Pharmacological Treatment of Medication-Related Osteonecrosis of the Jaw (MRONJ) with Pentoxifylline and Tocopherol – Report of Two Cases

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Abstract

In the present study, we discuss the cases of 62- and 71-year-old patients with osteonecrosis of the mandible, which had been treated for multiple myeloma (MM). The best-understood complications of MM are changes in the skeletal system, the nervous system, and the kidneys. Major symptoms affecting the bones are osteolysis and hypercalcemia. To reduce excessive bone turnover, patients receive bisphosphonate group drugs. The study aims to present cases of pharmacological treatment with pentoxylin and tocopherol (PENTO method) in patients with MRONJ during bisphosphonate treatment. The applied PENTO therapy caused the resolution of inflammatory symptoms and reduced pain and discomfort resulting from purulent extra-oral and intra-oral fistulas. All the actions undertaken helped avoid mutilating surgical procedures.

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Introduction

The currently applied holistic approach to patient health, especially in palliative care, significantly increases the quality of mental and physical life. A group of drugs with an established position in palliative care are bisphosphonates. They are implemented to treat postmenopausal osteoporosis, multiple myeloma, Paget's disease, and neoplastic bone metastases and reduce pain associated with them, especially in the disease's terminal stages. [1,2,3] The application of these drugs in patients with breast cancer, for instance, prolongs the symptomless period before metastases set in and soothes the accompanying bone pain. [4] This pain occurs in 60% -90% of patients in the terminal stages of a disease, with 30% of patients presenting with persistent pain. [5]

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Bisphosphonates are generally well tolerated and considered safe. However, such therapy happens to induce adverse reactions like fatigue, hypocalcemia, anemia, or flu-like symptoms. With oral administration of bisphosphonates, digestive disorders may occur, including heartburn, constipation, diarrhea, and severe abdominal pains. On the other hand, intravenous administration is likely to cause electrolyte disorders. A rare but possible complication of prolonged use of bisphosphonates is jaw bone osteonecrosis related to excessive inhibition of bone turnover. [6,7,8,9] Medication-related necrosis occurs mainly in the mandible, probably because of its structure and vascularization. [10] Additionally, numerous data indicate significant differences in complications incidence depending on the drug administration route. [11] Drugs administered by the intravenous route cause necrosis more often than when administered orally. The osteonecrosis rate of the mandibular bone is 0.2% -6.7% and 0.004% -0.2% for the intravenous and oral routes, respectively. [12]

The first publication to have described a series of 36 cases of MRONJ was presented in 2003. [13] Further papers focused on MRONJ

etiology, risk factors and symptoms presence correlation, evaluation of the disease course, and the most effective treatment. [11,14,15,16,17] To establish the disease stage, the American Association of Oral and Maxillofacial Surgeons (AAMOS) developed a numerical MRONJ scale in 2014 (Tab. 1). [18]

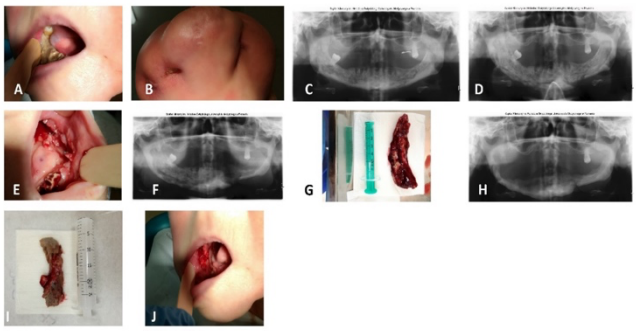

Figure 1. A Necrotically altered mandibular body. B Bilateral extra-oral fistulas in the submandibular area. C Check-up pantomographic picture taken before treatment. A clear sclerotic zone is seen involving the body, angles on both sides, and unresorbed extraction sockets in the anterior segment of the mandible. D Follow-up pantomogram took after two months of therapy. The discontinuity of the outer lamina of the mandibular body is seen (arrow). Clinical examination did not reveal any pathological mobility of the segments. E Picture was taken after removing a mobile sequester from the mandibular body on the left side. F A follow-up pantomogram was taken after 4 months of therapy. Reduced thickness of the mandible on the left side is seen after the removal of a sequester and a low mineralized inner lamina of the mandibular body on the left side. G Histopathological specimen involving a bony sequester on the left side. H A follow-up pantomogram took after 6 months of therapy. Reduced thickness of the mandible on the right side is seen after removing a sequester and increased mineralization of the mandibular body inner lamina on the left side. I Histopathological specimen involving a sequester on the right side, containing tooth 48. J A mobile sequester post-removal status of the mandibular body on the right side.

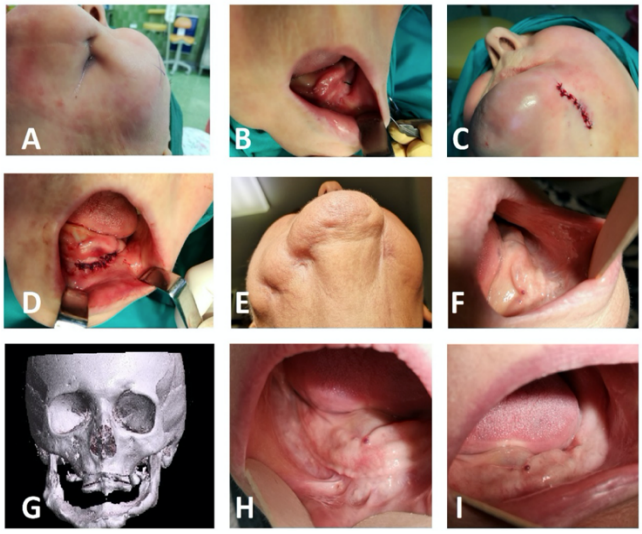

Figure 2. A A remaining active salivary fistula on the left side. B Salivary fistula on the left side with the probe placed in its lumen. C Status after fistula canal excision and extra-oral suturing. D Status after fistula canal excision and intra-oral suturing. E Follow-up after 3 months. No fistula present extra-orally. F Follow-up after 3 months. No fistula present intra-orally. G Craniofacial CT scan, a 3D image taken 6 months after salivary fistula treatment. H Follow-up 6 months after extra-oral fistula treatment. No disturbance intra-orally. I Follow-up 6 months after treatment of extra-oral fistula. No disturbance intraorally.

Osteonecrosis of the jaw bones is treated with surgical debridement. Often, such procedures leave patients with mutilating facial injuries and significantly influence their life comfort. Alternative methods are being looked for, which would include no surgical interventions. According to reports, patients may benefit from the treatment of jaw bones- osteonecrosis with methylxanthine group medicines, like pentoxifylline. [19,20,21,22]

The PENTO method (PENtoxifylline - TOcopherol) is one of the few pharmacological methods to treat osteonecrosis of the jaws, which can improve the patient's condition and accelerate disease treatment. [23] Pentoxifylline is a commonly used drug for intermittent claudication associated with peripheral arterial disease.

It is a methylated derivative of xanthine, which improves peripheral blood flow, the elasticity of erythrocyte membranes, microcirculation, tissue oxygenation, and reduces blood viscosity. [22,24] Tocopherol, on the other

hand, has strong antioxidant properties. Among others, it prevents oxidation of structures present in cell membranes, hinders free radicals formation, and accelerates their "scavenging". [25] Pentoxifylline at 800 mg and tocopherol at a dose of 800-1000 IU daily has been used in treating osteoradionecrosis (ORN). [26] Significant regression of inflammatory changes observed in patients with ORN gave grounds for using these drugs in the treatment of MRONJ. [26] The available publications indicate the need for further research to determine the optimal protocol for managing patients suffering from medication-related mandibular osteitis.

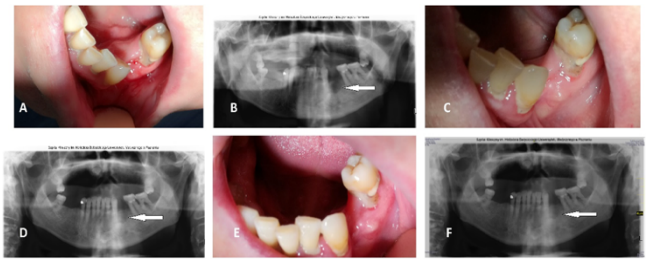

Figure 3. A Necrotic mandibular alveolar process with an intra-oral fistula. Clinical positive probing to the bone, exposed bone B A control OPG has taken before treatment. A seen sclerotic zone involving the alveolar process on the left lateral fragment of the mandible (arrow) C The condition after 12-week therapy is the alveolar process of the mandible covered with the gum. Clinically negative probing D A follow-up OPG taken after the 12-week therapy Regression of the mandibular alveolar process sclerotic zone is observed (arrow) E After 24-week therapy mandibular alveolar process is covered with the gum. Clinically negative probing with no pain on palpation F A follow-up OPG was taken after 24 weeks of the therapy. A progressing recession of the mandibular alveolar process sclerotic zone is seen (arrow).

Materials and methods

Written informed consent was obtained from the patients for all the diagnostic and therapeutic procedures, and publishing the photographs, and radiographs of these cases.

Case 1

A 62-year-old female patient was admitted to the Department of Maxillofacial Surgery of the Clinical Hospital for the diagnosis and treatment of the alveolar part of the mandible. On admission, despite prior antibiotic therapy (clindamycin 600 mg twice daily for 14 days), she reported pain (NRS 7-9), sensory disturbances in the V3 region, dysgeusia, recurrent bleeding, and halitosis. Inflammation appeared following teeth removal in this area of the mandible due to periodontitis. Immediately after the procedure, the patient did not receive any antibiotic therapy, nor was any alveoloplasty performed.

She gave a history of multiple myeloma for four years , hypothyroidism, arterial hypertension, paroxysmal supraventricular tachycardia, and a 20% drop in body weight over the last year (BMI 20.33). For the past two years, the patient received monthly intravenous bisphosphonates (pamidronate 90 mg every four weeks). She received a total of 21 doses. On the University of Connecticut mandibular necrosis risk numerical scale, she was classified as being high-risk (> 15 points). [27] Clinical examination revealed exposed necrotic bone of the mandibular body in the area of teeth 38-48, evidence of infection, pain, bone necrosis extending beyond the alveolar process (i.e., the lower border), bilateral, purulent extra-oral fistulas submandibular and osteolysis involving the lower border of the mandible (Fig. 1 A-B).

A pantomogram revealed a clear sclerotic zone, including the body and angles on both sides and unresorbed post-extraction sockets in the anterior segment of the mandible (Figure 1 C). The presented image is classified as stage 3 of MRONJ according to AAMOS (Tab. 1). [18] Laboratory tests displayed pancytopenia, renal failure (myeloma nephropathy), and increased inflammatory markers (CRP 88.2 g/dl). Escherichia coli bacteria were cultivated without pathological resistance to routine antibiotics in the bacteriological examination of the smear taken from the lesion. Histopathological examination showed no neoplastic changes.

Initially, the patient was scheduled to undergo surgery under general anesthesia to remove necrotic lesions, but due to comorbidities and no vital indications for the procedure, the patient was disqualified from anaesthesia. It was decided to implement pharmacological treatment using the PENTO method, including pentoxifylline at 400 mg (2x1 tablet over 24h) and tocopherol at the dose of 400 IU (2x1 tablet over 24h). During treatment, the patient was reassessed regularly. After two months, no pathological mandibular mobility was found on

the clinical examination, although an external lamina discontinuity was found on radiographs (Fig. 1 D).

The next follow-up visit after four months of therapy revealed mobility of the bone sequester on the left side with no signs of mandibular fracture. The mobile bone fragment was removed under local anaesthesia without a secondary surgical wound secure (Fig. 1 E-G). During the third scheduled visit (after 6 months of treatment), a passive purulent fistula on the left and a necrotic changed part of the mandible on the right side, including tooth 48, were found. The movable alveolar process on the right side was removed, similarly to the sequester on the left side (Fig. 1 H-J).

A9 months of being on medication, the patient presented no purulent fistulas, exposed mandibular bones, or pathological mobility. A salivary fistula, present at that time on the left side, was secured under local anaesthesia (Fig. 2 A-D). During the treatment, most complaints were eliminated, and the pain was reduced (NRS 3-5); only a subjective distortion in the sense of taste remained. BMI improved from 20.33 to 23.88. Follow-up examinations 3 months after salivary fistula treatment did not reveal any signs of osteitis (Fig. 2 E-F). Computed tomography did not show any foci of osteolysis (Fig. 2 G). Follow-up examinations 6 months after the salivary fistula treatment did not reveal any signs of osteitis (Fig. 2 H-I). No side effects of the therapy were reported during pharmacological treatment. As no active necrotic foci were present, pharmacological treatment was discontinued after 20 months. The patient remains under the control of the Maxillofacial Surgery Out-Patient Clinic. Relapse is not observed.

Case 2

A male 71-year-old patient was admitted to the Department of Maxillofacial Surgery of the Clinical Hospital for the diagnosis and treatment of mandibular alveolar bone inflammation. On admission, he reported: pain (NRS 2-3), taste disturbance, dry mouth, and halitosis despite previous empiric antibiotic therapy (amoxicillin with clavulanic acid 1.0 g twice a day for 14 days). Inflammation occurred following teeth removal from this mandible area due to periodontitis 8 months ago. Immediately after the procedure, the patient received no antibiotics, and no alveoplasty was performed. History showed multiple myeloma for four years, peripheral polyneuropathy, and overweight, despite a 10% decrease in body weight over the last year (BMI 25.56). For the past three years, the patient received a monthly dose of intravenous bisphosphonates (12 doses of pamidronate of 90 mg for 4 weeks, 10 doses of zoledronic acid of 40 mg for 4 weeks). Altogether, he received 22 doses. According to the University of Connecticut mandibular necrosis numerical scale, the patient was classified as high risk (> 15 points). [27] Clinical examination revealed exposed necrotic bone of the mandibular body at the region of teeth 34-35, evidence of infection, pain on palpation, and a positive probing test (Fig. 3 A). The pantomographic radiograph displayed a clear oval sclerotic zone involving the mandibular alveolar process on the left (Fig. 3 B). The presented image is classified as stage 1 of MRONJ according to AAMOS (Table 1). [18] No significant deviations were observed in laboratory tests. A bacteriological examination of the smear taken from the lesion did not show any alert pathogens. Histopathological examination displayed no neoplastic changes.

MRONJ stage	
0	No signs of osteonecrosis, patients treated with drugs inducing MRONJ and bisphosphonates
I	Exposed necrotic bone or positive probing test to the bone, with no evidence of infection
II	Exposed necrotic bone or positive probing test, evidence of infection, pain, oral mucositis with or without purulent drainage
III	Exposed necrotic bone, positive probing test to the bone, evident infection signs, pain, and at least 1 of the following: osteonecrosis extending beyond the region of alveolar bone (inferior border and ramus of the mandible, maxillary sinus, zygomatic arch), pathologic fracture, extra-oral fistula, oral-maxillary communication, oral-nasal communication, osteolysis extending to the inferior border of the mandible or sinus floor

Table 1. MRONJ scale according to the American Association of Oral and Maxillofacial Surgeons (AAOMS). [18]

The patient gave no consent for surgical intervention to remove necrotic lesions because he was concerned about the underlying disease's possible progression and local disorder deterioration. Pharmacological treatment with the PENTO method was implemented, including pentoxifylline at 400 mg (2x1 tablet per 24h) and tocopherol at the dose of 400 IU (2x1 tablet per 24h). During treatment, the patient was reassessed regularly. After three months, the clinical examination revealed the epithelialized area of teeth 34-35, and the probing test was

negative. On X-rays, mineralization of the examined area was observed (Fig. 3 C-D). The second follow-up visit after 6 months of therapy confirmed the healing of the alveolar process region; the OPG confirmed further mineralization and regression of the sclerotic zone of the inflamed bone (Fig. 3 E-F). The treatment successfully eliminated subjective symptoms, including pain (NRS 0). In the follow-up, clinical examinations after 3 and 6 months, no signs of osteitis were observed. Pharmacological treatment did not produce any side effects. As no active necrosis foci were present, pharmacological treatment was discontinued after 12 months. The patient currently remains under the control of the Maxillofacial Surgery Out-Patient Clinic. Relapse is not observed.

Our presented cases show positive results of MRONJ pharmacological treatment with the PENTO method (Table 2).

Discussion

In the presented cases, medication-related necrosis appeared following multiple myeloma therapy. Bone metastases are present in 95% of patients suffering from multiple myeloma, which results in the implementation of antiresorptive.[28]

The most frightening symptom of cancer disease, according to patients and their families, is the feeling of pain. Pain severity in bone metastases ranges from 7.19-7.95 +/- 1.36-1.98 on the NRS scale.[29] Bisphosphonates reduce the number of metastases causing general and vertebral fractures, significantly affecting the patient's quality of life. [30] However, they do not affect life expectancy or disease progression-free survival rate.[30]

Although complications related to osteonecrosis of the jaws occur in about 1.5% of people on antiresorptive drugs, an increase in their number can be expected as the results of oncological treatment are improving, and so is the life of the patients, which is getting longer. Surgery to remove inflamed tissue is the standard treatment for osteonecrosis of the jaws. Modern medicine enables reconstructive procedures with microvascular flaps in radiation and medication-related osteitis.[31,32] Such procedures performed in preoperatively irradiated sites produce an increased risk of flap failure, reoperation, and purulent fistulas.[32] When deciding on reconstructive procedures, one should consider an increased risk of complications and prolonged hospital treatment, significantly reducing the patient's quality of life.

Treatment with pentoxifylline and tocopherol (the PENTO method) described in the literature confirms its effectiveness not only in bone inflammations due to radiation but also in the prophylaxis of surgical tooth extraction. [34,35] Studies are also available on combined preparations containing pentoxifylline, tocopherol, and disodium clodronate (PENTOCLO−PENtoxifylline - TOcopherol - CLOdronate), on which we can get our hopes high for truly better therapeutic outcomes.[36,37,38] According to the words of Hippocrates - "Morbum evitare quam curare facilius est", the use of PENTOCLO can eliminate the most severe complication of bisphosphonate therapy, which is undoubtedly medication related bone necrosis, and thus save the patient from the need for treatment.

Conclusions

The presented cases show encouraging results of MRONJ pharmacological treatment with the PENTO method. This therapy eliminates osteitis, the bothersome complication of bisphosphonate therapy. The method used may increase safety while using bisphosphonates. Continuation of bisphosphonate therapy will protect the skeletal system in cancer patients, which is an evident benefit for them. Reducing the accompanying pain severity will positively affect the patient's quality of life. Moreover, the PENTO method offers other advantages such as low price, good drug tolerance, safe use, and, as it is a home therapy - no need for hospitalization. The presented cases may contribute to the above-described therapy promotion and confirm the opinion on its effectiveness.

Declaration of Interest

The authors report no conflict of interest.

Cases	Location	Risk of osteonecrosis of the jaw[1]	Antiresorptive therapy	Doses	Preliminary examination[2]	Examination after 2-3 months[2]	Examination after 5-6 months[2]	Examination after 8-9 months[2]	Examination after 11-12 months[2]	Time of PENTO therapy (months)
1	the right side of the mandible	significant	intravenous (IV) bisphosphonates	21	III	III	III	0	0	20
	the left side of the mandible				III	III	0	0	0	
2	the left side of the mandible	significant		22	I	0	0	0	0	12

Table 2. The comparison of treatment effects with the PENTO method in both cases.
1. University of Connecticut Osteonecrosis Numerical Scale (UCONNS) 2015.
2. MRONJ staging system American Association of Oral and Maxillofacial Surgeons–AAOMS 2014.

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