ADDENDUM - 8/31/06

Yes, it is true that I much prefer Aredia over Zometa. In early 2004, I wrote a paper about bisphosphonate-related osteonecrosis or ONJ osteonecrosis of the jaw. In that paper, I speculated that eventually we would find that as many as 10-15% of patients on long-term bisphosphonates were destined to develop this complication. I additionally speculated that Zometa would be found to be associated with this much more commonly than Aredia. Durie reported in 2005 in a New England Journal of Medicine article the ONJ occurred in 10% of patients who were treated only with Zometa, and in 4% of those who were treated only with Aredia. Without censoring, the mean time to onset of ONJ was 18 months among patients receiving Zometa, and six years for those receiving Aredia.

Other investigators, Maerevoet, M., et al., New England Journal of Medicine, 2005, found ONJ after a median time of 39 months in those treated with Aredia, and 18 months in those treated with Zometa. In the August 2006 issue of Oncology, the authors point out that the approximate time to onset of ONJ in patients treated with Zometa appears to be 18 months, while patients with Aredia probably 39-72 months.

To me, it is very suspicious that ONJ only began to be diagnosed in 2003, which coincided with the availability of Zometa.

ADDENDUM - 10/11/05

I initially wrote a paper regarding bisphosphonate-associated osteonecrosis in December of 2003. I have updated the paper on a number of occasions. I believe this current addendum from October 11, 2005 validates the views and conclusions that I have previously reported. The September 2005 issue of Oncology News International, page 10, reports that Zometa won FDA approval for treating bone metastases in 2002. That same year, the FDA began to receive spontaneous reports of development of osteonecrosis of the jaw (ONJ) in cancer patients taking Aredia and/or Zometa. Nine cases were reported that year. In 2003, 60 cases were reported, and I am proud to state that I
contacted Novartis in December 2003 to report on ten cases. By May 2004, an additional 69 cases had been reported, and as of February 22, 2005, a total of 875 cases had been reported.

I had speculated in December 2003 that I felt ultimately perhaps 10 or 15% of men who were treated with monthly intravenous bisphosphonates over many years would be at significant risk for developing ONJ. This *Oncology News International* article references some work by Dr. Brian Durie at Cedars-Sinai Medical Center in Los Angeles. He is a specialist in treating multiple myeloma. They did an online survey and 62 of 904 myeloma patients treated with intravenous bisphosphonate had developed ONJ, and another 54 had suspicious findings. I would point out, however, that in multiple myeloma, patients are often treated with every three-week intravenous bisphosphonates since they have such remarkable anticancer activity against myeloma cells. Of 299 breast cancer patients, 13 had developed ONJ, and another 23 had suspicious findings. The same survey indicated another point that I had speculated upon in my 2003 paper. They found that ONJ occurred faster in patients treated with Zometa than with Aredia, and occurred faster in patients who switched from Aredia to Zometa. Among myeloma patients, the mean time from diagnosis of myeloma to ONJ took 72 months for patients treated with Aredia only; 70 months for patients treated with Aredia and then Zometa, but in those patients treated only with Zometa, it only took 18 months to develop this. As my paper also described, the first suspicion that the patient may have ONJ occurred following tooth extraction where there would be complications including delayed wound healing. About one-third of patients presented with spontaneous eruption of a piece of bone near their teeth. As a result of these findings, I strongly recommend that patients receive a thorough dental exam prior to beginning bisphosphonate therapy, and certainly prior to a second dose. If it is absolutely necessary to have a tooth pulled, it should be done prior to starting bisphosphonates, or before the second dose. Patients on bisphosphonates should be discouraged from having elective oral surgery, and need to talk to Mary or Christine, my Physician Assistants, prior to scheduling any dental work. As my paper explains later, root canals are considered the treatment of choice, and then just allowing a tooth to fall out. For your safety, please do not allow a tooth to be pulled without our clearance.
Novartis, the manufacturer of Zometa and Aredia, noted that as of December 2004, 119 cases of ONJ had developed among 1.9 million patients treated with Aredia, and 248 cases in 1 million patients treated with Zometa worldwide. Their most recent count of 875 ONJ case reports represented only 0.0003% of the 2.9 million patients treated with the two Novartis drugs, although they did admit this likely represented an underestimate of all cases. Interestingly, in a review of 4,032 patients treated at M.D. Anderson Hospital, of the first 963 charts reviewed, ONJ occurred in 18 of 780 patients, with one of the following three cancers: breast (11); multiple myeloma (6), and thyroid (1). No cases were reported among patients with other cancers, including prostate, and several other cancers. The M.D. Anderson doctor concluded that the balance of benefit to risk for Zometa and Aredia remains favorable.

Dr. Bob and Compassionate Oncology Medical Group reduced the frequency of administration of intravenous bisphosphonates so that most men are treated only once every three months, and almost always with Aredia. However, for men on hormone blockade, particularly those who might only receive a single cycle of hormone blockade, I recommend using Aredia more frequently to help prevent the development of osteoporosis. I do not recommend the use of Zometa, except in patients with definite bone metastases. For those men who do have documented bone metastases, the frequency of administration of Aredia and/or Zometa is determined on an individual patient basis.

End of 10/11/05 Addendum

In late 2003, I observed that an unusual number of my patients were having dental problems. The typical example was that after one or more teeth were pulled, patients had difficulty with wound healing. I believe that this clinical presentation is usually due to osteonecrosis of the maxilla and/or mandible (upper and lower jaw bones).

Prior to 2002, there were only approximately 32 case reports in the medical literature describing chemotherapy-associated osteonecrosis of bone. Osteonecrosis means that the bone is breaking down and partially dissolving in places. Only three of these 32 patients had developed osteonecrosis of a bone in their oral cavity. In our patients, I do not believe this condition is a complication of chemotherapy. Instead I believe it is a complication from the use of intravenous bisphosphonates, specifically Aredia and/or Zometa.
A letter to the editor in the *Journal of Clinical Oncology*, Volume 21, Number 22, November 15, 2003, pages 4253-4254 by Cesar Migliorati reported five patients with spontaneous bone necrosis of the mandible (lower jaw bone) following tooth extraction. They called this drug-induced avascular bone necrosis. This was the only reference to this condition published in medical oncology literature as of the date of this article. I prefer the term osteonecrosis of jaws (maxilla and/or mandible).

In a letter to the editor by Robert Marx, D.D.S from Miami, Florida, to the *Journal of Oral Maxillofacial Surgery*, Volume 61, 2003, pages 1115-1118, is another report describing this problem. He reported 36 cases of painful bone exposures in the mandible and/or maxilla that were unresponsive to surgical or medical treatments. All of these patients were receiving either Aredia or Zometa. None of these 36 patients had prostate cancer; 18 had multiple myeloma (a type of bone cancer); 17 had metastatic breast cancer, and one had osteoporosis. Most patients presented with painful, exposed bone in the mandible, maxilla, or both. The symptoms simulated conditions such as dental abscesses, toothaches, denture sore spots, or osteomyelitis (infection of bone). Removal of painful teeth resulted in exposed bone and/or difficulty with wound healing. Twenty-eight of the patients had delayed wound healing; the remaining eight developed exposed bone spontaneously.

Zometa and Aredia are known to have very potent antiangiogenic activity. In bones, both Aredia and Zometa work by inhibiting osteoclasts (which cause bone resorption). It is thought that some of this inhibition is due to antiangiogenesis. In normal bone, you must first have resorption of bone by osteoclasts before you can have bone buildup by osteoblasts. The maxilla and mandible are thought to be constantly remodeling at a rate much higher than most bones. The jaw bones also have one of the richest blood supplies in the body. An example of this rich blood supply is the amount of bleeding that occurs after a dental extraction. By inhibiting osteoclasts in the jaw bones, IV bisphosphonates can cause an imbalance in bone remodeling that results in osteonecrosis. Throughout the rest of the body Zometa and Aredia cause a marked increase in bone build up which strengthens bones and treats osteoporosis. Paradoxically the same medicine that strengthens bones throughout the rest of the body may be the cause of osteonecrosis of jaws. As of August 2004, only a small
percentage of patients treated with an IV bisphosphonate have developed this complication. Both Aredia and Zometa help to prevent or delay the appearance of new bone metastases, bone fractures, bone pain, and the need for radiation therapy to treat bone pain. These effects are called skeletal related events. I use IV bisphosphonates because they reduce and postpone skeletal related events and are the most potent medicines I have to prevent and/or treat osteoporosis/osteopenia. Therefore, for most of our patients, I still recommend using an IV bisphosphonate, but I have altered my practice, and for most patients, I only give these medications every two to three months. Previously I recommended monthly treatment. For men receiving hormone blockade (HB), I usually treat monthly. When HB is completed, I treat less frequently.

In December 2003, I reported my concerns to Novartis Pharmaceuticals, the manufacturer of Aredia and Zometa. They told me that more than 2,500,000 patients worldwide had been treated with one or both of these drugs, and there were only rare cases of this complication reported. They did not believe anyone had yet proven a connection between the use of bisphosphonates and this complication, especially since most of the patients had also simultaneously received chemotherapy agents and/or steroids.

I spoke to Dr. Jim Berenson, a nationally recognized expert in multiple myeloma and bone metastases. Since multiple myeloma is a type of bone cancer, a major part of the therapy is giving intravenous bisphosphonates. Patients with myeloma are usually treated with Aredia and Zometa every three weeks. I treat our prostate cancer patients every four weeks. He, too, had observed that a number of his patients were having dental problems, specifically difficulty with wound healing following dental extractions. As a result of my reports and reports from a few other clinicians, in January 2004, Novartis changed their package insert to state that rare cases of osteonecrosis have been reported to them, but they describe this possible complication as a casual relationship, cause and effect not yet proven. I am convinced that this complication is from bisphosphonates, although I cannot yet prove it. Therefore, it is my opinion, not proven fact.

In February 2004, Dr. Berenson told me that anecdotally he has found that some patients improve to some extent with an antibiotic, Biaxin XL 500, one twice a day for 14 days. I have tried this and it only helped treat infectious complications,
not the abnormal bone itself. Over time, I found Cleocin to be the most effective antibiotic.

The best x-ray or scan study to diagnose osteonecrosis is what is called a dental Panorex view. Only dentists have the type of machine to obtain the Panorex view. I usually also order a CT scan of the jaw bones.

Dr. Berenson and I try to refer our patients to an oral surgeon at UCLA, Dr. Alan Felsenfeld. His phone number is (310) 825-0834. I recommend that all of our patients with any dental symptoms consult with Dr. Felsenfeld prior to allowing any extractions. He has the largest experience to date dealing with this complication. And, he is a great doctor with a superb bedside manner.

I also strongly recommend that any of our patients who are being treated with Aredia or Zometa not allow a dental extraction without first discussing it with us. Patients with osteonecrosis should never allow a dental implant since the abnormal jaw bone will prevent implants from healing. Our usual recommendation is to have a root canal procedure done (this is safe), and then just let the tooth fall out naturally. If one of our patients develops osteonecrosis, I usually recommend temporarily or permanently discontinuing their Aredia or Zometa, although this may not help. For some patients with bone metastases, I believe that the benefits of Zometa/Aredia may be too compelling to discontinue their use, even if osteonecrosis develops.

I made the observation that I have been using Aredia to treat prostate cancer patients since at least the early 1990's. In the past, I actually gave higher doses of Aredia than I currently use. In spite of that, I never had a patient develop this complication prior to 2003. Zometa has only been commercially available since 2002. Therefore, to me, it seems that Zometa is much more likely to cause this condition than Aredia. Dr. Berenson agreed with this opinion, but stated that he has some patients who have only been treated with Aredia and have developed osteonecrosis. The few published articles also confirm that some patients treated with Aredia alone have developed osteonecrosis. The report by Dr. Robert Marx includes 24 patients who had been treated with Aredia alone.

I spoke to our Zometa representative in mid-February 2004, and she told me that up until the last several weeks, Dr. Berenson
and our group were the only oncologists who had identified and reported this problem to Novartis. However, in February, an oral surgery group in Miami, and a second oral surgery group on Long Island, began to identify patients with this problem. To me, it is obvious that I will see many more cases of this over the next many months to several years.

An article in the *Journal of Oral and Maxillofacial Surgery*, Volume 62: 527-534, 2004, by Ruggiero, Salvatore, et al., is entitled, “Osteonecrosis of the Jaws Associated with the Use of Bisphosphonates: A Review of 63 Cases.” This study involved patients seen in the Oral Surgery Clinics of Long Island Jewish Medical Center and University of Maryland Medical Systems. They had noted that a growing number of patients were referred for evaluation and management of “refractory osteomyelitis” of varying duration. The typical presentation was a nonhealing extraction socket or spontaneous exposed jaw bone. Prior to 2001, this rare clinical scenario was seen only in patients who previously had radiation therapy to their jaw bones, and numbered only one or two cases per year. From February 2001 to June 2003, a total of 63 patients were identified. There were 45 female patients and 18 male patients ranging in age from 43 to 89, mean age 62. Only three of the patients had prostate cancer. Most of the rest had multiple myeloma or breast cancer. Fifty-six patients were taking an intravenous bisphosphonate; seven an oral bisphosphonate. The duration of treatment ranged from six to 48 months. Fifty-four of the patients had a complication after dental extraction; nine (14%) had no history of a prior dental procedure, but presented with spontaneous exposure of an alveolar bone. Some patients also had chronic maxillary sinusitis presumably from osteonecrosis. There is no known effective therapy for patients who develop this complication. Surgery almost always makes it worse. Do not allow surgery. Please discuss your plans with me before any type of dental procedure. The Ruggiero article explains that in the past three years, only four patients who were not receiving a bisphosphonate presented with osteonecrosis of jaws. Three of these patients had prior radiation therapy to the jaw area, and one had a primary bone disorder. It has been known for many decades that radiation therapy that includes a jaw bone in its field usually results in osteonecrosis. It is hoped that more modern radiation therapy techniques will be able to reduce the incidence of this side effect.

I stress that patients should not allow any extractions of their teeth if they are or have been treated with intravenous
bisphosphonates. Stopping bisphosphonate treatment has not had a major impact on the progression of this process. The article above points out that five patients had persistent bone necrosis, and even developed new regions of exposed bone despite discontinuing their bisphosphonate. I believe that Aredia (pamidronate) may be less likely to cause this complication, since I only began seeing this complication in the past several years. Whether or not there is a different risk from using Aredia versus Zometa is not certain. I believe Aredia may ultimately be shown to cause osteonecrosis much less often than Zometa.

In June 2004, Novartis issued a 4-page paper entitled, “Expert Panel Recommendations for the Prevention, Diagnosis, and Treatment of Osteonecrosis of the Jaws.” The paper states, “a casual relationship between bisphosphonate therapy and osteonecrosis of the jaws has not been established.” Additional points from the panel: Osteonecrosis of the jaws may remain asymptomatic for many weeks or months, and may only be recognized by the presence of exposed bone in the oral cavity. These lesions are most frequently symptomatic when sites become secondarily infected, there is trauma to the soft tissues, and/or the sharp edges of exposed bone occur. Typical signs and symptoms may include pain, soft tissue swelling, infection, loosening of teeth, drainage and/or exposed bone.” The latter may occur spontaneously, or more commonly at the site of a prior tooth extraction. Other signs and symptoms that may occur include sudden change in the health of periodontal or gum tissue, failure of the gums to heal, undiagnosed mouth pain, loose teeth, or infection. Biopsy is specifically not recommended. For patients currently receiving bisphosphonate therapy, the panel recommends that you aggressively manage dental infections nonsurgically using root canal treatment if at all possible. Root canal therapy is far safer than extractions. A dental procedure, coronal amputation with subsequent root canal therapy on retained roots, is recommended to avoid the need for tooth extraction and, therefore, the potential development of osteonecrosis. Management of patients with osteonecrosis of the jaws includes doing only minimal bony debridement. This means the only goal is filing down some of the edges of tooth or exposed bone to reduce sharp edges, thereby reducing trauma to the surrounding tissues such as your tongue. A removable appliance may be used to cover and protect the exposed bone. Biopsy absolutely is not recommended. Cultures are strongly recommended. The panel suggests using oral rinses with 0.12% chlorhexidine gluconate
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(Peridex) several times a day. Dentures can be worn, but should be adjusted to minimize any further trauma, and should be removed at night. To date, cessation of bisphosphonate therapy appears to have no effect on established osteonecrosis. Antibiotics following dental surgery may be appropriate for this type of patient, and should be continued postoperatively for at least ten days. However, this is a clinical judgment. Hyperbaric oxygen is not beneficial, and dental implants are contraindicated, and may result in further osteonecrosis.

Obviously, the fact that Novartis convened an expert panel and published this report five months after stating that there were fewer than 100 cases of osteonecrosis ever reported to them tells us that this complication is real, and that the incidence of it is increasing dramatically. I believe the reason that most patients are unaware of this complication is because the vast majority of physicians are also unaware that intravenous bisphosphonates may be the cause of osteonecrosis of the jaws. Most patients do not report dental problems to their oncologist and/or urologist believing that there is no medical reason to volunteer this information.

As of August 2004, Compassionate Oncology believes that Novartis will ultimately be instructed by the FDA to send a warning letter to the medical and dental professions reporting that IV bisphosphonates can cause osteonecrosis of the jaws. I speculate that ultimately more than 10% of patients treated every month with an IV bisphosphonate over many years may develop osteonecrosis. I also believe that less frequent (perhaps every two to three months) administration of an IV bisphosphonate may dramatically decrease (or hopefully eliminate) the possibility for developing this complication. I believe that Compassionate Oncology is the only practice that has these outspoken opinions, at least as of 2004, but I predict that many others will ultimately agree with us.

Unrelated to osteonecrosis, I am also of the opinion that Aredia is less likely to cause kidney problems compared to Zometa.

As always --
Be happy,
Be well,
Live long and prosper,

DR. Bob

DR. BOB

Revised 10/11/05
This paper is from Novartis, the company that makes Zometa and Aredia. It was published June 2004. We were the second group to report this complication to Novartis.

Background
Osteonecrosis of the jaws is a rare potential complication in cancer patients receiving radiation, chemotherapy, or other cancer treatment regimens, or in patients with tumors/infectious embolic events. Recently, there have been reports of osteonecrosis of the jaws in cancer patients receiving concomitant anticancer therapy (chemotherapy, steroid therapy, or head and neck radiotherapy) and an intravenous bisphosphonate. There are multiple recognized conditions and risk factors associated with the development of osteonecrosis (not limited to the jaws) in cancer patients. These factors include trauma, female sex, advanced age, edentulous regions, combination cancer therapy (eg, head and neck radiotherapy, chemotherapy, or steroid therapy), blood dyscrasias/metastatic disease, anemia, coagulopathy, surgical dental procedures, alcohol or tobacco use, and prior infection. In the cases reported to date, the majority of patients were receiving long-term chemotherapy and many were receiving short-term intermittent steroid therapy with concomitant bisphosphonate therapy for their cancer and symptom management. In the majority of cases, patients could be managed in a pain-free state with continued exposed bone using a nonsurgical approach consisting of oral systemic antibiotics and 0.12% chlorhexidine gluconate antiseptic containing oral rinses. Surgical intervention was counterproductive and often produced further exposed bone. Bisphosphonates and other cancer therapies were continued in the majority of patients.

A causal relationship between bisphosphonate therapy and osteonecrosis of the jaws has not been established. However, to better understand the pathogenesis and management of patients with osteonecrosis of the jaws, a panel of experts representing oral surgery, oral medicine/oral oncology, endocrinology, and medical oncology convened recently to discuss identification of risk factors for osteonecrosis of the jaws, and to develop clinical guidelines for prevention, early diagnosis, management, and multidisciplinary treatment of osteonecrosis of the jaws in patients with cancer. Additionally, the panel developed recommendations to reduce the incidence of osteonecrosis of the jaws in cancer patients receiving bisphosphonate therapy as well as for patients with clinical osteonecrosis of the jaws who are already receiving bisphosphonates and may require oral surgery. The panel's recommendations are presented here to help guide physicians in patient management.

Clinical Presentation and Diagnosis of Osteonecrosis of the Jaws
- Osteonecrosis of the jaws may remain asymptomatic for many weeks or months and may only be recognized by the presence of the exposed bone in the oral cavity. These lesions are most frequently symptomatic when sites become secondarily infected or there is trauma to the soft tissues via the sharp edges of the exposed bone.
- Typical signs and symptoms include pain, soft-tissue swelling and infection, loosening of teeth, drainage, and exposed bone, which may occur spontaneously or more commonly at the site of previous tooth extraction. Some patients may present with atypical complaints, such as "numbness," the feeling of a "heavy jaw," and various dysesthesias.
- Signs and symptoms that may occur before the development of clinical osteonecrosis include a sudden change in the health of periodontal or mucosal tissues, failure of the oral mucosa to heal, undiagnosed oral pain, loose teeth, or soft-tissue infection.
- If osteonecrosis is suspected, panoramic and tomographic imaging may be performed to rule out other etiologies (eg, cysts or impacted teeth). Smaller intraoral films can also be used to demonstrate subtle bone changes.
- Microbial cultures may provide a differential diagnosis for comorbid oral infections.
- Tissue biopsy should be performed only if metastatic disease is suspected. If a biopsy is performed to rule out metastatic tumor, microbial cultures (aerobic and anaerobic) may provide identification of the pathogens causing secondary infections (Note: actinomycosis organisms are often seen microscopically or identified upon culture.)
Potential Risk Factors for the Development of Osteonecrosis of the Jaws

- The precise risk factors for osteonecrosis of the jaws have not been identified. Risk factors may include:
  - Concomitant therapy with steroids, chemotherapy, and IV bisphosphonates (in few instances after short dosing)
  - Dental extraction, infectious disease, and/or trauma
  - Occasionally the concomitant risk factors may not be apparent

- Other risk factors that have been previously identified for osteonecrosis (not limited to the jaws) include:
  - Head and neck radiotherapy, chemotherapy, immunotherapy, or other cancer treatment regimens
  - Female gender, coagulopathies, infections, periodontal disease, bony exostosis, previous invasive dental procedures, dental prostheses, arthritis, blood dyscrasias, vascular disorders, alcohol abuse, smoking, and malnutrition. Controversially, anesthetics with vasoconstrictors (ie, novocaine) have been reported as potentially contributing to some cases of osteonecrosis

Potential Preventive Measures Prior to the Initiation of IV Bisphosphonate Therapy

- Avoid any elective jaw procedure that will require bone to heal.
- Recommend a routine clinical dental exam that may include a panoramic jaw radiograph to detect potential dental and periodontal infections.
- If bisphosphonate therapy can be briefly delayed without the risk of a skeletal-related complication, teeth with a poor prognosis or in need of extraction should be extracted and other dental surgeries should be completed prior to the initiation of bisphosphonate therapy. The benefit or risk of withholding bisphosphonate therapy has not been evaluated to date. Therefore, the decision to withhold bisphosphonate treatment must be made by the treating oncologist in consultation with an oral maxillofacial surgeon or another dental specialist.
  - Suggested preventive dentistry before initiation of chemotherapy, immunotherapy, and/or bisphosphonate therapy may include:
    - Remove abscessed and nonrestorable teeth and involved periodontal tissues
    - Functional rehabilitation of salvageable dentition, including endodontic therapy
    - Dental prophylaxis, caries control, and stabilizing restorative dental care
    - Examine dentures to ensure proper fit (remove dentures at night)
    - Oral self-care hygiene education
    - Prophylactic antibiotics are not indicated before routine dentistry unless otherwise required for prophylaxis of bacteremia in those patients at risk (eg, those with an indwelling catheter)
- Educate patients regarding the importance of good dental hygiene and symptom reporting
  - Suggest regularly scheduled hard- and soft-tissue oral assessments, possibly every 3 to 4 months, depending on risk
- Oncologists should perform a brief visual inspection of the oral cavity at baseline and at every follow-up visit

Dental Treatment for Patients Currently Receiving Bisphosphonate Therapy

- Maintain excellent oral hygiene to reduce the risk of dental and periodontal infections
- Check and adjust removable dentures for potential soft-tissue injury, especially tissue overlying bone
- Perform routine dental cleanings, being sure to avoid soft-tissue injury
- Aggressively manage dental infections nonsurgically with root canal treatment, if possible or with minimal surgical intervention
- Endodontic (root canal) therapy is preferable to extractions when possible. It may be necessary to carry out coronal amputation with subsequent root canal therapy on retained roots to avoid the need for tooth extraction and, therefore, the potential development of osteonecrosis
Management of Patients With Osteonecrosis of the Jaws

- Consultation with an oral surgeon or dental oncologist
- A nonsurgical approach may prevent further osseous injury
  - Minimal bony debridement only to reduce sharp edges so as to reduce trauma to surrounding or opposing tissues (e.g., lateral tongue where lingual mandibular bone is exposed)
  - A removable appliance may be used to cover and protect the exposed bone
  - A protective stent may be of benefit for patients with exposed bone that causes trauma to adjacent tissues and in patients where the osteonecrotic site is repeatedly traumatized during normal oral function. A thin, vinyl, vacuformed mouthguard or thin acrylic stent may be used, provided that the device does not further traumatize the osteonecrotic site and that it can be kept free of bacterial plaque and debris
  - Biopsy should be performed only if metastasis to the jaw is suspected. A portion of the biopsy should be submitted for microbial analysis as well as culture from the biopsy site
- Intermittent or continuous antibiotic therapy may be beneficial (cultures should be collected to determine the appropriate antibiotic therapy). The goal of antibiotic therapy is to prevent secondary soft-tissue infection and, therefore, pain as well as to prevent osteomyelitis. At this time, the duration of antibiotic therapy and the benefit of oral antiseptic rinses have not been defined, but pain control and disease control have been observed with this management strategy. The decision to treat with an antibiotic is a clinical judgment that should be made by an oral maxillofacial surgeon or other dental specialist in consultation with the treating physician/oncologist. Cultures, including those for aerobic, anaerobic, viral, and fungal species, may be collected to determine the appropriate antimicrobial intervention.
  - Antibiotics that have been found useful for osteonecrosis include:
    - Penicillin VK 500 mg or amoxicillin 500 mg; both 4 times daily (QID) initially and twice daily (BID) for maintenance
    - If penicillin allergic:
      - Clindamycin 150 to 300 mg QID
      - Vibramycin 100 mg once daily (QD)
      - Erythromycin ethylsuccinate 400 mg 3 times daily (TID)
    - Antifungals when required:
      - Nystatin oral suspension 5 to 15 mL QID or 100,000 IU/mL
      - Mycelex troches ( clotrimazole 10 mg ) x 5/day
      - Fluconazole 200 mg initially, then 100 mg QD
      - Other potential systemic antifungals include itraconazole or ketoconazole
    - Antivirals, if required:
      - Acyclovir 400 mg BID
      - Valacyclovir hydrochloride 500 mg to 2 g BID
    - 0.12% chlorhexidine gluconate (Peridex*) oral rinses or minocycline hydrochloride (Arestin*) periodontal pockets can be used
- Dentures can be worn, but should be adjusted to minimize soft-tissue trauma or irritation, especially in light of ongoing antibiotic therapy, and should be removed at night
- All patients should be monitored every 3 months or sooner if symptoms continue or worsen
- Cessation or interruption of bisphosphonate therapy may be considered in severe cases. However, close coordination between the dental specialist and the medical oncologist is recommended, taking into consideration the risk of skeletal complications (including hypercalcemia of malignancy) versus the risk of osteonecrosis. To date, cessation of bisphosphonate therapy appears to have no effect on established osteonecrosis. However, further study is needed
If surgery is required in patients with established osteonecrosis, cessation or interruption of bisphosphonate therapy may be considered taking into account the potential risk of further osteonecrosis versus the risk of skeletal complications or hypercalcemia of malignancy. It is unknown whether or not there is benefit to cessation of bisphosphonate therapy. However, cessation of bisphosphonate therapy may be prudent in some patients if the risk of osteonecrosis outweighs the risk of skeletal complications or hypercalcemia of malignancy. Therefore, the decision to stop bisphosphonate therapy must be coordinated between the treating oncologist and an oral surgeon. Antibiotics following dental surgery may be appropriate in this patient population and should be continued postoperatively for at least 10 days. However, this is a clinical judgment that must be made in collaboration with the treating oncologist. Cultures taken from the extraction site at the time of oral surgery can provide guidance in making this decision.

Hyperbaric oxygen has not been shown to be effective and, therefore, is not recommended.

Osseointegrated dental implants are contraindicated and may result in further osteonecrosis.

References


* The expert panel representatives were as follows: Kathryn Damato, RDH, MS, CCRP, University of Connecticut Health Center, Farmington, Conn; Julie Gralow, MD, University of Washington Medical Center, Seattle, Wash; Ana Hoff, MD, University of Texas MD Anderson Cancer Center, Houston, Tex; Joseph Huryn, DDS, Memorial Sloan-Kettering Cancer Center, New York, NY; Robert Marx, DDS, University of Miami School of Medicine, Miami, Fla; Salvatore Ruggiero, DMD, MD, Long Island Jewish Medical Center, New Hyde Park, NY; Mark Schubert, DDS, MDS, Seattle Cancer Care Alliance, Seattle, Wash; Bela Toth, DDS, MS, University of Texas MD Anderson Cancer Center, Houston, Tex; Vicente Valero, MD, FACP, The University of Texas MD Anderson Cancer Center, Houston, Tex.