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 (HBO_2) therapy.

Patients and Methods: A total of 16 patients, ranging in age from 43 to 78 years, with BP-ONJ were treated with adjunctive HBO_2 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 analysis were calculated.

Results: The median time on BP therapy before appearance of ONJ symptoms was 18 months, and that from symptom onset to HBO_2 therapy was 12 months. Fourteen of 16 patients (87.5%) improved in stage. The size and number of ONJ lesions were decreased after HBO_2 therapy ($P < .001$ and $P = .008$, respectively; Wilcoxon signed-rank test). Immediately after HBO_2 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 HBO_2 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 HBO_2 therapy may benefit patients with BP-ONJ; however, the outcome is improved with cessation of BP administration.

J Oral Maxillofac Surg 65:1321-1327, 2007

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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0278-2391/07/6507-0010$32.00/0
doi:10.1016/j.joms.2007.03.019

Table 1. STAGING CRITERIA

Grade	Size, Diameter*
1A	Single lesion <0.5 cm
1B	Multiple lesions, largest <0.5 cm
2A	Single lesion 0.5 to 0.99 cm
2B	Multiple lesions, largest 0.5 to 0.99 cm
3A	Single lesion 1 to 2 cm
3B	Multiple lesions, largest 1 to 2 cm
4A	Single lesion >2 cm
4B	Multiple lesions, largest >2 cm

*Lesion size measured as the largest diameter.

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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%[8] 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.[9] However, osteoclast apoptosis (alendronate-induced apoptosis) can be suppressed by osteoclastogenic cytokines (tumor necrosis factor α, macrophage colony-stimulating factor, receptor activator of Nfκ-B [RANKL], and interleukin-6α).[10] These signals are known to be oxygen-sensitive;[11-13] therefore, we reasoned that hyperbaric oxygen (HBO_2) therapy might influence their activity. Reactive oxygen species stimulate the expression of RANKL and the Nfκ-B transcription factor, which are essential to avoid osteopetrosis.[14,15] This article reports on 16 patients with BP-ONJ recently treated with HBO_2 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.[16] After evaluation and identification, each patient's oral condition was recorded at 4 time points: *1*) immediately before HBO_2 therapy, *2*) on completion of HBO_2 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 HBO_2 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 HBO_2 therapy. The principal outcome was the clinical response (Table 2). The crude odds for a patient to show improvement in stage after HBO_2 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 HBO_2 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 HBO_2 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 HBO_2 therapy.

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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Table 3. LESION SIZE AND NUMBER

Size	Before HBO_2 Therapy		After HBO_2 Therapy	
	Frequency	Percent	Frequency	Percent
No lesion	0	0	6	37.5
<0.5 cm	2	12.5	4	25
0.5 to 1.0 cm	2	12.5	3	18.8
1.0 to 2.0 cm	7	43.8	3	18.8
>2.0 cm	5	31.3	0	0
Total	16	100	16	100
				$P < .001$*
Number				
0	0	0	8	40
1	12	60	8	40
Multiple	8	40	4	20
Total	20†	100	20†	100
				$P = .008$*

The size and number of the ONJ lesions decreased significantly when pre-HBO_2 and post-HBO_2 observations were compared ($P < .001$, size; $P = .008$, number by Wilcoxon's signed-rank test). Four patients received 2 sessions each. All sessions were included under the assumption that patients who were treated twice had no residual beneficial effect from HBO and that their before and after assessments were independent observations.

*Wilcoxon's signed-rank test.

†Four patients underwent 2 HBO_2 sessions

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Table 4. CLINICAL RESPONSE AFTER HBO_2 THERAPY AND AT TIME OF FOLLOW-UP

	After HBO_2 Therapy		At Time of Follow-Up	
	Frequency	Percent	Frequency	Percent
Remission	7	43.8	8	50
Stable	8	50	2	12.5
Progression	1	6.3	6	37.5
Total	16	100	16	100

Immediately after HBO_2, 7 of 16 patients (44%) were in remission with complete gingival coverage of bone that had been exposed before therapy. This percentage improved slightly to 50% wi th follow-up because one patient continued to heal after HBO_2 therapy. At the time of follow-up, 10 of the 16 patients (62.5%) either remained in remission or reported that their signs and symptoms had stabilized.

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Time-to-failure analysis was performed on all subjects who showed improvement with HBO_2. To determine the length of improvement after treatment, the interval from the onset of HBO_2 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 HBO_2 therapy more than once. The response to each treatment episode in relation to continued BP therapy and concurrent HBO_2 therapy and chemotherapy was considered separately. SPSS version 8.0 for Windows (SPPS 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 HBO_2 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 HBO_2 therapy was 12 months (mean, 13 months; minimum, 4 months; maximum, 25 months). All patients were treated twice

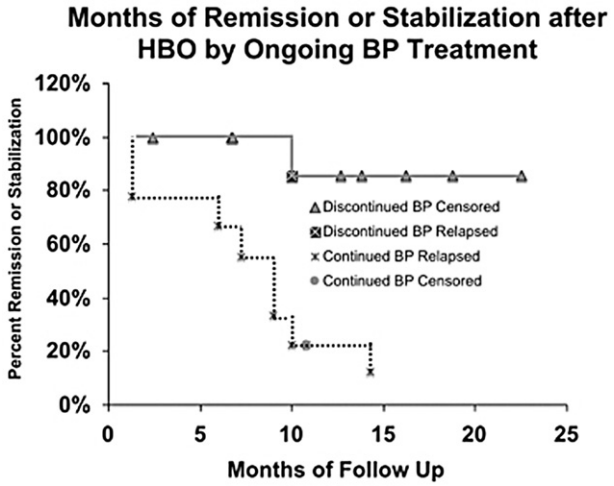

FIGURE 1. Kaplan-Meier curves for the 15 patients who were in remission or had stabilized immediately after HBO_2 therapy, comparing those who discontinued BP therapy and those who continued on BP therapy. The respective mean durations of beneficial effect were 20.1 months (95% CI = 17.5 to 23.9) versus 8.5 months (95% CI = 7.1 to 9.8) ($P = .006$; log-rank test). The mean duration of healing for all patients was 16.0 months (95% CI = 12.2 to 19.9). The patients who continued BP therapy were more likely to relapse during follow-up.

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Table 5. TREATMENT RESPONSE BY CONTINUED USE OF BP IN PATIENTS TREATED WITH 2 COURSES OF HBO_2

Patient	HBO_2 Course	Continued BP	Response After HBO_2	Response During Follow-Up	Months of Follow-Up
A11	1	Yes	Improved	Deteriorated	6
	2	Yes	No change	Deteriorated	14
A14	1	Yes	Improved	Deteriorated	16
	2	No	Improved	Stable	7
A6	1	Yes	Improved	Deteriorated	21
	2	No	Improved	Stable	10
A7	1	Yes	No change	Deteriorated	7
	2	Yes	No change	Deteriorated	1

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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 HBO_2 therapy to after HBO_2 therapy ($P < .001$ for size and .008 for number; Wilcoxon's signed-rank test). Fourteen of the 16 patients (87.5%) showed some improvement in stage after HBO_2 therapy. Table 3 presents the frequency of lesions by size and number before and after HBO_2 therapy. As shown, there was no significant association of change in stage after HBO_2 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 HBO_2

The clinical outcomes recorded after HBO_2 therapy and on follow-up are listed in Table 4. Immediately after HBO_2 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 HBO_2 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 HBO_2 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 HBO_2 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 HBO_2 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 HBO_2 therapy. Although HBO_2 therapy improved outcome in the immediate post-treatment period in some patients, those who continued BP during HBO_2 therapy deteriorated during follow-up.

Discussion

In a small group of patients with BP-ONJ, adjunctive HBO_2 therapy with a goal of 40 sessions led to remission or improvement in 62.5% of patients. Benefits from HBO_2 therapy also have been reported in patients treated at other institutions;[17-19] 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–HBO_2-treated patients.[7] 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 HBO_2 therapy, the causal relationship between treatment efficacy and BP-ONJ is uncertain. The efficacy of HBO_2 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 HBO_2 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-

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.[20] 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.[21] In any event, BP-ONJ is an escalating problem that will require careful attention to therapy optimization.

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Appendix: Individual Patient Histories

63F. Lesion: mandible. BP indication: breast cancer in remission. Latency of symptom onset: 19 months. Continued BP during HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: stable. Months of follow-up: 11. 5/2/04 begin Zometa (estimated date); 8/3/04 end Zometa; 9/3/04 begin Aredia; 10/3/04 nonhealing extraction; 5/23/5 HBO_2 consult; 6/3/5 end Aredia; 7/5/05 begin HBO_2; 9/27/05 debridement; 10/08/05 end HBO_2; 5/24/06 doing well.

69F. Lesion: maxilla. BP indication: breast cancer in remission. Latency of symptom onset: 16 months. Continued BP during HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: deteriorated. Months of follow-up: 21. 06/29/01 begin Zometa; 10/02 nonhealing extraction; 10/03 oral surgery visit for nonhealing wound site; 10/14/03 HBO_2 consult; 11/12/03 begin HBO_2; 12/8/03 debridement; 12/15/03 end HBO_2, wound closed; 12/29/03 OS F/U notes show good results; 10/6/04 OS notes report complete healing; 8/1/05 begin HBO_2 repeat series for small pocket in maxilla; 8/5/05 end HBO_2 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 HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: 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 HBO_2 consult; 3/16/04 debridement; 3/06/05 lesions completely healed; 6/22/06 no pain; no exposed bone; pink tissue. Implant stable.

53M. Lesion: mandible. BP indication: multiple myeloma in remission. Latency of symptom onset: 36 months. Discontinued BP during HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: stable. Months of follow-up: 7. 2001 begin bisphosphonate; 7/3 extraction; 7/4 oral surgeon consult for nonhealing extraction site; 8/23/04 HBO_2 consult; 10/8/04 OS follow-up, "tissues pink without . . . exposed

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 HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: 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 HBO_2 consult; 10/25/04 begin HBO_2; 11/16/04 debridement; 11/30/04 end HBO_2; 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 HBO_2. Immediate response to HBO_2: not improved. Follow-up after HBO_2: improved. Months of follow-up: 13. Unknown when BP started; 12/4/04 nonhealing extraction; 4/27/05 HBO_2 consult; 05/09/05 begin HBO_2 (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 HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: 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 HBO_2 consult for fistula; 03/27/06 begin HBO_2; 04/17/06 repeat debridement; 04/25/06 end HBO_2 (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 HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: stable. Months of follow-up: 18. 5/01/04 begin Zometa, then Aredia; 10/30/04 nonhealing extraction; 2/15/05 begin HBO_2; 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 HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: 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 HBO_2 started; 5/9/05 HBO_2 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.

56M. Lesion: mandible. BP indication: multiple myeloma in remission. Latency of symptom onset: 48 months. Discontinued BP during HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: improved. Months of follow-up: 13. 2002 begin Zometa; 2003 to 2004 pain and mouth lesions, multiple oncologist visits; 5/23/05 HBO_2 consult and start HBO_2 therapy; 8/16/05 debridement and hardware placement; 8/30/05 end HBO_2; 6/7/06 no sores, no pain or pain medication use by telephone interview; 8/28/2006 revision of prosthesis.

52M. Lesion: mandible and maxilla, BP indication: Waldenström's macroglobulinemia in remission. Latency of symptom onset: 43 months. Discontinued BP during HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: 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 HBO_2; 8/10/05 debridement and closure; 9/2/05 end HBO_2; 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 HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: 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 2×2 mm of exposed bone; 9/16/03 HBO_2 consult; 10/6/03 first HBO_2 session; 10/23/03 healed; 10/29/03 HBO_2 progress note, "site healed"; 10/31/03 last HBO_2 session; 11/6/03 relapse with small area of exposed bone; 2/17/04 sequestrectomy 5×5 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 HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: deteriorated. Months of follow-up: 32. 1/03 began Zometa; 3/03 multiple dental extractions; 7/03 seen in oral surgery clinic for "chronic osteomyelitis"; 10/2/03 HBO_2 consult (continued on Zometa); 10/8/03 begin HBO_2 (continued on Zometa); 01/15/04 end HBO_2; 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; 8/22/05 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 HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: 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 HBO_2 consult; 6/10/03 begin HBO_2; 7/11/03 end HBO_2; 3/1/04 new site noted, previous site well healed; 3/22/04 begin second HBO_2 series; 4/2/04 end second HBO_2 series (20 sessions only); 10/10/04 patient died.

43F. Lesion: mandible. BP indication: Breast cancer; active. Latency of symptom onset: 16 months. Continued BP during HBO_2. Immediate response to HBO_2: improved. Follow-up after HBO_2: deteriorated. Months of follow-up: 6. 2001 previous bisphosphonate treatment; 2/21/02 nonhealing extraction; 10/02 begin Zometa; 11/4/03 HBO_2 consult; 1/5/04 begin HBO_2; 1/26/04 oral surgery debridement; 3/1/04 end HBO_2 still with open sores but smaller; 5/24/06 open sores; occasional pain; on Aredia.

63M. Lesion: mandible and maxilla. BP indication: multiple myeloma in remission. Latency of symptom onset: 18 months. Continued BP during HBO_2. Immediate response to HBO_2: not improved. Follow-up after HBO_2: deteriorated. Months of follow-up: 1. 12/18/03 first indications of lesions; 1/29/04 HBO_2 consult note; 4/29/04 HBO_2 clinic note mild improvement only; 10/28/04 HOA notes indicate open areas of exposed bone.