BONE & MUSCULOSKELETAL STUDY GROUP
MASCC/ISOO/ASCO Guideline:
Medication-Related Osteonecrosis of the Jaw

Citation:

Abstract:
Purpose: To provide guidance regarding best practices in the prevention and management of medication-related osteonecrosis of the jaw (MRONJ) in patients with cancer.
Methods: Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and ASCO convened a multidisciplinary Expert Panel to evaluate the evidence and formulate recommendations. Guideline development involved a systematic review of the literature and a formal consensus process. PubMed and EMBASE were searched for studies of the prevention and management of MRONJ related to bone-modifying agents (BMAs) for oncologic indications published between January 2009 and December 2017. Results from an earlier systematic review (2003 to 2008) were also included.
Results: The systematic review identified 132 publications, only 10 of which were randomized controlled trials. Recommendations underwent two rounds of consensus voting.
Recommendations: Currently, MRONJ is defined by (1) current or previous treatment with a BMA or angiogenic inhibitor, (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region and that has persisted for longer than 8 weeks, and (3) no history of radiation therapy to the jaws or metastatic disease to the jaws. In patients who initiate a BMA, preventive care includes comprehensive dental assessments, discussion of modifiable risk factors, and avoidance of elective dentoalveolar surgery (ie, surgery that involves the teeth or contiguous alveolar bone) during BMA treatment. It remains uncertain whether BMAs should be discontinued before dentoalveolar surgery. Staging of MRONJ should be performed by a clinician with experience in the management of MRONJ. Conservative measures comprise the initial approach to MRONJ treatment. Ongoing collaboration among the dentist, dental specialist, and oncologist is essential to optimal patient care.
**Guideline Question**
What are the recommended best practices for preventing and managing medication-related osteonecrosis of the jaw (MRONJ) in patients with cancer?

**Clinical question 1.**
What is the preferred terminology and definition for osteonecrosis of the jaw (maxilla and mandible) associated with pharmacologic therapies in oncology patients?

**Recommendation 1.1.**
It is recommended that the term medication-related osteonecrosis of the jaw be used when referring to bone necrosis associated with pharmacologic therapies.

*type: formal consensus; evidence quality: insufficient; strength of recommendation: weak*

**Recommendation 1.2.**
Clinicians should confirm the presence of all three of the following criteria to establish a diagnosis of MRONJ: (1) current or previous treatment with a BMA or angiogenic inhibitor, (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region and that has persisted for longer than 8 weeks, and (3) no history of radiation therapy to the jaws or metastatic disease to the jaws.

*type: formal consensus; evidence quality: insufficient; strength of recommendation: weak*

**Clinical question 2.**
What steps should be taken to reduce the risk of MRONJ?

**Recommendation 2.1.**
Coordination of care: for patients with cancer who are scheduled to receive a BMA in a nonurgent setting, oral care assessment (including a comprehensive dental, periodontal, and oral radiographic exam when feasible to do so) should be undertaken before initiating therapy. Based on the assessment, a dental care plan should be developed and implemented. The care plan should be co-ordinated between the dentist and the oncologist to ensure that medically necessary dental procedures are undertaken before the initiation of the BMA. Follow-up by the dentist should then be performed on a routine schedule, for example every 6 months once therapy with a BMA has commenced.

*type: evidence-based; evidence quality: low/intermediate; strength of recommendation: moderate*

**Recommendation 2.2.**
Modifiable risk factors: members of the multidisciplinary team should address modifiable risk factors for MRONJ with the patient as early as possible. These risk factors include poor oral health, invasive dental procedures, ill-fitting dentures, uncontrolled diabetes mellitus, and tobacco use.

*type: formal consensus; evidence quality: insufficient; strength of recommendation: moderate*

**Recommendation 2.3.**
Elective dentoalveolar surgery: elective dentoalveolar surgical procedures (eg, non-medically necessary extractions, alveoloplasties, and implants) should not be performed during active therapy with a BMA at an oncologic dose. Exceptions may be considered when a dental specialist with expertise in the prevention and treatment of MRONJ has reviewed the benefits and risks of the proposed invasive procedure with the patient and the oncology team.

**Recommendation 2.4.**
Dentoalveolar surgery follow-up: if dentoalveolar surgery is performed, patients should be evaluated by the dental specialist on a systematic and frequently scheduled basis (eg, every 6 to 8 weeks) until full mucosal coverage of the surgical site has occurred. Communication with the oncologist regarding the status of healing is encouraged, particularly when considering future use of BMA.

**type: formal consensus; evidence quality: insufficient; strength of recommendation: moderate**

**Clinical question 3.**
How should MRONJ be staged?

**Recommendation 3.1.**
A well-established staging system should be used to quantify the severity and extent of MRONJ and to guide management decisions. Options include the 2014 American Association of Oral and Maxillofacial Surgeons staging system, the Common Terminology Criteria for Adverse Events version 5.0, and the 2017 International Task Force on Osteonecrosis of the Jaw staging system for MRONJ. The same system should be used throughout the patient’s MRONJ course of care. Diagnostic imaging may be used as an adjunct to these staging systems.

**type: formal consensus; evidence quality: insufficient; strength of recommendation: weak**

**Recommendation 3.2.**
Optimally, staging should be performed by a clinician who is experienced with the management of MRONJ.

**type: formal consensus; evidence quality: insufficient; strength of recommendation: weak**

**Clinical question 4.**
How should MRONJ be managed?
**Recommendation 4.1.**
Initial treatment of MRONJ: conservative measures comprise the initial approach to treatment of MRONJ. Conservative measures may include antimicrobial mouth rinses, antibiotics if clinically indicated, effective oral hygiene, and conservative surgical interventions, for example, removal of a superficial bone spicule.

*type: formal consensus; evidence quality: insufficient; strength of recommendation: moderate*

**Recommendation 4.2.**
Treatment of refractory MRONJ: aggressive surgical interventions (eg, mucosal flap elevation, block resection of necrotic bone, or soft tissue closure) may be used if MRONJ results in persistent symptoms or affects function despite initial conservative treatment. Aggressive surgical intervention is not recommended for asymptomatic bone exposure. In advance of the aggressive surgical intervention, the multidisciplinary care team and patient should thoroughly discuss the risks and benefits of the proposed intervention.

*type: formal consensus; evidence quality: insufficient; strength of recommendation: weak*

**Clinical question 5.**
Should BMAs be temporarily discontinued after a diagnosis of MRONJ has been made?

**Recommendation 5.**
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.

*type: formal consensus; evidence quality: insufficient; strength of recommendation: weak*

**Clinical question 6.**
What outcome measures should be used in clinical practice to describe the response of the MRONJ lesion to treatment?

**Recommendation 6.**
During the course of MRONJ treatment, the dentist/dental specialist should communicate with the medical oncologist the objective and subjective status of the lesion—resolved, improving, stable, or progressive. The clinical course of MRONJ may affect local and/or systemic treatment decisions with respect to cessation or recommencement of BMAs.

*type: formal consensus; evidence quality: insufficient; strength of recommendation: weak*
## Grading of Recommendations and Levels of Evidence

<table>
<thead>
<tr>
<th>Types of recommendations</th>
<th>Details</th>
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<tbody>
<tr>
<td>Evidence-based</td>
<td>There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.</td>
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<tr>
<td>Formal consensus</td>
<td>The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement.</td>
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<tr>
<td>Informal consensus</td>
<td>The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion.</td>
</tr>
<tr>
<td>No recommendation</td>
<td>There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.</td>
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## Quality of the evidence

<table>
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<tr>
<td>High</td>
<td>High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits v harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.</td>
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<tr>
<td>Intermediate</td>
<td>Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.</td>
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<tr>
<td>Low</td>
<td>Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.</td>
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<tr>
<td>Insufficient</td>
<td>Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.</td>
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## Strength of the recommendation
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<td>Strong</td>
<td>There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists’ agreement.</td>
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<tr>
<td>Moderate</td>
<td>There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists’ agreement.</td>
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<tr>
<td>Weak</td>
<td>There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists’ agreement.</td>
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