Medication Related Osteonecrosis of the Jaw

Cancer and Bone Invasion

Tumors that have invaded the bones cause the bone to wear away, leaving small holes, called osteolytic lesions. This process of bone erosion is called resorption and leaves bones weak and fragile. Tumors can also stimulate abnormal bone formation, resulting in areas of bone build-up called osteosclerotic lesions, which can be painful. These areas of build-up are weak and unstable and can easily break or collapse. Both of these processes put patients with cancer that has spread to the bone, or multiple myeloma, at risk for fractures, a faster spread of bone metastases, spinal cord compression (when the bone in the spine compresses the spinal cord) and hypercalcemia (increased levels of calcium in the blood caused by bone breakdown, which can cause severe problems). Several medications have the ability to prevent or slow these complications, including denosumab and a class of medications called bisphosphonates.

What are Bisphosphonates?

Bisphosphonates are a group of medications that slow the bone destroying activity that occurs with bone metastases (cancer that has spread to the bone) or Multiple Myeloma (cancer of plasma cells, which invade and destroy bone). Bisphosphonates work by slowing the wearing away (also called resorption) of bone and the abnormal build-up of unstable bone. These problems can lead to what doctors call "skeletal related events". These events include the previously listed fractures, increased bone metastases, spinal cord compression and hypercalcemia. Bisphosphonates are used to help improve bone strength in many diseases associated with bone resorption, including cancer and osteoporosis.

Currently approved bisphosphonates include:

- Alendronate (Fosamax®)
- Etidronate (Didronel®)
- Ibandronate (Boniva®) – currently used for only for osteoporosis
- Pamidronate (Aredia®) (given intravenously)
- Risedronate (Actonel®)
- Tiludronate (Skelid®)
- Zoledronic acid (Zometa®) (given intravenously)

Other Medications Associated with ONJ

Another medication used to slow or prevent bone breakdown and bone complications is denosumab (Xgeva®). Denosumab is a type of monoclonal antibody, which is a medicine designed to target a specific protein or cell – in this case, the target is a protein called RANKL, which is necessary for bone breakdown and is over produced in bone metastases. By targeting RANKL, denosumab inhibits bone breakdown. In addition, a class of medications called anti-angiogenesis inhibitors, which work by interfering with a tumors blood supply, are a known cause of ONJ. These medications are used in many cancer treatment regimens.

What is Osteonecrosis of the Jaw?

Osteonecrosis is exposed bone of the maxilla (upper jaw bone) or mandible (lower jaw bone). These bones are normally covered by gum tissue. In the case of osteonecrosis of the jaw (ONJ), the bone is exposed, either through an opening in the gum tissue or with the gum tissue missing entirely. Typical symptoms associated with ONJ are: pain, swelling or infection of the gums, loosening of the teeth, and exposed bone (often at the site of a previous tooth extraction). Some patients may report
numbness or tingling in the jaw or a "heavy" feeling jaw. ONJ may have no symptoms for weeks or months and may only be recognized by the presence of exposed bone.

The exact cause of ONJ is not known, but potential causes include: dental work, infection, inflammation, and the inhibition of angiogenesis. Originally, the cause was thought to be related to dental work while taking these medications. However, further research found that this dental work was often done because of underlying dental disease, which is often associated with inflammation of the gum tissue or infection. Anti-angiogenic medications inhibit blood supply, which can lead to bone damage. Research has found that bisphosphonates also have some affect on angiogenesis. ONJ is a rare complication, but as patients with bone metastases are living longer and being treated with medications associated with this complication for many years, it is important to be aware of this complication.

ONJ should not be confused with osteoradionecrosis of the jaw, which is caused by radiation therapy and is treated differently than ONJ.

**Prevention is the Key**

What experts have learned is that most cases were associated with some type of dental event, and if these are avoided, ONJ may be as well. Any patient who is going to start receiving a medication associated with ONJ should be seen by an oral maxillofacial surgeon or dental oncologist familiar with ONJ. If there are any dental concerns (requiring dental surgeries, extractions, root canals, or removal of abscessed teeth), therapy with the medication should be delayed (if possible) until the dental concerns are addressed and several weeks have passed, to allow for healing. Dental exams should include cleaning, examining of denture fit, and patient education regarding oral care while on these medications.

Patients receiving bisphosphonates should have regularly scheduled oral assessments, perhaps as often as every 3-4 months. They should maintain good oral hygiene and have routine dental cleanings (with care to avoid injury to tissues).

If invasive dental procedures are absolutely necessary, some have suggested that temporarily stopping the at-risk medications may result in improved healing. However, there is no evidence that this helps prevent ONJ in oncology patients. These medications remain in the body for many months after the last dose, meaning you would need several months or more off the medication to make stopping the therapy worthwhile. These medications clearly benefit patients at high risk of bone complications and, unfortunately, no other class of medications have this benefit. The patient and provider must weigh the patient's risk with the benefit derived from these medications. Further research into appropriate management is ongoing.

**How do we treat ONJ?**

Patients with suspected ONJ should have panoramic and/or intra-oral x-rays performed to rule out other dental problems (impacted teeth, cysts, bone changes). These patients should be seen and evaluated by an oral maxillofacial surgeon or dental oncologist familiar with ONJ. Primary goals of treatment of ONJ are to reduce pain, treat or prevent infection, and minimize progression.

Oral rinses with chlorhexidine (Peridex®) should be used 3-4 times a day, indefinitely. Dentures can be worn, but may require some resizing or cushioning to prevent further injury. An appliance can be used to cover and protect the exposed bone. Antibiotics can be beneficial and the area may be tested to determine what bacteria is present, which will guide the choice of which antibiotic to use.

Non-surgical approaches are often preferred, as surgery on these bones may not heal well and may worsen the problem. However, in more advanced cases, surgical removal of the involved bone can improve quality of life, reduce pain, prevent this area from spreading, and help promote soft tissue healing. When used, surgery may include the surgical removal of foreign material and/or dead, damaged, or infected tissue or bone and in some cases, reconstruction of the bone.

**Conclusions**

ONJ is a relatively newly recognized concern for patients receiving certain medications. It is thought to be quite rare, but is probably underreported given the lack of understanding regarding this problem. As a patient, follow recommendations for prevention and report any signs of ONJ to your healthcare team.