GUIDELINE FOR THE USE OF DENOSUMAB FOR HYPERCALCAEMIA OF MALIGNANCY

TARGET AUDIENCE	Predominantly specialist palliative care, with information for primary care and secondary care clinicians involved in palliative care
PATIENT GROUP	Patients with hypercalcaemia of malignancy

Clinical Guidelines Summary

- Denosumab is a human monoclonal antibody that can be used for the treatment of hypercalcaemia of malignancy (Unlicensed indication in the UK).
- Denosumab may be considered instead of standard treatment with zolendronic acid where the condition is refractory to bisphosphonate therapy or where bisphosphonates are contraindicated due to severe renal impairment, under the guidance of the Specialist Palliative Care Team.
- In exceptional circumstances it may be considered for community based patients under the care of the Community Specialist Palliative Care Team that are either unable, or do not wish, to attend hospital for bisphosphonate therapy. This would be following very careful consideration of the potential risks and benefits of treatment, including discussion with the patient and family about the use of off licence medications.
- Typical dosing and monitoring schedule:
  - Day 1 120mg sc denosumab
  - Day 5 Clinical assessment and bloods to check calcium
  - Day 8 Further 120mg sc denosumab if patient remains symptomatic of a high calcium
  - Day 13 Clinical assessment and bloods to check calcium
  - Day 15 Further 120mg sc denosumab if patient remains symptomatic of a high calcium
  - Day 20 Clinical assessment and bloods to check calcium
- Patients with severe renal impairment (creatinine clearance <30ml/min) or receiving dialysis are at greater risk of hypocalcaemia
- Osteonecrosis of the jaw is a well-known and common side-effect in patients receiving Denosumab for hypercalcaemia of malignancy

Guideline Body

This guideline should be considered in conjunction with the NHSL guideline on Management of Hypercalcaemia.

Introduction

Denosumab is a human monoclonal antibody that inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption.

Preparation

Denosumab (Xgeva®) 70mg/ml, 120mg vial

Indication

Hypercalcaemia of malignancy (unlicensed indication in the UK):

- refractory to bisphosphonate therapy, or
- where bisphosphonates are contraindicated due to severe renal impairment.

In exceptional circumstances it may be considered for community based patients under the care of the Community Specialist Palliative Care Team that are either unable, or do not wish, to attend hospital for bisphosphonate therapy. This would be following very careful consideration of the potential risks and benefits of treatment, including discussion with the patient and family about the use of off licence medications.

Dose and Administration

- The licenced dose and administration is 120mg SC every 4 weeks with additional doses on days 8 and 15 of the first month
- Administer by slow SC injection into the thigh, abdomen or upper arm
- A 27-gauge needle is recommended for administration
- No dose adjustment is required in renal impairment.

Notes:

- Xgeva® is for subcutaneous route only. Do not administer intravenously or intramuscularly
- **Do not shake the vial**
- Before administration, visually inspect the vial. The solution may contain trace amounts of translucent to white proteinaceous particles. Do not inject the solution if it is cloudy or discoloured.

Monitoring

Calcium should be checked prior to receiving the first dose and between 5 and 14 days post-dose.

Additional monitoring should be considered in patients with risk factors for hypocalcaemia e.g. severe renal impairment.

It will be the responsibility of the community SPC team to arrange for blood sampling (via the community nurse team) and to ensure the results are checked.

Typical dosing and monitoring schedule:

Day 1 120mg sc denosumab

Day 5 Clinical assessment and bloods to check calcium

Day 8 Further 120mg sc denosumab if patient remains symptomatic of a high calcium

Day 13 Clinical assessment and bloods to check calcium

Day 15 Further 120mg sc denosumab if patient remains symptomatic of a high calcium

Day 20 Clinical assessment and bloods to check calcium

Cautions

- Patients with severe renal impairment (creatinine clearance <30ml/min) or receiving dialysis are at greater risk of hypocalcaemia
- The safety and efficacy of Denosumab has not been studied in patients with hepatic impairment
- Osteonecrosis of the jaw is a well-known and common side-effect in patients receiving Denosumab for hypercalcaemia of malignancy
  - Risk factors include smoking, old age, poor oral hygiene, invasive dental procedures, comorbidities, advanced cancer, previous treatment with bisphosphonates, and concomitant treatments (including chemotherapy, anti-angiogenic biologics, corticosteroids, and radiotherapy to head and neck).
  - A dental examination and appropriate preventative dentistry is recommended as soon as possible after treatment, if appropriate with consideration to expected prognosis. However, patients treated under this guideline are likely to be those with a very limited prognosis and longer term complications such as osteonecrosis of the jaw may not be clinically relevant.

Contraindications

- Dental or jaw conditions requiring surgery or unhealed lesions from dental or oral surgery. However, in the case of life threatening or highly symptomatic hypercalcaemia in an individual with a prognosis of short weeks, where there is no viable alternative this would be a relative contraindication.
- Hypersensitivity to active ingredient or excipients. Xgeva® contains Sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

Side effects

Very common (>10%): breathlessness, diarrhoea, hypocalcaemia, musculoskeletal pain.

Common (<10%, >1%): hypophosphataemia, hyperhidrosis, osteonecrosis of the jaw, tooth extraction, rash.

Rare (<0.1%, >0.01%): atypical femoral fracture.

Not known: osteonecrosis of external auditory canal.

Clinically significant hypersensitivity including anaphylaxis has been reported with use of Xgeva®.

Practice points

- Store in a refrigerator long-term (2-8°C). May be removed and stored at room temperature, in the original container for up to 30 days.
- To reduce discomfort at the site of injection, allow the vial to reach room temperature before use. This generally takes 15 to 30 minutes. Do not warm in any other way.
- Xgeva® is ordered as per normal ordering procedures. Delivery may take longer than usual, allow up to three days.
- St Andrews Hospice stock two vials. Kilbryde Hospice may borrow and replace if required.

Ordering via a community pharmacy will take up to five working days. Boots, 40-42 Graham Street, Airdrie hold one vial for use under specialist palliative care advice.

References/Evidence

1. https://nhslguidelines.scot.nhs.uk/media/2138/guideline-management-of-malignant-hypercalcaemia-sep-22-v11.pdf
2. Xgeva 120mg solution for injection. Summary of Product Characteristics (SPC) Amgen Ltd. www.medicines.org.uk/emc accessed on 10.05.2023
3. Denosumab monograph. Palliative Care Formulary via Medicines Complete https://www.medicinescomplete.com accessed on 10.05.2023
4. British National Formulary (BNF). https://bnf.nice.org.uk accessed on 10.05.2023

Appendices

1. Governance information for Guidance document

Lead Author(s):	Linda Johnstone, Macmillan Area Lead Pharmacist Palliative Care Dr Kerry McWilliams, Consultant in palliative Medicine
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Date	Lead Author	Change	Version No.
		e.g. Review, revise and update of policy in line with contemporary professional structures and practice	1
			2
			3
		.	4
			5

2.You can include additional appendices with complimentary information that doesn't fit into the main text of your guideline, but is crucial and supports its understanding.

https://nhslguidelines.scot.nhs.uk/media/2138/guideline-management-of-malignant-hypercalcaemia-sep-22-v11.pdf

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