

BONE PROTECTION IN MYELOMA

INDICATIONS

- Long-term bisphosphonate therapy: This is the primary subject of this protocol. **Prophylactic treatment should be given to all patients with myeloma requiring treatment, whether or not bone lesions are evident** as per the BCSH Guidelines 2010¹ **and should continue for at least 2 years.**² Discontinuing bisphosphonates after 2 years' treatment in patients with well controlled disease, and restarting at relapse/progression is a reasonable approach. Therapy can be withheld 2 weeks prior to undergoing ASCT and re-initiated 2 months post-ASCT

Denosumab is NOT routinely funded for bone protection in myeloma. For patients with renal impairment who are not eligible to receive bisphosphonates, Individual funding request must be approved prior to initiation of therapy.

EVIDENCE

- The 2012 Cochrane review suggested that adding bisphosphonates to the treatment of multiple myeloma reduces vertebral fracture, probably pain and possibly the incidence of hypercalcaemia.³
 - For every 10 patients with myeloma treated with bisphosphonates one patient will avoid a vertebral fracture.
 - The Nordic myeloma study group compared the effect of two doses of (30 mg or 90 mg) pamidronate on health-related quality of life and skeletal morbidity in patients with newly diagnosed multiple myeloma in a randomised phase 3 trial. Primary outcome of physical function after 12 months and secondary outcome of time to first SRE were not significantly different in a 4 year follow up between the two drug doses.⁴
 - Efficacy and safety of 120 mg Denosumab SC every 4 weeks or 4 mg zoledronic acid (dose-adjusted for reduced renal function) IV every 4 weeks were compared in three randomised, double blind, active controlled studies, in IV-bisphosphonate naïve patients with advanced malignancies involving bone: adults with breast cancer (study 1), other solid tumours or multiple myeloma (study 2), and castrate-resistant prostate cancer (study 3). Denosumab reduced the risk of developing a SRE, and developing multiple SREs (first and subsequent) in patients with bone metastases from solid tumours and multiple myeloma^{5,6}
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CHOICE OF Bone protection AGENT

- Myeloma IX suggests zoledronic acid significantly reduces skeletal events and may improve survival when compared with clodronate.⁷
- Intravenous zoledronate 4 mg monthly is equivalent in efficacy to pamidronate 90 mg monthly and has the advantage of a shorter infusion time (15 minutes versus 90 minutes for pamidronate). However, the risk of osteonecrosis of the jaw (ONJ) may be higher with zoledronate than with pamidronate.²
- Pamidronate 30 mg is non inferior to a standard 90 mg dose of pamidronate.⁴
- Based on Myeloma IX, newly diagnosed patients should be offered treatment with zoledronic acid. Clodronate is an acceptable alternative in patients with renal impairment including dialysis or in patients with poor venous access or if the patient prefers oral treatment or wishes to reduce hospital visits.
- Zoledronic acid has not been shown to be superior to Pamidronate and therefore Pamidronate is a reasonable alternative for all patients.

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- Alendronic acid, Etidronate and ibandronate should be avoided.
- Denosumab can be considered for patients with renal impairment and unable to receive/ tolerate bisphosphonates. Prior funding arrangement has to be secured.

BEFORE COMMENCING TREATMENT

It is recommended that all patients should have a comprehensive dental examination and appropriate preventive dentistry before starting bisphosphonate therapy, at least when the intravenous agents are being used. This may not be possible if the bisphosphonate is needed urgently but should be arranged at the earliest opportunity. This examination should be repeated every 6 months whilst bisphosphonates are being used.

Patients should be advised on the risks of ONJ as per section below and appropriate written information provided to patients, e.g. Myeloma UK MUK leaflet / Macmillan leaflet.

TREATMENT DETAILS

i. Zoledronic acid:

A 4 mg dose reconstituted and diluted for infusion (in 100 mL Sodium chloride 0.9% or Glucose 5%) is given in no less than a 15-minute intravenous infusion every 4 weeks.

ii. Pamidronate:

Pamidronate 30 mg IV infusion in 250 mL 0.9% normal saline over 30 minutes once every 4-weeks.

iii. Sodium Clodronate:

A continuous dose equivalent to 1600 mg sodium clodronate should be given orally either as single or 2 divided doses

Bonefos 1600 mg daily PO (400 mg capsules and 800 mg tablets available)

Note: Sodium Clodronate should be taken on an empty stomach, often most conveniently at bedtime. Food, especially calcium-containing products, e.g. milk, should be avoided for 2 hours before and after treatment. Side effects, which may include nausea, diarrhoea and asymptomatic hypocalcaemia, do not usually require dose adjustments or cessation of treatment.

iv. Denosumab:

The dose is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. Before administration, Denosumab solution should be inspected visually. It may contain trace amounts of translucent to white proteinaceous particles. Do not inject the solution if it is 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 the entire contents of the vial slowly. A 27-gauge needle is recommended for administration. **(Denosumab is not currently commissioned for this indication)**

MONITORING DURING THERAPY WITH PAMIDRONATE OR ZOLEDRONIC ACID

Before every infusion:

1. Check serum creatinine has been performed within the last 8 weeks and dose modify accordingly. **Infusion should be withheld if renal deterioration without other apparent cause.** Monitor serum calcium, electrolytes, magnesium and phosphate at intervals. Therapy

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can be re-started when serum creatinine returns to a value within 10% of baseline.² Therapy should be withheld if adjusted Calcium is less than 2.05 mmol/l

2. Ensure well hydrated prior to each treatment.
3. Calcium and vitamin D supplementation (Calcichew D3 Forte, or Adcal D3) is recommended at a dose of 1-2 tablets daily when patients are on Zoledronic acid and patients developing hypocalcemia on Pamidronate. Monthly review of calcium levels is required.

USE IN PATIENTS WITH RENAL IMPAIRMENT ⁸⁻¹¹

Bisphosphonate	Renal
Bonefos (sodium clodronate)	CrCl 50 – 80 mL/min 1600mg od (100%) CrCl 30-<50 mL/min 1200mg od CrCl 10-<30 mL/min 800mg od CrCl < 10 mL/min clinical decision No data exists on its use in dialysis patients- clinical decision
Pamidronate disodium	CrCl 61 – 90 mL/min: no dose reduction CrCl 30 – 60 mL/min: no dose reduction. Infusion rate should not exceed 90 mg/4hr (~22 mg/hour) CrCl <30 mL/min: it should not be administered unless life-threatening hypercalcaemia where benefit outweighs risk
Zoledronic acid	CrCl > 60 mL/min 4.0 mg CrCl 50-60 mL/min 3.5 mg CrCl 40-49 mL/min 3.3 mg CrCl 30-39 mL/min 3.0 mg
Denosumab	No dose reduction required

CAUTIONS

- Doses and frequencies should not be exceeded and infusion times should not be shorter than those recommended by the manufacturer
- Care is required with all bisphosphonates in patients with moderate to severe renal failure

DURATION OF TREATMENT

There is little data to guide optimal duration of bisphosphonate therapy. However, the risks of ONJ seem to increase with time of bisphosphonate exposure. The ASCO Clinical Guideline Update Committee suggests bisphosphonates to be given for a period of 2 years at which time physicians should consider discontinuing them in patients with responsive or stable disease. In patients in remission, the frequency can be reduced to once every 2-3 months (after the first 24 months)

Therapy should be resumed on relapse with new-onset skeletal-related events.²

OSTEONECROSIS OF THE JAW

The risks of ONJ in myeloma patients on bisphosphonates are difficult to assess but appear to be between 0.83 and 11%. The risk of ONJ seems to be higher with the more potent agents (zoledronic acid has been associated with more cases than pamidronate) and cases on oral agents including clodronate are extremely rare. Patients should be informed of this potential risk before starting treatment (see ONJ patient information from Myeloma UK ¹²).

Patients should have a thorough dental examination and appropriate preventative dentistry before starting therapy. Active oral infections should be treated and sites at high risk of infection should be eliminated. Repeat dental check-ups should occur every 6 months whilst on treatment. Patients should maintain good oral **hygiene** and avoid invasive dental procedures if possible whilst on therapy. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ but referral to an oral/maxillofacial surgeon should be considered. Infrequent use of pamidronate guided by bone biomarkers or alternatively sodium clodronate should be considered in patients with previous ONJ.

Filling and cleaning does not require interruption of bisphosphonate therapy. If dental extractions/implants are required during therapy and cannot be avoided, then treatment interruption is required. There is no evidence based guideline to direct duration of interruption, around 6-8 weeks is common practice. It may help to retain roots, if possible in case of dental extractions to reduce risk of long term ONJ.

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REVIEW

Name	Revision	Date	Version	Review date
Dr Jaimal Kothari Consultant	Indication section, evidence section, choice of treatment section, denosumab added, treatment details, renal impairment and reference section updated	May 2016	3.0	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated indication, treatment details, renal impairment and references	July 2017	3.1	June 2018
Myeloma Protocol Review 2019	Updated indication, choice of bone protection agent, monitoring prior to therapy, renal impairment and references	June 2018	3.2	June 2019

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