate to severe renal failure (eGFR < 30) is contraindicated and should be only considered when potential benefits outweigh the risks and safer medication can't be used.

Disodium Pamidronate rarely causes acute renal failure in patients with normal or mildly impaired renal function. Renal failure has occurred with Zoledronic acid, especially with high doses, but it is uncommon with Ibandronic acid.

5. Treatment in renal impairment

- 5.1 It is important to be cautious when treating hypercalcaemia in renal failure attention should be paid to rehydration and on-going monitoring of renal function because the drug itself can cause renal tubular damage and acute renal failure. Zoledronic acid must be dose adjusted for patients with mild-moderate renal impairment, where Disodium Pamidronate is safer in mild-moderate renal impairment but must not exceed a rate of 90mg/4hr.
- 5.2 Where eGFR < 30, PCF8 (Palliative Care Formulary) states consider using ibandronate or denosumab and seek specialist renal/endocrinology advice.

6. Management of treatment resistant and/or recurrent hypercalcaemia

- 6.1 If at 7-10 days post bisphosphonate infusion, the corrected calcium level is greater than 3.0mmol/l or symptoms of hypercalcaemia persist, it may be appropriate to consider another bisphosphonate infusion. At least 7 days should elapse before a further treatment is given to ensure a maximal response to the initial dose, although the Palliative Care formulary suggests waiting three weeks. Options for treatment include:
 - Repeat the same dose of bisphosphonate
 - Increased dose of same bisphosphonate
 - Change to alternative bisphosphonate
- 6.2 Further episodes of hypercalcemia may be treated as 6.1. Relapsing hypercalcaemia usually does not respond as well to bisphosphonates as in the initial episode.
- 6.3 For patients with hypercalcaemia resistant to bisphosphonates (initial or recurrent), Denosumab should be considered.
- 6.4 If levels normalise, consider ongoing plan for monitoring and therapy, referring to Oncology or Specialist Palliative Care as needed. Calcium should be re-checked if symptoms recur and at four weekly intervals if risk of recurrent hypercalcaemia and regular (monthly) infusions of bisphosphonates should be considered

7. Role of other agents in the treatment of malignant hypercalcaemia

- 7.1 Denosumab
Denosumab is a human monoclonal antibody that binds to RANKL, a receptor activator of osteoclasts. It is used primarily in preventing skeletal related events in patients with bone metastases of some solid tumours however recent small trial studies have shown it to be effective in treating hypercalcaemia in resistant cases.

Denosumab is administered as a subcutaneous injection. Side effects include osteonecrosis of the jaw, dyspnoea and diarrhoea. It is more expensive than bisphosphonate therapy hence further economic review is warranted. It does not cause renal toxicity therefore may be useful for patients with renal impairment who may not be able to receive bisphosphonates.

7.2 Calcitonin

Calcitonin should only be used in exceptional circumstances when the corrected calcium level is extremely high and there is a clinical indication for the rapid reduction of the calcium level e.g. symptomatic cardiac arrhythmias.

Calcitonin should be given in addition to a bisphosphonate. It reduces the calcium level rapidly whilst the slower acting bisphosphonate will take longer to work but have a longer lasting effect. The dose is 100 IU every 6-8 hours to a maximum of 400IU in 24 hours. It is administered as a subcutaneous or intramuscular injection. It is highly emetogenic; an antiemetic should be co-prescribed.

7.2 Corticosteroids

The role of steroids in severe hypercalcaemia is confined to haematological tumours that respond to the cytostatic effects of steroids including myeloma, leukaemia and lymphoma.

7.3 Gallium Nitrate

Effective but not used in clinical practice in the UK.

8. Subcutaneous administration of bisphosphonates

8.1 For some patients, it is not appropriate for or too burdensome for them to have intravenous therapy of bisphosphonates. It is possible to consider a subcutaneous route instead for administration of therapy. There are case reports (level 4 evidence) available describing administration of subcutaneous bisphosphonates, although these are mostly using clodronate which is not routinely available in the UK^(1, 2). It is important to note that this must be conducted alongside adequate hydration.

8.2 Administration

Pamidronate disodium: 90mg diluted in 1 litre of sodium chloride 0.9% over 12-24 hours

Zoledronic acid: There are no published guidelines for administration but this guideline would like to reference the case report from Mountbattern Hospice 'Zoledronic acid was typically added to 500mL of sodium chloride 0.9% and infused subcutaneously under gravity using a 'BD Safe-Tintima' subcutaneous cannula over approximately 12 hours'⁽³⁾.

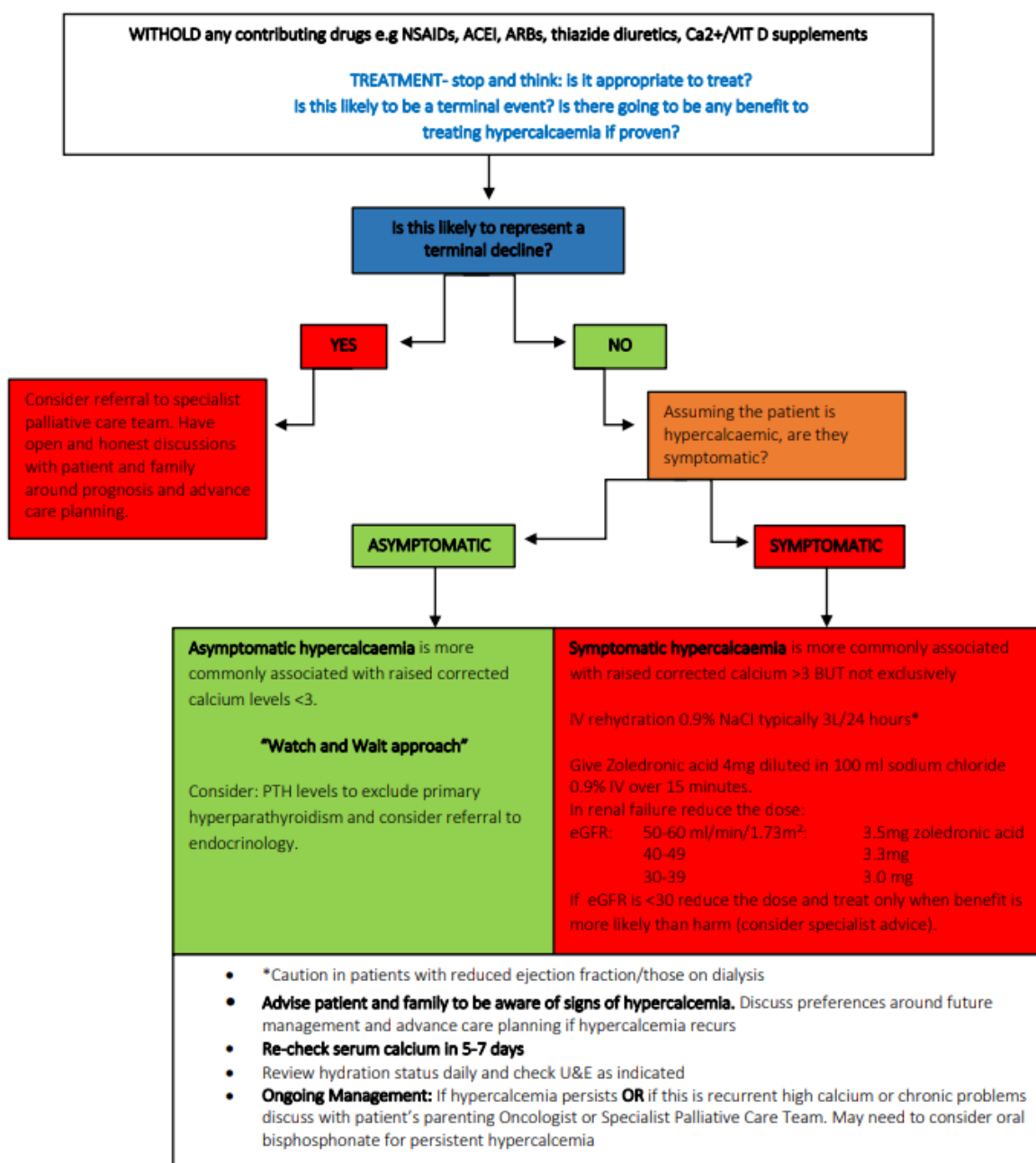
9. References

1. Roemer-Bécuwe C, Vigano A, Romano F, Neumann C, Hanson J, Quan HK, Walker P. Safety of subcutaneous clodronate and efficacy in hypercalcemia of malignancy: a novel route of administration. *J Pain Symptom Manage*. 2003 Sep;26(3):843-8. doi: 10.1016/s0885-3924(03)00252-5
2. Walker P, Watanabe S, Lawlor P, Hanson J, Pereira J, Bruera E. Subcutaneous clodronate: a study evaluating efficacy in hypercalcemia of malignancy and local toxicity. *Ann Oncol*. 1997 Sep;8(9):915-6. doi: 10.1023/a:1008274608267
3. Ramdany H, Curtin J, Howard P. Zoledronic acid by subcutaneous infusion in palliative medicine. *BMJ Support Palliat Care*. 2022 Sep 13:spcare-2022-003878. doi: 10.1136/spcare-2022-003878. Epub ahead of print.

10. Appendices

1. Management of Hypercalcaemia of Malignancy

Typical presentation of hypercalcaemia:	Investigations:
<ul style="list-style-type: none"> ➤ Nausea and Vomiting ➤ Confusion ➤ Polydipsia and polyuria ➤ Constipation and abdominal pain ➤ Clinical dehydration ➤ Agitation, decreased consciousness, seizures <p>“Bones, stones, groans and moans”</p>	<ul style="list-style-type: none"> ➤ FBC, Urea and Electrolytes, Liver function tests ➤ Bone profile (adjusted calcium) ➤ PTH level <ul style="list-style-type: none"> ○ Low in hypercalcaemia if malignancy ○ If high – consider primary hyperparathyroidism ➤ ECG ➤ Assessment of fluid status



2. Summary of action of bisphosphates

	zoledronic acid	disodium pamidronate
Intravenous (IV) dose	4mg	30 to 90mg
Onset of effect	<4 days	<3 days
Maximum effect	4 to 7 days	5 to 7 days
Duration of effect	4 weeks	2.5 weeks