Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline

Yarom et al.
Introduction

- This guideline focuses on the prevention and management of MRONJ in patients with cancer who receive bone modifying agents (BMAs) for oncologic indications.

- The guideline does not address BMAs used for osteoporosis nor does the guideline address the prevention or management of MRONJ due to medications other than BMAs.

- Throughout this guideline, the Expert Panel emphasizes the importance of collaboration among the cancer care team, dentists, and dental specialists.
  
  - *Dentists* may be community-based or hospital-based, and are the providers who typically complete the pre-cancer-therapy dental evaluation and long-term preventive management.
  
  - *Dental Specialists* as cited in this publication refers to dentists with expertise in the clinical management of MRONJ. This individual may be an oral medicine specialist, oral maxillofacial surgeon, hospital dentist, clinical oral pathologist, and/or periodontist.
Guideline Development Methodology

The guideline development included:

• A systematic literature review
• The formal consensus process
• An expert panel provided critical review and evidence interpretation to inform guideline recommendations
• Final guideline approval by ASCO CPGC and MASCC Guidelines Committee

The full ASCO Guideline methodology supplement can be found at:

www.asco.org/guideline-methodology
Clinical Questions

This clinical practice guideline addresses:

1) What is the preferred terminology and definition for osteonecrosis of the jaw associated with pharmacologic therapies in oncology patients?

2) What steps should be taken to reduce the risk of MRONJ in patients with cancer?

3) How should MRONJ be staged?

4) How should MRONJ be managed?

5) Should BMAs be temporarily discontinued after a diagnosis of MRONJ has been established?

6) What outcome measures should be utilized in clinical practice to describe the response of the MRONJ lesion to treatment?
Target Population and Audience

Target Population
Adult patients with cancer who are receiving bone modifying agents (BMAs) for any oncologic indication.

Target Audience
Oncologists and other physicians, dentists, dental specialists, oncology nurses, clinical researchers, oncology pharmacists, advanced practitioners, and patients with cancer.
Summary of Recommendations

**CLINICAL QUESTION 1**
What is the preferred terminology and definition for osteonecrosis of the jaw associated with pharmacologic therapies in oncology patients?

**Recommendation 1.1**
It is recommended that the term “medication-related osteonecrosis of the jaw” (MRONJ) 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 in order 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 extra-oral 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).
Summary of Recommendations

CLINICAL QUESTION 2
What steps should be taken to reduce the risk of MRONJ?

**Recommendation 2.1**
(Coordination of Care): For cancer patients scheduled to receive a BMA in a non-urgent setting, oral care assessment (including a comprehensive dental, periodontal, and oral radiographic exam when feasible to do so) should be undertaken prior to initiating therapy. Based on the assessment, a dental care plan should be developed and implemented. The care plan should be coordinated between the dentist and the oncologist to ensure that medically necessary dental procedures are undertaken prior to initiation of the BMA. Follow-up by the dentist should then be performed on a routine schedule (e.g., every six 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)
Summary of Recommendations

**Recommendation 2.3**
(Elective Dentoalveolar Surgery): Elective dentoalveolar surgical procedures (e.g. 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 prevention and treatment of MRONJ has reviewed the benefits and risks of the proposed invasive procedure with the patient and the oncology team. (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate)

**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 (e.g., every 6-8 weeks), until full mucosal coverage of the surgical site has occurred. Communication with the oncologist regarding status of healing is encouraged particularly when considering future use of BMA (Table 2). (Type: Formal consensus; Evidence quality: Insufficient; Strength of recommendation: Moderate)

**Recommendation 2.5**
Temporary discontinuation of BMAs prior to dentoalveolar surgery). For patients with cancer who are receiving a BMA at an oncologic dose, there is insufficient evidence to support or refute the need for discontinuation of the BMA prior to dentoalveolar surgery. 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: Informal consensus; Evidence quality: Insufficient; Strength of recommendation: Weak)

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Summary of Recommendations

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 AAOMS staging system, the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 and the 2017 International Task Force on ONJ 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 experienced with the management of MRONJ. (Type: Formal consensus; Evidence quality: Insufficient; Strength of recommendation: Weak)
Summary of Recommendations

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 (e.g., 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 (e.g. mucosal flap elevation, block resection of necrotic bone, soft tissue closure) may be used if MRONJ results in persistent symptoms or impacts 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 the patient should thoroughly discuss the risks and benefits of the proposed intervention. (Type: Formal consensus; Evidence quality: Insufficient; Strength of recommendation: Weak)
Summary of Recommendations

CLINICAL QUESTION 5
Should bone-modifying agents (BMA) be temporarily discontinued in patients with suspected or established MRONJ?

Recommendation 5
For patients 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)
Summary of Recommendations

CLINICAL QUESTION 6
What Outcome Measures Should Be Utilized 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 impact local and/or systemic treatment decisions with respect to cessation or recommencement of BMAs. (Type: Formal consensus; Evidence quality: Insufficient; Strength of recommendation: Weak)
Patient and Clinician Communication

- To ensure optimal symptom management, clinicians should assess symptoms throughout therapy.

- Discussion with patients about the importance of modifiable risk factors for MRONJ and lifelong commitment to oral care is fundamental to MRONJ prevention.

- If patients need assistance identifying a dentist or dental specialist in the United States, options include contacting a nearby dental school (https://www.adea.org/dentalschools/) or professional organizations such as the American Academy of Oral Medicine (www.aaom.com/) or the American Association of Oral and Maxillofacial Surgeons (www.aaoms.org/).
Health Disparities

- There are a number of social determinants that contribute to which patients have access to oral health care in general, and medically necessary oral care in context of cancer treatment in particular.

- These determinants include the patient’s socioeconomic status and degree of health literacy, as well as access to oral health care information and interprofessional oncology protocols that incorporate management of oral complications of cancer treatment.

- Racial and ethnic disparities in health care contribute significantly to limited access to medical and dental care in the United States.

- Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.
Future Research

- Optimal treatment for patients with MRONJ remains to be established. New research, including RCTs, is warranted.

- The Expert Panel encourages the creation of predictive tools for the development of MRONJ, such as bone turnover markers and genetic markers.

- There should also be future consideration of a staging system that incorporates both clinical and radiographic diagnostic criteria.
Additional Resources

More information, including a Data Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/supportive-care-guidelines

Patient information is available at www.cancer.net
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