Medication-related osteonecrosis of the jaw

Guidance for the oncology multidisciplinary team

Report of a working party on behalf of the UK Chemotherapy Board

December 2019
About the UK Chemotherapy Board

The UK Chemotherapy Board is the national overarching body which provides guidance, oversight and support for the continuing development of chemotherapy (SACT – systemic anticancer therapy) services in the UK. Its core membership comprises representatives of the Association of Cancer Physicians (ACP), the Royal College of Radiologists (RCR), the Royal College of Physicians (RCP), the Royal College of Pathologists (RCPath), the British Oncology Pharmacy Association (BOPA) and the UK Oncology Nursing Society (UKONS). The Board also has representation from the four UK nations and from other organisations closely involved in chemotherapy services.

About this guidance

This guidance has been produced by a multidisciplinary working party on behalf of the UK Chemotherapy Board (see appendix 1) which includes specialist representation from medical, dental and nursing teams across the UK. It has been endorsed by the Clinical Standards Committee of the Faculty of Dental Surgery of the Royal College of Surgeons of England.

Scope of guidance

It is common practice in oncology to prescribe bone-modifying agents (BMAs) or anti-angiogenic drugs (AADs) for a range of cancers. The association of these drugs in medication-related osteonecrosis of the jaw (MRONJ) has led to a wealth of published guidance. However, much of this guidance is focused and weighted towards the dental specialty with minimal information to assist oncologists. As regular prescribers of these medications, it is essential that appropriate information in both preventing and managing MRONJ is available for responsible treatment planning. Hence, this guidance has been assembled to aid oncologists and the wider team in understanding the condition and subsequently provide optimum clinical care. The guidance will aid all stakeholders within an oncology directorate. In addition, it will provide a source of information for trainees at all levels.

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Disclaimer

The information contained in this guidance is a consensus of the development and consultation groups’ views on current treatment. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance process. Care has been taken in the preparation of the information contained in the guidance. Nevertheless, any person seeking to consult the guidance, apply its recommendations or use its content is expected to use independent, personal medical and/or clinical judgement in the context of the individual clinical circumstances, or to seek out the supervision of a qualified clinician. The group makes no representation or guarantee of any kind whatsoever regarding the guidance content or its use or application and disclaim any responsibility for its use or application in any way.
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1. Introduction

This guidance focuses on all aspects of medication-related osteonecrosis of the jaw (MRONJ) in relation to oncology patients. It aims to fulfil three functions:

- Primarily, it is a single source of collective information for oncology teams focused around the prevention and management of MRONJ.
- Secondly, it proposes protocols that oncology departments can adapt and amend accordingly to fit local delivery of services.
- Thirdly, it provides a series of simple communication adjuncts that can be adapted to assist communication between the oncology multidisciplinary team, patients, dental practitioners and hospital dental specialists.

Collaboration between the cancer care team, dentists and dental specialists is repeatedly emphasised and encouraged throughout the guidance.

Definition of MRONJ

MRONJ is defined as exposed bone, or bone that can be probed through an intraoral or extraoral fistula, in the maxillofacial region that has persisted for more than 8 weeks in patients with a history of treatment with antiresorptive or anti-angiogenic drugs, and where there has been no history of radiation therapy to the jaw or no obvious metastatic disease to the jaws (Ruggiero et al 2014).

Indications for bone-modifying agents (BMAs)

- Patients with breast cancer in the adjuvant setting to reduce the risk of bone metastases
- Patients with metastatic bone disease
- Myeloma
- Treatment of hypercalcaemia of malignancy

Types of BMA

- Intravenous bisphosphonates – zoledronic acid/ibandronic acid/pamidronate
- Oral bisphosphonates – clodronate/ibandronic acid
- RANKL antibody – denosumab
Table 1: Medications that can cause MRONJ

<table>
<thead>
<tr>
<th>Medications associated with MRONJ arranged by type of drug</th>
<th>Tyrosine kinase inhibitors</th>
<th>Immunosuppressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Sunitinib</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Cabozantinib</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Imatinib</td>
<td>Thalidomide</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Sorafenib</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Ibandronic acid</td>
<td>Regorafenib</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Axitinib</td>
<td>Ipilimumab</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>Infliximab</td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td>Romosozumab</td>
</tr>
<tr>
<td>Selective estrogen modulator receptors (SERM)</td>
<td>Bevacizumab</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Denosumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fusion proteins</td>
<td></td>
</tr>
<tr>
<td>Radiopharmaceuticals</td>
<td>Aflibercept</td>
<td></td>
</tr>
<tr>
<td>Radium 223</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Incidence**

The risk of MRONJ is present in all patients treated with either BMAs or AADs (anti-angiogenic drugs) but varies between differing regimens for metastatic and non-metastatic cancer. The current guidance reflects the incidence in oncology patients only. It is beyond the scope of this document to explore MRONJ incidence in the non-neoplastic setting. It should be noted that previous use of BMAs eg in osteoporosis, may increase the risk of MRONJ.

**MRONJ in the metastatic setting**

Systematic and meta-analyses have reported MRONJ in the metastatic setting in relation to BMAs medication to range from 0–12% (Lee et al 2014; Khan et al 2015; Kuhl et al 2012; Qi et al 2014). The risk of MRONJ is increased by various risk factors which include type of agent, duration of treatment, total cumulative dose and dental intervention – particularly extraction. The overall risk of MRONJ for patients exposed to zoledronic acid is approximately 1% (Mauri et al 2009; Coleman et al 2011; Scagliotti et al 2012; Qi et al 2014; Ruggiero et al 2014; SDCEP 2017; Yarom et al 2019). In cancer patients exposed to denosumab, the risk of MRONJ ranges from 0.7%–1.9% (Scagliotti et al 2012; Qi et al 2014; Ruggiero et al 2014; Yarom et al 2019).

The risk for MRONJ in cancer patients exposed to bevacizumab is 0.2%. The risk may be higher among patients exposed to both bevacizumab and zoledronic acid, reported as 0.9% (90 cases per 10,000) (Guarneri et al 2010; Ruggiero et al 2014). No incidence for the various other drugs implicated in MRONJ can be determined suggesting the overall rate to be extremely low and generally rare.
MRONJ in the adjuvant setting

The frequency of MRONJ from oral bisphosphonates in the early breast cancer setting is 0.06% to 0.7% of the bisphosphonate-exposed patient population. This is a higher frequency to that documented in the osteoporosis population (0.004%, Lo et al 2010) and highlights that oncology patients are deemed to have an elevated risk (Patel et al 2018).

The potential for MRONJ in early breast cancer studies notably increases when intravenous zoledronic acid is used with reported frequencies of up to 1.5% of patients (Paterson et al 2012; Coleman et al 2013; von Minckwitz et al 2013; Rathbone et al 2013; Gnant et al 2015; Gralow et al 2015; Patel et al 2018). Similar to the MRONJ risk from bisphosphonate use in metastatic cancer and osteoporosis, the risk with adjuvant zoledronic acid appears to increase with both treatment duration (3 years versus 5 years) and dose intensity (cumulative doses of 28 mg to 76 mg) (Paterson et al 2012; Coleman et al 2013; von Minckwitz et al 2013; Rathbone et al 2013; Gnant et al 2015; Gralow et al 2015; Patel et al 2018).
2. Guidelines

a. Pre-treatment: adjuvant and metastatic cancer

Adjuvant bisphosphonates (breast only)

All patients who are identified as requiring adjuvant bisphosphonates should have the following:

1. Dental alert card (for patient, appendix 3A)
2. Dental check-up (letter to primary dental practitioner, appendix 3B, with option for a formal reply, appendix 3C)
3. Pre-treatment baseline bloods including creatinine, calcium and vitamin D
4. Patient information sheet listing common side effects (see Macmillan and Cancer Research UK (CRUK) section 5a) and highlighting MRONJ and spontaneous fractures
5. Informed consent to treatment (see CRUK regimen-specific consent forms, section 5b)

Bisphosphonates/denosumab in the metastatic setting

6. Dental alert card (for patient, appendix 3A)
7. Consider dental check-up with hospital specialist (oral/maxillofacial/specialist dental surgeon (trust referral, appendix 3D), with option for formal reply (appendix 3E)
8. Pre-treatment baseline bloods including creatinine, calcium and vitamin D
9. Patient information sheet listing common side effects (see Macmillan/CRUK) and highlighting MRONJ and spontaneous fractures
10. Informed consent to treatment (see CRUK regimen-specific consent forms, section 5b)

Dental review

All patients should have dental review prior to starting bisphosphonates or denosumab. Dental treatment prior to starting medication may involve:

- extraction of teeth with a poor prognosis
- remedial dental work
- minimisation of periodontal disease
- improve/replace poor dentures
- high fluoride toothpaste for those at risk of caries
- advice on brushing, interdental cleaning, mouthwash, diet, smoking.

All invasive dental work such as extractions or oral surgery should have completely healed before initiating therapy, and a minimum of 4 weeks after a dental procedure that exposes or manipulates bone. Each case has to be considered individually as there will be some cases where cancer therapy can be delayed slightly and others where it is more urgent. A risk–benefit analysis therefore needs to be made.

It may be necessary to initiate bisphosphonate or denosumab therapy in a patient with metastatic disease presenting with hypercalcaemia as an emergency, in which case the dental check-up must be done promptly after stabilisation.
Vitamin D/calcium

1. Some units give a single dose of 100,000 units of colecalciferol orally 2 weeks prior to starting treatment to reduce the risk of profound hypocalcaemia.

2. Vitamin D deficiency. Adults who are vitamin D deficient can be treated with 50,000 IU of vitamin D2 or vitamin D3 (colecalciferol) once a week for 6 weeks (total 300,000 IU), or equivalent daily dose 7,000 IU for 8–12 weeks. This should be followed by maintenance therapy of 1,500–2,000 IU/day.

3. Calcium and vitamin D supplementation should be continued throughout adjuvant therapy with the equivalent of 1,000 mg of calcium daily and 800 IU of vitamin D – AdCal D3 forte twice daily or the equivalent. This should also be used in the metastatic setting but is contraindicated in the presence of hypercalcaemia.

Table 2: Renal function

<p>| 1. Zoledronic acid – calculate dose based on creatinine clearance (CrCl) |</p>
<table>
<thead>
<tr>
<th>Baseline CrCl</th>
<th>Dose of zoledronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 60 ml/min</td>
<td>4 mg</td>
</tr>
<tr>
<td>50–60 ml/min</td>
<td>3.5 mg</td>
</tr>
<tr>
<td>40–49 ml/min</td>
<td>3.3 mg</td>
</tr>
<tr>
<td>30–39 ml/min</td>
<td>3 mg</td>
</tr>
<tr>
<td>&lt;30 ml/min</td>
<td>Not recommended</td>
</tr>
<tr>
<td>For metastatic breast patients consider denosumab</td>
<td></td>
</tr>
</tbody>
</table>

<p>| 2. Sodium clodronate |</p>
<table>
<thead>
<tr>
<th>Baseline CrCl</th>
<th>Dose of sodium clodronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 ml/min</td>
<td>1,600 mg daily</td>
</tr>
<tr>
<td>30–49 ml/min</td>
<td>1,200 mg daily</td>
</tr>
<tr>
<td>10–29 ml/min</td>
<td>800 mg daily</td>
</tr>
<tr>
<td>&lt;10 ml/min</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

<p>| 3. Ibandronic acid |</p>
<table>
<thead>
<tr>
<th>CrCl (renal clearance is linearly related to CrCl)</th>
<th>Dose of ibandronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30 ml/min</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>&lt;30 ml/min</td>
<td>Ibandronic acid not recommended</td>
</tr>
<tr>
<td>For patients with metastatic breast cancer consider denosumab</td>
<td></td>
</tr>
</tbody>
</table>

| 4. Denosumab |
| No dose reduction necessary for renal dysfunction. |
b. During treatment

It is important to assess patients’ oral health at every clinic appointment once they have commenced treatment with denosumab or bisphosphonates. This guidance applies to all patients whether on adjuvant treatment or for metastatic disease.

Patients are advised to see their primary dental practitioner at least every 6 months.

It is good practice to continue to educate patients on how to decrease the risks of MRONJ including the following:

- Promote good oral hygiene: regular dental check-ups (at least twice a year). Clean teeth at least twice a day.
- Reduce frequency of sugary drinks and snacks and reduce alcohol intake.
- Encourage patients to inform their doctor or dentist immediately if they experience any problems with their mouth and teeth.
- For preventative care and dietary advice involve support from the hygienist and dietitian to reduce risk of oral disease (RCS 2018).

During clinic appointments check for symptoms and ask the patient about any dental problems they may be experiencing including: pain, swelling and numbness in the mouth, offensive odour, loose teeth and ulcers. If the patient has developed any of these symptoms it is recommended that they are urgently referred to the oral/maxillofacial/specialist dental surgeon.

The decision to cease or suspend antiresorptive medication should be made in conjunction with both the dental specialist and oncologist.

Also consider referral to a dietitian and speech and language therapy team (SALT) if there are concerns about managing nutrition for a patient with suspected or confirmed MRONJ.

MRONJ should be treated as an adverse drug reaction by the patient’s healthcare team, including hospital doctor, primary dental practitioner and GP. Suspected adverse drug reactions should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) using the Yellow Card Scheme. There are many ways to report a Yellow Card (see section 5d).

c. Post treatment

For patients receiving adjuvant treatment the following is recommended:

- continue to have regular dental check-ups
- report any symptoms of MRONJ
- remain vigilant.

d. Established MRONJ

The most common dental intervention leading to MRONJ is dental extraction.

It is important to acknowledge that MRONJ is an adverse effect of treatment with BMAs and AADs and although invasive dental treatment is a risk factor, it does not cause the disease (SDCEP 2017).
A recent systematic review estimated the incidence of MRONJ after tooth extraction in oncology patients as 2.9% (Gaudin et al. 2015). Several studies report that among patients with MRONJ, tooth extraction is a common predisposing event ranging from 52 to 61% (Fehm et al. 2009; Vahtsevanos et al. 2009; Saad et al. 2012). However, MRONJ can occur ‘spontaneously’ without the patient having undergone any recent invasive dental treatment.

Dental implant treatment in patients who have had parenteral BMAs is less well understood. Their provision following commencement of BMAs and AADs in the metastatic setting is contraindicated. There is no direct guidance for their use in the adjuvant setting. Dental guidance (Ruggiero et al. 2014; SDCEP 2017) suggests caution in patients in the low risk category of MRONJ.

**Duration of BMAs**

The risk of MRONJ is thought to increase with cumulative doses, particularly with bisphosphonates, due to their long half-life. In contrast, denosumab has a 6-month washout period, although in a metastatic setting cessation of the drug for this period of time may not be clinically appropriate.

Among cancer patients exposed to zoledronic acid or denosumab, the incidence of developing MRONJ was, respectively, 0.6% and 0.5% at 1 year, 0.9% and 1.1% at 2 years, and 1.3% and 1.1% at 3 years, with the risk for MRONJ among denosumab-exposed subjects plateauing between years 2 and 3 (Henry et al. 2011).

**Concurrent medications**

Many of the concurrent medications implicated in increasing the risk of MRONJ have also been reported to cause this complication (section 1, table 1). There is conflicting evidence for the role of corticosteroids in increasing the risk of MRONJ (Lazarovici et al. 2009; Kos et al. 2010; Saad et al. 2012).

**Presentation of MRONJ**

MRONJ can occur spontaneously but commonly invasive dental intervention is often implicated as the main causative factor. Symptoms can include pain, facial cellulitis, infection, offensive odour, swelling and altered sensation of nerve distribution. Clinical examination often reveals exposed jaw bone but this is not always necessary for a diagnosis of MRONJ.

**Classification of MRONJ**

There are various classifications proposed for MRONJ, however, the AAOMS 2014 (Ruggiero et al. 2014) remains the most widely used and accepted. An adapted version based on the readership is present below with corresponding recommended management (table 3).

**Treatment of MRONJ**

The presence of established MRONJ can be debilitating and impact on basic oral functions. To date, no treatment strategies have guaranteed cure. The primary treatment is focused towards symptom management. In general surgery is avoided.

Where traumatic or loose sequestration occurs, or if symptoms fail to resolve with conservative approaches, surgery may need to be considered in exceptional circumstances. In extensive and severe MRONJ cases treatment is via vascularised free tissue transfer.
The oral/maxillofacial/specialist dentist team should endeavour to build a strong line of communication with the oncology team. This allows both specialties to optimally manage the patient for the best outcome.

Table 3: AAOMS 2014 MRONJ classification *(adapted)*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of exposed/necrotic bone. Clinical or radiographic features suggestive of MRONJ</td>
<td>Systemic management, including the use of pain medication and antibiotics</td>
</tr>
</tbody>
</table>
| 1     | Asymptomatic exposed and necrotic dento-alveolar bone with no associated infection | Antibacterial mouth rinse  
Clinical follow-up on a quarterly basis  
Patient education and review of indications for continued BMA or AA therapy |
| 2     | Symptomatic exposed and necrotic dento-alveolar bone with associated infection | Symptomatic treatment with oral antibiotics  
Oral antibacterial mouth rinse  
Pain control  
Debridement to relieve soft tissue irritation and infection control |
| 3     | Exposed and necrotic bone leading to invasion of vital structures, fractured jaw or extraoral fistula | Antibacterial mouth rinse  
Antibiotic therapy and pain control  
Surgical debridement/resection for longer term palliation of infection and pain |

Continuation of BMAs in the presence of MRONJ

For patients who are diagnosed with MRONJ while being treated with BMAs, there is insufficient evidence to support or refute the discontinuation of the BMAs. Administration of the BMA may be deferred at the discretion of the treating physician, in conjunction with discussion with the patient and the oral health provider (Yarom et al 2019). Denosumab has a shorter half-life than bisphosphonates.
3. Pathways

These pathways have been devised to facilitate the management of the patient in the following settings:

a. Pre-treatment: adjuvant and metastatic cancer (appendix 2A)

All oncology patients who are started on medications associated with MRONJ (this includes the bone-modifying agents denosumab and bisphosphonates and anti-angiogenic drugs) should have a full dental assessment and extraction of teeth with a poor prognosis prior to starting treatment. This aims to reduce the risk of MRONJ.

b. Dental pathway on treatment (appendix 2B)

All oncology patients who are being treated with medications which are associated with a risk of MRONJ require prompt and appropriate management of dental symptoms. However other dental problems may arise and if there appears an obvious cause of dental pain (for example a broken tooth or cavity) then it is reasonable for primary dental practitioners to assess patients in the first instance. Suspected MRONJ should be managed by specialist dental services.

c. Established MRONJ (appendix 2C)

All oncology patients who are being treated with medications which are associated with a risk of MRONJ require prompt and appropriate management of dental symptoms.

MRONJ is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region, present for more than 8 weeks in patients with a history of treatment with medications related to MRONJ.

Any unexplained dental symptoms or symptoms suggestive of MRONJ should be referred for specialist assessment.

These pathways are available to download and for trusts to add local information.
4. Communication aids

The following communication aids have been developed to be downloaded and for trusts to add local information as required. These are also available separately as downloadable editable PDFs.

a. Dental alert card for patients (appendix 3A)

This card can be given to the patient and/or carer when the concept of denosumab/bisphosphonates is first introduced, or at any stage of the patient pathway. The card acts as a reminder to alert the dental practitioner that the patient is taking these drugs, to have regular check-ups, and not to restart this type of medication if they have had recent dental work which exposes or manipulates bone.

b. Letter to primary dental practitioner (appendix 3B)

This letter should be given to the patient to give to their dental practitioner as a referral to carry out work prior to starting denosumab/bisphosphonates.

c. Reply from primary dental practitioner (appendix 3C)

This pro forma can be attached to the letter for the primary dental practitioner to confirm that they have made an assessment for this patient prior to starting denosumab/bisphosphonates. The reply indicates whether dental work is required and also whether referral to the oral/maxillofacial/specialist dental surgeon is advised.

d. Trust referral to oral/maxillofacial/specialist dental surgeon (appendix 3D)

This referral can be through an electronic patient record (EPR) or paper-based referral system.

e. Reply from oral/maxillofacial/specialist dental surgeon (appendix 3E)

This can be paper-based and given to the patient to give to the oral/maxillofacial/specialist dental surgeon to complete, or through an electronic system.

f. Prompts for pre-treatment consultation (appendix 3F)

These can be used as stickers or as electronic prompts at the time of first prescribing denosumab/bisphosphonates.

g. Stickers for handheld records/cancer treatment record/hospital notes (appendix 3F)

These stickers can be used to put on the patient’s handheld records and the patient’s notes as required to act as a reminder for the patient and hospital staff that the patient is taking denosumab/bisphosphonates. They can also be used as electronic prompts on electronic prescribing system.
5. Useful links and further reading

a. Patient information
   - Macmillan Cancer Support (2019): Zoledronic acid patient information
   - Cancer Research UK: Zoledronic acid treatment
   - Macmillan Cancer Support: Denosumab therapy

b. Regimen-specific consent forms
   - Cancer Research UK: Denosumab
   - Cancer Research UK: Zoledronic acid

c. Guidance and references
   - MHRA. Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk. MHRA Drug Safety Update Denosumab Bisphosphonates. Published 20 July 2015.

d. MHRA reporting
   - online at www.mhra.gov.uk/yellowcard
   - via the Yellow Card app available in the Apple App Store or Google Play Store
   - through SystmOne, Vision, and MiDatabank clinical IT systems
   - by emailing yellowcard@mhra.gov.uk or by downloading printable forms from the Yellow Card website and sending them freepost to ‘Yellow Card’
   - by completing Yellow Card forms in the BNF, NPF, MIMS, or PAGB OTC directory
   - by calling the Yellow Card reporting line on 0800 731 6789 (10am to 2pm Monday–Friday).

Healthcare professionals and patients can also report Yellow Cards for all medicines, medical device adverse incidents, defective medicines, counterfeit or fake medicines or medical devices, and safety concerns with e-cigarettes or their refill containers on the Yellow Card website.
6. References


Appendix 1: Members of the working party

- Samreen Ahmed, professor of medical oncology, Leicester Royal Infirmary
- Kazumi Chia, specialty trainee in clinical oncology, London/Kent, Surrey and Sussex
- Alison Clayton, consultant medical oncologist, Belfast City Hospital, Northern Ireland
- Sharmistha Ghosh, associate specialist in medical oncology, Guy’s and St Thomas’ NHS Foundation Trust, London
- Jennifer Kahan, specialty trainee in clinical oncology, South West Wales Cancer Centre
- Janine Mansi, consultant medical oncologist, Guy’s and St Thomas’ NHS Foundation Trust, London
- Karen McAdam, consultant medical oncologist, North West Anglia NHS Foundation Trust
- Alasdair McKechnie, honorary consultant oral and maxillofacial surgeon, University of Leeds
- Lara Mitchell, metastatic bone disease specialist nurse, Leicester Royal Infirmary
- Vinod Patel, consultant oral surgeon, Guy’s and St Thomas’ NHS Foundation Trust, London
- Norma Sidek, consultant clinical oncologist, Beatson Cancer Centre, Scotland
- Nikki Tanna, consultant oral surgeon, University College Hospital NHS Foundation Trust, London
Appendix 2: Pathways

Appendix 2A: Dental health for oncology patients prior to starting treatment associated with MRONJ

All oncology patients who are started on medications associated with MRONJ (this includes the bone-modifying agents denosumab and bisphosphonates and anti-angiogenic drugs) should have a full dental assessment and management of pre-existing dental disease prior to starting treatment. This aims to reduce the risk of MRONJ.

Patient to be treated with medication associated with osteonecrosis of the jaw.

Provide patient with:
> Patient information leaflet on drug
> Dental alert card
> Letter to primary dental practitioner requesting full dental check-up and management

Patient attends own primary dental practitioner. Full dental check-up and management including extractions prior to commencing treatment.

If patient does not have usual primary dentist they will need to register with a practice. Online NHS Dental Service Finder will list possible dentists in the local area.

Full dental check-up and management including extractions prior to commencing treatment.

If extractions occur wait 4 weeks before commencing treatment. Any dental issues should be referred to primary dental practitioner or, if there is concern regarding MRONJ, specialist dental services. See appendix 3B and 3D

Informed consent to oncological treatment including risk of MRONJ.

At each treatment appointment chemotherapy nurses should:
> ensure pre-treatment dental check was completed
> monitor and report any dental concerns
> ensure regular dental follow-up.

Regular dental check-up every 6 months or more frequently if required.
Appendix 2B: Management of dental pain in oncology patients at risk of MRONJ

All oncology patients who are being treated with medications which are associated with a risk of MRONJ require prompt and appropriate management of dental symptoms.

MRONJ is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region, present for more than 8 weeks in patients with a history of treatment with medications related to MRONJ.

However other dental problems may arise and if there appears an obvious cause of dental pain (for example a broken tooth or cavity) then it is reasonable for primary dental practitioners to assess patients in the first instance. Suspected MRONJ should be managed by specialist dental services.
Appendix 2C: Management of suspected MRONJ

All oncology patients who are being treated with medications which are associated with a risk of MRONJ require prompt and appropriate management of dental symptoms.

MRONJ is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region, present for more than 8 weeks in patients with a history of treatment with medications related to MRONJ.

Any unexplained dental symptoms or symptoms suggestive of MRONJ should be referred for specialist assessment.

- Odontalgia without obvious cause in patients at risk of MRONJ should be investigated.
- Risk factors include:
  - Recent dental intervention especially extraction
  - Use of bone-modifying agents such as denosumab and bisphosphonates
  - Anti-angiogenic drugs such as tyrosine kinase inhibitors
  - Long duration of medication associated with MRONJ

- Patient on medication associated with MRONJ.
- Clinical symptoms or signs suspicious of MRONJ.
- Reviewing clinician (oncology or primary dental practitioner) to refer to local specialist service oral/maxillofacial/dental.
- Clinical and radiographic assessment, and commencement of management.
- Oral/maxillofacial/dental specialist to correspond with oncology team to relay MRONJ management plan to align with oncology management.
Appendix 3: Communication aids

Appendix 3A: Dental alert card: to give to patient when decision has been made to start treatment with MRONJ-associated drug

Front of card

Name of trust

To be shown to your dentist before any dental assessment

Name
Date of birth
NHS number
Name of responsible consultant
Name of department

Note that bisphosphonate/denosome should not be given until at least 4 weeks after dental extraction or longer if necessary.

Back of card

This patient is taking/has received drug treatment which is associated with a risk of developing medication-related osteonecrosis of the jaw (MRONJ)

Request to dentist
Please:
> perform a dental review at least every 6 months (including those wearing dentures)
> provide oral hygiene instruction
> carry out any necessary conservative dental treatments
> avoid any procedure which exposes or manipulates bone
> make an urgent referral to the oral surgery/maxillofacial/specialist dentist if a dental extraction is required

A referral form can be downloaded from
Appendix 3B: Letter for primary dental practitioner

Dear dentist,

The above patient has been seen in the oncology clinic and will start taking medication that has been associated with a risk of developing medication-related osteonecrosis of the jaw (MRONJ).

Name of drug

Route of administration

Frequency and duration

Before starting the above drug therapy
Please carry out a dental assessment and any necessary treatments especially extraction of teeth with a poor prognosis. Undergoing invasive dental procedures once established on the above therapy will significantly increase a patient’s risk of developing osteonecrosis of the jaw. For this reason, any dental extractions should be performed prior to starting the above drug treatment allowing at least 4 weeks for the socket to heal.

After starting the above drug therapy
Please see your patient at least every 6 months to reinforce the importance of good oral hygiene, screen for any dental health problems and in particular, assess for any signs or symptoms of MRONJ. If a dental extraction becomes necessary once the patient is on MRONJ-associated drug therapy, specialist management will be required. In this case, please refer the patient for assessment to your local oral/maxillofacial/specialist dental surgery department.

Further information about MRONJ can be found in the 2017 Scottish Dental Clinical Effectiveness Programme (SDCEP) guidance available at www.sdcep.org.uk.

Thank you for your help.
Dental assessment

For patients prior to commencing MRONJ-associated drug therapy
1. Comprehensive extraoral and intraoral examination
2. Radiographic assessment of teeth including panoramic (OPG) and long cone periapical radiographs, as clinically necessary
3. Evaluation of third molars
4. Identify and control any periodontal disease
5. Perform any necessary extractions as soon as possible
6. Ensure dentures are atraumatic and comfortable
7. Eliminate sharp edges of teeth or restorations
8. Scaling of teeth
9. Oral hygiene instruction
10. Arrangement of regular review of dental health

Dental care of patients receiving MRONJ-associated drug therapy

Procedures to be avoided whenever possible
- Dental extractions
- Oral periodontal surgery that exposes or manipulates bone
- Dental implants

Permitted treatments
Routine dental care is not contraindicated in patients treated with antiresorptive medication and may help prevent the need for dental extractions.
- Scaling and root planing
- Routine restorations
- Placement of crowns and bridges
- Root canal treatment
- Use of local anaesthesia as necessary

Extractions, oral surgery and implants in patients receiving MRONJ-associated drug therapy require specialist management so please refer the patient to the oral surgery/maxillofacial department for further assessment.

Signs and symptoms of medication-related osteonecrosis of the jaw (MRONJ)

Symptoms
- Pain – severe or persistent
- Swelling, tenderness or abnormality of gingiva
- Offensive odour
- Paresthesia due to peripheral nerve involvement
- Poor healing after dental work
- Patients may be asymptomatic

Signs
- Absent or delayed healing of hard or soft tissue after dental extractions
- An area of exposed non-vital bone
- Necrotic bone with surrounding inflammation and tenderness of gingival and mucosal tissues
- Secondary infection of necrotic bone
- Paresthesia due to peripheral nerve compression
- Microfractures
- Spreading necrosis to involve adjacent teeth, usually with evidence of pre-existing periodontal disease

If MRONJ is suspected, please refer the patient urgently to the oral surgery/maxillofacial department
## Appendix 3C: Reply from primary dental practitioner

(Form could be electronic or printed)

<table>
<thead>
<tr>
<th>Primary dental practitioner review</th>
</tr>
</thead>
</table>

### Prior to initiation of medication-associated with osteonecrosis of the jaw

#### Patient details

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>Telephone</th>
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<tbody>
<tr>
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</table>

<table>
<thead>
<tr>
<th>Date of birth</th>
<th>Email</th>
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<table>
<thead>
<tr>
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<th>Hospital ID</th>
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</table>

<table>
<thead>
<tr>
<th>Referring consultant</th>
<th>Referring department</th>
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</tbody>
</table>

### Outcome of review from primary dental practitioner

Based on my review of the patient today, this patient

- [ ] Does not require any active treatment at this time
- [ ] Requires further dental treatment at the practice

#### Details

- [ ] I would like further advice/treatment by the hospital specialist (oral/maxillofacial/specialist dental surgeon)

<table>
<thead>
<tr>
<th>Routine</th>
<th>Urgent</th>
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<tbody>
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<table>
<thead>
<tr>
<th>Indication</th>
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<tbody>
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<td></td>
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</table>

<table>
<thead>
<tr>
<th>Dentist’s name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>Practice</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
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</tbody>
</table>

### Thank you

Thank you for your review of this patient. We would appreciate your findings reported to the oncology unit at the earliest convenience and within 72 hours of next planned appointment.
Appendix 3D: Referral pro forma: requesting oral/maxillofacial/specialist dental surgeon review of a patient taking medication associated with MRONJ

**Referral for oral / maxillofacial / specialist dentist review**

Patients on or due to start medication associated with osteonecrosis of the jaw

<table>
<thead>
<tr>
<th>Patient details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
</tr>
<tr>
<td>Address</td>
</tr>
<tr>
<td>Email</td>
</tr>
<tr>
<td>Date of birth</td>
</tr>
<tr>
<td>NHS number</td>
</tr>
<tr>
<td>Referring consultant</td>
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<tr>
<td>Contact telephone number</td>
</tr>
<tr>
<td>Diagnosis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Planned oncological treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for referral</td>
</tr>
<tr>
<td>Urgency of referral</td>
</tr>
<tr>
<td>Does patient have?</td>
</tr>
<tr>
<td>Dental problem</td>
</tr>
<tr>
<td>If yes</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does patient have a dentist?</td>
</tr>
<tr>
<td>Planned start date/next administration of bisphosphonate/denosumab</td>
</tr>
<tr>
<td>Other medication</td>
</tr>
<tr>
<td>Other information</td>
</tr>
<tr>
<td>Name of clinician (print)</td>
</tr>
</tbody>
</table>
Appendix 3E: Reply from oral/maxillofacial/specialist dental surgeon – electronic or pro forma

## Reply from oral / maxillofacial / specialist dental surgeon

### Patients on or due to start medication associated with osteonecrosis of the jaw

**Patient details**

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Email</td>
<td>Telephone</td>
</tr>
<tr>
<td>Date of birth</td>
<td>Hospital ID</td>
</tr>
<tr>
<td>NHS number</td>
<td>Date of review</td>
</tr>
<tr>
<td>Referring consultant</td>
<td>Referring department</td>
</tr>
<tr>
<td>Contact telephone number</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Planned oncological treatment</td>
<td></td>
</tr>
</tbody>
</table>

**Reason for referral**

- [ ] Pre-treatment
- [ ] During treatment

**Date of review**

**Hospital dental specialist**

Based on my review of the patient today, this patient

- [ ] Does not require any active treatment at this time
- [ ] Requires dental treatment with the primary dental practitioner

**Recommended treatment**

- [ ] Requires specialist dental treatment

**Please specify**

**Oral/maxillofacial/specialist dental surgeon**

<table>
<thead>
<tr>
<th>Name</th>
<th>Contact details</th>
</tr>
</thead>
</table>
Appendix 3F: Selection of communication aids

Sticker to be placed in cancer treatment records (patient-held records)

For patients on or due to start medication associated with a risk of osteonecrosis of the jaw e.g. denosumab/bisphosphonates

<table>
<thead>
<tr>
<th>Name of dentist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of dental check-up</td>
</tr>
<tr>
<td>Next dental check-up (at least 6 monthly)</td>
</tr>
<tr>
<td>Phone number to ring regarding dental problems</td>
</tr>
</tbody>
</table>

Ask about symptoms of: jaw pain, tooth mobility, gum swelling/redness or inflammation and ulceration, offensive odour, poor healing after dental surgery, exposed bone.

Advise on good dental hygiene

- clean teeth at least twice a day
- reduce frequency of sugary drinks, snacks and alcohol intake
- see a hygienist and/or dietitian

Sticker for hospital notes

For patients on or due to start medication associated with osteonecrosis of the jaw, e.g. denosumab/bisphosphonates

- Dental check-up prior to starting
- Dental work completed before starting

Treatment

Date due to start treatment

Oncology consultant

Contact number

Referral to hospital oral/maxillofacial/specialist dental surgeon

<table>
<thead>
<tr>
<th>Required</th>
<th>Date</th>
<th>Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not required</td>
<td>Date</td>
<td></td>
</tr>
</tbody>
</table>

Advice given

- Risk of medication-related osteonecrosis of the jaw (MRONJ)
- Regular dental check-ups (at least 6 monthly)

Check Dental problems, renal function prior to administration

Note: no treatment to start until at least 4 weeks after dental procedure which exposes or manipulates bone. Discuss with dentist or specialist as required.
Checklist prior to starting denosumab/bisphosphonates

- Advice given about regular dental check-ups (at least 6 monthly)
- Dental check-up prior to starting
- Dental work completed before starting

Date due to start treatment: ______________

- Advice given about medication-related osteonecrosis of the jaw (MRONJ)
- Renal function and calcium prior to administration
- Advice given re good dental hygiene:
  - clean teeth at least twice a day
  - reduce frequency of sugary drinks, snacks and alcohol intake
  - hygienist and/or dietary advice

NB no treatment to start until at least 4 weeks after dental procedure which exposes or manipulates bone, or longer if appropriate.

Checklist for electronic notes: denosumab/bisphosphonates

Pre-infusion or subcutaneous administration

- Dental problems
- Dental check-up (at least 6 monthly)
- Renal function
- Calcium
- Good dental hygiene:
  - clean teeth at least twice a day
  - reduce frequency of sugary drinks, snacks and alcohol intake
  - hygienist or dietary advice

NB no treatment unless at least 4 weeks after dental procedure that exposes or manipulates bone, or longer if appropriate.
Medication-related osteonecrosis of the jaw
Guidance for the oncology multidisciplinary team

This guidance has been produced by a multidisciplinary working party on behalf of the UK Chemotherapy Board, which includes specialist representation from medical, dental and nursing teams across the UK. It has been endorsed by the Clinical Standards Committee of the Faculty of Dental Surgery of the Royal College of Surgeons of England.

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