

BIPHOSPHONATE ASSOCIATED OSTEONECROSIS OF THE JAWS: A RETROSPECTIVE CASE SERIES AND REVIEW OF THE LITERATURE

Boneta O¹, Kraft K¹, Daniels D. ²

¹Duke Center for Hyperbaric Medicine and Environmental Physiology, Durham, North Carolina,

²Department of Oncology, Duke University Medical Center, Durham, North Carolina

INTRODUCTION: Reports of osteonecrosis of the jaw (ONJ) associated with intravenous bisphosphonate (BP) therapy for the management of bone disease from cancer, in patients without prior radiation therapy, first appeared in the oral surgery literature in 2003. Since that time there have been less than 100 reported cases in the medical literature. There have been no reports in the Hyperbaric Medicine literature. We report 14 patients with this condition referred for evaluation at the Duke Center for Hyperbaric Medicine and Environmental Physiology between June 2003 and March 2005.

BACKGROUND: In late 2003, we noticed a small cluster of patients diagnosed with chronic osteomyelitis (OM) of the jaw who were not responding as expected to conventional therapy (antibiotics and surgical debridement) and adjuvant HBO2. This patient group, appeared to fair worse after surgical debridement despite adjuvant HBO2. We questioned the diagnosis and reviewed the literature.

Prior to 2001, the incidence of non-radiation induced ONJ was relatively rare. But around 2003, there was a sharp rise in the number of cases of ONJ which has been described as epidemic.¹ The first preliminary report in a letter to the editor was by Marx in 2003 (36 patients) and followed by Ruggiero's case series of 63 patients in 2004. Both Marx and Ruggiero found an association between IV BP (pamidronate and/or zoledronate) therapy and ONJ.^{1,2} Our chronic OM patients who were responding poorly to therapy all had a history of IV BP therapy and findings similar to those reported by Marx and Ruggiero.

BPs are frequently used in patients with multiple myeloma (MM) and some metastatic cancers for the management of hypercalcemia. These neoplasms release various stimulatory factors that increase osteoclastic activity. Pamidronate and zoledronate's mechanism of action is not fully understood but they are potent inhibitors of osteoclast activity thus impair bone resorption and the remodeling cycle of bone. Studies of endothelial cell exposed to BP show decreased proliferation and increased apoptosis as well as antiangiogenic effects.³ Effects of BP therapy can be prolonged since they have very long half-lives in bone.

METHODS: A retrospective chart review of all patients referred to the Duke Center for Hyperbaric Medicine with a history of intravenous BP therapy and non-healing oral wounds with no prior history of radiation therapy to the head and neck was conducted. Fourteen cases were identified: 2 with pamidronate use, 10 with zoledronate use, and 2 who had used both. For each case, 16 pieces of information were collected using the Duke Hyperbaric Medicine database and the Duke University Medical Center medical record. Approval for the study was obtained from the Duke University Medical Center IRB.

RESULTS: Our patients ranged in age from 43-78 years of age with a median age of 61.7. Thirteen of the fourteen patients had hypercalcemia secondary to a malignancy and one had hypercalcemia but did not have an underlying malignancy.

| | | | |
|-------------------|--------------|--------------------|------------|
| Sex | Male 9 | Female 5 | |
| Race | Caucasian 10 | African American 4 | |
| Malignancy | MM 8 | Met Breast CA 2 | Other CA 3 |

All patients presented with a history of painful non-healing lesions.

| | | | |
|-------------------------|--------------------|---------------|-------------|
| Site of Lesion | Mandible 11 | Maxilla 1 | Both Jaws 2 |
| Initiating Event | Dental Procedure 9 | Spontaneous 5 | |

Duration of BP therapy ranged from 4 – 102 months with a mean of 51.9 months.

| | |
|---|----|
| Discont. BP prior to HBO2 | 9 |
| Discont. BP but will restart post HBO2 | 10 |
| Cont. BP therapy through HBO2 | 8 |

13 of 14 patients had undergone chemotherapy (14 different agents either singly or in combination) and 2 out of 14 were undergoing chemotherapy at the time of their HBO2 therapy. 4 out of 14 were taking steroids at the time of their HBO2 therapy.

Prior to referral for HBO2, 8 of the 14 patients had undergone surgical debridement and 10 of 14 had undergone or were still undergoing antibiotic therapy. 3 of 14 patients had not yet undergone surgery or antibiotic therapy at the time of their HBO2 evaluation. These patients had been recently diagnosed by their dentist / oral surgeon as osteonecrosis without OM. All 14 patients were worsening despite the type of intervention used.

As of 12 May 2005, 12 of the 14 patients had completed their HBO2 therapy and two are waiting to start therapy. Of the 12 patients who completed HBO2 therapy we observed the following outcomes:

| HBO2 Courses | No. of Pts | No. of Dives | Outcome |
|--------------|------------|--------------|----------------------|
| 1 | 10 | 36-40 | Stable 4, Resolved 6 |
| 2 | 1 | 60 | Resolved |
| 3 | 1 | 120 | Resolved |

REFERENCES:

- Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) Induced Avascular Necrosis of the Jaws: A Growing Epidemic. *Journal of Oral Maxillofacial Surgery*. 2003; 61:1115-1118.
- Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the Jaws Associated With the Use of Bisphosphonates: A Review of 63 Cases. *Journal of Oral Maxillofacial Surgery*. 2004; 62:527-534.
- Fournier P, Boissier S, Filleul S, Guglielmi J, Cabon F, Colombel M, Clezardin P. Bisphosphonates inhibit Angiogenesis *in Vitro* and Testosterone-stimulated Vascular Regrowth in the Ventral Prostate in Castrated Rats. *Cancer Research*. 2002; 62:6538-6544.
- Durie GM, Katz M, McCoy J, Crowley J. Osteonecrosis of the Jaws in Myeloma: Time dependent Correlation with Aredia and Zometa Use. Paper presented at: 46th American Society of Hematology (ASH) Annual Meeting; December 3, 2004; San Diego, California.
- Migliorati CA. Bisphosphonates and Oral Cavity Avascular Bone Necrosis. *Journal of Clinical Oncology*. 2003; 22:4253-4258.
- Oncologic Drugs Advisory Committee Report, Appendix 11: Expert Panel Recommendation for the Prevention, Diagnosis and Treatment of Osteonecrosis of the Jaw, report prepared for Novartis Pharmaceuticals Corporation, March 4, 2005.

All HBO2 treatments were delivered at 2 ATA for 2 hours with no airbreaks. Follow-up, of the treated patients ranged from 0-22 months after their final HBO2 treatment months with a mean of 8.6 months.

DISCUSSION: BP therapy is the only common factor to our 14 patients. The temporal association between BP therapy and the development of ONJ is suspicious but does not establish cause and effect. Durie recently reported his survey results of 1203 patients (75 with confirmed ONJ) who had received BP therapy and had either MM or breast cancer and found that duration of bisphosphonate therapy was associated with an increased risk of ONJ and that chemotherapy and steroids was not associated with the development of ONJ. There was an association with prior history of dental problems and ONJ.⁴

BP associated ONJ is refractory to treatment and surgical intervention has been associated with worsening of the disease process. At this time, non-surgical palliative care is considered the best course of action.^{1,5} In patients who develop OM, control of the infection with antibiotics, chlorhexidine mouthwash, and wound irrigation is recommended. Debridement should be limited to soft-textured sequestered bone.^{1,6} Preventive dentistry prior to initiation of BP therapy is recommended along with thorough patient education regarding oral hygiene.⁶

To date, the use of HBO2 has not been proven effective in the treatment of this disorder and has not been recommended.^{2,5, 6} However, our experience in the 12 patients that have completed a course of 40 HBO2 treatments is that 50% healed. Significantly, the 50% that did not heal did not deteriorate further. Of the 50% that did not heal, 33% received additional HBO2 and eventually healed. In all, 75% of our patients have gone on to heal their ONJ post-HBO2 therapy. Follow-up on these patients is limited and we do not know if our short term success will translate into long-term healing.

CONCLUSION: It is important to obtain a full history in patients presenting with oral non-healing wounds and ask about a history of prior BP use. If the history is positive for the use of BPs, ONJ must be in the differential diagnosis, with or without concomitant OM.

Further research is needed to evaluate the relationship between IV BP therapy and ONJ and to determine optimal therapy for patients with ONJ. Conservative, palliative care is indicated and though HBO2 has not yet been proven effective, it shows promise. A prospective clinical trial evaluating the efficacy of HBO2 in the treatment of BP induced ONJ is needed.