PROTOCOL

Systemic Anti Cancer Therapy Protocol

Denosumab (XGEVA)
Giant cell tumour of the bone

PROTOCOL REF: MPHADGCSA
Version No. 1.2

Approved for use in:

- The treatment of adults and skeletally mature adolescents, with giant cell tumour of bone that is unresectable, or where surgical resection is likely to result in severe morbidity.
- Neo adjuvant use in giant cell tumour of the bone

Dosage:

Drug	Dose	Route	Frequency	
Denosumab	**120mg**	Subcutaneous injection	Cycle 1	Day 1 / 8 / 15
			Cycle 2 +	Day 1
			Repeated every 28 days	

Following 1 year of treatment cycles may be extended to 2 months or 3 months at clinician discretion.

Administration:

- Inspect vial prior to administration, do not use if cloudy or discoloured
- Do not shake excessively.
- To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25°C) before injecting and inject slowly.

- A 27 gauge needle is recommended for the administration of denosumab.
- Single subcutaneous injection into the thigh, abdomen or upper arm.
- Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present.
- Calcium and vitamin D doses may be increased, reduced or stopped based on clinical need.
- Pre-existing hypocalcaemia must be corrected prior to initiating therapy.
- Hypocalcaemia can occur at any time during therapy and most commonly occurs during the first 6 months of dosing. If hypocalcaemia occurs check vitamin D levels and then consider additional supplementation
- Patients with rare hereditary problems of fructose intolerance should not use denosumab.

Day		Drug	Dose	Route
Cycle 1	Day 1 / 8 /15	Denosumab	120mg	Sub-cutaneous injection in thigh, abdomen or upper arm
Cycle 2 +	Day 1			
Continuously		Adcal D3 chewable tablets 1.5g/400units	2 tablets	Orally ONCE a day

Contraindications:

- Hypersensitivity to the active substance or to any of the excipients listed in the SPC.
- Severe, untreated hypocalcaemia
- Unhealed lesions from dental or oral surgery

Emetogenic risk:

Mild emetogenic potential.

Supportive treatments:

Adcal D3 chewable tablets 1.5g/400units D3; TWO tablets ONCE daily

Dosing in renal and hepatic impairment:

Renal	Patients with creatinine clearance < 30 mL/min (Severe renal impairment) or on dialysis are at increased risk of developing hypocalcaemia. The risk of developing hypocalcaemia and accompanying elevations in parathyroid hormone increases with increasing degree of renal impairment. Regular monitoring of calcium levels recommended.

Hepatic	No specific study in patients with hepatic impairment was performed. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms.

Interactions:

No interaction studies have been performed.

Please refer to the SPC

Main toxicities:

Very common	
Hypocalcaemia **Musculoskeletal pain** **Diarrhoea** **Dyspnoea**	• Symptoms of hypocalcaemia include; paraesthesias or muscle stiffness, twitching, spasms and muscle cramps. • Symptoms of **severe hypocalcaemia** include; QT interval prolongation, tetany, seizures, altered mental status (including coma) In clinical trials discontinuation due to this side-effect was uncommon.

Other adverse drug reactions	
Osteonecrosis of the jaw (ONJ)	• The jawbone becomes necrotic, exposed, and does not heal within 8 weeks. • Risk factors include invasive dental procedures (e.g., tooth extraction, dental implants, and oral surgery), poor oral hygiene, or other pre-existing dental disease. • Patients should have a dental examination prior to treatment. • If any invasive dental procedures need to be undertaken, treatment should be delayed until any oral lesions have healed (recommended duration 6 weeks). • All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups and immediately report any oral symptoms such as dental mobility, pain, or swelling. • If invasive dental work is required then treatment will be withheld for 6 weeks or until dentist or oral surgeon confirms that is safe to resume treatment. • Patients who experience ONJ should be managed in collaboration with a dentist or oral surgeon. • Treatment with denosumab should be interrupted until the condition resolves and the contributing risk factors are mitigated where possible. • Alternatively, the decision to resume treatment can be made by clinical team managing their care in conjunction with the dentist/oral surgeon and the patient.
Hypophosphataemia	Refer to the CCC Hypophosphataemia guidelines for replacement.

Atypical femoral fracture	• Risk increased with longer duration of treatment. • May occur with little or no trauma. • Patients should be advised to report new or unusual thigh, hip, or groin pain. • Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.
Skin toxicity/rash	Lichenoid drug eruptions
Osteonecrosis of the external auditory canal	• Possible risk factors include steroid use and chemotherapy and/or local risk factors such as infection or trauma. • Symptoms include the presentation of chronic ear infections.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 D15	Cycle 2	Prior to cycle 3	Cycle 3	Cycle 4	Ongoing
Informed Consent	X							
Clinical Assessment	X				X			Every three months as clinically indicated
Dental check	X							Pre cycle 1 and if clinically indicated
SACT Assessment (to include PS and toxicities)	X	X		X		X	X	Every cycle
Bone profile	X		X	X		X	X	Every cycle
U&E & serum creatinine (renal profile)	X	X		X		X	X	Every Cycle
Magnesium								If clinically indicated (hypocalcaemia and concurrent chemotherapy that affects Magnesium e.g. platinum)
Calcium	X		X	X		X	X	Every cycle
CrCl (Cockcroft and Gault)	X			X		X	X	Every cycle
CT scan**/ MRI scan	X							Every 3-6 months and if clinically indicated
ECG								If clinically indicated (suspected Hypocalcaemia induced QT prolongation)
Main observations (blood pressure, respiratory rate etc)	X			X		X	X	Every cycle
Blood glucose								If clinically indicated
Weight recorded	X	X		X		X	X	Every cycle
Blood glucose	X							Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Prior to cycle 1 day 1- confirm patient has completed baseline dental check.

Proceed on day 1 of cycle 1 and subsequent cycles if:

Adjusted Calcium ≥ Lower Limit Normal (LLN*)	CrCl (creatinine clearance calculated using Cockcroft and Gault equation) ≥ 30ml/min

Delay 1 week** on day 1 if:

Adjusted Calcium < Lower Limit Normal (LLN*)	CrCl (creatinine clearance calculated using Cockcroft and Gault equation) < 30ml/min

*Please refer to adjusted calcium range specific to the biochemistry laboratory that has processed the sample.
****** Unless a decision is made by a clinical team to continue with treatment with appropriate intervention (monitoring and/or increased supplementation).

When assessing blood results it is important to check for trends in adjusted calcium and creatinine clearance. If the trend denotes a decline in-:

- Adjusted calcium- then provided patient is adherent with supplementation, consult with a medical team or appropriate non-medical prescriber with regards to increasing supplementation dose.
- Serum creatinine ≥ 15% then consult with the appropriate clinical team (refer to 'Dosing in Renal and Hepatic impairment' section).

Following any deferral- confirm patient adherence with calcium and vitamin D supplementation.

If patient deferred for 2 consecutive weeks despite patient adherence with supplementation- please check vitamin D level. It is important to ensure all patients

receiving denosumab treatment are vitamin D replete. Contact clinical team if vitamin D level is low.

References:

1. Amgen Denosumab Health Care Professional Letter. Denosumab 120mg (XGEVA®▼): Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia (July 2014).
2. NICE TA265 – Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours (October 2012). Accessed on 6th February 2023 via https://www.nice.org.uk/guidance/ta265/chapter/1
3. Guidance Prevention of Skeletal-Related Events in Patients with Bone Metastases, CCC Clinical Procedure, v1. Society for Endocrinology. Emergency Management of Acute Hypocalcaemia in Adult Patients (2016). Accessed on 6th February 2023 via www.endocrinology.org
4. Summary of Product Characteristics (SmPC) for Denosumab (Last updated 22nd November 2019). Accessed on 6th February 2023 via https://www.medicines.org.uk/emc/product/4675/smpc
5. Sant C, Blay JY et al. Denosumab in patients with giant cell tumor of the bone: a multi-centre, open label phase 2 trial. The Lancet [internet] November 2019;20(12):1627-1628 Available from: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30660-6/fulltext

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
1.2	12/0723	**Rob Challoner (Pharmacist)**	New regimen protocol. Following review with Dr Ali. Formatting changes, Adcal D3 dose amended to 2 tabs OD to match TTO packs