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(Revised)

**BISPHOSPHONATES AND OSTEONECROSIS OF THE
MAXILLA AND/OR MANDIBLE (JAW BONES)**

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.

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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-

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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 buildup 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

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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

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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

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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 (Peridex) several times a day. Dentures can be worn, but should be adjusted to minimize any further trauma,

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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,

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Live long and prosper,

DR. BOB

10/11/05