Clinical Guideline
BONE PROTECTION IN MYELOMA

SETTING Division of Specialised Services

FOR STAFF Medical, Nursing and Pharmacy Staff of Bristol Haematology & Oncology Centre (BHOC)

PATIENTS Adult patients with myeloma

1. BACKGROUND

Bone loss is a well-recognised complication of myeloma, resulting from the disease, intensive chemotherapy and corticosteroid usage. Vitamin D deficiency, inactivity, hypogonadism, renal failure with secondary hyperparathyroidisim and radiotherapy may also contribute.[1]

Adding bisphosphonates to the treatment of multiple myeloma reduces vertebral fracture, probably pain and possibly the incidence of hypercalcaemia.[2] Zoledronic acid, which is the current standard of care, has been shown to reduce skeletal related events (SREs), preserve bone density and prolong progression-free and overall survival.[3]

This guideline describes the treatment options available for bone protection in myeloma.

2. GENERAL PRINCIPLES AND RECOMMENDATIONS

Prophylactic bisphosphonate treatment should be given to all patients with myeloma requiring systemic treatment, with or without evidence of lytic bone lesions or compression fracture of the spine from osteopenia .

There is currently no clear evidence to guide optimal duration of bisphopshonate therapy. The risks of osteonecrosis necrosis of the jaw (ONJ) seems to increase with time of bisphosphonate exposure. **Discontinuing after 2 years' treatment for patients with well controlled disease, and restarting at relapse with new-onset SREs Is recommended by ASCO's expert panel.** For patients with well controlled disease, consideration may be given to reducing the frequency of infusions to once every 2 to 3 months after the first 12 months of treatment.[6]

For patients undergoing autologous stem cell transplant (ASCT) bisphosphonate therapy can be withheld 2 weeks prior to undergoing ASCT and re-initiated 2 months post-ASCT.

Calcium and vitamin D supplementation, dietary advice, weight-bearing exercise, hormone replacement therapy (HRT) and minimisation of exposure and duration of corticosteroids and chemotherapy should also be considered in order to preserve bone.[1] HRT should be offered to male and female patients where appropriate with specialist advice.

3. CHOICE OF BISPHOSPHONATE

Results from the Myeloma IX trial suggest that intravenous zoledronic acid significantly reduces SREs and may improve survival when compared with oral sodium clodronate. [7] Zoledronic acid should therefore be offered as first line treatment for newly diagnosed patients at BHOC.[8]

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Intravenous disodium pamidronate is a reasonable alternative for patients where zoledronic acid is not tolerated or contra-indicated.[8]

Oral sodium clodronate is an acceptable alternative for:-

- patients with renal impairment
- patients with poor venous access
- patients who prefer an oral treatment option
- patients who wish to reduce hospital visits.

Alendronate, etidronate and risedronate should be avoided.

Ibandronate is associated with less nephrotoxicity than zoledronate. A recent meta-analysis demonstrated that both IV and oral ibandronate significantly reduced the incidence of SREs and bone pain in patients with multiple myeloma relative to placebo but it has not been shown to demonstrate a survival benefit.[9] Ibandronate is not included in the NICE Clinical Guideline for myeloma for preventing bone disease or managing non-spinal bone disease.

Denosumab (Xgeva®) is a monoclonal antibody that targets receptor activator of nuclear factor kappa-B ligand. Denosumab (Xgeva®) has demonstrated non-inferiority to zoledronic acid for the prevention of SREs, with fewer adverse events related to renal toxicity.. ASCO's expert panel therefore recommend it as an alternative bone modifying agent in this setting,[5] however individual funding must be sought as it is not routinely commissioned in this setting.

4. BASELINE INVESTIGATIONS AND TESTS BEFORE STARTING TREATMENT

Investigation	Validity period
Dental examination	3 months, unless any ongoing dental issues
Creatinine	14 days
Calcium	28 days
Magnesium	28 days
Phosphate	28 days

Dental examination: All patients should have a comprehensive dental examination and appropriate preventive dentistry before starting bisphosphonate therapy. Active oral infections should be treated, and sites that are high risk for infection should be eliminated.[5] The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations e.g. hypercalcaemia.

Invasive dental procedures should be avoided whilst on 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 8-12 weeks is common practice. It may help to retain roots, if possible in case of dental extractions to reduce risk of long term ONJ. Filling and cleaning does not require interruption of bisphosphonate therapy.

Patients should be advised on the risks of ONJ and appropriate written information provided e.g. Macmillan or Myeloma UK information leaflet. All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups (at least 6 monthly), and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge

during treatment.

Renal function: Check serum creatinine and calculate creatinine clearance (CrCl) before initiation of bisphosphonate therapy. Patients with mild to moderate renal impairment may require lower doses- see section 6 for dosing guidance in renal impairment. Care is required with all bisphosphonates in patients with moderate to severe renal failure.
Ensure patient is well hydrated.

Calcium, Phosphate, Magnesium: Hypocalcaemia, hypophosphataemia, or hypomagnesaemia may occur with bisphosphonate treatment. Check baseline levels and correct where appropriate. Calcium and vitamin D supplementation is recommended for patients on zoledronic acid (unless hypercalcaemic) and for patients developing hypocalcemia on pamidronate.

Adcal D3 is the supplement of choice at BHOC at a dose of 1- 2 tablets daily (each tab contains 500mg calcium and 400iu Vitamin D). Other calcium & vitamin D supplements may be prescribed by GPs in accordance with the BNSSG formulary.

5. TESTS BEFORE EACH BISPHOSPHONATE INFUSION

Investigation	Validity period
Creatinine	7 days
Calcium	7 days
Phosphate	7 days
Magnesium	3 months
Vit D	3 months
Urinary albumin	3- 6 months

Ensure patient is well hydrated prior to each treatment. Check serum creatinine and calculate creatinine clearance before each dose.. If serum creatinine rises significantly from baseline value, a doctor should be informed and consideration should be given to withholding bisphosphonate therapy until the serum creatinine returns to within 10% of the baseline level.

Treatment should be deferred if the patient has hypocalcaemia or hypophosphataemia.

ASCO's expert panel recommends intermittent evaluation (every 3-6 months) for the presence of albuminuria on a spot urine sample for patients on zoledronic acid or pamidronate. In patients who experience unexplained albuminuria, a 24 hour urine collection should be obtained to assess for >500mg/24 hours of urinary albumin, and discontinuation of the drug is advised until renal problems are resolved. These patients should be reassessed every 3 to 4 weeks - with a 24 hour urine collection for total protein and urine protein electrophoresis – and pamidronate should be reinstituted over a longer infusion time(≥ 4 hours) when renal function returns to baseline.[5]

6. DOSAGE, FREQUENCY AND ADMINISTRATION

Drug and route	CrCl (ml/min)	Dose	Frequency	Infusion fluid & time
Zoledronic acid -IV [12]	> 60	4.0 mg	Every 4 weeks	100ml Sodium Chloride 0.9% over 15 mins
	50-60	3.5 mg		
	40-49	3.3 mg		
	30-39	3.0 mg		
	<30	Not recommended		
Clodronate disodium (Loron)®- Oral [13]	> 30	1040 mg OD	Continuous	Not applicable
	10-30	520 mg OD		
	< 10	Contra-indicated		
Sodium clodronate (Bonefos)®- Oral [14]	50- 80	1600 mg OD	Continuous	Not applicable
	30-49	1200 mg OD		
	10-29	800 mg OD		
	< 10	Contra-indicated		
Disodium pamidronate- IV[15]	> 60	30 mg*	Every 4 weeks	250ml Sodium Chloride 0.9% over 90 minutes[15]
	30-60	30 mg*		250ml Sodium Chloride 0.9% over 4 hours[16]
	<30		Only use in cases of life-threatening tumour-induced hypercalcaemia when the benefit outweighs the potential risk	
Denosumab (Xgeva)- SC	No modification required	120mg	Every 4 weeks (*note this is not routinely commissioned so individual funding must be sought)*	

Sodium clodronate is classified as an amber drug in the BNSSG formulary[17] therefore GP's may prescribe in accordance with the shared care protocol available at: http://www.bnssgformulary.nhs.uk/Shared-Care-Protocols/

*Pamidronate 90mg monthly is equivalent in efficacy to Zoledronic acid 4mg monthly. Pamidronate 30mg has been shown to be non-inferior to a standard 90 mg dose of pamidronate.[18]

7. ADVERSE EFFECTS

Adverse effects of bisphosphonate therapy may include osteonecrosis of the jaw (ONJ), atypical fractures of the femur, hypocalcaemia, headache, nausea, vomiting, decreased appetite, fever, flu-like syndrome (including fatigue, rigors, malaise and flushing) and electrolyte disturbances.

Refer to the individual drug's Summary of Product Characteristics for a full list of side effects, accessible via www.medicines.org.uk

Osteonecrosis of the jaw: The risks of ONJ in myeloma 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. See section 4 regarding dental examination and oral hygiene.

Continuation of a bone-targeting agent in the setting of ONJ has to be individualised and dependent on a risk-benefit ratio and the severity of bone disease.[5]

8. DRUG INTERACTIONS

Caution is advised when bisphosphonates are administered with aminoglycosides, calcitonin or loop diuretics since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required.

Caution is indicated with other potentially nephrotoxic drugs. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

Refer to the individual drug's Summary of Product Characteristics for a full list of drug interactions, accessible via www.medicines.org.uk

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RELATED DOCUMENTS

SAFETY Consult Summary of Product Characteristics, Network Protocol and/ or Trial protocol for dosing guidance, indications, contraindications, adverse effects and interactions.

QUERIES Contact Pharmacy extension 22349
Contact Lead Divisional Pharmacist Haematology & Oncology bleep 3329.

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