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Management of bisphosphonate-associated osteonecrosis: pentoxifylline and tocopherol in addition to antimicrobial therapy. An initial case series

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Background. Studies of the use of pentoxifylline and α-tocopherol in osteoradionecrosis of the jaw have suggested their efficacy in this condition. We report an initial case series of pentoxifylline and α-tocopherol for patients with bisphosphonate-associated osteonecrosis (BON).

Methods. Six cases referred for management of BON were provided pentoxifylline and α-tocopherol in addition to antimicrobial therapy, and followed for a mean of 10 months.

Results. A 74% decrease in area of bony exposure and symptom control was achieved in these cases.

Discussion. Pentoxifylline with α-tocopherol may represent a strategy for management of BON. Controlled trials in cases of BON appear warranted. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:593-596)**

Bisphosphonate-associated osteonecrosis (BON) is a recently recognized oral complication with hundreds of cases reported worldwide.[1] BON is reported primarily among cancer patients treated with potent bisphosphonates (BP), including zoledronic acid, pamidronate, and others administered intravenously.[1,2] Among patients treated with oral BP for osteoporosis, BON is a rare potential complication.[3,4] A significant correlation has been reported between the administered dose and duration of BP and BON in cancer patients.[5] Comorbid risk factors identified include tobacco use, diabetes mellitus, concurrent immunosuppressive therapy, medications with antiangiogenic effects, and ongoing cancer chemotherapy.[6] General guidelines have been developed for the prevention and care of patients prescribed BP, primarily based on expert opinion.[7-13] It is strongly recommended that all patients planned to receive BP treatment, and those already undergoing treatment, receive thorough dental assessments and appropriate preventive dental management before initiation of these drugs.[7]

Osteoradionecrosis (ORN) and other late radiation complications have been associated with radiation-induced fibrosis (RIF), which has led to studies that focus on a fibro-atrophic mechanism in the pathogenesis of ORN, rather than vascular insufficiency.[11] Combined pentoxifylline and α-tocopherol (PT) significantly reduce RIF[14] modulating fibroblast activity, perhaps because of their impact on cytokine production. A phase II clinical trial with PT induced a 66% regression of the RIF surface area after 12 months of treatment.[15] These results were confirmed in an experimental RIF model where a 70% regression of RIF volume was observed

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after 6 months of treatment.[16] These results were replicated in a phase II trial of uterine fibro-atrophy[16] and clinical studies of ORN.[13,15,17,18] Another study of breast cancer patients showed long-term benefits with a 68% reduction of RIF in breast tissue 2 years after treatment with PT therapy.[12] Based on these findings and the similar pathogenesis to radiation-induced fibrosis in ORN, trials of PT were conducted. Case series and a phase II trial of patients treated for mandibular ORN with PT and antibiotic therapy document improvement in most patients.[13,15,17,19]

Pentoxifylline improves peripheral blood flow, reduces viscosity of blood, increases flexibility of red blood cell membranes, improves microcirculation, and enhances tissue oxygenation.[12] In addition, pentoxifylline has anti–tumor necrosis factor alpha (anti-TNFα) effects, inhibits dermal fibroblasts, and increases collagenase activity.[13] Decreased levels of TNFα and reduced production of interleukin (IL)-12 have been observed among patients with acute coronary syndromes treated with pentoxifylline compared with placebo.[14] Decrease in the anti-inflammatory cytokine IL-10 and increase in transforming growth factor beta (TGFβ) have also been shown.[14] Pentoxifylline also reduces the synthesis of proinflammatory cytokines, including TNFα in recurrent aphthous lesions.[20] Furthermore, a decrease in the duration of soft tissue necrosis was reported in radiation-associated necrosis.[21] In a study of experimental periodontitis in rats, bone loss was decreased with pentoxifylline.[22]

A number of mechanisms of action of α-tocopherol may decrease inflammation and stimulate healing. α-Tocopherol impairs tissue fibrosis and is a potent oxygen radical scavenger that may reduce damage caused by free radicals impacting necrosis.[17] α-Tocopherol scavenges reactive oxygen species generated during oxidative stress, thereby protecting cell membranes, and inhibits TGF*h*1 and pro-collagen gene expression.[23] α-Tocopherol improves endothelial function in patients with hypercholesterolemia or advanced atherosclerosis.[23] It has also been reported to produce a proinflammatory effect induced by low-dose atrovastatin among patients with ischemic heart failure.[24] Studies of dietary α-tocopherol supplementation resulted in significantly lower TNFα production in animals,[25] reduced inflammation in patients with diabetes or who smoked, and prevention of the early signs of dermal necrosis.[26]

Studies of PT in RIF and ORN prompted us to assess the utility of this combination in addition to standard antimicrobial therapy in a series of cases of BON of the jaws.

METHODS

Consecutive patients with persisting BON of the jaws were referred for management. Pentoxifylline and

Table I. Patient characteristics

Patient no., age, sex	*Bisphosphonate treatment begins (months before therapy initiation)*	*Osteonecrosis diagnosis (months before treatment initiation)*	*Pentoxifylline initiation (month year)*	*Size of bony exposure at initial visit, mm*	*Size of bony exposure at most recent follow-up, mm*	*Follow-up, mo*	*% Decrease in area of bony exposure*
1. 58 y F	19 mo (zoledronate)	7 mo	06 2008	4 × 9	4 × 8	3	16%
2. 89 y F	126 mo (pamidronate)	57 mo	10 2007	10 × 5	2 × 2	19	92%
	30 mo (zoledronate)						
3. 64 y F	103 mo (aredia)	74 mo	10 2007	15 × 10	5 × 5	12	83%
4. 85 y F	62 mo (fosamax)	0.5 mo	11 2007	5 × 10	2 × 1.5	12	94%
5. 81 y F	36 mo (ibandronate)	5 mo	11 2008	20 × 10	0 × 0	10	100%
	12 mo (alendronate)						
6. 77 y M	60 mo (zoledronate)	0.5 mo	11 2008	15 × 5	8 × 4	9	57%

Patients 1, 2, 3: presented with pain, purulence and continued systemic antibiotics.
Patient 4: presented with pain, no clinical evidence of infection, and was not provided systemic antibiotics.
Patients 5, 6: presented with roughness at the site of exposure, Patient 6 had prior swelling and pain and was previously on antibiotics; both presented without pain and were not provided systemic antibiotics during treatment with combined pentoxifylline and α-tocopherol.

α-tocopherol were both prescribed at 400 mg twice daily with chlorhexidine rinses. Four of the 6 patients had used chlorhexidine rinse (0.12%) before treatment with PT. All of the patients used chlorhexidine (10-15 mL rinsed more than 30 seconds, twice daily) with PT. Outcomes assessed included symptoms, signs, and measure of the area of exposed bone. All patients provided informed consent.

RESULTS AND DISCUSSION

A summary of the patients is presented in Table I. Of the patients presented in this series, 4 of 6 were previously treated with chlorhexidine rinses and 4 with systemic antibiotics owing to purulence, before initiation of the PT. Chlorhexidine rinses were provided to all patients during the treatment with PT and the antibiotics that were started before PT treatment were continued in 3 patients. Five patients were female and 1 was male, with a mean age of 75 years. Four patients had a history of cancer and 2 had a history of severe osteoporosis, and all but one was treated with intravenous BP. For those maintained on oral agents, the mean duration of oral alendronate was 62 months. In those receiving intravenous (IV) BP, the duration on drug ranged from 19 months to 126 months (mean, 71 months). Four of these patients had an extensive history of years of fluctuating symptomatic BON. Of the 6 patients, 1 remained stable, 4 improved with a decrease in bone exposure along with improvement in symptoms, and 1 case resolved. One had a small sequestrum easily mobilized and removed before resolution. In one case, symptoms and bone exposure increased following initial improvement on PT and α-tocopherol when these agents were discontinued for 3 months, and improved upon resuming these agents. The mean reduction in area of exposed bone in all patients was 74%, at a mean follow-up of 10 months. All patients were without pain, erythema, or purulence following initiation of treatment with PT. The improved clinical outcomes should be compared with the history of fluctuating symptoms and progression in lesion size before the addition of PT. The medications were well tolerated with no adverse effects identified. Potential comorbid risk factors were present in 4 patients and included use of tobacco, prednisone, lenalidomide, and lack of oral hygiene (Table I).

The primary goal is prevention of BON by expert dental assessment and dental management before the initiation of BP treatment.[8,9] For patients who present with painful exposed bone, nonsurgical care using a regimen of 0.12% chlorhexidine mouth rinse, systemic antibiotics (in the presence of secondary infection), pain management, and cessation of tobacco and alcohol use are recommended.[9] In cases of advanced BON where control of bone destruction or infection is not possible, or in cases of pathologic fracture, alveolectomy or resection of affected bone may be necessary. The findings in the 6 patients who were treated with PT here suggest that this drug combination with antimicrobial agents may have utility in the medical management of BON. The patients in this series improved with the introduction of PT and α-tocopherol without noticeable adverse effects. Future studies of potential therapeutic and prophylactic efficacy of this therapy for high-risk patients should be considered.

REFERENCES

1. Migliorati CA, Siegel MA, Elting LS. Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. Lancet Oncol 2006;7:508-14.
2. Michaelson MD, Smith MR. Bisphosphonates for treatment and prevention of bone metastases. J Clin Oncol 2005;23:8219-24.
3. Cartsos VM, Zhu S, Zavras AI. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. J Am Dent Assoc 2008;139:23-30.
4. Grbic JT, Landesberg R, Lin SQ, Mesenbrink P, Reid IR, Leung PC, et al. Health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial research group. Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in the health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial. J Am Dent Assoc 2008;139:32-40.
5. Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. J Clin Oncol 2006;24:945-52.
6. Khamaisi M, Regev E, Yarom N, Avni B, Leitersdorf E, Raz I, et al. Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. J Clin Endocrinol Metab 2007;92:1172-5.
7. Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg. 2007;65:369-76.
8. Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo SB. Managing the care of patients with bisphosphonate-associated osteonecrosis: an American Academy of Oral Medicine position paper. J Am Dent Assoc 2005;136:1658-68.
9. Edwards BJ, Hellstein JW, Jacobsen PL, Kaltman S, Mariotti A, Migliorati CA; American Dental Association Council on Scientific Affairs Expert Panel on Bisphosphonate-Associated Osteonecrosis of the Jaw. Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: an advisory statement from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc 2008;139:1674-7.
10. Edwards BJ, Hellstein JW, Jacobsen PL, Kaltman S, Mariotti A, Migliorati CA, et al. Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: an advisory statement from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc 2008;139:1674-7.
11. Teng MS, Futran ND. Osteoradionecrosis of the mandible. Curr Opin Otolaryngol Head Neck Surg 2005;13:217-21.
12. Delanian S. Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. J Clin Oncol 2005;23:8570-9.

13. Delanian S, Depondt J, Lefaix JL. Major healing of refractory mandible osteoradionecrosis after treatment combining pentoxifylline and tocopherol: a phase II trial. Head Neck 2005;27:114-23.
14. Altenburg A, Abdel-Naser MB, Seeber H, Abdallah M, Zouboulis CC. Practical aspects of management of recurrent aphthous stomatitis. J Europ Acad Dermatol Venereol 2007;21:1019-26.
15. Delanian S, Lefaix JL. Complete healing of severe osteoradionecrosis with treatment combining pentoxifylline, tocopherol and clodronate. Br J Radiol 2002;75:467-9.
16. Delanaian S, Balla-Mekias S, Lefaix J-L. Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. J Clin Oncol 1999;17:3283-90.
17. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. Br J Oral Maxillofac Surg 2008;46:63-60.
18. Futran ND, Trotti A, Gwede C. Pentoxifylline in the treatment of radiation-related soft tissue injury: preliminary observations. Laryngoscope 1997;107:391-5.
19. Fernandes JL, de Oliveira RT, Mamoni RL, Coelho OR, Nicolau JC, Blotta MH, et al. Pentoxifylline reduces pro-inflammatory and increases anti-inflammatory activity in patients with coronary artery disease-a randomized placebo-controlled study. Atherosclerosis 2008;196:434-42.
20. Dion M, Hussey D, Doornbos J, Vigliotti A, Wen B, Anderson B. Preliminary results of a pilot study of pentoxifylline in the treatment of late radiation soft tissue necrosis. Int J Radiat Oncol Biol Phys 1990;19:401-7.
21. Lima V, Vidal FD, Rocha FA, Brito GA, Ribeiro RA. Effects of tumor necrosis factor-alpha inhibitors pentoxifylline and thalidomide on alveolar bone loss in short-term experimental periodontal disease in rats. J Periodontol 2004;75:162-8.
22. Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. Radiother Oncol 2004;73:119-31.
23. Tousoulis D, Antoniades C, Vassiliadou C, Toutouza M, Pitsavos C, Tentolouris C, et al.. Effects of combined administration of low dose atorvastatin and vitamin E on inflammatory markers and endothelial function in patients with heart failure Eur J Heart Fail 2005;7:1126-32.
24. Han SN, Wu D, Ha WK, Beharka A, Smith DE, Bender BS, et al. Vitamin E supplementation increases T helper 1 cytokine production in old mice infected with influenza virus. Immunol 2000;100:487-93.
25. Mol MJ, de Rijke YB, Demacker PN, Stalenhoef AF. Plasma levels of lipid and cholesterol oxidation products and cytokines in diabetes mellitus and cigarette smoking: effects of vitamin E treatment. Atherosclerosis 1997;129:169-76.
26. Houwing R, Overgoor M, Kon M, Jansen G, van Asbeck BS, Haalboom JR. Pressure-induced skin lesions in pigs: reperfusion injury and the effects of vitamin E. J Wound Care 2000;9:36-40.

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