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 .

Calcium and vitamin D supplementation, dietary advice, weight-bearing exercise, minimisation of exposure and duration of corticosteroids and chemotherapy should also be considered in order to preserve bone.[1]

DURATION OF TREATMENT

There is currently no clear evidence to guide optimal duration of bisphosphonate therapy. The risks of osteonecrosis 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.

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]

Author(s) A Preston, Divisional Lead Pharmacist Haematology, Dr JM Bird, Consultant Haematologist, Dr J Griffin, Consultant Haematologist and Dr L Wolger, Consultant Haematologist.

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

Oral sodium clodronate is an acceptable alternative if zoledronic acid and pamidronate are contraindicated, not tolerated or not suitable. Examples might include:-

- patients with renal impairment (e.g.Creatinine clearance < 30ml/min)
- 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 (the NICE technology appraisal for preventing SREs in multiple myeloma was terminated due to no evidence submission from Amgen).

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
Vitamin D	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 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.

Guidance for dentists in primary care is included in *Oral Health Management of Patients Prescribed Bisphosphonates: Dental Clinical Guidance, Scottish Dental Clinical Effectiveness Programme* (available at www.sdcep.org.uk).[20]
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 and Vitamin D
Calcium and vitamin D supplementation is recommended for patients on zoledronic acid (unless hypercalcaemic) and for patients developing hypocalcemia on other bisphosphonates.

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.
Note Colecalciferol is contraindicated in severe renal impairment as it is ineffective. Alfacalcidol may be prescribed in severe renal impairment for patients under specialist care
https://remedy.bnssgccg.nhs.uk/media/3244/ssg-adult-vitamin-d-prescribing-guidance.pdf

Phosphate and Magnesium: Hypophosphataemia, or hypomagnesaemia may occur with bisphosphonate treatment. Check baseline levels and correct where appropriate. Magnesium supplementation guidelines available via on BBSSG formulary:-
https://remedy.bnssgccg.nhs.uk/media/3248/magnesium-supplementation-2015-v4.pdf
Phosphate supplementation advice available in BHOC Guideline- Management of Hypophosphatemia.

5. TESTS BEFORE EACH BISPHOSPHONATE INFUSION

Investigation	Validity period
Creatinine	14 days
Calcium	14 days
Phosphate	14 days
Magnesium	3 months
Vitamin 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]

7. DOSAGE, FREQUENCY AND ADMINISTRATION

Dose 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 impairment

Drug and route	CrCl (ml/min)	Dose	Frequency	Infusion fluid & time
Zoledronic acid -IV [12]	> 60	4.0 mg	Every 4 to 12 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	Administration information below
	10-30	520 mg OD		
	< 10	Contra-indicated		
Sodium clodronate (Bonefos®) - Oral [14]	50- 80	1600 mg OD	Continuous	Administration information below
	30-49	1200 mg OD		
	10-29	800 mg OD		
	< 10	Contra-indicated		
Disodium pamidronate-IV[15]	> 60	30 mg*	Every 4 to 12 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 dose modification required	120mg	Every 4 weeks	Subcutaneous injection into the thigh, abdomen or upper arm. Refer to product information before administering (link below).

* Denosumab (Xgeva®) is not routinely commissioned so individual funding must be sought. Product information can be found at https://www.medicines.org.uk/emc/product/4675/smpc

Sodium Clodronate- method of administration

The film-coated tablets may be taken as a single dose or in two equally divided doses if necessary to improve gastrointestinal tolerance.

The single daily dose and the first dose of two should preferably be taken in the morning on an empty stomach together with a glass of water. The patient should then refrain from eating, drinking (other than plain water), and taking any other oral drugs for one hour. Remain in upright position to prevent upper abdominal pain.

When twice daily dosing is used, the first dose should be taken as recommended above. The second dose should be taken between meals, more than two hours after and one hour before eating, drinking (other than plain water), or taking any other oral drugs.

Clodronate should in no case be taken with milk, food or drugs containing calcium or other divalent cations because they impair the absorption of clodronate.

The oral bioavailability of bisphosphonates is poor. Bioequivalence studies have shown appreciable differences in bioavailability between different oral formulations of clodronate disodium, as well as marked inter and intra patient variability. Dose adjustment may be required if the formulation is changed.

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:

https://remedy.bnssgccg.nhs.uk/media/3376/sodium-clodronate-myeloma-uhb-09.pdf

8. 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.

Orally administered, mainly nitrogen-containing, bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when clodronate disodium is given to patients with active upper gastrointestinal problems (e.g. known Barrett's oesophagus, dysphagia, other oesophageal diseases, gastritis, duodenitis or ulcers).

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%.Risk factors for developing ONJ that should be considered are: potency of bisphosphonate (highest for zoledronate), route of administration, cumulative dose, duration and type of malignant disease, concomitant treatment, smoking, comorbid conditions, and history of dental disease[19]. 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]

Osteonecrosis of the external auditory canal: Benign idiopathic osteonecrosis of the external

auditory canal has been reported very rarely with bisphosphonate treatment, mainly in patients receiving long-term therapy (2 years or longer). Consider if patients present with ear symptoms, including chronic ear infections, or suspected cholesteatoma.[19]

Risk factors for developing osteonecrosis of the external auditory canal include: steroid use, chemotherapy, infection, an ear operation, or cotton-bud use.

Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during treatment with a bisphosphonate.

9. 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

References

1. Snowden JA, Greenfield DM, Bird JM et al. Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. Br J Haematol. Jan 2017 [Epub ahead of print 10.1111/bjh.14514 available at http://onlinelibrary.wiley.com/doi/10.1111/bjh.14514/full].
2. Mhaskar R, Redzepovic J, Wheatley K. Bisphosphonates in multiple myeloma: a network meta- analysis. Cochrane Database Systematic Reviews. May 2012: 16; 5.
3. Morgan, G., Davies, F., Gregory, W., et al. Long-term follow-up of MRC Myeloma IX trial: survival outcomes with bisphosphonate and thalidomide treatment. Clinical Cancer Research 2013: 19; 6030–6038.
4. Snowden JA, Ahmedzai S, Ashcroft J, D'Sa S, Littlewood T, Low E, Lucraft H, Maclean R, Feyler S, Pratt G, Bird J. British Committee for Standards in Haematology in conjunction with the UK Myeloma Forum (UKMF). Guidelines for Supportive Care in Myeloma. Sept 2010.
5. Anderson K, Ismalail N, Flynn, P.J et al. Rose of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2018 Mar 10; 36 (8): 812-818.
6. Himelstein AL, Foster JC, Khatcheressian JL et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients with Bone Metastases: A Randomized Clinical Trial. JAMA 2017 Jan 3; 317(1):48-58.
7. Morgan GJ, Davies FE, Gregory WM, et al. National Cancer Research Institute Haematological Oncology Clinical Study Group. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet. 2010 Dec 11;376 (9757):1989-99.
8. National Institute for Health and Care Excellence Clinical Guideline 35. Myeloma: diagnosis and management. Feb 2016. Last updated Oct 2018. Available at https://www.nice.org.uk/guidance/ng35/chapter/Recommendations#preventing-and-managing-bone-disease
9. Chun-Jing Geng, Qian Liang, Jian-Hong Zhong et al. Ibandronate to treat skeletal-related events and bone pain in metastatic bone disease or multiple myeloma: a meta-analysis of

randomised clinical trials. BMJ Open: 5; 6 http://dx.doi.org/10.1136/bmjopen-2014-007258
10. Henry DH, Costa L, Goldwasser F et al. Randomized, doubleblind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011; 29: 1125–1132.
11. Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer 2012; 48: 3082–3092
12. Novartis. Summary of Product Characteristics [Internet]. Zometa 4mg/100ml Solution for Infusion (Zoledronic acid). Last revised 21st June 2016 [cited Feb 2017]. Available from URL: http://www.medicines.org.uk/emc/medicine/25058
13. Intrapharm. Summary of Product Characteristics [Internet]. Loron 520mg film-coated tablets (clodronate disodium). Last revised 13th Aug 2018 [cited July 2020]. Available from URL: http://www.medicines.org.uk/emc/medicine/26632
14. Bayer. Summary of Product Characteristics [Internet]. Bonefos 400mg capsules (sodium clodronate). Last revised 16th June 2016 [cited Feb 2017]. Available from URL: http://www.medicines.org.uk/emc/medicine/309
15. Wockhardt. Summary of Product Characteristics [Internet]. Disodium Pamidronate 15mg/ml Concentrate for Solution for Infusion (30mg strength). Last revised 5th Dec 2016 [cited Feb 2017]. Available from URL: http://www.medicines.org.uk/emc/medicine/32688
16. Bird JM, Owen RG, D'Sa S et al. on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH), UK Myeloma Forum. Guidelines for the Diagnosis and Management of Multiple Myeloma 2013 update of 2010 Guideline. Available at http://www.ukmf.org.uk/wp-content/uploads/2014/01/MYELOMA_GUIDELINE_updated_29_aug_RG_jzw_31-copy.pdf
17. The Bristol, North Somerset, & South Gloucestershire (BNSSG) Joint Formulary [Internet]. Available at URL: http://www.bnssgformulary.nhs.uk/
18. Gimsing P, Carlson K, Turesson I, et al. Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind randomised controlled trial. Lancet Oncol 2010 Oct; 11(10):973-82.
19. British National Formulary [Internet]. Available at URL: https://bnf.nice.org.uk/drug/zoledronic-acid.html#importantSafetyInformations
20. Oral Health Management of Patients Prescribed Bisphosphonates: Dental Clinical Guidance, Scottish Dental Clinical Effectiveness Programme, April 2011. Available at https://www.sdcep.org.uk/published-guidance/medication-related-osteonecrosis-of-the-jaw/

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 bleep 3329.

Author(s) A Preston, Divisional Lead Pharmacist Haematology, Dr JM Bird, Consultant Haematologist, Dr J Griffin, Consultant Haematologist and Dr L Wolger, Consultant Haematologist.