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	May 2019
Document Purpose and Intended Audience	To support specialist palliative care clinicians in hospices and hospital trusts to manage and treat hypercalcaemia related to malignancy.
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References	Palliative Care Formulary 6th Edition 2018 Twycross, R. Symptom Management in Advanced Cancer British National Formulary 71st Edition 2016 NHS Scotland – Scottish Palliative Care Guidelines – accessed via www.palliativecareguidelines.scot.nhs.uk www.medicines.org.uk West Midlands Palliative Care Physicians Guidelines for the use of drugs in symptom control Cheshire and Merseyside Palliative and End of Life Care Strategic Clinical Network Standards and Guidelines: Guideline for the Management of Cancer-related Hypercalcaemia (2018).
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)	May 2022
Approval Signatures	SPAGG Chair: Jon Tomas SPAGG Secretary: Heena Khiroya
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Management of Hypercalcaemia of Malignancy

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 Dr Brenda Ward and Dr Radka Klezlova. Paragraphs about aetiology of hypercalcaemia of malignancy and other treatment options - Calcitonin and Denosumab were added.
0.4	Jan 2020	Insertion of management chart Dr Anna Lock and Dr Radka Klezlova

1. **Scope of the Guideline**

This guideline has been produced to support the care of palliative patients with hypercalcaemia related to malignancy admitted to a hospice or hospital. These guidelines set out the diagnosis, assessment and management of hypercalcaemia and include a summary page (see page 6) detailing management.

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.

2.3 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 protein.

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

Measured serum calcium mmol/l + 0.02 x (40 –[albumin g/l]) = corrected calcium mmol/l

2.2. 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 Breast Myeloma Head and neck Kidney Cervix Lymphoma	Lung – small cell Large bowel Stomach Prostate

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.

2.7 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.

2.6 It is important to differentiate hypercalcaemia of malignancy from a benign hypercalcaemia in a patient with cancer. In the presence of raised calcium, a normal or increased serum parathyroid hormone (PTH) is pathological.
The prognosis of hypercalcaemia in a cancer patient with coexistent hyperparathyroidism is years, but a true HM has a median survival of 2 months.

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.

3.4 It is important however to assess the stage of disease, 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.

4. Treatment

Stop and think! Is it appropriate to treat? Or is the patient moribund and in 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 compare to Disodium Pamidronate and it is usually the preferred bisphosphonate in treatment of HM in patients with normal or mildly impaired renal function . Ibandronate is also the third generation bisphosphonate with better renal profile. Other bisphosphonates are Clodronate, Etidronate and Alendronate.
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

4.6 The dose of any bisphosphonate should be adjusted in renal insufficiency and attention paid to rehydration and on-going monitoring of renal function because the drug itself can cause renal tubular damage and acute renal failure.

4.7 Where eGFR < 30, PCF5 (Palliative Care Formulary) states consider using ibandronate or denosumab and seek specialist renal/endocrinology advice.

4.8 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 is 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.

4.9 Summary of action of bisphosphonates

	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**

5. Management of treatment resistant and/or recurrent hypercalcaemia

5.1 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. Options for treatment include:

- Repeat the same dose of bisphosphonate
- Increased dose of same bisphosphonate
- Change to alternative bisphosphonate

5.2 Further episodes of hypercalcemia may be treated as 5.1. Relapsing hypercalcaemia usually does not respond as well to bisphosphonates as in the initial episode.

5.3 For patients with hypercalcaemia resistant to bisphosphonates (initial or recurrent), Denosumab should be considered.
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.

6. Role of other agents available in the treatment of malignant hypercalcaemia

6.1 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.

6.2 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.

6.3 Gallium Nitrate
Effective but not used in clinical practice in the UK.

HYPERCALCAEMIA OF MALIGNANCY MANAGEMENT

SEVERITY OF HYPERCALCAEMIA

Corrected calcium < 3.0 mmol/l:
May be asymptomatic. Does not require urgent treatment, advisable to treat if symptomatic.

Corrected calcium 3.0-3.5 mmol/l:
Usually symptomatic.
Treatment is indicated as below unless inappropriate to treat.

Corrected calcium >3.5 mmol/l:
Emergency, fatal if untreated. urgent treatment is required unless inappropriate to treat.

Mild:
Fatigue, lethargy, weakness, cognitive dysfunction, anorexia, nausea, constipation

Severe:
Polyuria, dehydration, renal failure, vomiting, drowsiness, confusion, delirium, worsening of pain

Very severe:
Coma, seizures,
cardiac arrest due to arrhythmia, myoclonus

INVESTIGATIONS

History and physical examination:
Assess symptoms, cognitive impairment and fluid balance status

Drug history-STOP:
calcium supplements
thiazide diuretics,
vitamin D and A products,
nephrotoxic drugs if possible

Blood tests:
Corrected calcium or ionised calcium
Urea, creatinine, electrolytes
+/- PTH, if diagnosis unclear

If high calcium and normal or high PTH:-
Consider hyperparathyroidism

If high calcium and low PTH:-
Malignancy or other rare causes

TREATMENT- stop and think: is it appropriate to treat?

STEP 1 - REHYDRATION

Patient not at risk of fluid overload:
IV hydration with Sodium Chloride 0.9% 2-3 litres over 24 hours. Monitor hydration status, renal function and electrolytes. If K^+ normal or low, use ready-made potassium infusions as per local policy.

Patient at risk of fluid overload:
Careful IV rehydration, consider loop diuretics if fluid overloaded, continue according to hydration status. Monitor hydration status, renal function and electrolytes.

STEP 2 - BISPHOSPHONATES (consider formulary status and calcium level)

Action within <4 days ***Lasts for 4 weeks***
Zoledronic acid 4mg diluted in 100 ml sodium chloride 0.9% IV over 15 minutes.
In renal failure **reduce** the dose:
eGFR: 50-60 ml/min/1.73m²: 3.5mg zoledronic acid
40-49 ml/min/1.73m²: 3.3mg zoledronic acid
30-39ml/min/1.73m²: 3.0mg zoledronic acid
If eGFR is <30 reduce the dose and treat only when benefit is more likely than harm (consider specialist advice).

Action within <3 days ***Lasts for 2.5 weeks***
Pamidronate 90mg IV diluted in 500ml in sodium chloride 0.9% over 2 hours.
In moderate renal impairment
eGFR >30ml/min/1.73m² administer 90 mg over 4 hours.
If eGFR is < 30 reduce the dose and treat only when clinical benefit is more likely than harm (consider specialist advice).

STEP 3 – IF REMAINS HYPERCALCAEMIC AT FIVE DAYS FURTHER TREATMENT SHOULD BE PLANNED IN CONJUNCTION WITH SPECIALIST TEAM

First line choice
Repeat bisphosphonate
in 7 days' time
or, use Zoledronic acid IV 4mg if Pamidronate was given first line.

Second line choices
- **Ibandronic acid (oral)**

May be prescribed alongside a shared care arrangement with GP. Dose adjustments needed from eGFR = <50ml/min
- **Corticosteroids**

Use in lymphoma & myeloma, **no** effect in solid tumours.
- **Seek specialist advice**

Specialist use only - Denosumab
Seek advice with oncology – vitamin D replacement may be needed.
Fatal cases of hypocalcaemia have been reported

STEP 4– FOLLOW UP

Dependent on symptoms and treatment choice, check calcium after 3-5 days
Review hydration status daily and check U&E's as indicated. Advise patient and relatives to be aware of symptoms of hypercalcaemia. Discuss future management and advance care planning with patient and family. Repeat calcium within a month, earlier if symptoms recur. Continue regular monitoring. Consider maintenance with an oral bisphosphonate for persistent hypercalcaemia.