THE USE OF BISPHOSPHONATES AND DENOSUMAB FOR MALIGNANT BONE PAIN

MAY 2015
GUIDELINE DEVELOPMENT GROUP

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With special thanks to . . .

Invited Expert:

• Dr Susan O’Reilly

Consultant Medical Oncologist
Clatterbridge Cancer Centre
After discussion we agreed to focus the review of the existing standards and guidelines around the use of bisphosphonates and denosumab for the management of malignant bone pain.
The aims of these guidelines are:

• To provide guidelines concerning the indications, efficacy, and tolerability of bisphosphonates and denosumab in managing malignant bone pain.

• In patients with advanced cancer of age 18 years and over, known to specialist palliative care services.
OUR CLINICAL QUESTIONS

• In patients needing Specialist Palliative Care*(P), do Bisphosphonates (I) improve cancer related bone pain (O) compared with usual treatment* (C)?

• In patients needing Specialist Palliative Care* (P), does Denosumab (I) improve cancer related bone pain (O) compared with usual treatment* (C)?
LITERATURE SEARCH: BISPHOSPHONATES

Medline, EMBASE, CINAHL databases:

Search terms:

Pamidronate OR Zometa OR Zoledronic OR Pamidronate OR Bisphosphonates OR Diphosphonates AND “Bone Pain” OR “Musculoskeletal Pain” AND (Cancer OR Neoplasm) AND (“Palliative Care” OR “Hospice” OR “Terminal Care”)
LITERATURE SEARCH: DENOSUMAB

Medline, EMBASE, CINAHL databases:

Search terms:

Denosumab OR Xygeva
AND
“Bone Pain” OR “Musculoskeletal Pain”
AND
(Cancer OR Neoplasm)
LITERATURE REVIEW

- Cochrane database also searched
- Review of previously included references

Terms searched in ALL TEXT

**Date** – No limit – Current

**Limits** – English Language, Humans, Adults – 18 years or over
LITERATURE SEARCH: BISPHOSPHONATES

- 102 abstracts identified
- 95 abstracts reviewed after duplicates removed
- 22 articles identified

Articles excluded:

- 2 – not relevant to clinical question
- 0 – foreign language
- 0 – review articles
- 0 – could not obtain
- 6 – poor quality
- 0 – abstract only

- 14 relevant articles
LITERATURE SEARCH: DENOSUMAB

- 33 abstracts identified
- 30 abstracts reviewed after duplicates removed
- 2 articles identified

- Articles excluded: 0

- 2 relevant articles
<table>
<thead>
<tr>
<th>Study Name</th>
<th>Type of Study</th>
<th>Level of Evidence</th>
<th>Summary of Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety and pain palliation of zoledronic acid in patients with breast cancer, prostate cancer, or multiple myeloma who previously received bisphosphonate therapy. Vogel et al, Oncologist, 2004;9(6):687-95.</td>
<td>Single system/longitudinal</td>
<td>3</td>
<td>Pain scores reduced after treatment with Zoledronic Acid. Not RCT</td>
</tr>
</tbody>
</table>
IMPROVED QUALITY OF LIFE AFTER LONG-TERM TREATMENT WITH IBANDRONATE IN PATIENTS WITH METASTATIC BONE DISEASE DUE TO BREAST CANCER

DIEL ET AL, 2004

• Characteristics: multi-centre randomised, double-blind, placebo-controlled trial of 466 women with breast cancer

• Analysis: A number of quality of life measures were taken including pain score (1-4) and analgesic score.

• Outcome: 6mg Ibandronate group demonstrated a lower mean bone pain score at the last assessment compared to baseline. The mean change was significantly different to the placebo group (p<0.001). This suggested that Ibandronate had a beneficial effect on bone pain.

• Limitations: Dose was open label, high drop-out rate (insufficient patients to meet initial power calculations)
Effect of Zoledronic Acid on Pain Associated with Bone Metastasis in Patients with Prostate Cancer

Weinfurt KP et al, 2006

• Characteristics; multi-centre, randomised, double-blind, placebo controlled study. 422 patients with prostate cancer received Zoledronic Acid or placebo every 3 weeks for study duration

• Analysis; Proportion of cases in which a patient in Zoledronic Acid group had a more favourable pain response than a patient in placebo group. Patients pain was assessed with BPI at 11 points over a 60 week period

• Outcome; Over the duration of the trial a patient using Zoledronic Acid had a 33% chance of having a favourable response compared to placebo patient (p=0.036). Concluding that zoledronic acid may help to avert the pain experienced by patients with metastatic bone disease from prostate cancer

• Limitations; 90 day intervals between pain assessments, pain episodes may be missed. No reference to any other analgesia or interventions such as radiotherapy
• **Characteristics:** SR, 6915 patients included in pain analysis.

• **Analysis:** Systematic review- meta-analysis not possible due to heterogeneity of pain scoring methods. All included studies were controlled trials.

• **Outcome:** Statistically significant improvements in pain noted with: Zoledronic acid 4mg IV, Pamidronate 90mg IV, Ibandronate 6mg IV, Clodronate orally, Pamidronate orally and ibandronate 50mg orally. 2 studies comparing relative efficacy of different bisphosphonates demonstrated preference for IV formulations (either zoledronic acid or pamidronate).

• **Limitations:** Heterogeneity of pain assessment made meta-analysis impossible.
Characteristics: Systematic review, 1281 patients included in pain analysis.

Analysis: Systematic review with meta-analysis

Outcome: Statistically significant improvements in pain noted with bisphosphonates (group), RR 0.75 (95% CI 0.6-0.95) compared to placebo or no treatment.

Limitations: pain was a secondary analysis within this review. Large heterogeneity of studies. Sensitivity analysis showed that results lost significance for the blinded studies, whilst the non-blinded studies favoured bisphosphonates over placebo.
BISPHOSPHONATES FOR ADVANCED PROSTATE CANCER
COCHRANE SYSTEMATIC REVIEW.

- **Characteristics:** Systematic review, 1955 patients included in pain analysis.

- **Analysis:** Systematic review with meta-analysis

- **Outcome:** Non-statistically significant improvements in pain noted with bisphosphonates (group), OR 1.54, (95% CI 0.97 to 2.44, P = 0.07) compared to placebo or no treatment.

- **Limitations:** Heterogeneity of studies made combined analysis difficult.
BISPHOSPHONATES FOR THE RELIEF OF PAIN SECONDARY TO BONE METASTASES, COCHRANE SYSTEMATIC REVIEW, WONG RKS, WIFFEN PJ, 2002

- **Characteristics:** Systematic Review, 3682 subjects in 30 RCTs
- **Analysis:** Systematic Review with Meta-analysis
- **Outcome:** pooled results for the proportion of patients with pain relief at 12 weeks showed benefits for the treatment group OR 2.37 (95% CI 1.61-3.5) with NNT 6, NNH 16. Unable to recommend the most effective bisphosphonate
- **Limitations:** only limited data could be included in meta-analysis due to lack of consensus on pain endpoint reporting
LITERATURE REVIEW:
BISPHOSPHONATES

Dr Anthony Thompson
Dr Andrea Graham
A RCT TO COMPARE THE EFFICACY OF BISPHOSPHONATES IN THE MANAGEMENT OF PAINFUL BONE METASTASES, CHOUDHURY ET AL, I JOURNAL PALLIATIVE CARE, 2011;17(3);210-218

Characteristics: randomised controlled trail, prospective, single institution. No placebo, 256 patients with painful bone metastases

Analysis: Pain score 5+, all had radiotherapy, single or 5 fractions. Randomised to ZA 4mg, ibandronate 6mg, Pamidronate 90mg every 3-4 weeks. Assessed at 1,2,3, 6 months and every 6 months to end of trial

Outcome: No difference at 3 months or end of study, but pain scores less at 6 months only significant for ZA. No difference in opioid use in 3 arms, all had reduced hypercalcaemia events

Concluded 6 months of IV Bisphosphonate reduced painful bone metastases and less hypercalcemia too.
LITERATURE REVIEW: BISPHOSPHONATES

Dr Joanna Roberts
Dr Clare Horlick
## INCLUDED ARTICLES

<table>
<thead>
<tr>
<th>Study Name</th>
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<th>Level of Evidence</th>
<th>Summary of Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate treatment in patients with malignant osteolytic bone disease and pain: a prospective randomized double-blind trial. Koeberle et al, Supportive Care in Cancer, 1999; 7(1): 21-27.</td>
<td>RCT</td>
<td>1++</td>
<td>Reduction in bone pain at both 60mg and 90mg</td>
</tr>
</tbody>
</table>

- **Characteristics:** Single institution, prospective, randomised, double blind trial. 70 patients with advanced malignant bone disease were randomised to 60mg vs. 90mg of IV Pamidronate every 3 weeks for 6 cycles.

- **Analysis:** Pain parameters, analgesic consumption and performance status were assessed at baseline and throughout the study.

- **Outcome:** Significant reduction of pain intensity by 60% in 60mg group vs. 63% in 90mg group (no significant difference). Significant reduction in pain intensity after 2 infusions.

- **Limitations:** small trial, under powered trial, confounded by concomitant treatment with chemo/RXT

- **Characteristics:** Single-centre, open, randomised control trial. 81 patients randomised to oral Pamidronate and 80 control patients with breast cancer.

- **Analysis:** Assessed events of morbidity due to bone metastasis including occurrence of severe bone pain requiring RXT or surgery.

- **Outcome:** Event rates for bone pain in Pamidronate group were reduced by 30% compared to control (statistically significant). A dose dependent effect was also observed but came with risk of GI toxicity.

- **Limitations:** Study was not blinded, confounded by patients also receiving chemotherapy or hormone treatment.
LITERATURE REVIEW: DENOSUMAB

Dr Joanna Roberts
Dr Clare Horlick
CLINICAL BENEFIT IN PATIENTS WITH METASTATIC BONE DISEASE: RESULTS OF A PHASE 3 STUDY OF DENOSUMAB VERSUS ZOLEDRONIC ACID. VADHAN-RAJ ET AL, ANNALS OF ONCOLOGY, 2012; 23(12): 3045-3051.

• **Characteristics:** Multicentre, randomised, double-blind, double dummy phase 3 trial of 1776 patients with advanced cancer or multiple myeloma (excluding breast and prostate cancer)

• **Analysis:** Numerous outcome measures including analgesic use and patient reported pain severity and interference using BPI score at baseline and every 4 weeks

• **Outcome:** 2 point reduction in BPI in both Denosumab and Zoledronic acid with no significant difference. Denosumab delayed time to significant pain increase by 2 points in the BPI

• **Limitations:** High drop out rate with unclear reasons identified, breast and prostate cancer excluded
In general the articles examined were of reasonable quality, but there were issues regarding consistency of pain scores, allowable oncological treatment during trials, and correcting for analgesic use.

There is a good body of evidence for the effectiveness of bisphosphonates in reducing malignant bone pain.

The best quality evidence is for zoledronic acid, but no recommendations can be made regarding the superiority of one bisphosphonate over another.

There is also evidence that denosumab is effective for malignant bone pain, with a similar reduction in pain scores to zoledronic acid.
NICE RECOMMENDATIONS

NICE has recommended the use of Denosumab for the prevention of skeletal related events, including the management of malignant bone pain in adults with bone metastases from breast cancer and from solid tumours other than prostate if:

- bisphosphonates would otherwise be prescribed, and
- the manufacturer provides Denosumab with the discount agreed in the patient access scheme.

Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer.

Patients with bone metastases from solid tumour currently receiving Denosumab whose disease does not meet the above criteria can continue treatment until they and their clinician consider it appropriate to stop.
NICE COST EFFECTIVENESS RECOMMENDATIONS

• In people with breast cancer that has spread to the bone NICE has recommended denosumab because it works better, and because it works better, it is likely to cost the NHS less overall than other treatments available on the NHS.

• In people with cancer that has spread to the bone from solid tumours, except breast and prostate cancer, NICE recommended denosumab because it works better than bisphosphonates. Although it also costs more than other treatments, this was justified by the benefits it provided.

• In people with prostate cancer that has spread to the bone denosumab does not provide enough benefit to patients to justify its high cost so NICE did not recommend it.
AUDIT OF CURRENT PRACTICE

DR JENNY SMITH
HELEN THOMAS
BARBARA HUMPHRIES
LYNNE PARTINGTON
DATA COLLECTION

Period
• 19th January- 2nd March 2015

Collection Method
• Case Note Audit
• Evaluation of Professional Practice
• Disseminated to all SPCSGs
Patient and Carer Involvement:

WHAT DO PATIENTS NEED AND WANT?
USER INVOLVEMENT

• Project underway surveying patients receiving bisphosphonates for pain, about information they have received, and their preferences. (What, how, format)

• Patients also to be asked for their views on information already available (Drug company, Macmillan)
PROPOSED NEW STANDARDS AND GUIDELINES

DR CLARE HORLICK
GUIDELINES FOR THE USE OF BISPHOSPHONATES AND DENOSUMAB FOR MALIGNANT BONE PAIN

DR CLARE HORLICK
INTRODUCTION

• Metastatic bone disease is a relatively common site of disease in advanced cancer; affecting 75% of breast and prostate cancer patients with advanced disease, and 15-40% of patients with lung, colon and kidney cancers.\textsuperscript{1,2} Metastatic bone disease causes osteolysis and also abnormal bone formation. In addition there is a complex interaction between tumour related growth factors, and cytokine release which leads to osteoclast-mediated bone destruction and tumour growth.\textsuperscript{1}

• Metastatic bone disease causes significant morbidity and is associated with skeletal related events (SRE), including bone pain; which can have a significant impact on quality of life. As treatments for advanced cancer improve, patients are living longer with metastatic disease, including with associated bone pain. It is therefore important to identify effective long term treatments for metastatic bone pain.
• Treatment options include analgesics, radiotherapy, surgery and chemotherapy, as well bone-targeted therapies including bisphosphonates and denosumab.³

• Bisphosphonates are synthetic analogues of pyrophosphate, a natural regulator of bone metabolism found abundantly in bone matrix. They inhibit differentiation of osteoclast precursors and induce osteoclast apoptosis leading to a decrease in bone resorption. ⁴,⁵

• Zoledronic acid and disodium pamidronate are the most widely used bisphosphonates for the management of metastatic bone disease, including the management of bone pain. Ibandronic acid and sodium clodronate which are both available in oral and intravenous form are alternatives. ⁶,⁷
• Denosumab (XYGEVA) is also used for to manage problems related to metastatic bone disease, including bone pain. Denosumab is a human monoclonal antibody with a high affinity and specificity for human RANKL; it is given as a subcutaneous injection. Metastatic bone disease releases cytokines that enhance RANKL expression, therefore activating osteoclast-mediated bone destruction. Through inhibiting RANKL expression denosumab reduces osteoclast-mediated bone destruction, and associated SREs, including bone pain.¹

• The following guidance is an update of Guidelines for the Use of Bisphosphonates in the Management of Malignant Bone Pain originally developed in 2000, re—audited in 2008 and updated 2009. ⁸
ASSESSMENT AND MANAGEMENT OF BONE PAIN

- Treatment with opiates, NSAIDS and other adjuvant analgesics should be optimised before using bisphosphonates or denosumab to manage pain due to bone metastases. It should also be considered whether referral for radiotherapy or orthopaedic intervention is clinically appropriate. For further information, see ‘Guidelines for the Prevention of Pathological Fracture in Palliative Care’.

- Bisphosphonates (and where clinically appropriate denosumab), should be considered as an option for the management of bone pain due to metastatic disease. There is a large body of evidence that bisphosphonates are effective in treating pain from metastatic bone disease in patients with breast cancer, prostate cancer and multiple myeloma, as well as other solid tumours. Denosumab is also recommended as a treatment option for patients with painful bone metastases from breast and other solid tumours, however its use is not recommended for patients with prostate cancer.
BISPHOSPHONATES & DENOSUMAB IN MALIGNANT BONE PAIN

- There is evidence that both bisphosphonates and denosumab are effective in treating pain from bone metastases. Decisions to treat should be based on an individual assessment of each patient’s general medical condition, and expected survival time. 14
BISPHOSPHONATES

• In general bisphosphonates are recommended as a treatment option for malignant bone pain, after analgesics and other treatments have been optimised. However there is also evidence of the benefit of the earlier preventative use of bisphosphonates, particularly in breast cancer, prostate cancer and multiple myeloma in terms of delaying the onset of SREs, including the onset of bone pain. ³

• There is a large body of evidence to support the use of bisphosphonates as a treatment for bone pain related to skeletal metastases. However, it is not possible to recommend the superiority of one bisphosphonates over another in terms of reducing bone pain due to bone metastases. The evidence for the use of the most commonly prescribed bisphosphonates is therefore detailed below:
• For bisphosphonates the best quality evidence for effectiveness in reducing pain from bone metastases is for zoledronic acid versus control.\textsuperscript{4, 16} It has been shown in studies of zoledronic acid use that the maximum response in terms of reduced bone pain is likely to be observed by four weeks post-treatment. \textsuperscript{4}

• There is also evidence that disodium pamidronate is effective in reducing malignant bone pain given intravenously for a range of cancer types.\textsuperscript{17, 18} In a direct dosage comparison of the intravenous preparation there was no significant difference in reduction in bone pain between 60mg and 90mg infusions; although the 90mg group tended towards non-significant improvements in terms of reduced pain, but greater gastrointestinal toxicity.\textsuperscript{17} A lower dose of 60mg could therefore be considered in those patients who are unable to tolerate the recommended 90mg infusion dose. \textsuperscript{10}
Sodium clodronate is an alternative treatment option for bone pain in patients with breast cancer and multiple myeloma. Oral administration is often poorly tolerated; however it can also be given intravenously or subcutaneously. Ibandronic acid is currently only licensed for the management of bone metastases in patients with metastatic breast cancer; it can be administered orally or intravenously.

If effective, bisphosphonates infusions should be repeated at regular intervals; as described in Table 1 below. A patient who fails to respond to the first dose of a bisphosphonates in terms of a reduction in bone pain, should receive one further dose before being considered a non-responder. Patients treated with oral bisphosphonates who continue to experience bone pain, may benefit from a switch to an intravenous bisphosphonates. Continuation of treatment beyond two years should be based on an individual risk assessment.
DENOSUMAB

- There is evidence that denosumab is effective in terms of reducing pain from metastatic bone disease.\textsuperscript{3,7} In patients with solid tumours and multiple myeloma denosumab was found to lead to an equivalent significant reduction in pain scores as zoledronic acid. In a comparison of denosumab versus zoledronic acid although there was no difference in terms of analgesic efficacy, there was evidence of a delayed onset to the development of moderate to severe pain in those patients treated with denosumab, as well as a non-significant trend for reduced pain interference with activities of daily living. \textsuperscript{3,7}
• Although there is no clear evidence for the superiority of denosumab compared with bisphosphonates in managing pain due to metastatic bone disease, the use of denosumab does have potential advantages. This is particularly in terms of ease of administration via subcutaneous injection rather than intravenous infusion, and the better safety profile of denosumab in renal impairment. ³,¹⁹

• It may therefore be considered as an alternative option for the management of malignant bone pain, in those who are unable to tolerate bisphosphonates.
Table 1: Use of bisphosphonates and denosumab in the management of malignant bone pain. 4,6,7,19,20

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route of administration</th>
<th>Diluent</th>
<th>Rate of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic Acid</td>
<td>4mg</td>
<td>Intravenously</td>
<td>100ml sodium chloride 0.9% or dextrose 5%</td>
<td>15-30 minutes Repeat every 4 weeks</td>
</tr>
<tr>
<td>Disodium Pamidronate</td>
<td>60-90mg</td>
<td>Intravenously</td>
<td>250-500ml sodium chloride 0.9%</td>
<td>Rate not exceeding 1mg/minute Repeat every 4 weeks</td>
</tr>
<tr>
<td>Ibandronic Acid</td>
<td>6mg</td>
<td>Intravenously</td>
<td>100ml sodium chloride 0.9% or dextrose 5%</td>
<td>15 minutes Repeated every 4-6 weeks</td>
</tr>
<tr>
<td></td>
<td>50mg</td>
<td>Orally</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Sodium Clodronate</td>
<td>600mg-1500mg</td>
<td>Intravenously</td>
<td>500ml sodium chloride 0.9% or dextrose 5%</td>
<td>Depends on dose Range 2-4 hrs</td>
</tr>
<tr>
<td></td>
<td>1600mg</td>
<td>Orally</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Xygeva 120mg</td>
<td>Subcutaneously</td>
<td>N/A</td>
<td>Repeat every 4 weeks</td>
</tr>
</tbody>
</table>
COMMON SIDE EFFECTS OF TREATMENT: BISPHOSPHONATES

• Bisphosphonates are known to have a number of side effects, which prescribers should be aware of, and which should be discussed with patients. These include a ‘flare’ of bone pain and a rise in body temperature and accompanying flu-like symptoms that resembles a typical acute phase response.\(^6,19\)

• An increase in nausea has also been observed in those treated with bisphosphonates compared with placebo.\(^4,21\) This generally occurs after the first infusion and less frequently after following infusions.\(^20\)
RENAL IMPAIRMENT

- Renal toxicity can also be an associated problem with bisphosphonate use, and serum creatinine should be checked and hydration status assessed, prior to each treatment. The risk of renal impairment is directly related to drug infusion time and dosage. When using bisphosphonates for the treatment of bone pain, and where there is persistent renal deterioration but a need for treatment, it may be appropriate to consider either a dose reduction or a longer infusion time.

- The use of zoledronic acid, disodium pamidronate and sodium clodronate for the management of malignant bone pain is not recommended in patients with severe renal impairment (eGFR<30mls/min). For further information please see Table 2 below and ‘The Renal Handbook’. 

6,10
<table>
<thead>
<tr>
<th>eGFR (mls/min)</th>
<th>Zoledronic Acid</th>
<th>Disodium Pamidronate</th>
<th>Intravenous Ibandronic Acid</th>
<th>Oral Ibandronic Acid</th>
<th>Intravenous Sodium Clodronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>4mg</td>
<td>60-90mg over 4-6 hours</td>
<td>6mg over 15 minutes</td>
<td>50mg daily</td>
<td>600-1500mg</td>
</tr>
<tr>
<td>50-60</td>
<td>3.5mg</td>
<td>60-90mg over 4-6 hours</td>
<td>6mg over 1 hour</td>
<td>50mg daily</td>
<td>25% dose reduction recommended</td>
</tr>
<tr>
<td>40-49</td>
<td>3.3mg</td>
<td>60-90mg over 4-6 hours</td>
<td>4mg over 1 hour</td>
<td>50mg daily</td>
<td>25-50% dose reduction recommended</td>
</tr>
<tr>
<td>30-39</td>
<td>3mg</td>
<td>60-90mg over 4-6 hours</td>
<td>4mg over 1 hour</td>
<td>50mg daily</td>
<td>25-50% dose reduction recommended</td>
</tr>
<tr>
<td>&lt;30</td>
<td><em>Not recommended for use for malignant bone pain</em></td>
<td>2mg over 1 hour PCF</td>
<td>50mg weekly</td>
<td><em>Not recommended for use for malignant bone pain</em></td>
<td></td>
</tr>
</tbody>
</table>
ELECTROLYTE IMBALANCE

• Serum calcium should also be checked prior to each infusion as hypocalcaemia is a well recognised complication of bisphosphonates treatment. Often hypocalcaemia co-exists with other biochemical abnormalities, including renal impairment and hypomagnesaemia. 6 Patients treated with zoledronic acid and disodium pamidronate should be prescribed oral calcium supplements 500mg daily and vitamin D 400IU daily, unless there is co-existing Hypercalcaemia. 4, 6, 19

• For patients receiving Ibandronic Acid or Sodium Clodronate, calcium and vitamin D supplements should also be considered, and any pre-existing hypocalcaemia should be corrected. 19

• For information regarding the use of bisphosphonates to manage Hypercalcaemia see ‘Guidelines for the Treatment of Cancer related Hypercalcaemia’.
OSTEONECROSIS OF THE JAW

• Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates. Clinical features include exposed bone in the maxillofacial area, which occurs in association with dental surgery or can appear spontaneously, with no evidence of healing. 6,23 A working diagnosis is made when there is no evidence of healing after 6 weeks of appropriate evaluation and dental care, and no evidence of metastatic bone disease in the jaw or osteoradionecrosis. 23

• Where clinically appropriate, patients should have a dental examination and any dental treatment required before starting bisphosphonates treatment. Patients should be educated regarding the importance of good oral hygiene to reduce the risk of dental infection and periodontal infections. Patients receiving bisphosphonates and who have dental problems other than ONJ should receive the least invasive dental treatment. 4,6,19,23
• Written information regarding bisphosphonates therapy and preventative measures for ONJ should be made available to patients. 10

• Length of exposure to bisphosphonates is strongly associated with development of ONJ. It is extremely rare for patients receiving less than 12 treatments to develop ONJ. Therefore if a patient has a poor prognosis and it is anticipated that they are only going to receive a few infusions for bone pain, dental checks may not be essential or appropriate. 23

• In patients who develop ONJ whilst receiving bisphosphonates, the decision to stop or continue treatment should be made on an individual patient basis. Cessation of bisphosphonates treatment may not have an effect on established osteonecrosis. Referral to the local dental hospital, an oral surgeon or dental oncologist should be considered and invasive dental procedures should be avoided if possible. 20,23
DENOSUMAB

• Denosumab has a similar side effect profile to the bisphosphonates, although unlike the bisphosphonates, does not impair renal function. No dose adjustment is therefore needed in patients with renal impairment, including in those with an eGFR <30ml/min. Closer monitoring of electrolytes is however required, as described below.19

• Similarly to the bisphosphonates, denosumab is also associated with a risk of developing hypocalcaemia; this risk increases with increasing renal impairment. Hypocalcaemia most commonly occurs in the first few weeks of treatment, but it can also occur later. Serum calcium should therefore be checked before the first dose and within two weeks of the initial dose. It may be appropriate to monitor some patients more frequently in patients with severe renal impairment (eGFR<30mls/min). To prevent hypocalcaemia calcium 500mg supplements and vitamin D 400IU daily should also be prescribed, unless there is co-existing hypercalcaemia.19
• Denosumab is also associated with a risk of developing ONJ, the same precautions as for patients receiving bisphosphonates should be followed. This includes a dental examination and appropriate preventative dentistry prior to starting treatment. \(^{19}\)

• Written information regarding denosumab treatment and preventative measures for ONJ should be made available to patients.\(^{10}\)
STANDARDS

1. It should be documented that treatment with opiates and NSAIDs adjuvant analgesics has been optimised before using bisphosphonates for malignant bone pain. 4,10 [Grade D]

2. The decision to use bisphosphonates or denosumab for the management of malignant bone pain should be clearly documented in the case notes, including the dose and rate to be prescribed. 10 [Grade D]

3. Subsequent infusions of the bisphosphonate should be given as per the recommended regimen for each drug.

4. A patient who fails to respond to the first dose of a bisphosphonate given for the treatment of malignant bone pain, should, if clinically appropriate, receive one further dose two consecutive doses at a 4 weekly interval before being considered a non-responder. 4,10,12 [Grade B]
STANDARDS

5. The serum creatinine and adjusted calcium should be checked prior to each bisphosphonate infusion.\(^6,^{19,20}\) [Grade B]

6. Patients prescribed \textit{zoledronic acid bisphosphonates} or \textit{denosumab} should be prescribed calcium and vitamin D supplements, unless contraindicated.\(^6,^{10,19}\) [Grade D]

7. Verbal information should be given to all patients regarding the use of bisphosphonates and denosumab for malignant bone pain, and their potential adverse effects; this should be documented in the case notes.\(^{10}\) [Grade D]

8. Written patient information regarding bisphosphonates and denosumab and their potential adverse effects should be \textit{available provided}.\(^{10}\) [Grade D]
REFERENCES


4. Wong RKS, Wiffen PPJ, Bisphosphonates for pain secondary to bone metastases Cochrane Database of Systematic Reviews, 2002.


DISCUSSION POINTS

Should we include oral and intravenous bisphosphonates in this guidance?

Should we include denosumab in these guidelines?

To what extent should we recommend the use of denosumab?
THANK YOU