Hyperbaric Oxygen Treatment and Bisphosphonate-Induced Osteonecrosis of the Jaw: A Case Series

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Purpose: Bisphosphonate (BP)-associated osteonecrosis of the jaw (ONJ) is an emerging problem with few therapeutic options. Our pilot study of BP-ONJ investigated a possible role for hyperbaric oxygen (HBO₂) therapy.

Patients and Methods: A total of 16 patients, ranging in age from 43 to 78 years, were treated with HPV-ONJ between July 2003 and April 2006. Staging was based on the size and number of oral lesions. Clinical response after treatment and at distant follow-up; the odds of remission, stabilization, or relapse; and time to failure were calculated.

Results: The median time on BP therapy before appearance of ONJ symptoms was 18 months, and that from symptom onset to HBO₂ therapy was 12 months. Fourteen of 16 patients (87.5%) improved in stage. The size and number of ONJ lesions were decreased after HBO₂ therapy (P < .001 and P = .008, respectively; Wilcoxon signed-rank test). Immediately after HBO₂ therapy, 7 of 16 patients (44%) were in remission and 8 (50%) had stabilized; however, stabilization without remission was sustained in only 2 patients. At follow-up, 10 of the patients (62.5%) were still in remission or had stabilized. The 7 patients who continued on BP treatment during HBO₂ therapy had a shorter time to failure (8.5 months; 95% confidence interval [CI] = 7.1 to 9.8) than those who discontinued the drug (20.1 months; 95% CI = 17.5 to 23.9; P = .006 by the log-rank test). Clinical response was not associated with cancer type or malignancy remission status.

Conclusions: Adjunctive HBO₂ therapy may benefit patients with BP-ONJ; however, the outcome is improved with cessation of BP administration.

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Before treatment with bisphosphonate (BP)-based osteoclast-inhibiting drugs was available, osteonecrosis of the jaws (ONJ) was uncommon. The first preliminary report of BP-ONJ in 36 patients was published by Marx in 2003.¹ This was followed in 2004 by Ruggiero’s series of 63 patients.² Both authors found an association between intravenous (IV) BP therapy and ONJ, and other reports corroborating this association have appeared since that time.³,⁷

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BPs, particularly compounds containing an aliphatic chain with an amino group in the R2 position (pamidronate, alendronate, and zoledronate), are widely used to treat breast cancer, prostate cancer, multiple myeloma, and nonmalignant bone disease. The agents are clinically efficacious. ONJ has been reported as a complication in as many as 10% and as few as less than 1% of patients taking these drugs (A. Hoff, personal communication, March 31, 2006). The disease is serious, and treatment options are lacking.

The biology of BP-induced ONJ is complex. Nitrogen-containing BPs inhibit geranylgeranyl-diphosphate synthesis with subsequent deregulation of the guanosine 5'-triphosphate binding proteins required for intracellular vesicular transport. Compromised vesicular transport blocks osteoclast bone resorption activity, promoting apoptosis. However, osteoclast apoptosis (alendronate-induced apoptosis) can be suppressed by osteoclastogenic cytokines (tumor necrosis factor α, macrophage colony-stimulating factor, receptor activator of NfκB [RANKL], and interleukin-6α). These signals are known to be oxygen-sensitive; therefore, we reasoned that hyperbaric oxygen (HBO2) therapy might influence their activity. Reactive oxygen species stimulate the expression of RANKL and the NfκB transcription factor, which are essential to avoid osteopetrosis. This article reports on 16 patients with BP-ONJ recently treated with HBO2 on a compassionate basis at Duke University Medical Center.

### Patients and Methods

Institutional review board approval, including a waiver of written consent, was obtained for all patients, and a database search was used to screen all patients with BP-associated ONJ treated at Duke University Medical Center between July 2003 and April 2006. BP-ONJ was defined as exposed maxillofacial bone after BP treatment occurring either spontaneously or induced by dental surgery, exhibiting no evidence of healing after 6 weeks of standard dental care, and demonstrating no evidence of metastatic disease in the jaw or osteoradionecrosis. After evaluation and identification, each patient’s oral condition was recorded at 4 time points: 1) immediately before HBO2 therapy, 2) on completion of HBO2 therapy, 3) at the time of any clinic visit at which a relapse was reported if it occurred, and 4) at the time of the last contact, usually a telephone call made to the patient at least 1 month after the completion of therapy.

### METHOD OF DATA ANALYSIS

Uniform criteria were used to classify the patient’s stage or extent of oral pathology before treatment. The oral condition at the time of referral and before HBO2 treatment was recorded based on the clinic notes, photographs, or the consultant’s physical examination. Staging criteria were based on the size and number of the oral lesions and are listed in Table 1. Staging was also performed after HBO2 therapy. The principal outcome was the clinical response (Table 2). The crude odds for a patient to show improvement in stage after HBO2 therapy was calculated for the entire group. Logistic regression was used to assess the effects of various cofactors on changes in stage and clinical response. Lesion size and lesion number before and after HBO2 were analyzed separately.

Clinical outcomes were categorized using the criteria in Table 2. Remission was defined as the complete regrowth of gingiva over an area of previously exposed bone plus the resolution of oral pain. Radiologic studies of the extent of bone changes were not available for all subjects and were not used. The crude odds of achieving remission, disease stabilization, or clinical deterioration (relapse) after HBO2 therapy were calculated for the group as a whole. Logistic regression was used to assess the effects of cofactors, including disease stage before treatment, continuation of BP, and months of BP treatment before HBO2 therapy.

### Table 1. STAGING CRITERIA

<table>
<thead>
<tr>
<th>Grade</th>
<th>Size, Diameter*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Single lesion &lt;0.5 cm</td>
</tr>
<tr>
<td>1B</td>
<td>Multiple lesions, largest &lt;0.5 cm</td>
</tr>
<tr>
<td>2A</td>
<td>Single lesion 0.5 to 0.99 cm</td>
</tr>
<tr>
<td>2B</td>
<td>Multiple lesions, largest 0.5 to 0.99 cm</td>
</tr>
<tr>
<td>3A</td>
<td>Single lesion 1 to 2 cm</td>
</tr>
<tr>
<td>3B</td>
<td>Multiple lesions, largest 1 to 2 cm</td>
</tr>
<tr>
<td>4A</td>
<td>Single lesion &gt;2 cm</td>
</tr>
<tr>
<td>4B</td>
<td>Multiple lesions, largest &gt;2 cm</td>
</tr>
</tbody>
</table>

*Lesion size measured as the largest diameter.

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### Table 2. CLINICAL RESPONSE CRITERIA

1. Remission: complete regrowth of the oral mucosa over previously exposed bone plus cessation of oral pain.
2. Not in remission: incomplete bone coverage and/or the presence of fistulae or pain.
   a. Stable: clinical improvement or stabilization of previously progressive breakdown or improvement in pain.
   b. Refractory: no effect or progressive breakdown of gingival or worsening pain.

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Time-to-failure analysis was performed on all subjects who showed improvement with HBO2. To determine the length of improvement after treatment, the interval from the onset of HBO2 therapy until a change in either the stage or outcome criteria became evident was recorded. Follow-up ended in August 2006, and patients who continued to improve were right-censored at that time. Four subjects underwent HBO2 therapy more than once. The response to each treatment episode in relation to continued BP therapy and concurrent HBO2 therapy and chemotherapy was considered separately. SPSS version 8.0 for Windows (SPSS Inc, Chicago, IL) was used for all statistical calculations; a \( P \) value of .05 was considered significant.

### Results

**Patient Demographics and General Descriptions**

A total of 16 patients (6 females and 10 males), ranging in age from 43 to 78 years, were identified from the database search criteria. Twelve patients had mandibular lesions, 2 had maxillary lesions, and 2 had lesions in both bones. Multiple myeloma was the indication for BP treatment for 10 patients, whereas the others received BP during treatment for breast cancer (3 patients), sarcoidosis (1 patient), prostate cancer (1 patient), and Waldenstrom’s macroglobulinemia (1 patient). Of the 15 patients with malignancies, 13 were in remission. Two patients with breast cancer and 1 patient with multiple myeloma received chemotherapy during HBO2 therapy. The median time on BP therapy before onset of symptoms was 18 months (mean, 26 months; minimum, 2 months; maximum, 60 months). The median time from the onset of ONJ symptoms to the start of HBO2 therapy was 12 months (mean, 13 months; minimum, 4 months; maximum, 25 months). All patients were treated twice.
daily for 2 hours with 100% oxygen at 202.65 kPa (2 atm absolute), with a goal of 40 treatment sessions. The actual mean number of sessions was 37 (minimum, 24; maximum, 40).

SIZE AND NUMBER OF LESIONS

The size and numbers of the ONJ lesions decreased significantly from before HBO2 therapy to after HBO2 therapy ($P < .001$ for size and $0.008$ for number; Wilcoxon’s signed-rank test). Fourteen of the 16 patients (87.5%) showed some improvement in stage after HBO2 therapy. Table 3 presents the frequency of lesions by size and number before and after HBO2 therapy. As shown, there was no significant association of change in stage after HBO2 therapy with cancer type (categorized by multiple myeloma vs other) or remission status of the primary malignancy when analyzed by logistic regression.

CLINICAL OUTCOME AFTER HBO2

The clinical outcomes recorded after HBO2 therapy and on follow-up are listed in Table 4. Immediately after HBO2 therapy, 7 of the 16 patients (44%) were in remission with complete gingival coverage of bone that had been exposed before therapy. This percentage improved slightly to 50% at follow-up, because 1 patient continued to heal after HBO2 therapy. At the time of follow-up, 10 of the 16 patients either remained in remission or reported that their signs and symptoms had stabilized.

TIME-TO-FAILURE ANALYSIS

Six of the 15 patients who were in remission or had stabilized immediately after HBO2 therapy experienced relapse or deterioration in stage or clinical outcome category during follow-up. A Kaplan-Meier analysis showed that the mean duration of a beneficial effect was 16.0 months (95% confidence interval [CI] = 12.2 to 19.9). The mean duration of healing was 8.5 months (95% CI = 7.1 to 9.8) in the 7 patients who continued receiving BP treatment during HBO2 therapy, compared with 20.1 months (95% CI = 17.5 to 23.9) in those in whom the drug was discontinued ($P = .006$; log-rank test). Figure 1 shows the time to failure curves for both groups.

SUBGROUP OF PATIENTS TREATED WITH 2 HBO2 SESSIONS

Table 5 presents the response to each treatment episode in relation to ongoing BP therapy in the 4 patients who underwent more than 1 session of HBO2 therapy. Although HBO2 therapy improved outcome in the immediate post-treatment period in some patients, those who continued BP during HBO2 therapy deteriorated during follow-up.

Discussion

In a small group of patients with BP-ONJ, adjunctive HBO2 therapy with a goal of 40 sessions led to remission or improvement in 62.5% of patients. Benefits from HBO2 therapy also have been reported in patients treated at other institutions; however, our findings suggest that cessation of further BP administration is necessary to achieve remission. Our findings agree with the conclusions of a previous report of 11 non–HBO2-treated patients. Taken together, these preliminary results are encouraging but call for further investigation aimed at determining optimal therapy for patients with ONJ. Because of the varying times between the appearance of symptoms and the initiation of HBO2 therapy, the causal relationship between treatment efficacy and BP-ONJ is uncertain. The efficacy of HBO2 therapy in treating this condition will be evaluated in a planned prospective randomized controlled trial of 70 patients at Duke University. The patients will be randomized to receive 40 HBO2 sessions over a 4-week period in addition to routine oral surgery therapy for ONJ. Both groups will be followed for a 2-year period. The analysis will compare remission rates between the 2 groups while controlling for age, gender, previous local trauma or surgery, tumor type, diabetes, immunosuppression, duration of BP therapy, indication for BP ther-

<table>
<thead>
<tr>
<th>Patient</th>
<th>HBO2 Course</th>
<th>Continued BP</th>
<th>Response After HBO2</th>
<th>Response During Follow-Up</th>
<th>Months of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>A11</td>
<td>1</td>
<td>Yes</td>
<td>Improved</td>
<td>Deteriorated</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Yes</td>
<td>No change</td>
<td>Deteriorated</td>
<td>14</td>
</tr>
<tr>
<td>A14</td>
<td>1</td>
<td>Yes</td>
<td>Improved</td>
<td>Deteriorated</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>No</td>
<td>Improved</td>
<td>Stable</td>
<td>7</td>
</tr>
<tr>
<td>A6</td>
<td>1</td>
<td>Yes</td>
<td>Improved</td>
<td>Deteriorated</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>No</td>
<td>Improved</td>
<td>Stable</td>
<td>10</td>
</tr>
<tr>
<td>A7</td>
<td>1</td>
<td>Yes</td>
<td>No change</td>
<td>Deteriorated</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Yes</td>
<td>No change</td>
<td>Deteriorated</td>
<td>1</td>
</tr>
</tbody>
</table>

apy, infection, use of corticosteroids or thalidomide, and dental hygiene.

The rationale for a randomized controlled trial is that current treatment has proven suboptimal. Present management recommendations include preventive dentistry before initiation of BP therapy, thorough patient education regarding oral hygiene, control of secondary infection, and debridement limited to soft-textured sequestrated bone. Whether these routine measures are effective remains unknown. Three-phase bone scanning [99Tc(m)-MDP] is reportedly a useful screening test for detecting subclinical BP-ONJ in patients who have received BP therapy, and computed tomography and magnetic resonance imaging are useful for defining the features and extent of osteolytic lesions. In any event, BP-ONJ is an escalating problem that will require careful attention to therapy optimization.

References


Appendix: Individual Patient Histories

65F. Lesion: mandible. BP indication: breast cancer in remission. Latency of symptom onset: 19 months. Continued BP during HBO2. Immediate response to HBO2: improved. Follow-up after HBO2: stable. Months of follow-up: 11. 5/2/04 begin Zometa (estimated date); 8/8/04 end Zometa; 9/3/04 begin Aredia; 10/3/04 non-healing extraction; 5/25/5 HBO2 consult; 6/3/5 end Aredia; 7/5/05 begin HBO2; 9/27/05 debridement; 10/8/05 end HBO2; 5/24/06 doing well.

69F. Lesion: maxilla. BP indication: breast cancer in remission. Latency of symptom onset: 16 months. Continued BP during HBO2. Immediate response to HBO2: improved. Follow-up after HBO2: deteriorated. Months of follow-up: 21. 06/29/01 begin Zometa; 10/02 non-healing extraction; 10/03 oral surgery visit for nonhealing wound site; 10/14/03 HBO2 consult; 11/12/03 begin HBO2; 12/8/03 debridement; 12/15/03 end HBO2, wound closed; 12/29/03 OS F/U notes show good results; 10/6/04 OS notes report complete healing; 8/1/05 begin HBO2 repeat series for small pocket in maxilla; 8/5/05 end HBO2 repeat series; 9/15/05 OS notes show good healing; 5/24/06 last report, patient continues well and healed.

57M. Lesion: mandible. BP indication: multiple myeloma in remission. Latency of symptom onset: 60 months. Discontinued BP during HBO2. Immediate response to HBO2: improved. Follow-up after HBO2: stable. Months of follow-up: 16. 8/01 dental extraction; 08/02 problems first noted (not precisely described); 7/10/03 two 8 × 10 mm lesions of exposed bone; 1/22/04 lesions enlarged to 2 × 2 cm; 2/20/05 HBO2 consult; 3/16/04 debridement; 3/06/05 lesions completely healed; 6/22/06 no pain; no exposed bone; pink tissue. Implant stable.

bone”; 3/5/05 telephone follow-up, healed and doing well.

70M. Lesion: mandible. BP indication: multiple myeloma in remission. Latency of symptom onset: 12 months. Discontinued BP during HBO₂. Immediate response to HBO₂: improved. Follow-up after HBO₂: stable. Months of follow-up: 23. 5/1/03 begin Zometa; 11/03 nonhealing wound of mandible noted; 5/7/04 end Zometa; 9/30/04 HBO₂ consult; 10/25/04 begin HBO₂; 11/16/04 debridement; 11/30/04 end HBO₂; 12/9/04 oral surgery follow-up, “healed well”; 3/2/05 oral surgery follow-up, “no pain or sores”; 5/3/06 oral surgery follow-up, “no pain or sores”; 6/1/06 oral surgery follow-up, “no pain no exposed bone”; 9/1/06 telephone follow-up, doing well.

45F. Lesion: mandible. BP indication: multiple myeloma in remission. Latency of symptom onset: unknown. Discontinued BP during HBO₂. Immediate response to HBO₂: not improved. Follow-up after HBO₂: improved. Months of follow-up: 13. Unknown when BP started; 12/4/04 nonhealing extraction; 4/27/05 HBO₂ consult; 05/09/05 begin HBO₂ (poor compliance); 05/24/06 telephone follow-up “no pain or sores.”

62M. Lesion: maxilla. BP indication: multiple myeloma in remission. Latency of symptom onset: 40 months. Discontinued BP during HBO₂. Immediate response to HBO₂: improved. Follow-up after HBO₂: stable. Months of follow-up: 2.4. 9/00 begin bisphosphonates (estimated date); 09/17/03 end Zometa; 12/15/03 partial debridement; necrosis unresolved; 05/23/05 culture confirmed osteomyelitis; 02/22/06 HBO₂ consult for fistula; 03/27/06 begin HBO₂; 04/17/06 repeat debridement; 04/25/06 end HBO₂ (fistula closed); 6/7/06 doing well by telephone interview.

59M. Lesion: mandible. BP indication: multiple myeloma in remission. Latency of symptom onset: 40 months. Discontinued BP during HBO₂. Immediate response to HBO₂: improved. Follow-up after HBO₂: stable. Months of follow-up: 18. 5/01/04 begin Zometa, then Aredia; 10/30/04 nonhealing extraction; 2/15/05 begin HBO₂; 3/8/05 debridement and closure; 4/1/05 doing well; 4/1/06 off Zometa approximately 1 year; 8/06 visited OS, no lesions; 9/1/06 telephone follow-up, doing very well.

78F. Lesion: mandible. BP indication: multiple myeloma in remission. Latency of symptom onset: 33 months. Discontinued BP during HBO₂. Immediate response to HBO₂: improved. Follow-up after HBO₂: improved. Months of follow-up: 14. 1/2/05 Zometa start date; 1/05 discontinued Zometa; 3/11/05 2 lesions noted; 4/4/05 HBO₂ started; 5/9/05 HBO₂ ended, lesions smaller but bone not covered; 5/24/05 surgical debridement and closure; 10/05 relapse with tissue breakdown and exposed bone; 3/6 ongoing exposed bone and pain surgery; 5/24/06 telephone interview, no open sores or pain.


52M. Lesion: mandible and maxilla. BP indication: Waldenström's macroglobulinemia in remission. Latency of symptom onset: 43 months. Discontinued BP during HBO₂. Immediate response to HBO₂: improved. Follow-up after HBO₂: deteriorated. Months of follow-up: 11. 7/00 (dates not precise) begin bisphosphonate; 7/04 nonhealing dental extraction and end Zometa; 7/17/05 begin HBO₂; 8/10/05 debridement and closure; 9/2/05 end HBO₂; 2/06 doing well by telephone interview; 5/25/06 relapse.

52F. Lesion: mandible. BP indication: sarcoidosis. Latency of symptom onset: 13 months. Continued BP during HBO₂. Immediate response to HBO₂: improved. Follow-up after HBO₂: deteriorated. Months of follow-up: 31.5. History of sarcoidosis treated with both steroids and methotrexate, 11/27/01 pamidronate prescribed 90 mg/month; 11/27/01 first symptoms; 12/02 tooth extraction; 7/10/03 aggressive debridement with primary closure; 8/26/03 2 x 2 mm of exposed bone; 9/16/03 HBO₂ consult; 10/6/03 first HBO₂ session; 10/23/03 healed; 10/29/03 HBO₂ progress note, "site healed"; 10/31/03 last HBO₂ session; 11/6/03 relapse with small area of exposed bone; 2/17/04 sequestrectomy 5 x 5 cm by tooth 31; 3/8/04 biopsy showed acute osteomyelitis; 7/05 telephone follow-up revealed breakdown; 5/06 further debridements, more symptoms; 6/2/06 pain persisting.

72M. Lesion: mandible. BP indication: Prostate cancer in remission. Latency of symptom onset: 2 months. Continued BP during HBO₂. Immediate response to HBO₂: improved. Follow-up after HBO₂: deteriorated. Months of follow-up: 32. 1/03 began Zometa; 3/03 multiple dental extractions; 7/05 seen in oral surgery clinic for “chronic osteomyelitis”; 10/2/03 HBO₂ consult (continued on Zometa); 10/8/03 begin HBO₂ (continued on Zometa); 01/15/04 end HBO₂; 01/08/04 debridement (Zometa discontinued); 3/25/04 near-complete resolution of exposed bone; 1/1/05 initial relapse; 5/24/06 relapse with gingival breakdown; 8/22/06 persistent exposure of mandibular ridge bilaterally along the crest. Surrounding gingival tissues are pink and healthy, with no evidence of infection.
77M. Lesion: mandible. BP indication: multiple myeloma; active. Latency of symptom onset: unknown. Continued BP during HBO₂. Immediate response to HBO₂: improved. Follow-up after HBO₂: deteriorated. Months of follow-up: 16. 5/8/02 exposed bone noted; 5/8/03 OS notes report a 2 × 4 cm area of exposed bone 1 year old; 5/13/03 HBO₂ consult; 6/10/03 begin HBO₂; 7/11/03 end HBO₂; 3/1/04 new site noted, previous site well healed; 3/22/04 begin second HBO₂ series; 4/2/04 end second HBO₂ series (20 sessions only); 10/10/04 patient died.
