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.


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.8 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.14 Combined pentoxifylline and α-tocopherol (PT) significantly reduce RIF14 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.
after 6 months of treatment. These results were replicated in a phase II trial of uterine fibro-atrophy and clinical studies of ORN. 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. 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.

Pentoxifylline improves peripheral blood flow, reduces viscosity of blood, increases flexibility of red blood cell membranes, improves microcirculation, and enhances tissue oxygenation. In addition, pentoxifylline has anti–tumor necrosis factor alpha (anti-TNFα) effects, inhibits dermal fibroblasts, and increases collagenase activity. 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. Decrease in the anti-inflammatory cytokine IL-10 and increased transforming growth factor beta (TGFβ) have also been shown. Pentoxifylline also reduces the synthesis of proinflammatory cytokines, including TNFα in recurrent aphthous ulcers. Furthermore, a decrease in the duration of soft tissue necrosis was reported in radiation-associated necrosis. In a study of experimental periodontitis in rats, bone loss was decreased with pentoxifylline.

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. α-Tocopherol scavenges reactive oxygen species generated during oxidative stress, thereby protecting cell membranes, and inhibits TGFβ1 and pro-collagen gene expression. It has also been reported to produce a proinflammatory effect induced by low-dose atorvastatin among patients with ischemic heart failure. Studies of dietary α-tocopherol supplementation resulted in significantly lower TNFα production in animals, reduced inflammation in patients with diabetes or who smoked, and prevention of the early signs of dermal necrosis.

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>
<thead>
<tr>
<th>Patient no., age, sex</th>
<th>Bisphosphonate treatment begins (months before therapy initiation)</th>
<th>Osteonecrosis diagnosis (months before treatment initiation)</th>
<th>Pentoxifylline initiation (months before therapy initiation)</th>
<th>% Decrease in area of bony exposure</th>
<th>Follow-up, mo</th>
<th>Size of bony exposure at initial visit, mm</th>
<th>Size of bony exposure at most recent follow-up, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 58 y F 19 mo (zoledronate)</td>
<td>7 mo</td>
<td>06 2008</td>
<td>4</td>
<td>3</td>
<td>16%</td>
<td>4 × 8</td>
<td></td>
</tr>
<tr>
<td>2. 89 y F 126 mo (pamidronate)</td>
<td>57 mo</td>
<td>10 2007</td>
<td>2 × 2</td>
<td>19</td>
<td>92%</td>
<td>5 × 5</td>
<td></td>
</tr>
<tr>
<td>3. 64 y F 103 mo (aredia)</td>
<td>74 mo</td>
<td>11 2007</td>
<td>5 × 5</td>
<td>19</td>
<td>92%</td>
<td>20 × 10</td>
<td></td>
</tr>
<tr>
<td>4. 85 y F 62 mo (fosamax)</td>
<td>60 mo (alendronate)</td>
<td>5 mo</td>
<td>0 × 0</td>
<td>10</td>
<td>90%</td>
<td>8 × 4</td>
<td></td>
</tr>
<tr>
<td>5. 81 y F 36 mo (ibandronate)</td>
<td>74 mo</td>
<td>11 2008</td>
<td>5 × 5</td>
<td>10</td>
<td>100%</td>
<td>15 × 10</td>
<td></td>
</tr>
<tr>
<td>6. 77 y M 60 mo (zoledronate)</td>
<td>0.5 mo</td>
<td>11 2008</td>
<td>0.5 mo</td>
<td>9</td>
<td>57%</td>
<td>8 × 4</td>
<td></td>
</tr>
</tbody>
</table>

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.
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. 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. In cases of advanced BON where control of bone destruction or infection is not possible, or in cases of pathologic fracture, alvelectomy 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


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