Background

Osteonecrosis of the jaw (ONJ) is an uncommon event that has been reported in cancer patients receiving complex treatment regimens, including radiation, chemotherapy, and other cancer treatments. Recently, there have been reports of ONJ in cancer patients whose treatment regimens include an intravenous (IV) bisphosphonate.\(^1\)\(^2\) Additionally, ONJ has been reported in a very small number of patients who are receiving oral bisphosphonates for noncancer indications.\(^3\)\(^4\)\(^7\)\(^16\) Practical guidelines for the prevention, diagnosis, and management of ONJ in patients with cancer were recently published.\(^22\) However, there is currently no consensus definition for ONJ. Moreover, the pathogenesis of ONJ, which likely involves a combination of many risk factors, is poorly understood, and research efforts in this area are ongoing.

In February 2006, Novartis convened an international advisory board of experts in the fields of oral surgery and pathology, medical oncology, metabolic bone disease, and orthopedics. The panel reviewed existing data and provided updated recommendations on the clinical diagnosis of ONJ and further developed recommendations for the prevention and management of ONJ in patients with cancer who are receiving IV bisphosphonates. Novartis' recommendations, based on the panel's input, are presented here to help guide medical and dental healthcare professionals in early diagnosis and patient management.

Clinical Presentation and Working Diagnosis of ONJ

Novartis recommends a 2-stage approach to identify patients with ONJ.

1. **The clinical features of suspected ONJ** are exposed bone in the maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing. Patients with these clinical features should be referred for appropriate dental evaluation and care as soon as possible.

2. **A working diagnosis of ONJ** is made when there is no evidence of healing after 6 weeks of appropriate evaluation and dental care and no evidence of metastatic disease in the jaw or osteoradionecrosis.

Severity and Lesion Size Staging for ONJ

The staging criteria listed below in Tables 1 and 2 were supported by this advisory panel and are endorsed by Novartis.

*Table 1. ONJ Severity Grading*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptom severity</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
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Table 2. ONJ Lesion Size Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Size, diameter*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Single lesion &lt; 0.5 cm</td>
</tr>
<tr>
<td>1B</td>
<td>Multiple lesions, largest &lt; 0.5 cm</td>
</tr>
<tr>
<td>2A</td>
<td>Single lesion 0.5 to 0.99 cm</td>
</tr>
<tr>
<td>2B</td>
<td>Multiple lesions, largest 0.5 to 0.99 cm</td>
</tr>
<tr>
<td>3A</td>
<td>Single lesion 1 to 2 cm</td>
</tr>
<tr>
<td>3B</td>
<td>Multiple lesions, largest 1 to 2 cm</td>
</tr>
<tr>
<td>4A</td>
<td>Single lesion &gt; 2 cm</td>
</tr>
<tr>
<td>4B</td>
<td>Multiple lesions, largest &gt; 2 cm</td>
</tr>
</tbody>
</table>

*Lesion size measured as the largest diameter.

Updated Recommendations for the Prevention and Management of ONJ in Patients With Cancer

The expert panel addressed a series of questions related to the prevention and management of ONJ in patients with cancer whose treatment regimens include IV bisphosphonates. These are endorsed by Novartis and listed below. In all cases, an open discussion between the treating physician and the patient is strongly recommended.

1. **Should a dental examination and preventive dentistry be performed before starting bisphosphonate therapy?**
   - It is recommended that patients be encouraged to have a dental examination before they start bisphosphonate therapy
   - If the dental professional determines that the patient requires a surgical dental procedure, then it is recommended that it be completed before initiation of bisphosphonate therapy when possible

2. **How often should a dental examination be recommended while on bisphosphonate therapy?**
   - Patients are encouraged to seek appropriate dental maintenance care approximately every 6 months or more frequently, when appropriate
   - Patients should maintain good oral hygiene
   - Routine restorative treatments and dental hygiene procedures may be performed
3. For oncology patients on bisphosphonate therapy who have dental problems (other than ONJ)

A) Should dental treatment be modified?

- If possible, the least invasive (nonsurgical) dental treatment is recommended

B) Should bisphosphonate therapy be withheld before and after dental treatment? If so, for how long?

- There are no prospective data. However, if tooth extraction or other dental surgery is required while on bisphosphonate therapy, consider withholding bisphosphonate therapy until the site of the surgical procedure has healed

- For patients with high risk of hypercalcemia of malignancy or skeletal-related events, consideration should be given to maintaining bisphosphonate therapy

4. For oncology patients on bisphosphonate therapy with a working diagnosis of ONJ

A) Should bisphosphonate therapy be discontinued, temporarily withheld, or continued?

- No prospective data exist

- For patients at high risk of hypercalcemia of malignancy or skeletal-related events, consideration should be given to maintaining bisphosphonate therapy. Patients not at high risk for hypercalcemia of malignancy or skeletal-related events should be evaluated, and the discontinuation of bisphosphonates should be considered. In all cases, close coordination between the oral surgeon and treating oncologist is recommended

- Some factors that may correlate with an increased risk of hypercalcemia or skeletal-related events include
  - Progression of the underlying malignancy
  - Prior skeletal-related event in a patient with a solid tumor
  - Presence of more than 3 bone lesions in a patient with a solid tumor

B) What are the current treatment options for ONJ?

- Current management of ONJ is empiric. At present, a conservative approach is recommended. This includes antibiotics, oral rinses, pain control, and limited debridement. Cases refractory to conservative management may benefit from investigational therapies. The roles of surgical treatment and hyperbaric oxygen therapy are still under investigation
Conclusion

Osteonecrosis of the jaw is an uncommon but significant complication that occurs in cancer patients whose treatment regimens include IV bisphosphonates. As with all medical therapies, the potential risks and benefits should be discussed openly with the patient. Novartis has a comprehensive ONJ research plan that includes preclinical and clinical research aimed at providing more definitive guidance for the management of ONJ with regard to the following issues: the pathogenesis and risk factors for ONJ, identifying patients at risk for ONJ, and effective preventive measures and treatments for ONJ.

References