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Pentoxifylline and Tocopherol in the Management of Cancer Patients with Medication-related Osteonecrosis of the Jaw: an observational retrospective study of initial case series

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Abstract

Introduction—Very few studies have evaluated the efficacy of pentoxifylline and tocopherol (PENT-E) in the management of medication-related osteonecrosis of the jaw (MRONJ), though studies have shown its therapeutic and prophylactic benefit in the management of osteoradionecrosis. We report the outcomes of MRONJ managed with PENT-E in patients with metastatic bone disease/multiple myeloma.

Patients and Methods—Seven patients diagnosed with refractory established cases of MRONJ due to anti-resorptive medications for management of metastatic bone tumors/multiple myeloma were provided PENT-E for a mean period of 16.8 months (range: 3 – 48 months).

Results—At latest follow-up visit, all patients demonstrated relief of symptoms. There was radiographic evidence of new bone fill of prior radiolucent defect in all patients. Two patients had resolution of exposed bone, 2 patients had partial resolution, in 1 patient no change in exposed bone and 1 patient with 3 sites of exposed bone prior to starting PENT-E had resolution of 1 site, partial resolution in another site and no change on the third site. PENT-E was well-tolerated in all patients.

Conclusion—Our case series illustrates that PENT-E could be a safe and effective adjunct in the management of MRONJ.

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Introduction

Malignancy such as multiple myeloma and metastases to the bone, a common occurrence in advance-stage disease, may necessitate the use of bone-modifying agents such as anti-resorptive medications, including pamidronate and zolendronate (intravenous bisphosphonates), denosumab (humanized monoclonal antibody) and anti-angiogenics such as sunitinib (tyrosine kinase inhibitor) and bevacizumab (humanized monoclonal antibody).

Medication-related osteonecrosis of the jaw (MRONJ) is a well-known complication of bone-modifying agents used in the prevention of skeletal-related events such as bone fracture, spinal cord compression, radiotherapy or surgery in patients with metastatic disease and patients with osteoporosis or osteopenia[1-5]. The risk of developing MRONJ in patients treated for metastatic disease is higher compared to patients treated for osteoporosis[6]. Steroids, tobacco, immunosuppressive therapy use and comorbidities such as a medical history of diabetes mellitus have been associated with an increased risk for MRONJ[7-9]. In approximately 60% of patients, surgical procedures such as dental extraction, periodontal surgery, or implant placement are considered the major precipitating factors for the development of MRONJ[9-11].

Clinical management of MRONJ remains controversial, with no established treatment guidelines. Different therapeutic approaches such as chlorhexidine 0.12% or 2% rinse, antibiotic therapy, hyperbaric oxygen (HBO), low level laser therapy (LLLT), laser surgery, conservative surgery, extensive surgery with or without fluorescence light or plasma rich protein (PRP), and pentoxifylline and tocopherol (PENT-E) have been utilized in the management of MRONJ, with variable success rates[1, 2, 4, 12-23].

Patients whose osteoradionecrosis (ORN) is managed by PENT-E have demonstrated significant symptom improvement. A newly proposed theory of pathophysiology of radiation-induced fibrosis accounts for the treatment's effectiveness[24, 25]. Pentoxifylline was originally approved by the FDA for the management of peripheral artery disease such as ischemic heart disease and intermittent claudication. It improves peripheral blood flow by enhancing vasodilation, reducing blood viscosity and increases erythrocyte flexibility[26]. It also induces anti-tumor necrosis factor alpha (anti-TNFα) effects, inhibiting inflammation and decreasing fibrosis[24, 27]. Tocopherol is a potent oxygen radical scavenger that reduces free radical damage generated during oxidative stress and protects cell membranes [28]. It also reduces inflammation and tissue fibrosis[24, 27].

To date, only two reports have demonstrated the effect of PENT-E on MRONJ[21, 22]. In one study of 6 patients, all patients with MRONJ experienced improvement after treatment with PENT-E, including a 74% decrease in area of bone exposure, without adverse effects[21]. The second report detailed a patient treated yearly with zoledronic acid for the management of osteoporosis. This patient demonstrated complete bone remodeling after PENT-E treatment[22].

The aim of this observational study is to report the outcomes of MRONJ in patients with metastatic bone disease/multiple myeloma managed with PENT-E.

Patients and Methods

The observational study was approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board. Seven patients diagnosed with refractory established MRONJ were referred to Dental Service for evaluation of oral complaints including exposed bone, jaw pain and non-healing extraction sites. They were prescribed PENT-E (pentoxifylline 400mg BID and vitamin E 400 IU BID). All patients had been treated with anti-resorptive medication for management of metastatic bone tumors/multiple myeloma. Clinical and radiographic records were examined to determine if PENT-E provided therapeutic benefit to these patients. Outcomes assessed were symptoms, signs and the area of exposed bone. The outcome of the area of exposed bone was divided into 4 categories: resolution (complete mucosal coverage of prior exposed bone); partial resolution (reduction in size of exposed bone); no change; and progression (increase in size of exposed bone). All patients were also treated with chlorhexidine 0.12% rinse and prescribed antibiotic therapy Augmentin 875mg BID or Clindamycin 300mg QID for seven days or longer as indicated for active infection.

Results

Table 1 summarizes treatment outcomes. There were seven patients (female n = 4, male n = 3; ages 53-68 years). Four patients were being managed for metastatic breast cancer, 2 patients for multiple myeloma and 1 patient metastatic gastrointestinal stromal tumor. Three patients were managed with zoledronic acid only, 1 patient with denosumab only and the remaining 3 patients had a combination of zoledronic acid with either denosumab, sunitinib, or alendronic acid. Anti-resorptive dose ranged from 8 – 100 doses. Three patients were classified as MRONJ stage 3 (cases 1-3), three patients were MRONJ stage 2 (cases 4-6) and one patient was MRONJ stage 0 (case 7).

Prior to commencement of PENT-E, 6 patients had an area of exposed bone (cases 1-6), 4 patients had a radiolucent lesion identified on panoramic radiograph (cases 1-3, 7), and 4 expressed purulent discharge (Cases 1-4). All patients experienced pain at presentation.

Patients were placed on PENT-E for a mean period of 16.8 months (range: 3 – 48 months). At the most recent follow-up visit, all patients demonstrated symptom relief; no patient presented with pain or discharge. On radiographic evaluation there was evidence of new bone fill of radiolucent defect in 4 patients (cases 1-3, 7) (Figures 1 – 3). Sequestrum was removed in 2 patients (Cases 1 and 4), due to outwardly loose necrotic bone. Two patients had resolution of exposed bone (Cases 1 and 3) (Figure 1) and 2 patients had partial resolution (Cases 4 and 6). In one patient there was no change in exposed bone (Case 2), and one patient with 3 sites of exposed bone prior to PENT-E treatment had resolution of 1 site, partial resolution of another site and no change in exposure area of the third site (Case 5). PENT-E was well tolerated with no adverse effects identified in all patients.

Discussion

This observational study reports the outcome of MRONJ in patients with metastatic bone disease/multiple myeloma managed with PENT-E. In this present study, all patients demonstrated relief of symptoms and patients who presented with radiolucent defect

demonstrated significant new bone formation in the defect at our last follow-up time. PENT-E has demonstrated promising results in the management of radiation-induced fibrosis in soft tissue and established ORN[25, 29, 30], with a recent study showing therapeutic benefit in the prophylactic use of PENT-E in patients who required dental extractions after head and neck radiotherapy. In that study, 390 dental extractions were performed in 82 patients who had been irradiated to the head and neck; only one patient developed ORN post-dental extraction[31], suggesting a promising application for PENT-E in the management of MRONJ.

In the face of a lack of consensus treatment guidelines, different therapeutic approaches have been employed in the management of MRONJ, all with different outcomes. Nonsurgical options entail the use of antimicrobials such as chlorhexidine 0.12% or 2% rinse or antibiotics. Common antibiotics employed include amoxicillin, amoxicillin with clavulanic acid, clindamycin and/or metronidazole, HBO and low-level laser therapy (LLLT). Surgical options entail conservative surgery (sequestrectomy and/or superficial debridement of sequestrum), extensive surgery (alveoloplasty, resection), and laser surgery. Combination treatments are common, including HBO before and after extensive surgery, HBO or PENT-E with antimicrobial treatment, and others[13, 15, 20, 21].

In the 2 previous reports of PENT-E use in the management of MRONJ and in our study [21, 22], the pentoxifylline and tocopherol combination therapy has provided effective relief of patient's symptoms. PENT-E is easily prescribed, less expensive and better tolerated compared to other treatment options such as HBO and extensive surgery. As opposed to surgical procedures which are a well known precipitating factor to the development of MRONJ, it may occur spontaneously secondary to associated endodontic or periodontal infections [16]. The use of PENT-E may be considered prophylactically. Limitations to this study are its retrospective nature and an observational study with few patients. Further studies on the therapeutic and prophylactic efficacy of PENT-E in a large cohort of MRONJ patients are needed.

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Statement of Clinical Relevance

Pentoxifylline and tocopherol were found to be safe and effective in the management of medication-related osteonecrosis of the jaw

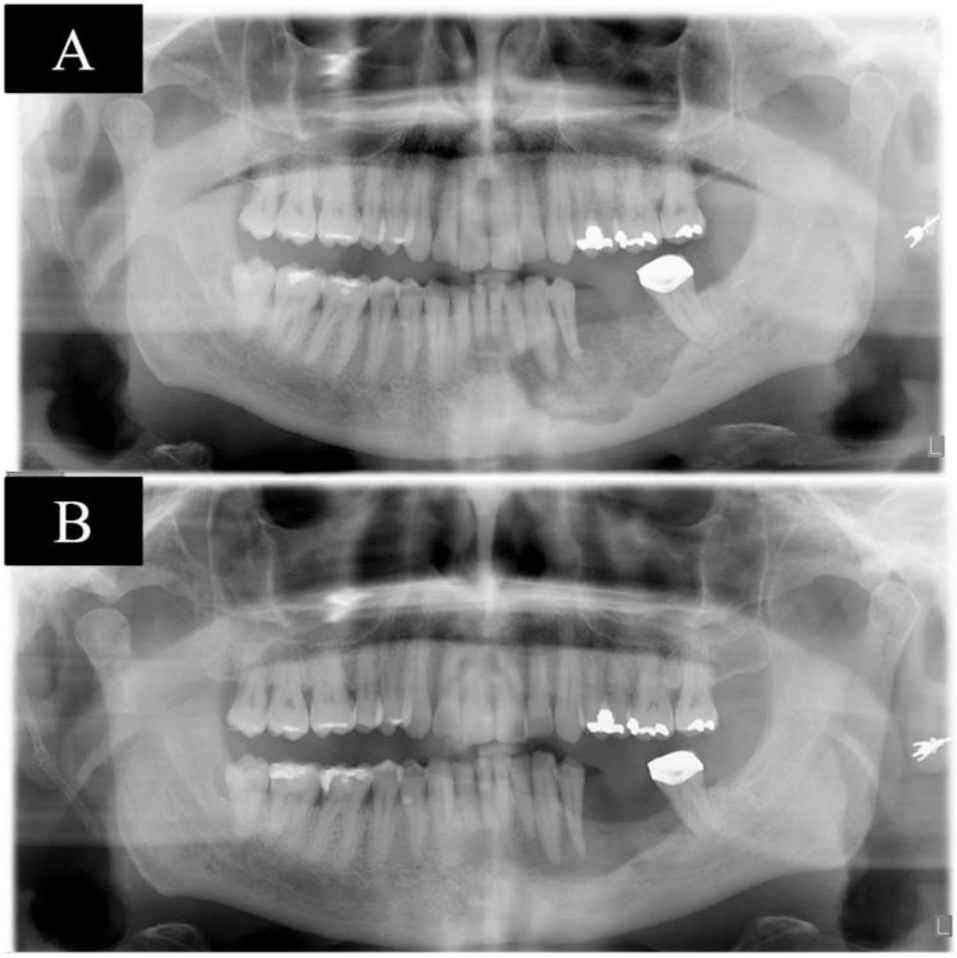

Figure 1. shows pre-therapy panoramic radiograph with a radiolucent defect (A), panoramic radiograph shows a radiographic bone fill after 34 months of therapy (B), case 1

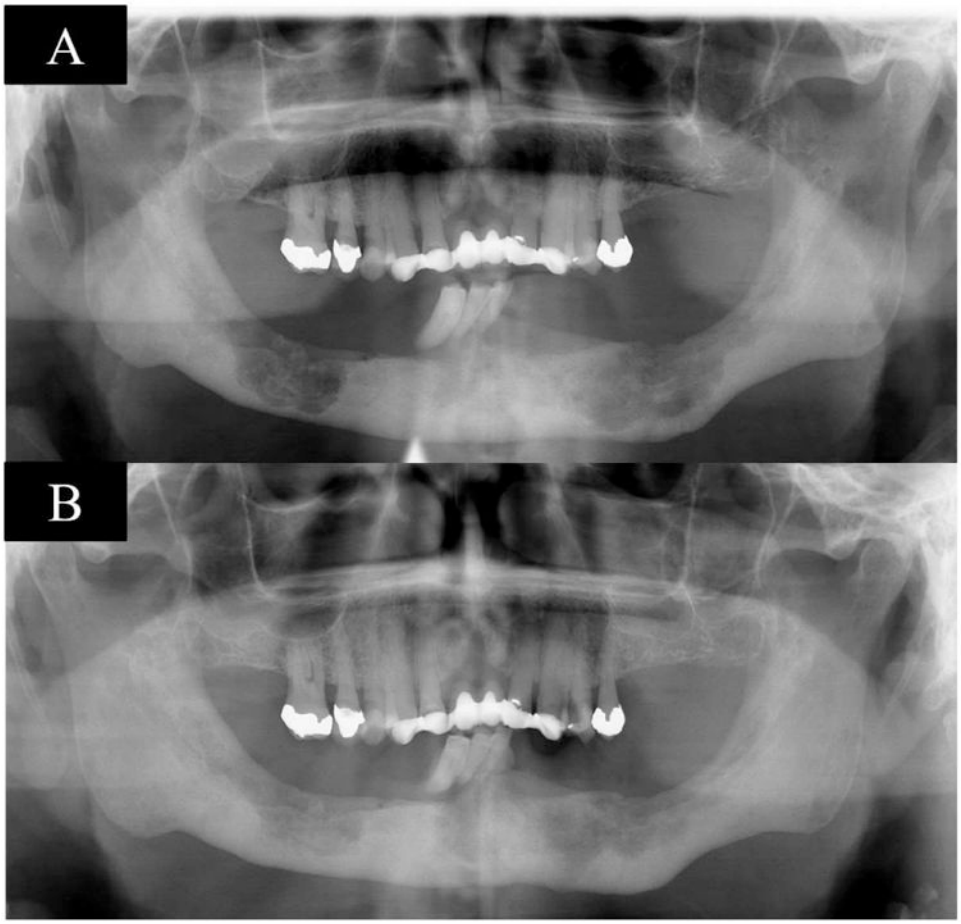

Figure 2. shows pre-therapy panoramic radiograph with bilateral radiolucent defects (A), panoramic radiograph shows bilateral radiographic bone fill after 11 months of therapy (B), case 2

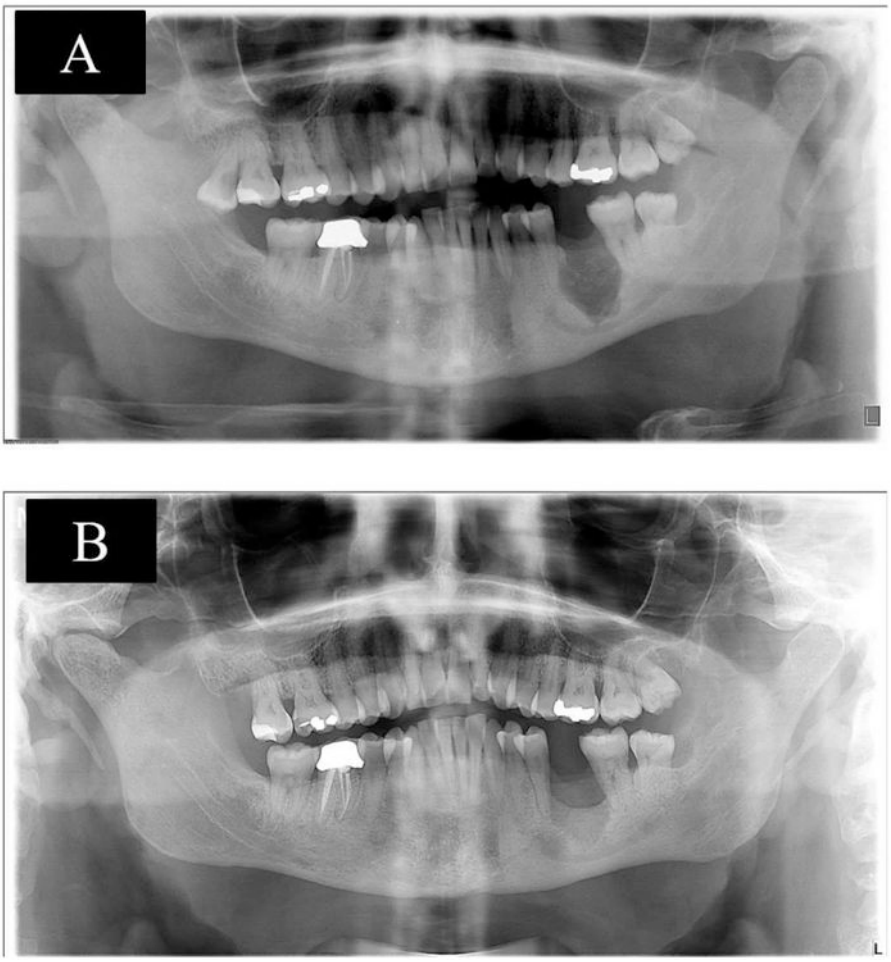

Figure 3. shows pre-therapy panoramic radiograph with a radiolucent defect (A), panoramic radiograph shows a radiographic bone fill after 22 months of therapy (B), case 3

Table 1

Characteristics of MRONJ Patients managed with PENT-E

Age(y) /Sex /Stage	No. of doses prior to ONJ	Clinical presentation prior to PENT-E	Radiographic findings prior to PENT-E	Duration on PENT-E till last follow-up	Clinical presentation at last follow-up	Radiographic findings at last follow-up
1. 63/M /3	40, Z + S	Pain, purulent discharge, mandibular bone exposure (55 mm)	Radiolucent defect reaching the basal bone	48 months	No pain, discharge or bone exposure	Radiolucent bony defect filling
2. 66 /M /3	35Z + 11 A	Pain, purulent discharge, bilateral mandibular bone exposure	Radiolucent defects reaching the basal bone	13 months	No pain, discharge, bone exposure unchanged	Radiolucent bony defect filling
3. 54 /M /3	40, Z	Pain, purulent discharge, mandibular bone exposure	Radiolucent defect reaching the basal bone	22 months	No pain, discharge or bone exposure	Radiolucent bony defect filling
4. 62/F /2	7Z + 2D	Pain, discharge and bone exposure	No radiographic findings	3 months	No pain or discharge, bone exposure reduced in size	NA
5. 57/F /2	8, D	Pain and bone exposure: right maxilla (8 mm), left maxilla (6 mm) and mandible	No radiographic findings	5 months	No pain or bone exposure on the right maxilla, bone exposure on the left maxilla reduced to 2 mm. The mandibular bone exposure unchanged	NA
6. 68 /F /2	100, Z	Pain, bilateral mandibular bone exposure	No radiographic findings	3 months	No pain, bone exposure reduced in size	NA
7. 53 /F /0	63, Z	Pain, swelling, no exposed bone	Radiolucent defect	24 months	No pain or swelling	Radiolucent bony defect filling

Z – Zolendronic acid, S – Sunitinib, A – Alendronic acid, D - Denosumab, NA - Not applicable