



American Association of Oral and Maxillofacial Surgeons
Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw—2009 Update
Approved by the Board of Trustees January 2009

Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws: Salvatore L. Ruggiero, DMD, MD, Associate Professor, Division of Oral and Maxillofacial Surgery, Stony Brook School of Dental Medicine, Attending, Long Island Jewish Medical Center, New Hyde Park, NY, New York Center for Orthognathic and Maxillofacial Surgery, Lake Success, NY; Thomas B. Dodson, DMD, MPH, Visiting Oral and Maxillofacial Surgeon and Director, Center for Applied Clinical Investigations, Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital, Associate Professor, Harvard School of Dental Medicine, Boston, MA; Leon A. Assael, DMD, Professor and Chairman, Oral and Maxillofacial Surgery, Oregon Health and Science University, Portland, OR; Regina Landesberg, DMD, PhD, Associate Professor, Columbia University, SDOS Division OMFS, New York, NY; Robert E. Marx, DDS, Professor of Surgery and Chief, Division of Oral and Maxillofacial Surgery, University of Miami School of Medicine, Miami, FL; Bhoomi Mehrotra, MD, Division of Hematology-Medical Oncology, Long Island Jewish Medical Center, New Hyde Park, NY.

Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) adversely affects the quality of life, producing significant morbidity in afflicted patients. Strategies for management of patients with or at risk for BRONJ were set forth in the American Association of Oral and Maxillofacial Surgeons (AAOMS) *Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws (Position Paper)* and approved by the Board of Trustees in September 2006¹. The *Position Paper* was developed by a Task Force appointed by the Board and composed of clinicians with extensive experience in caring for these patients and basic science researchers. The knowledge base and experience in addressing BRONJ has expanded, necessitating modifications and refinements to the original *Position Paper*. The Task Force was re-convened in August 2008 to review the 2006 recommendations, appraise the current literature, and revise the *Position Paper* and recommendations, where indicated. This update contains revisions to diagnosis and staging and management strategies, and highlights the status of basic science research. AAOMS considers it vitally important that this information be disseminated to other dental and medical specialties.

Purpose

The purpose of this updated position paper is to provide:

1. perspectives on the risk of developing BRONJ and the risks and benefits of bisphosphonates in order to facilitate medical decision-making of both the treating physician and the patient;

2. guidance to clinicians regarding the differential diagnosis of BRONJ in patients with a history of treatment with intravenous (IV) or oral bisphosphonates; and
3. guidance to clinicians on possible BRONJ prevention measures and management of patients with BRONJ based on the presenting stage of the disease.

Background

Indications and benefits of bisphosphonate therapy

Intravenous (IV) bisphosphonates are primarily used and effective in the treatment and management of cancer-related conditions including hypercalcemia of malignancy, skeletal-related events associated with bone metastases in the context of solid tumors such as breast cancer, prostate cancer and lung cancer, and management of lytic lesions in the setting of multiple myeloma.²⁻¹³ While bisphosphonates have not been shown to improve cancer-specific survival, they have had a significant positive effect on the quality of life for patients with advanced cancer involving the skeleton. Before 2001, pamidronate (Aredia[®]) was the only drug approved in the United States for treatment of metastatic bone disease. In 2002, zoledronic acid (Zometa[®]) was approved for this indication by the US Food and Drug Administration (FDA).¹³ More recently, a once yearly infusion of zoledronate (Reclast[®]) and a parenteral formulation of ibandronate (Boniva[®]) administered every three months have been approved by the FDA for management of osteoporosis.¹⁴

Oral bisphosphonates are approved to treat osteoporosis and are frequently used to treat osteopenia as well.¹⁵ They are also used for a variety of less common conditions such as Paget's disease of bone, and osteogenesis imperfecta of childhood.¹⁶⁻¹⁷ By far the most prevalent and common indication, however, is osteoporosis.¹⁸⁻¹⁹ Osteoporosis may arise in the context of other diseases such as inflammatory bowel disease or primary biliary cirrhosis, as the result of medications, most commonly steroids, or as a consequence of postmenopausal aging.²⁰⁻²²

Risks of bisphosphonate therapy

Oral and maxillofacial surgeons first recognized and reported cases of non-healing exposed bone in the maxillofacial region in patients treated with IV bisphosphonates.²³⁻²⁴ Since these initial reports, several case series and reviews have been published.²⁵⁻³² In September 2004, Novartis, the manufacturer of the IV bisphosphonates pamidronate (Aredia[®]) and zoledronic acid (Zometa[®]), notified healthcare professionals of additions to the labeling of these products, which provided cautionary language related to the development of osteonecrosis of the jaws.³³ This was followed in 2005 by a broader drug class warning of this complication for all bisphosphonates including the oral preparations.³⁴⁻³⁵ See Appendix 1 for list of bisphosphonate medications that are currently available in the United States.

Causality

Epidemiologic studies have established a compelling, albeit circumstantial, association between IV bisphosphonates and BRONJ in the setting of malignant disease. An association between IV bisphosphonate exposure and BRONJ may be hypothesized based on the following observations: 1) a positive correlation between bisphosphonate potency and risk for developing BRONJ; 2) a negative correlation between bisphosphonate potency and duration of bisphosphonate exposure prior to developing BRONJ; and 3) a positive correlation between duration of bisphosphonate exposure and developing BRONJ. However, the current level of evidence does not fully support

a cause and effect relationship between bisphosphonate exposure and necrosis of the jaw.³⁶ Although causality may never be proven, emerging experimental and epidemiologic studies have established a firm foundation for a strong association between monthly IV bisphosphonate therapy and BRONJ. The causal association between oral or IV bisphosphonates for treating osteoporosis and BRONJ is much more difficult to establish.

BRONJ Case Definition

To distinguish BRONJ from other delayed healing conditions, the following working definition of BRONJ has been adopted by the AAOMS and remains unchanged from the original *Position Paper*¹:

Patients may be considered to have BRONJ if all of the following three characteristics are present:

- 1. Current or previous treatment with a bisphosphonate;*
- 2. Exposed bone in the maxillofacial region that has persisted for more than eight weeks; and*
- 3. No history of radiation therapy to the jaws.*

It is important to understand that patients at risk for or with established BRONJ can also present with other common clinical conditions not to be confused with BRONJ. Commonly misdiagnosed conditions may include, but are not limited to alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology and TMJ disorders.

Estimated Incidence and Factors Associated with Development of BRONJ

IV bisphosphonates and incidence of BRONJ

The clinical efficacy of IV bisphosphonates for the treatment of hypercalcemia and bone metastases is well established.²⁻⁵ IV bisphosphonate exposure in the setting of managing malignancy remains the major risk factor for BRONJ. Based on case series, case-controlled and cohort studies, estimates of the cumulative incidence of BRONJ range from 0.8%-12%.³⁷⁻⁴⁵

Zoledronic acid (Reclast[®]) administered once per year for the treatment of osteoporosis was approved by the FDA in August 2007.¹⁴ A single, large, prospective placebo-controlled study established its efficacy for this indication through three years of treatment.⁴⁶ Two cases of osteonecrosis of the jaw were reported, one each in the treatment and control groups, suggesting a low risk of BRONJ with this treatment modality through three years.

Oral bisphosphonates and incidence of BRONJ

The clinical efficacy of oral bisphosphonates for the treatment of osteopenia/osteoporosis is well established and is reflected in the fact that over 190 million oral bisphosphonate prescriptions have been dispensed worldwide.⁴⁷ The specialty's experiences have identified several BRONJ cases related to oral bisphosphonates.^{24,26} Patients under treatment with oral bisphosphonate therapy are at a considerably lower risk for BRONJ than cancer patients treated with monthly IV bisphosphonates. Based on data from the manufacturer of alendronate (Merck), the incidence of BRONJ was calculated to be 0.7/100,000 person/years of exposure.⁴⁸ This was derived from the number of reported (not confirmed) cases that were deemed to likely represent BRONJ divided by the number of alendronate pills prescribed since approval of the drug, and converted to number of patient years. While this is the best available data to date, there may be serious under-

reporting and, as noted above, none confirmed. Surveillance data from Australia estimated the incidence of BRONJ for patients treated weekly with alendronate as 0.01-0.04%.⁴⁹ In a survey study of over 13, 000 Kaiser-Permanente members, the prevalence of BRONJ in patients receiving long-term oral bisphosphonate therapy was reported at 0.06% (1:1,700).⁵⁰ Felsenberg reported a prevalence of BRONJ among patients treated with bisphosphonates for osteoporosis of 0.00038%, based on reports of 3 cases to the German Central Registry of Necrosis of the Jaw.⁵¹

Based on available data, the risk of BRONJ for patients receiving IV bisphosphonates is significantly greater than the risk for patients receiving oral bisphosphonates. Regardless, given the large number of patients receiving oral bisphosphonates for the treatment of osteoporosis/osteopenia it is likely that most practitioners may encounter some patients with BRONJ. It is important to determine accurately the incidence of BRONJ in this population and to assess the risk associated with long-term use, i.e., greater than 3 years, of oral bisphosphonates. The low prevalence of BRONJ in osteoporosis patients poses a significant challenge for future clinical trials aimed at establishing accurate incidence data.

Risk factors

In the original *Position Paper* BRONJ risks were categorized as drug-related, local, and demographic or systemic factors.¹ Other medications, such as steroids, thalidomide, and other chemotherapeutic agents were thought to be risk factors, but no measurable associations were identified. Subsequently, two new sets of factors, genetic and preventative, are available to report.

I. Drug-related risk factors include:

A. Bisphosphonate potency: zoledronate (Zometa[®]) is more potent than pamidronate (Aredia[®]) and pamidronate (Aredia[®]) is more potent than the oral bisphosphonates; the IV route of administration results in a greater drug exposure than the oral route.^{37-38, 45, 52} Using a number of different risk measures, the BRONJ risk among cancer patients given IV bisphosphonate exposure ranged from 2.7 to 4.2, suggesting that cancer patients receiving IV bisphosphonates have a 2.7 to 4.2-fold increased risk for BRONJ than cancer patients not exposed to IV bisphosphonates.^{37, 53}

B. Duration of therapy: longer duration appears to be associated with increased risk.^{38, 45}

II. Local risk factors include:

- A. Dentoalveolar surgery, including, but not limited to^{37, 45, 52}
1. Extractions
 2. Dental implant placement
 3. Periapical surgery
 4. Periodontal surgery involving osseous injury

In the original *Position Paper*, local factors such as dentoalveolar procedures, local anatomic structures, e.g., tori, and concomitant dental disease were hypothesized to increase the risk for BRONJ in the setting of IV bisphosphonate exposure.¹ Patients receiving IV bisphosphonates and undergoing dentoalveolar surgery are at least seven

times more likely to develop BRONJ than patients who are not having dentoalveolar surgery.^{45, 52} In the setting of IV bisphosphonate exposure, four studies reported that dentoalveolar procedures or concomitant dental disease increased the risk for BRONJ between 5.3 (odds ratio) to 21 (relative risk).^{37, 52, 54-55} In other words, cancer patients treated with IV bisphosphonates who undergo dentoalveolar procedures have a 5 to 21-fold increased risk for BRONJ than cancer patients treated with IV bisphosphonates who do not undergo dentoalveolar procedures.

B. Local anatomy

1. Mandible
 - a. Lingual tori
 - b. Mylohyoid ridge
2. Maxilla
 - a. Palatal tori

It has been observed that lesions are found more commonly in the mandible than the maxilla (2:1 ratio) and more commonly in areas with thin mucosa overlying bony prominences such as tori, bony exostoses and the mylohyoid ridge.^{24, 26, 56} No data are available to provide risk estimates for anatomic structures and BRONJ.

C. Concomitant oral disease

Cancer patients exposed to IV bisphosphonates with a history of inflammatory dental disease, e.g., periodontal and dental abscesses, are at a seven-fold increased risk for developing BRONJ.⁴⁵

III. Demographic and systemic factors

In the original *Position Paper*, age, race, and cancer diagnosis with or without osteoporosis were reported as risk factors for BRONJ.¹ Seven studies report increasing age as consistently associated with BRONJ.^{38-39, 52, 54-55, 57-58} Sex was not statistically associated with BRONJ.^{38-39, 52, 54-55, 57} Race was reported in one study to be a risk factor, with Caucasians having an increased risk for BRONJ compared with blacks.⁵²

Other systemic factors or conditions, i.e., renal dialysis, low hemoglobin, obesity, and diabetes, were variably reported to increase the risk for BRONJ.^{53-54, 59} Malignancy type was not statistically associated with an increased risk for BRONJ, although the presence of metastatic disease reached near statistical significance, i.e., $p = 0.051$, in Wessel's report.^{38, 53}

In contrast to the original *Position Paper*, a few current studies noted an increased risk for BRONJ among patients exposed to chemotherapeutic agents, i.e., cyclophosphamide, erythropoietin, and steroids.^{54, 57} Others, however, failed to confirm the association between chemotherapeutic agents and BRONJ risk.^{37, 39, 52-53, 58} Wessel, et al, reported an increased risk for BRONJ among tobacco users, but no increased risk associated with alcohol exposure.⁵³

IV. Genetic factors

Sarasquete, et al, demonstrated that genetic perturbations, i.e. single nucleotide polymorphisms (SNPs), in the cytochrome P450-2C gene (CYP2C8) gene were associated with an increased risk for BRONJ among multiple myeloma patients treated with IV bisphosphonates.⁶⁰

V. Preventative factors

The AAOMS Taskforce on BRONJ recommended that patients undergo dental evaluations and receive necessary treatment prior to initiating IV bisphosphonates therapy.¹ In addition, given the long-term biologic activity of IV bisphosphonates, one may hypothesize that different dosing regimens may be equally effective and decrease the risk for BRONJ.

Using a retrospective cohort study design, Coso, et al, evaluated the BRONJ and skeletal-related events (SRE), e.g. pathologic fracture, in multiple myeloma patients using different dosing schedules for zoledronate.⁵⁸ These findings suggest that alternative dosing schedules that reduce IV bisphosphonate exposure have comparable outcomes in terms of preventing SREs and a decreased risk of BRONJ.

Since the original *Position Paper* on BRONJ, several studies have generated quantitative estimates of risk of BRONJ in the setting of IV bisphosphonates exposure. The two largest risk factors for BRONJ are IV bisphosphonate exposure and dentoalveolar procedures. Recent studies suggest that manipulation of IV bisphosphonates dosing may be effective in reducing SREs and minimizing BRONJ risk.⁵⁸ In addition, preventative dental interventions before initiating IV bisphosphonate treatment can also effectively reduce, but not eliminate, the risk of BRONJ.

Management Strategies for Patients Treated with Bisphosphonates

Prevention of BRONJ

Prior to treatment with monthly IV bisphosphonates, the patient should have a thorough oral examination, any unsalvageable teeth should be removed, all invasive dental procedures should be completed and optimal periodontal health should be achieved.

Three studies reported that preventative dental treatment decreased BRONJ risk among patients with malignancy treated with IV bisphosphonates.⁶¹⁻⁶³ These findings suggest that, while BRONJ is not eliminated, dental evaluations and treatment prior to initiating IV bisphosphonate therapy among cancer patients reduces BRONJ risk.

The risk of developing BRONJ associated with oral bisphosphonates, while exceedingly small, appears to increase when the duration of therapy exceeds three years. This time frame may be shortened in the presence of certain comorbidities, such as chronic corticosteroid use. *If systemic conditions permit*, the clinician may consider discontinuation of oral bisphosphonates for a period of three months prior to and three months following elective invasive dental surgery in order to lower the risk of BRONJ. The rationale for this approach is based on extrapolated data that demonstrate fluctuations of osteoclast function, which is related to bisphosphonate therapy, and recent outcomes studies that show improved outcome of BRONJ treatment with drug cessation.⁶¹⁻⁶⁴ Long-term, prospective studies are required to establish the efficacy of drug holidays in reducing the risk of BRONJ for patients receiving oral bisphosphonates. The risk

reduction may vary depending on the duration of bisphosphonate exposure. Modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

Treatment Goals

The major goals of treatment for patients at risk of developing or who have BRONJ are:

- Prioritization and support of continued oncologic treatment in patients receiving IV bisphosphonates.
 - Oncology patients can benefit greatly from the therapeutic effect of bisphosphonates by controlling bone pain and reducing the incidence of other skeletal complications.
- Preservation of quality of life through:
 - Patient education and reassurance
 - Control of pain
 - Control of secondary infection
 - Prevention of extension of lesion and development of new areas of necrosis

Treatment Strategies^{26, 31, 65-67}

A. Patients about to initiate intravenous bisphosphonate treatment

The treatment objective for this group of patients is to minimize the risk of developing BRONJ. Although a small percentage of patients receiving bisphosphonates develop osteonecrosis of the jaw spontaneously, the majority of affected patients experience this complication following dentoalveolar surgery.^{37, 45, 52} Therefore *if systemic conditions permit*, initiation of bisphosphonate therapy should be delayed until dental health is optimized.⁶¹⁻⁶³ This decision must be made in conjunction with the treating physician and dentist and other specialists involved in the care of the patient.

Non-restorable teeth and those with a poor prognosis should be extracted. Other necessary elective dentoalveolar surgery should also be completed at this time. Based on experience with osteoradionecrosis, it appears advisable that bisphosphonate therapy should be delayed, *if systemic conditions permit*, until the extraction site has mucosalized (14-21 days) or until there is adequate osseous healing. Dental prophylaxis, caries control and conservative restorative dentistry are critical to maintaining functionally sound teeth. This level of care must be continued indefinitely.

Patients with full or partial dentures should be examined for areas of mucosal trauma, especially along the lingual flange region. It is critical that patients be educated as to the importance of dental hygiene and regular dental evaluations, and specifically instructed to report any pain, swelling or exposed bone.

Medical oncologists should evaluate and manage patients scheduled to receive IV bisphosphonates similarly to those patients scheduled to initiate radiation therapy to the head and neck. The osteoradionecrosis prevention protocols are guidelines that are familiar to most oncologists and general dentists.

B. Asymptomatic patients receiving intravenous bisphosphonates

Maintaining good oral hygiene and dental care is of paramount importance in preventing dental disease that may require dentoalveolar surgery. Procedures that involve direct osseous injury should be avoided. Non-restorable teeth may be treated by removal of the crown and endodontic treatment of the remaining roots.⁶⁷ Placement of dental implants should be avoided in the oncology patient exposed to the more potent intravenous bisphosphonate medications (zoledronic acid and pamidronate) on a frequent dosing schedule (4-12 times per year).

Zoledronic acid (Reclast[®]) administered once per year for the treatment of osteoporosis was approved by the FDA in August 2007.¹⁴ A single, large, prospective placebo-controlled study established its efficacy for this indication through three years of treatment.⁴⁶ Two cases of osteonecrosis of the jaw were reported, one each in the treatment and control groups, suggesting a low risk of BRONJ with this treatment modality through three years. The efficacy of a drug holiday for patients receiving yearly zoledronic acid therapy and the appropriate timing of dentoalveolar surgery (if required) is unknown and therefore requires further study.

C. Asymptomatic patients receiving oral bisphosphonate therapy

Patients receiving oral bisphosphonates are also at risk for developing BRONJ, but to a much lesser degree than those treated with intravenous bisphosphonates.^{24, 26-27, 56}

BRONJ can develop spontaneously or after minor trauma. In general, these patients seem to have less severe manifestations of necrosis and respond more readily to stage specific treatment regimens.⁶⁸⁻⁶⁹ (See Table 1.) Elective dentoalveolar surgery does not appear to be contraindicated in this group. It is recommended that patients be adequately informed of the small risk of compromised bone healing. The utilization of bone turnover marker levels in conjunction with a drug holiday has been reported as an additional tool to guide treatment decisions in patients exposed to oral bisphosphonates.⁶⁸ The efficacy of utilizing a systemic marker of bone turnover to assess the risk of developing jaw necrosis in patients at risk will require further research before it can be considered a valid risk assessment tool. Long-term, prospective studies are also required to establish the efficacy of drug holidays in reducing the risk of BRONJ for these patients.

The risk of BRONJ may be associated with increased duration of treatment with oral bisphosphonates, i.e., \geq three years. There has been no information to suggest that monthly dosing of oral bisphosphonates, i.e., ibandronate (Boniva[®]), risedronate (Actonel[®]), is associated with either an elevated or reduced risk of BRONJ when compared with weekly dosing regimens. The risk of long-term oral bisphosphonate therapy clearly requires continued analysis and research.

Sound recommendations based on strong clinical research designs are still lacking for patients taking oral bisphosphonates. The Task Force strategies outlined below have remained essentially unchanged from those in the original *Position Paper* and are based on clinical experience of clinicians (expert opinion) involved in caring for these patients and case series.^{63, 65-68} The risk of developing BRONJ associated with oral

bisphosphonates increased when duration of therapy exceeded three years. Although the current level of evidence is not strong, the Task Force considers these strategies for patients receiving oral bisphosphonates as a prudent set of guidelines that will not compromise the long-term management of their osteoporosis. As more data become available and a better level of evidence is obtained, these strategies will be updated and modified as necessary.

For individuals who have taken an oral bisphosphonate for less than three years and have no clinical risk factors, no alteration or delay in the planned surgery is necessary. This includes any and all procedures common to oral and maxillofacial surgeons, periodontists and other dental providers.

It is suggested that if dental implants are placed, informed consent should be provided related to possible future implant failure and possible osteonecrosis of the jaws if the patient continues to take an oral bisphosphonate. Such patients should be placed on a regular recall schedule. It is also advisable to contact the provider who originally prescribed the oral bisphosphonate and suggest monitoring such patients and considering either alternate dosing of the bisphosphonate, drug holidays or an alternative to the bisphosphonate therapy.

For those patients who have taken an oral bisphosphonate for less than three years and have also taken corticosteroids concomitantly, the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate (drug holiday) for at least three months prior to oral surgery, if systemic conditions permit. The bisphosphonate should not be restarted until osseous healing has occurred. These strategies are based on the opinion of experts with significant clinical experience and the hypothesis that concomitant treatment with corticosteroids may increase the risk of developing BRONJ and that a “drug holiday” may mitigate this risk. Long-term, prospective studies are required to establish the efficacy of drug holidays in reducing the risk of BRONJ for these patients.

For those patients who have taken an oral bisphosphonate for more than three years with or without any concomitant prednisone or other steroid medication, the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate for three months prior to oral surgery, if systemic conditions permit. The bisphosphonate should not be restarted until osseous healing has occurred. These strategies are based on the opinion of experts and observational studies.⁶⁸

D. Patients with BRONJ

The treatment objectives for patients with an established diagnosis of BRONJ are to eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone necrosis.

These patients respond less predictably to the established surgical treatment algorithms for osteomyelitis or osteoradionecrosis. Surgical debridement has been variably effective in eradicating the necrotic bone.^{22-24, 29} It may be difficult to obtain a surgical margin

with viable bleeding bone as the entire jawbone has been exposed to the pharmacologic influence of the bisphosphonate. Therefore, surgical treatment should be delayed if possible and reserved for those patients with stage 3 disease or in those cases with well-defined sequestrum. Areas of necrotic bone that are a constant source of soft tissue irritation should be removed or recontoured without exposure of additional bone. Loose segments of bony sequestrum should be removed without exposing uninvolved bone.⁷⁰ The extraction of symptomatic teeth within exposed, necrotic bone should be considered, since it appears unlikely that the extraction will exacerbate the established necrotic process.

Patients with established BRONJ should avoid elective dentoalveolar surgical procedures, since these surgical sites may result in additional areas of exposed necrotic bone. Symptomatic patients with stage 3 disease may require resection and immediate reconstruction with a reconstruction plate or an obturator. Recent case series have described acceptable outcomes following surgical therapy for patients with stage 2 and stage 3 disease.⁶⁹ The potential for failure of the reconstruction plate because of the generalized effects of the bisphosphonate exposure needs to be recognized by the clinician and patient. Immediate reconstruction with non-vascularized or vascularized bone is still considered potentially problematic as necrotic bone may be present at the resection margins or develop at the recipient site.

The effectiveness of hyperbaric oxygen therapy as an adjunct to non-surgical and surgical treatment is under investigation at two institutions where a randomized controlled trial is underway.⁷¹ Preliminary results have shown some improvement in wound healing and long-term pain scores, but its use as the sole treatment modality for BRONJ cannot be supported at this time.

Case reports with small sample sizes have documented the use of other non-surgical treatment strategies, such as, platelet rich plasma, parathyroid hormone, and bone morphogenic protein.⁷² The efficacy of these treatment modalities needs to be established through additional research and controlled studies.

Staging and Treatment Strategies (See Table 1)

Staging

Since the publication of the original *Position Paper*, changes in the staging system are necessary so that patients could be more accurately stratified. Specifically, a Stage 0 category was added to include patients with non-specific symptoms, or clinical and radiographic abnormalities that may be due to bisphosphonate exposure. The risk of a patient with Stage 0 disease advancing to a higher disease stage is unknown at this time. The definition of Stage 3 disease was also amended to include and more appropriately categorize advanced maxillary disease.

In order to direct rational treatment guidelines and collect data to assess the prognosis in patients who have used either IV or oral bisphosphonates, the AAOMS proposes use of the following revised staging system:

Patients at risk

No apparent necrotic bone in asymptomatic patients who have been treated with IV or oral bisphosphonates.

Stage 0

Patients with no clinical evidence of necrotic bone, but present with non-specific symptoms or clinical and radiographic findings, such as,

Symptoms

- odontalgia not explained by an odontogenic cause
- dull, aching bone pain in the body of the mandible, which may radiate to the temporomandibular joint region
- sinus pain, which may be associated with inflammation and thickening of the maxillary sinus wall
- altered neurosensory function

Clinical Findings

- loosening of teeth not explained by chronic periodontal disease
- periapical/periodontal fistula that is not associated with pulpal necrosis due to caries

Radiographic Findings

- alveolar bone loss or resorption not attributable to chronic periodontal disease
- changes to trabecular pattern—dense woven bone and persistence of unremodeled bone in extraction sockets
- thickening/obscuring of periodontal ligament (thickening of the lamina dura and decreased size of the periodontal ligament space)
- inferior alveolar canal narrowing

These non-specific findings, which characterize Stage 0, may occur in patients with a prior history of Stage 1, 2, or 3 disease who have healed and have no clinical evidence of exposed bone.

Stage 1

Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection.

Stage 2

Exposed and necrotic bone in patients with pain and clinical evidence of infection.

Stage 3

Exposed and necrotic bone in patients with pain, infection, and one or more of the following:

- exposed necrotic bone extending beyond the region of alveolar bone, i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla
- pathologic fracture
- extra-oral fistula
- oral antral/oral nasal communication
- osteolysis extending to the inferior border of the mandible or sinus floor

Treatment strategies

At risk - Patients who are at risk of developing BRONJ by virtue of the fact that they have been exposed to a bisphosphonate do not require any treatment. However, these patients should be informed of the risks of developing BRONJ, as well as the signs and symptoms of this disease process.

Stage 0 – Provide symptomatic treatment, and conservatively manage other local factors, such as caries and periodontal disease. Systemic management may include the use of medication for chronic pain and control of infection with antibiotics, when indicated.

Stage 1 – These patients benefit from the use of oral antimicrobial rinses, such as chlorhexidine 0.12%. No surgical treatment is indicated.

Stage 2 – These patients benefit from the use of oral antimicrobial rinses in combination with antibiotic therapy. It is hypothesized that the pathogenesis of BRONJ may be related to factors adversely influencing bone remodeling. Additionally, BRONJ is not due to a primary infectious etiology. Most of the isolated microbes have been sensitive to the penicillin group of antibiotics. Quinolones, metronidazole, clindamycin, doxycycline and erythromycin have been used with success in those patients who are allergic to penicillin. Microbial cultures should also be analyzed for the presence of actinomyces species of bacteria. If this microbe is isolated, the antibiotic regimen should be adjusted accordingly. In some refractory cases, patients may require combination antibiotic therapy, long-term antibiotic maintenance, or a course of intravenous antibiotic therapy.

Stage 3 – These patients benefit from debridement, including resection, in combination with antibiotic therapy, which may offer long-term palliation with resolution of acute infection and pain.

Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.

Discontinuation of bisphosphonate therapy

IV bisphosphonates

Oncology patients benefit greatly from the therapeutic effects of bisphosphonates by controlling bone pain and the incidence of pathologic fractures. Discontinuation of IV bisphosphonates offers no short-term benefit. However *if systemic conditions permit*, long-term discontinuation may be beneficial in stabilizing established sites of BRONJ, reducing the risk of new site development and reducing clinical symptoms.⁶¹⁻⁶³ The risks and benefits of continuing bisphosphonate therapy should be made only by the treating oncologist in consultation with the OMS and the patient.

Oral bisphosphonates

Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease.⁶⁸ Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution following debridement surgery. *If systemic conditions permit*, modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

Table 1 Staging and Treatment Strategies

BRONJ [†] Staging	Treatment Strategies [‡]
At risk category No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	<ul style="list-style-type: none"> • No treatment indicated • Patient education
Stage 0 No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms	<ul style="list-style-type: none"> • Systemic management, including the use of pain medication and antibiotics
Stage 1 Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2 Exposed and necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	<ul style="list-style-type: none"> • Symptomatic treatment with oral antibiotics • Oral antibacterial mouth rinse • Pain control • Superficial debridement to relieve soft tissue irritation
Stage 3 Exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement/resection for longer term palliation of infection and pain

[†] Exposed bone in the maxillofacial region without resolution in 8-12 weeks in persons treated with a bisphosphonate who have not received radiation therapy to the jaws.

[‡] Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.

[‡] Discontinuation of the IV bisphosphonates shows no short-term benefit. However, *if systemic conditions permit*, long-term discontinuation may be beneficial in stabilizing established sites of BRONJ, reducing the risk of new site development, and reducing clinical symptoms. The risks and benefits of continuing bisphosphonate therapy should be made only by the treating oncologist in consultation with the OMS and the patient.

[‡] Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease. Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution following debridement surgery. *If systemic conditions permit*, modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

Future Research

The National Institutes of Health have provided funding opportunities for research on the pathophysiology of bisphosphonate-associated osteonecrosis of the jaw.⁷³ This has resulted in multiple research efforts focusing on several facets of this disease entity. The areas of investigation include, but are not limited to : 1) the effect of bisphosphonates on intra-oral soft tissue wound healing; 2) analysis of alveolar bone hemostasis and the response to bisphosphonate therapy; 3) antiangiogenic properties of bisphosphonates and their effects on jaw bone healing; 4) pharmacogenetic research; 5) development of valid BRONJ risk assessment tools.

Continued governmental and institutional support is required in order to elucidate the underlying pathophysiological mechanisms of BRONJ at the cellular and molecular level. Moreover, novel strategies for the prevention, risk reduction, and treatment of BRONJ need to be developed further so that more accurate judgments about risk, prognosis, treatment selection, and outcome can be established for patients with BRONJ.

DISCLAIMER

The American Association of Oral and Maxillofacial Surgeons is providing this position paper on Bisphosphonate related osteonecrosis of the jaw (BRONJ) to inform practitioners, patients and other interested parties. The position paper is based on a review of the existing literature and the clinical observations of an expert Task Force composed of oral and maxillofacial surgeons and oncologists experienced in the diagnosis, surgical and adjunctive treatment of diseases, injuries and defects involving both the functional and esthetic aspects of the hard and soft tissues of the oral and maxillofacial regions, epidemiologists, and basic researchers.

The position paper is informational in nature and is not intended to set any standards of care. AAOMS cautions all readers that the strategies described in the position paper are NOT practice parameters or guidelines and may NOT be suitable for every, or any, purpose or application. This position paper cannot substitute for the individual judgment brought to each clinical situation by the patient's oral and maxillofacial surgeon. As with all clinical materials, the position paper reflects the science related to BRONJ at the time of the paper's development, and it should be used with the clear understanding that continued research and practice may result in new knowledge or recommendations. AAOMS makes no express or implied warranty regarding the accuracy, content, completeness, reliability, operability, or legality of information contained within the position paper, including, without limitation, the warranties of merchantability, fitness for a particular purpose, and non-infringement of proprietary rights. In no event shall the AAOMS be liable to the user of the position paper or anyone else for any decision made or action taken by him or her in reliance on such information.

Appendix I Bisphosphonate Preparations Currently Available in the US

	Primary Indication	Nitrogen Containing	Dose	Route	Relative Potency*
Etidronate (Didronel)	Paget's Disease	No	300 -750 mg daily for 6 months	Oral	1
Tiludronate (Skelid)	Paget's Disease	No	400 mg daily for 3 months	Oral	50
Alendronate (Fosamax)	Osteoporosis	Yes	10 mg/day 70 mg/week	Oral	1,000
Risedronate (Actonel)	Osteoporosis	Yes	5 mg/day 35 mg/week	Oral	1,000
Ibandronate (Boniva)	Osteoporosis	Yes	2.5 mg/day 150 mg/month 3 mg every 3 months	Oral IV	1,000
Pamidronate (Aredia)	Bone Metastases	Yes	90 mg/3 weeks	IV	1,000 – 5,000
Zoledronate (Zometa)	Bone Metastases	Yes	4 mg/3 weeks	IV	10,000 +
(Reclast)	Osteoporosis		5 mg/year	IV	

*Relative to etidronate

References

1. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws. *J Oral Maxillofac Surg* 65:369, 2007
2. Nussbaum SR, Younger J, Vandepol CJ, et al. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: comparison of 30-, 60-, and 90-mg dosages. *Am J Med* 95:297, 1993
3. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled, clinical trials. *J Clin Oncology* 19:558, 2001
4. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer study Group. *N Eng J Med* 335:1785, 1996
5. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer study Group. *J Clin Oncol* 16:2038, 1998
6. Hillner BE, Ingle JN, Chelbowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 21:4042, 2003
7. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 94:1458, 2002
8. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst.* 96:879, 2004
9. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with non-small cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind placebo-controlled trial. *Cancer* 100:2613, 2004
10. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *N Engl J Med* 334:488, 1996

11. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *J Clin Oncol* 16:593, 1998
12. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III double-blind, comparative trial. *Cancer J* 7:377, 2002
13. Berenson JR, Hillner BE, Kyle RA, et al. American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 20:3719, 2002
14. United States Food and Drug Administration. Center for Drug Evaluation and Research. Available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetails>. Accessed November 11, 2008.
15. Physicians' Desk Reference. 57th ed. Montvale, NJ: Medical Economics; 2003.
16. Delmas PD, Meunier PJ. The management of Paget's disease of bone. *N Engl J Med* 336:558, 1997
17. Letocha AD, Cintas HL, Troendle JF, et al. Controlled trial of pamidronate in children with types III and IV osteogenesis imperfecta confirms vertebral gains but not short-term functional improvement. *J Bone Miner Res* 20:977, 2005
18. Watts NB. Bisphosphonate treatment of osteoporosis. *Clin Geriatr Med* 19:395, 2003
19. Delmas PD. The use of bisphosphonates in the treatment of osteoporosis. *Curr Opin Rheumatol* 17:462, 2005
20. Haderslev KV, Tjellesen L, Sorensen HA, Staun M. Alendronate increases lumbar spine bone mineral density in patients with Crohn's disease. *Gastroenterology* 119:639, 2000
21. Zein CO, Jorgensen RA, Clarke B, et al. Alendronate improves bone mineral density in primary biliary cirrhosis: a randomized placebo-controlled trial. *Hepatology* 42:762, 2005
22. Bone HG, Hosking D, Devogelaer JP, Tucci JR, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 350:1189, 2004
23. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic [Letter]. *J Oral Maxillofac Surg* 61:1115, 2003

24. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff S. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 62:527, 2004
25. Estilo CL, Van Posnak CH, Williams T, et al. Osteonecrosis of the maxilla and mandible in patients treated with bisphosphonates: a retrospective study. *J Clin Oncol. Proc Am Soc Clin Oncol* 22:8088, 2004
26. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention and treatment. *J Oral Maxillofac Surg* 63:1567, 2005
27. Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. *Cancer* 104:83, 2005
28. Purcell PM, Boyd IW. Bisphosphonates and osteonecrosis of the jaw. *Med J Aust* 182:417, 2005
29. Bagan JV, Jimenez Y, Murillo J, et al. Jaw osteonecrosis associated with bisphosphonates: multiple exposed areas and its relationship to teeth extractions. study of 20 cases [Letter]. *Oral Oncol* 42:327, 2006
30. Pires FR, Miranda A, Cardoso ES, et al. Oral avascular bone necrosis associated with chemotherapy and bisphosphonate therapy. *Oral Dis* 11:365, 2005
31. Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 144:753, 2006
32. Woo SB, Hande K, Richardson PG. Osteonecrosis of the jaws and bisphosphonates [Letter]. *N Engl J Med* 353:100, 2005
33. Hohnecker JA. Novartis "Dear Doctor" Precautions added to label of Aredia and Zometa. September 24, 2004.
34. United States Food and Drug Administration Oncologic Drugs Advisory Committee . Combidex briefing information. Available at: <http://www.fda.gov/ohms/dockets/ac/05/briefing/2005-4095b1.htm> Accessed August 14, 2006
35. US food and Drug Administration Office of Drug Safety Postmarketing Safety Review Available at: www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4095B2_03_04-FDA-TAB3.pdf - 03-02-2005 - Accessed August 14, 2006
36. Dodson TB. Intravenous bisphosphonate therapy and bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 67:XXX, 2009

37. Durie BGM, Katz M, Crowley J. Osteonecrosis of the jaws and bisphosphonates [Letter]. *N Engl J Med* 353:99, 2005
38. Bamias A, Kastritis E, Bamia C, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol* 23:8580, 2005
39. Dimopoulos MA, Kastritis E, Anagnostopoulos A, et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Haematologica* 91:968, 2006
40. Dimopoulos M, Kastritis E, Moulopoulos LA, Melakopoulos I, et al. The incidence of osteonecrosis of the jaw in patients with multiple myeloma who receive bisphosphonates depends on the type of bisphosphonate. *Blood*. (American Society of Hematology Annual Meeting Abstracts) 106:637, 2005
41. Tosi P, Zamagni E, Cangini D, et al. Bisphosphonates and osteonecrosis of the jaws: incidence in a homogeneous series of patients with newly diagnosed multiple myeloma treated with zoledronic acid. *Blood*. (American Society of Hematology Annual Meeting Abstracts) 106:3461, 2005
42. Pozzi S, Marcheselli R, Sacchi S, et al. Analysis of frequency and risk factors for developing bisphosphonate associated necrosis of the jaw. *Blood*. (American Society of Hematology Annual Meeting Abstracts) 106:5057, 2005
43. Cafro AM, Barbarano LA, Andriani A, et. al. Osteonecrosis of the jaw associated with chronic bisphosphonates therapy: an Italian experience. *Blood*. (American Society of Hematology Annual Meeting Abstracts) 106:5152, 2005
44. Zavras AI, Zhu S. Bisphosphonate are associated with increased risk for jaw surgery in medical claims data; is it osteonecrosis? *J Oral Maxillofac Surg* 64:917, 2006
45. Hoff AO, Toth BB, Altundag K, et al. Osteonecrosis of the jaw in patients receiving intravenous bisphosphonate therapy. *J Clin Oncol*. 2006 ASCO Annual Meeting Proceedings (post meeting edition). 2006;24:8528. Available at http://meeting.jco.org/cgi/content/abstract/24/18_suppl/8528. Accessed on August 14, 2006
46. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR, HORIZON Pivotal Fracture Trial: Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 356:1809, 2007
47. IMS HEALTH, NPA Plus™ May 2006

48. Report of the Council of Scientific Affairs. Expert panel recommendations: dental management of patients on oral bisphosphonate therapy. American Dental Association. June 2006. Available at <http://www.ada.org/prof/resources/topics/osteonecrosis.asp> Accessed June 29, 2006
49. Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. *J Oral Maxillofac Surg* 65:415, 2007.
50. Ault A. Jaw necrosis affects 1 in 1,700 on oral bisphosphonates. *Internal Medicine News* 41:23, August 1, 2008
51. Felsenberg D, Hoffmeister B. Necrosis of the jaw after high-dose bisphosphonate therapy. *Deutsches Arzteblatt* 103:3078, 2006
52. Badros A, Weikel D, Salama A, et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol* 24:945, 2006
53. Wessel JH, Dodson TB, Zavras AI: Zoledronate, smoking, and obesity are strong risk factors for osteonecrosis of the jaw: a case-control study. *J Oral Maxillofac Surg* 66:625, 2008
54. Jadu F, Lee L, Pharoah M, Reece D, Wang L: A retrospective study assessing the incidence, risk factors and comorbidities of pamidronate-related necrosis of the jaws in multiple myeloma patients. *Ann Oncol* 18:2015, 2007
55. Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, Nooka A, Sayegh G, Guarneri V, Desrouleaux K, Cui J, Adamus A, Gagel RF, Hortobagyi GN: Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res* 23:826, 2008
56. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. *Oral Surg Oral Med Oral Path Oral Radiol Endod* 102:433, 2006
57. Zervas K, Verrou E, Teleioudis Z, Vahtsevanos K, Banti A, Mihou D, Krikelis D, Terpos E: Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. *Br J Haematol* 134:620, 2006.
58. Corso A, Varettoni M, Zappasodi P, Klersy C, Mangiacavalli S, Pica G, Lazzarino M: A different schedule of zoledronic acid can reduce the risk of the osteonecrosis of the jaw in patients with multiple myeloma. *Leukemia* 21:1545, 2007

59. Khamaisi M, Regev E, Yarom N, Avni B, Leitersdorf E, Raz I, Elad S: Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. *J Clin Endocrinol Metab* 92:1172, 2007
60. Sarasquete ME, Garcia-Sanz R, Marin L, Alcoceba M, Chillon MC, Balanzategui A, Santamaria C, Rosinol L, de la Rubia J, Hernandez MT, Garcia-Navarro I, Lahuerta JJ, Gonzalez M, San Miguel JF: Bisphosphonate-related osteonecrosis of the jaw is associated with polymorphisms of the cytochrome P450 CYP2C8 in multiple myeloma: a genome-wide single nucleotide polymorphism analysis. *Blood* 112:2709, 2008
61. Dimopoulos MA, Kastritis E, Bamia C, Melakopoulos I, Gika D, Roussou M, Migkou M, Eleftherakis-Papaiakovou E, Christoulas D, Terpos E, Bamias A: Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. *Ann Oncol* , August 9, 2008 [Epub ahead of print]
62. Ripamonti CI, Maniezzo M, Campa T, Fagnoni E, Brunelli C, Saibene G, Bareggi C, Ascani L, Cislighi E: Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan. *Ann Oncol* July 22, 2008 [Epub ahead of print]
63. Mehrotra B, Fantasia J, Ruggiero SL. Outcomes of bisphosphonate related osteonecrosis of the jaw. Importance of staging and management. A large single institution update. *J Clin Oncol ASCO Meeting Abstracts* 26 suppl:20526, 2008
64. Rosen HN, Moses AC, Garber J, Iloputaife ID, Ross DS, Lee SL, Greenspan SL. Serum CTX: A new marker of bone resorption that shows treatment effect more often than other markers because of a low coefficient of variability and large changes with bisphosphonate therapy. *Calcif Tissue Int* 66:100, 2000
65. Ruggiero SL, Gralow J, Marx RE, Hoff AO, Schubert MM, Hury JM, et al. Practical guidelines for the prevention, diagnosis and treatment of osteonecrosis of the jaw in patients with cancer. *J Clin Oncol Pract* 2:7, 2006
66. Migliorati CA, Casiglia J, Epstein J, Siegel, MA, Woo SB. Managing the care of patients with bisphosphonate-associated osteonecrosis. *J Am Dent Assoc* 136:1658, 2005
67. American Association of Endodontists Position Statement Endodontic implications of bisphosphonate-associated osteonecrosis of the jaws. Available at: <http://www.aae.org/dentalpro/guidelines.htm>. Accessed on August 14, 2006.

68. Marx RE, Cillo JE, Ulloa JJ. Oral Bisphosphonates Induced Osteonecrosis: Risk Factors, Prediction of Risk Using Serum CTX Testing, Prevention, and Treatment. *J Oral Maxillofac Surg* 65:2397, 2007
69. Carlson EC. The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 67:XXX, 2009
70. Kademani D, Koka S, Lacy MQ, Rajkumar V. Primary surgical therapy for osteonecrosis of the jaw secondary to bisphosphonate therapy. *Mayo Clin Proc* 81:1100, 2006
71. Freiburger JJ. The utility of hyperbaric oxygen in the treatment of bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 67:XXX, 2009
72. Lee CY, David T, Nishime M. Use of platelet-rich plasma in the management of oral bisphosphonate-associated osteonecrosis of the jaw: a report of two cases. *J Oral Implantol* 33:371, 2007
73. National Institutes of Health Funding Opportunities and Notices Search Results. Available at http://grants.nih.gov/grants/guide/search_results.htm?text_curr=osteonecrosis&scope=pa-rfa&year=active&sort=&Search.x=10&Search.y=8 Accessed November 19, 2008