

BISPHOSPHONATES & DENTAL CONSIDERATIONS

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The below is information I have compiled and saved to my files regarding the use of bisphosphonates when treating osteopenia and osteoporosis, or when prescribed because of being administered androgen deprivation medications, particularly LHRH agonists or GnRH antagonists, that are known to have an effect on bone mineral density (BMD). A monoclonal antibody, Xgeva/denosumab, has also been approved to improve BMD. The same safeguards as explained below apply. PLEASE BE SURE TO READ ALL THE WAY TO THE END OF THIS PAPER TO RECOGNIZE THE EXTREME IMPORTANCE OF DENTAL CONSIDERATIONS PRIOR TO THE ADMINISTRATION OF BISPHOSPHONATES OR THE MONOCLONAL ANTIBODY XGEVA/DENOSUMAB. ADHERING TO THESE CONSIDERATIONS SERVES AS A PREVENTATIVE MEASURE TO AID IN THE INHIBITION OF OSTEONECROSIS OF THE JAW (ONJ).

To anyone expecting to be prescribed bisphosphonates as a treatment for the foregoing reasons, or actually any reason, the information below is important for the patient to review and fully discuss with both his physician prescribing the treatment and with his dentist prior to any administration of a bisphosphonate. The physician and dentist should be aware of each other in the event any dental work may become required once being treated with bisphosphonates.

Patients with other health issues should read the information at the following website before embarking on bisphosphonate treatment (a few examples: Chronic kidney disease stages 4 or 5, low serum calcium, osteomalacia, Vitamin D deficiency until it is corrected, serious esophageal disease, patients at bedrest who cannot stay upright for an hour):

<http://courses.washington.edu/bonephys/opbis.html>

Please take note, also, that Xgeva is not approved for patients with multiple myeloma or other cancers of the blood. An important role that Matthew Smith, MD, PhD, at Massachusetts General Hospital has determined in focusing on the

role of over-expression of RANK Ligand, a natural molecule that supports bone metabolism and bone integrity, is that Xgeva has shown to inactivate RANK Ligand and prevent bone destruction and fractures.

If being prescribed Fosamax (Alendronate), a less strong bisphosphonate in tablet form, the medication as 70mg tablets usually comes as four tablets in a folded packet to last four weeks. One tablet is taken per week, taken on the same day of every week, preferably taken immediately upon rising for the day while stomach is empty, taken with 6-8 oz. of water to thoroughly wash the tablet down, and no other meds or food are to be taken for at least 30 minutes. You must remain up and out of bed and active after taking this medication. When I had been taking Fosamax I made up a sign with the large letters FOSAMAX on it that I placed near my bed that could not help but catch my eye upon rising so that I would remember to take the pill immediately upon rising. I took mine every Sunday morning.

If a stronger, intravenous bisphosphonate is prescribed such as Zometa (Zoledronate) or Aredia (Pamidronate), or the monoclonal antibody Xgeva (denosumab), "insist" the initial dose be administered at a lowest dose possible and be administered over a longer than "usual" time frame to permit your system to tolerate the medication and minimize the chance of Acute Phase Response (APR) before increasing to what is considered a "normal" dose. Many Medical Oncologists use the argument "I've never heard of any of my patients experiencing any side effects." I seriously do not believe that to be fact, unless patients just fail to bring these side effects to the attention of their physician once they are over them. I've heard of way too many men who, within the next 28 to 36 hours after administration certainly did experience extremely uncomfortable side effects of flu-like symptoms, bone pain, kidney damage, and becoming bed-ridden for a few days after administration of intravenous bisphosphonates at full strength. The "normal" dose can be administered when returning for your second treatment. For Zometa, the initial dose to "insist" on is 1mg over at least 30 minutes. Your second and future dosage can be increased to what is considered "normal" - usually 4mg. For Aredia, the initial dose to "insist" on is 30mg over at least 1 1/2 hours. Your second and future dosage can be increased to what is considered "normal" which I believe is 60-90mg every two weeks thereafter. In the administration of either Zometa or Aredia at full dosage you have every right to "insist" that the infusion be timed to more than 30 minutes for Zometa and at least 1 1/2 to even 2 hours for Aredia. They may try to push the infusion to a shorter time period but stick to your "rights" and remind them that this is YOUR body in which the medication is being administered and you want as little side effect as possible.

Interesting to note is that Zoledronic acid (Zometa), in addition to its role in prevention of skeletal-related events, also directly suppresses cell proliferation and induces apoptosis in prostate cancer cells.

Xgeva/denosumab, rather than an infusion, is administered as a 120mg subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen.

I thought the below two advisories from Medical Oncologist Stephen Strum (who has specialized in research and treatment of recurring and advanced prostate cancer since 1983) may interest you:

Per Dr. Strum: “BEPs (Biological End Points) such as DpD (deoxypyridinoline) and b-CTX (C-Terminal Telopeptide, b-Crosslaps) should be used to decide on how often Xgeva is given. Remember too, the GOLDILOCKS maxim: "Not too hot, not too cold, but just right." This is true of all biological systems and the concept of BEPs is applicable here. We want to see the DpD and the CTx drop to low values but we can hold the Xgeva (or Zometa) if way way low to prevent what is called adynamic bone disease (ABD), which one day will be correlated with ONJ (osteonecrosis of the jaw).”

Further from Dr. Strum:

This is a group email. Its goal is to alert you to issues that relate to the potential for a serious side effect of bisphosphonate use in those having invasive dental work.

I believe I have one of the largest experiences with the use of bisphosphonates, both intravenous & oral. I have not seen the side effect called “avascular necrosis” or “osteonecrosis of the jaw”. Others have seen this & the reported incidence has been reported as between 1% & 5%. You will see in the attached file that some say that in those having dental extractions or dental implants this can be as high as 80%.

I suggest you read the attached file. If you wish more information do a Google search on bisphosphonates osteonecrosis or bisphosphonates avascular necrosis. I hope to soon have a website where these articles will be posted.

In the meantime, pay attention to the need for a DENTAL EVALUATION prior to starting on bisphosphonate therapy (especially intravenous bisphosphonates like Zometa or Aredia) & strongly consider dental

evaluations while on such therapy. Share the attached file with your dentist & any other pertinent medical reference(s). Avoid invasive dental procedures such as extractions or implants. If there is an issue challenging this, seek an oral surgeon or contact one of the authors specializing in avascular necrosis of the jaw relating to bisphosphonate therapy.

Lastly, I believe it is possible that I have not seen this problem because I advise my patients to use a comprehensive bone supplement such as Bone Up by Jarrow or Bone Assure or Bone Restore by Life Extension. (MY NOTE: Dr. Strum has now developed a formula called “Strum’s Intensive Bone Formula” available from Life Extension

<http://tinyurl.com/66lwqy5>

which contains: calcium 800mg, magnesium 400mg, zinc 10mg, boron 6mg, silica 5mg, Vit D-3 8,000 IU, Vit K (MK-7) 200mcg, potassium citrate 30 mEq, cissus quadrangularis 600mg in 10 capsules per day. Therefore, if using Strum's Intensive Bone Formula you would not likely be needing additional Vit D or Vit K, and the calcium dose is likely sufficient to not require additional calcium supplements. The potassium citrate alkalinizes your urine and helps promote bone formation. You need to monitor your serum potassium while on this supplement if you are on any drugs that cause potassium retention—be sure to discuss this with your local MD. This could be considered an expensive formula at around \$50 per month, but when considering that it replaces separate purchases of the vitamins listed, that price is not as significant.)

In the past, issues of bone brittleness relating to therapies using Fluoride or Bisphosphonates have come up. In both situations, I have found that such a problem relates to NOT supplying the patient with the needed raw materials to make healthy bone. And, one other point. This process is called avascular necrosis & drugs which inhibit angiogenesis might be working with bisphosphonates to create SYNERGISTIC TOXICITY. It is known that part of the mechanism of action of bisphosphonates is that of anti-angiogenesis. Therefore, think carefully when adding additional anti-angiogenesis agents to bisphosphonate therapy. This includes drugs like thalidomide, tetracyclines, and COX II inhibitors like Celebrex. These may be found to be risk factors.

“The Doctor of the Future will give no medicine, but will interest his patients in the care of the Human frame, in diet, and in the cause and prevention of disease.”

--Thomas Edison

“He is a better physician that keeps diseases off us, than he that cures them...prevention is so much better than healing because it saves the labour of being sick.”

Thomas Adams, 1618

**The superior doctor prevents sickness;
The mediocre doctor attends to impending sickness;
The inferior doctor treats actual sickness.**

--Chinese Proverb

He who cures a disease may be the skillfullest, but he that prevents it is the safest physician

--T. Fuller

My regards to all,

Stephen

**Stephen B. Strum MD, FACP
Medical Oncologist Specializing in Prostate Cancer**

(MY NOTE Regarding Jarrow Bone Up: Dr. Strum, recommends patients use Jarrow Bone Up 6 tablets daily to satisfy appropriate Calcium intake for any bone issues as well as about 8-10% of daily Vitamin D intake. He recommends taking 4 or 5 per day and pending calcium levels & ideally intact PTH levels one may need to add a little more. Jarrow's products involve taking 6 per day to equal 1,000mg Calcium so one has latitude in using less than the 6 per day. Also, ideally the intake of calcium is best done more towards the evening so he recommends weighting dosing in that way. All of this must take into account the use of bisphosphonate drugs, as well as any vitamin D supplementation. Jarrow Bone Up is likely available in most health food stores and can be ordered via the internet.

Example: <http://www.herbsmd.com/detail/Bone-Up-1621.htm>

Further to my note: With the availability of “Strum’s Intensive Bone Formula” since Dr. Strum’s earlier recommendation of Jarrow Bone Up, I would reason that his new formula will be much more effective to address bone issues.

PLEASE TAKE VERY SPECIAL NOTE OF THE FOLLOWING!

(Attachment to Dr. Strum’s report, above):

RECOMMENDATIONS TO PREVENT BISPHOSPHONATE AVASCULAR NECROSIS

Before Initiating Bisphosphonate Therapy

As soon as the treating oncologist prescribes bisphosphonate therapy (**MY NOTE: or XGEVA/DENOSUMAB, AND BEFORE BEGINNING THE MEDICATION**), the patient should be referred to an experienced dentist or oral and maxillofacial surgeon for an urgent examination. Close and ongoing communication between your physician and dentist is crucial, and commencement of bisphosphonate therapy should be deferred until dental and oral surgical treatments have been completed. **At the minimum, the dental examination should consist of clinical and panoramic radiographic examinations with individual periapical films where indicated. Dental treatment is aimed at eliminating infections and preventing the need for invasive dental procedures in the near and intermediate future.** This may include tooth removal, periodontal surgery, root canal treatment, caries control, dental restorations, and dentures. These patients should not be considered as candidates for dental implants, which have no crevicular epithelial attachment and therefore would predispose the patients in this group to bone exposure. **Impacted teeth that are completely covered by bone or soft tissue should be left undisturbed, but those with an oral communication are recommended to be removed and given a 1 month healing period.** Similarly, small lingual mandibular tori do not require removal whereas large, multilobed mandibular tori or midline palatal tori with thin overlying mucosa are recommended to be removed 1 month before the initiation of bisphosphonate therapy. **Prophylactic antibiotic coverage for noninvasive dental care is not required but is recommended for any invasive dental procedure**, and for this penicillin remains the drug of choice. **For individuals with a penicillin allergy, combination therapy using quinolones and metronidazole or erythromycin and metronidazole are good second choices and have proven efficacy in this group. Clindamycin alone is not**

recommended because of its lack of activity against actinomyces, Eikenella corrodens, and similar species that have been found to frequently colonize this exposed bone. As a general rule, if the patient requires only noninvasive dental care, such as dental cleanings (prophylaxis), fluoride carriers, dental restorations, dentures, and so forth, bisphosphonate therapy need not be delayed. If the patient requires invasive dental procedures such as **tooth removals, periodontal surgery, or root canal therapy, commencement of bisphosphonate therapy should be deferred for 1 month to allow sufficient time for bone recovery and healing.** Once the regimen of bisphosphonate therapy has begun, **a surveillance schedule of once every 4 months is recommended.**

WHILE RECEIVING BISPHOSPHONATE THERAPY Oncologists should consider referring all patients already receiving IV bisphosphonates to a dentist or oral and maxillofacial surgeon for an examination and a surveillance schedule. The dental team should carefully evaluate the **oral cavity for exposed bone in the areas most commonly affected, such as the posterior lingual area of the mandible, and for radiographic evidence of osteolysis, osteosclerosis, widened periodontal membrane spaces, and furcation involvements.** A dental cleaning and fluoride carriers should be considered, and **tooth removal should be avoided if at all possible. If the tooth is nonrestorable because of caries, root canal treatment and amputation of the crown is a better option than removing the tooth. Similarly, teeth that demonstrate 1 or 2 mobility should be splinted rather than removed.** If the mobility is 3 or more or is associated with a periodontal abscess, there is a strong possibility that osteonecrosis is already present and the abscess and/or granulation tissue is merely covering exposed bone. In these situations, removing the tooth and providing antibiotic treatment, as described in the previous section, is the only recourse. Elective surgery within the jaws, such as removal of third molar teeth or tori, periodontal surgery, or placement of dental implants, is strongly discouraged at this time. Denture wearing is acceptable, but the prosthesis should be examined for areas of excessive pressure or friction and given a soft reline if needed.

Bisphosphonate-Induced Exposed Bone

(Osteonecrosis/Osteopetrosis) of the Jaws: Risk Factors, Recognition, Prevention, and Treatment Robert E. Marx, DDS,* Yoh Sawatari, DDS, Michel Fortin, DMD, PhD, and Vishtasb Broumand, DMD, MD'

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Additionally, here is an extensive explanation of the effects of prostate cancer and treatment with androgen deprivation medications that are known to precipitate bone issues: <http://tinyurl.com/jlleo>

Disclaimer: Please recognize that I am not a Medical Doctor. I have been an avid student researching and studying prostate cancer as a survivor and continuing patient since 1992. **The comments or recommendations I make are not intended to be the procedure for you to now follow; rather, they are to be reviewed along with the comments or recommendations of others for your own further research, study, and discussion with the physician providing your prostate cancer care to come to your own, personal conclusion.**