A comparative study of the clinical characteristics of patients with medication-related osteonecrosis of the jaw and osteoporosis or malignancy

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Objective. This study aimed to compare the clinical characteristics of patients with medication-related osteonecrosis of the jaw (MRONJ) and osteoporosis vs malignancy.

Study Design. The study included patients hospitalized with MRONJ between July 2013 and April 2021. These patients were assigned to the osteoporosis or malignancy groups according to their primary disease. Characteristics and clinical variables were recorded and compared.

Results. Nighty-one patients (107 MRONJ lesions) were included, with 12 (14 lesions) in the osteoporosis group and 79 (93 lesions) in the malignancy group. The osteoporosis and malignancy groups differed in their respective incubation periods (57.0 ± 42.8 vs 29.3 ± 19.8 months, respectively; $P = .048$), bisphosphonates cumulative dose (16,487.4 ± 14,268.8 mg alendronate vs 104.0 ± 79.9 mg zoledronic; $P = .014$), and rate of patients receiving antiangiogenic agents (0/12, 0.0% vs 48/79, 60.8%; $P = .001$). The groups were similar in their treatment outcomes, measured as successful surgeries (11/12, 91.7% vs 59/79, 74.7%; $P = .351$).

Conclusions. For stage 2 or 3 MRONJ, patients with osteoporosis (exposed to oral bisphosphonates) developed MRONJ over a longer incubation period than patients with malignancy. The groups had similar responses to surgery. (Oral Surg Oral Med Oral Pathol Oral Radiol 2022;134:543−547)

Bisphosphonates are synthetic pyrophosphate analogs that act as antibone resorption agents by inhibiting osteoclast activity. They are commonly used clinically to treat malignant disease with bone metastases, osteoporosis, multiple myeloma, and other bone metabolic disease. Bisphosphonates are administered intravenously (e.g., zoledronic) for malignant disease with bone metastases or orally (e.g., alendronate) for osteoporosis, in which they have become the first-line treatment.[1] However, the widespread and long-term clinical use of bisphosphonates increases concerns about their safety and treatment-related complications.[2,3]

Medication-related osteonecrosis of the jaw (MRONJ) is a serious side effect of antiresorptive or antiangiogenic therapies.[4] It is characterized by bone necrosis in the maxillofacial region, with a fistula that probes to bone and drains purulent material. Extensive bone exposure, necrosis, and pathologic fractures occur in the advanced stages. Symptoms such as pain, halitosis, and marasmus adversely affect the patient's quality of life.

Previous reports, mostly focused on MRONJ associated with malignancies and after exposure to high-dose intravenously bisphosphonates,[5-7] showed an incidence of about 0.7% to 20.0%.[4] Patients with osteoporosis are also at risk of developing MRONJ after long-term oral bisphosphonates therapy, with an incidence of approximately 0.1% to 0.2%,[4] considerably lower than after intravenous administration. However, clinicians and research institutions might underestimate its clinical significance given that a large number of people, whose life expectancies are significantly longer than those of patients with malignancies, have osteoporosis. Hence, the present study aimed to compare the clinical characteristics of MRONJ in patients with osteoporosis and malignancies to provide a reference for clinical treatment.

Statement of Clinical Relevance

For stage 2 or 3 medication-related osteonecrosis of the jaw, patients with osteoporosis (exposed to oral bisphosphonates) developed medication-related osteonecrosis of the jaw over a longer incubation period than patients with malignancy, but the groups had similar responses to surgery.

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MATERIALS AND METHODS

The study population was composed of patients diagnosed with stage 2 or 3 MRONJ and hospitalized in the Department of Oral and Maxillofacial Surgery, Peking University Hospital of Stomatology (Beijing, China), between July 2013 and April 2021. This study was approved by the local ethics committee (approval No. PKUSSIRB-201949119) and carried out following the principles of the Declaration of Helsinki. The need for informed consent was waived based on the retrospective nature of the study.

MRONJ diagnosis was based on clinical and radiographic findings and the criteria recommended in the American Association of Oral and Maxillofacial Surgeons 2014 position paper.[4] The patients were divided into the osteoporosis and malignancy groups according to their primary disease. Current or previous oral treatment with 70 mg alendronate per week was required for the osteoporosis group; current or previous intravenous treatment with 4 mg zoledronic per month was required for the malignancy group. All patients were followed up for at least 3 months postoperatively. Patients with a history of radiation therapy to the jaw or apparent metastatic disease of the jaw and those followed up for under 3 months postoperatively were excluded.

Patient-related data were collected from the medical records; these data included age, sex, anatomic location of the lesions, disease stage on admission, bisphosphonates treatment duration, drug holiday, incubation period (time from drug administration to onset), preoperative MRONJ duration, cumulative bisphosphonates dose, receipt of antiangiogenic, corticosteroid therapy, treatment outcome, history of diabetes mellitus, and hemoglobin and serum albumin and calcium levels.

Surgery was considered successful when complete mucosal healing was observed and clinical symptoms were absent for 3 months after the surgery. Recurrence was defined as symptom recurrence, including soft tissue dehiscence, necrotic bone exposure, and surgical site infection, within 3 months postoperatively.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were performed. Data were compared between the groups by *t* test for continuous variables and the chi-squared test for categorical variables. Statistical significance was set at $P < .05$.

RESULTS

Ninety-one patients (107 lesions) were included in this study, with 12 (14 lesions) in the osteoporosis group and 79 (93 lesions) in the malignancy group.

All surgeries were performed under general anesthesia. For stage 2 lesions, debridement and saucerization were performed to resect the lesions completely, and the wounds were closed without tension using local mucoperiosteum flaps. Segmental mandibulectomy was performed for stage 3 mandibular lesions to resect the lesions completely. The mandible defect was reconstructed by a reconstruction plate and ipsilateral submandibular gland translocation, with or without submental perforator flap, as previously described.[8] Alternatively, a fibula-free flap was vascularized if the patient's general condition could tolerate microsurgery. For stage 3 maxillary lesions, the necrotic bone and infected tissue in the maxillary sinus were removed completely, and iodoform gauze was packed into the maxillary sinus cavity. In some cases, a buccal fat pad was used to help cover the bone defect. Platelet-rich fibrin was used to cover the bone surfaces in some cases. Biopsy of the bone was performed in all cases to confirm the diagnosis and exclude metastatic disease.

The follow-up period ranged from 3 to 79 months, with an average of 14.0 ± 13.3 months. Of the 107 MRONJ lesions, the surgeries for 70 (65.4%) were successful, whereas postoperative recurrence occurred in the remaining 37 (34.6%). Table I presents the descriptive statistics of the 2 groups.

The osteoporosis and malignancy groups were similar in age (65.9 ± 7.5 vs 63.9 ± 9.3 years; $P = .477$), and both groups were predominantly female (8/12; 66.7% vs 47/79; 59.5%; $P = .876$).

Mandibular lesions comprised half of those in the osteoporosis group (7/14; 50.0%) and more than half in the malignancy group (65/93; 69.9%), but the difference was insignificant ($P = .241$). Stage 3 lesions were predominant in both groups (9/12; 75.0% and 54/79; 68.4%; $P = .897$).

The duration of bisphosphonates treatment in the osteoporosis group was insignificantly longer than in the malignancy group (53.8 ± 45.0 vs 31.0 ± 21.0 months; $P = .111$), and the groups had similar drug holidays (11.7 ± 11.5 vs 10.6 ± 11.2 months; $P = .759$).

The incubation period in the osteoporosis group was longer than in the malignancy group (57.0 ± 42.8 vs 29.3 ± 19.8 months; $P = .048$), but the preoperative MRONJ duration was similar in both groups (13.9 ± 12.3 vs 12.3 ± 9.7 months; $P = .610$).

The bisphosphonates cumulative dose differed between the osteoporosis and malignancy groups (16 487.4 ± 14 268.8 mg of alendronate vs 104.0 ± 79.9 mg of zoledronic; $P = .014$). Compared with the malignancy group, the osteoporosis group had a lower proportion of co-administrated antiangiogenic agents (0/12; 0.0% vs 48/79; 60.8%; $P = .001$) and insignificantly higher proportion of successful surgeries (11/12; 91.7% vs 59/79; 74.7%; $P = .351$).

The osteoporosis and malignancy groups had similar proportions of patients with a history of diabetes

Table I. Patient and clinical characteristics of the 2 groups

Variable	*Malignancy, n = 79*	*Osteoporosis, n = 12*	*P value*
Age, y	63.9 ± 9.3	65.9 ± 7.5	.477*
Sex, female	47 (59.5%)	8 (66.7%)	.876†
Site, mandible	65 (69.9%)	7 (50.0%)	.241†
Stage 3	54 (68.4%)	9 (75.0%)	.897†
BPs treatment duration, mo	31.0 ± 21.0	53.8 ± 45.0	.111*
Drug holiday, mo	10.6 ± 11.2	11.7 ± 11.5	.759*
Incubation period	29.3 ± 19.8	57.0 ± 42.8	.048*
Preoperative MRONJ duration, mo	12.3 ± 9.7	13.9 ± 12.3	.610*
BPs cumulative dose, mg	104.0 ± 79.9	16 487.4 ± 14 268.8	.014*
BPs followed by antiangiogenic agents	48 (60.8%)	0 (0.0%)	.001†
Treatment outcome, mucosal healing	59 (74.7%)	11 (91.7%)	.351†
Diabetes mellitus	18 (22.8%)	2 (16.7%)	.918†
Corticosteroid therapy	38 (49.4%)	5 (41.7%)	.620†
Hemoglobin, g/L	113.7 ± 16.5	107.8 ± 18.2	.255*
Serum albumin, g/L	36.0 ± 3.7	33.8 ± 3.5	.061*
Serum calcium, mmol/L	2.2 ± 0.2	2.1 ± 0.1	.857*

*Independent-samples *t* test.
†Chi-squared test.
BPs, bisphosphonates; *MRONJ*, medication-related osteonecrosis of the jaw.
Data are presented as *n* (%) or mean ± standard deviation.

mellitus (2/12; 16.7% vs 18/79; 22.8%; $P = .918$) and corticosteroid therapy (5/12; 41.7% vs 38/79; 49.4%; $P = .620$).

When compared with the malignancy group, the osteoporosis group had insignificantly lower level of hemoglobin (107.8 ± 18.2 vs 113.7 ± 16.5 g/L; $P = .255$) and serum albumin (33.8 ± 3.5 vs 36.0 ± 3.7 g/L; $P = .061$), and similar serum calcium (2.1 ± 0.1 vs 2.2 ± 0.2 mmol/L; $P = .857$).

DISCUSSION

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures.[9] Its prevalence is increasing with the aging population, and its related complications seriously affect the population health and impose a heavy burden on the family and society.[10] Medications for osteoporosis are classified as antiresorptive agents, osteoanabolic agents, and others. Antiresorptive agents are the first-line osteoporosis treatment drugs, with bisphosphonates being the most widely used. As in malignant disease with bone metastases, patients with osteoporosis are at risk of MRONJ after bisphosphonates administration. Hence, the present study aimed to compare the clinical characteristics of MRONJ between patients with osteoporosis and malignancy.

Reportedly, long bisphosphonates treatment and high cumulative bisphosphonates dose are associated with an increased risk of developing MRONJ.[2,11] In the present study, the osteoporosis group had a longer incubation period (57.0 ± 42.8 vs 29.3 ± 19.8 months) and a higher cumulative bisphosphonates dose (16 487.4 ± 14 268.8 mg of alendronate vs 104.0 ± 79.9 mg of zoledronic) than the malignancy group. The cumulative bisphosphonates dose in the osteoporosis group was about 159 times higher than in the malignancy group; however, considering that oral alendronate was administered in the osteoporosis group whereas intravenous zoledronic was administered in the malignancy group, and the potency of the former is approximately 1/10 to 1/100 of the latter,[12] the actual cumulative bisphosphonates doses in the 2 groups may not be significantly different. The aforementioned results suggest that MRONJ develops after extended use of the less potent alendronate or within a short time with the more potent zoledronic. This finding supports the view that the risk of MRONJ is related to the actual cumulative bisphosphonates dose.

Antiangiogenic agents act directly on vascular endothelial cells, inhibiting angiogenesis and thus tumor growth. This treatment can be combined with chemotherapy to improve the oncotherapy effect. In this study, 60.8% of the patients in the malignancy group but none in the osteoporosis group were concurrently treated with antiangiogenic agents. This finding ascribes MRONJ development to the sole use of bisphosphonates in patients with osteoporosis.

Reportedly, stage 3 MRONJ occurs most commonly in patients receiving intravenous bisphosphonates therapy, whereas MRONJ rarely progresses beyond stage 2 in patients receiving oral bisphosphonates.[13,14] However, others have reported that the MRONJ stage distribution was similar in those receiving intravenous or oral bisphosphonates[15] and that the mode of

administration or indication for antiresorptive therapy was not associated with MRONJ severity.[16] In the present study, bisphosphonates were administered orally in the osteoporosis group and intravenously in the malignancy group, and stage 3 lesions were highly prevalent in both groups (9/12; 75.0% and 54/79; 68.4%), supporting the view that the MRONJ severity was independent of the mode of bisphosphonates administration and the indication for the antiresorptive therapy. Reportedly, the pace of progression varied among MRONJ lesions: some remained in an early stage (stages 1 and 2) for relatively long periods while others progressed rapidly to stage 3, even when the treatment was the same. There might be yet unidentified risk factors associated with the rapid progression of MRONJ to the advanced stage. Our previous study found that age $\leq$65 years, preoperative MRONJ duration $\geq$12 months, lesion located in the maxilla, and serum albumin $<$40 g/L might increase the risk for severe MRONJ.[16] Stage 3 MRONJ was predominant in both groups in the present study, which did not differ in any of the previously mentioned variables. It was reported that severe MRONJ might develop in Asian patients with osteoporosis after long-term oral bisphosphonates treatment; however, it is unknown whether the sensitivity to bisphosphonates differs between Asian patients and those in other countries.[15]

According to the American Association of Oral and Maxillofacial Surgeons 2014 position paper, operative treatment is not required for stage 1 and 2 lesions; surgery should be reserved for stage 3 and refractory stage 2 lesions.[4] However, an increasing number of studies suggest that surgical treatment is indicated for all MRONJ stages.[16-18] Early surgical treatment could help avoid lesion progression and preserve the patients' quality of life.[19,20] Also, the surgical treatment outcome in severe MRONJ cases is poor.[5,21-23] In this study, all MRONJ lesions were of stage 2 or 3, predominantly stage 3 in both groups. The proportions of successful surgeries in the 2 groups were similar. However, reportedly MRONJ caused by oral bisphosphonates treatment for osteoporosis was associated with more successful surgeries.[24,25] For example, it was reported that $>$90% of the MRONJ lesions could achieve complete healing in patients with osteoporosis, whereas only about 50% to 65% could achieve complete healing in patients with malignancies.[26,27] In the present study, oral alendronate was administered in the osteoporosis group, and the proportion of successful surgeries in this group was insignificantly higher than in the malignancy group. A possible explanation could be the high proportion of successful surgeries in the osteoporosis group in concordance with the rate reported in the literature, whereas it was higher than the reported rate in the malignancy group. Surgery was unsuccessful in only 1 of patients in the osteoporosis group. This patient could not be reoperated due to a poor general condition.

The main limitation of this study was the relatively small number of patients in the osteoporosis group, possibly because the use of bisphosphonates to treat osteoporosis has a shorter history than for malignancies in China. However, MRONJ incidence is expected to rise as the number of prescriptions increases.[28]

CONCLUSIONS

For stage 2 or 3 MRONJ, patients with osteoporosis (exposed to oral bisphosphonates) developed MRONJ over a longer incubation period than patients with malignancy. The groups had similar responses to surgery. The actual cumulative bisphosphonates doses might be similar in the 2 groups, considering the relative potencies of the bisphosphonates used.

DISCLOSURE

None.

REFERENCES

1. Kim SC, Kim MS, Sanfélix-Gimeno G, et al. Use of osteoporosis medications after hospitalization for hip fracture: a cross-national study. *Am J Med*. 2015;128. 519-26.e1.
2. Kim SH, Lee YK, Kim TY, Ha YC, Jang S, Kim HY. Incidence of and risk for osteonecrosis of the jaw in Korean osteoporosis patients treated with bisphosphonates: a nationwide cohort-study. *Bone*. 2021;143:115650.
3. Shibahara T, Morikawa T, Yago K, Kishimoto H, Imai Y, Kurita K. National survey on bisphosphonate-related osteonecrosis of the jaws in Japan. *J Oral Maxillofac Surg*. 2018;76:2105-2112.
4. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014;72:1938-1956.
5. Ristow O, Rückschloß T, Bodem J, et al. Double-layer closure techniques after bone surgery of medication-related osteonecrosis of the jaw—a single center cohort study. *J Craniomaxillofac Surg*. 2018;46:815-824.
6. Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schiødt M. Medication-related osteonecrosis of the jaw: prevention, diagnosis and management in patients with cancer and bone metastases. *Cancer Treat Rev*. 2018;69:177-187.
7. Otto S, Schnödt EM, Haidari S, et al. Autofluorescence-guided surgery for the treatment of medication-related osteonecrosis of the jaw (MRONJ): a retrospective single-center study. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2021;131:519-526.
8. Zhou W, Feng Z, An J, Wang H, Zhang Y. Combined reconstruction plate fixation and submandibular gland translocation for the management of medication-related osteonecrosis of the mandible. *Int J Oral Maxillofac Surg*. 2020;49:1584-1588.
9. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med*. 1993;94:646-650.
10. Lems WF, Raterman HG. Critical issues and current challenges in osteoporosis and fracture prevention. An overview of unmet needs. *Ther Adv Musculoskelet Dis*. 2017;9:299-316.
11. Zavras AI, Shanmugham JR. Bisphosphonates, osteoporosis, and osteonecrosis of the jaw: a critical review of a large nested case-control study. *J Evid Based Dent Pract*. 2016;16:136-138.

12. Badel T, Pavicin IS, Carek AJ, Rosin-Grget K, Grbesa D. Pathophysiology of osteonecrosis of the jaw in patients treated with bisphosphonate. *Coll Antropol*. 2013;37:645-651.
13. Assael LA. Oral bisphosphonates as a cause of bisphosphonate-related osteonecrosis of the jaws: clinical findings, assessment of risks, and preventive strategies. *J Oral Maxillofac Surg*. 2009;67 (suppl 5):35-43.
14. Aljohani S, Fliefel R, Ihbe J, Kühnisch J, Ehrenfeld M, Otto S. What is the effect of anti-resorptive drugs (ARDs) on the development of medication-related osteonecrosis of the jaw (MRONJ) in osteoporosis patients: a systematic review. *J Craniomaxillofac Surg*. 2017;45:1493-1502.
15. Urade M, Tanaka N, Furusawa K, et al. Nationwide survey for bisphosphonate-related osteonecrosis of the jaws in Japan. *J Oral Maxillofac Surg*. 2011;69:e364-e371.
16. Feng Z, An J, Zhang Y. Factors influencing severity of medication-related osteonecrosis of the jaw: a retrospective study. *J Oral Maxillofac Surg*. 2021;79:1683-1688.
17. Aljohani S, Troeltzsch M, Hafner S, Kaeppler G, Mast G, Otto S. Surgical treatment of medication-related osteonecrosis of the upper jaw: case series. *Oral Dis*. 2019;25:497-507.
18. Ristow O, Otto S, Troeltzsch M, Hohlweg-Majert B, Pautke C. Treatment perspectives for medication-related osteonecrosis of the jaw (MRONJ). *J Craniomaxillofac Surg*. 2015;43:290-293.
19. Hauer L, Jambura J, Hrusak D, et al. Surgical therapy for medication-related osteonecrosis of the jaw in osteoporotic patients treated with antiresorptive agents. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2020;164:100-107.
20. Ristow O, Rückschloß T, Müller M, et al. Is the conservative non-surgical management of medication-related osteonecrosis of the jaw an appropriate treatment option for early stages? A long-term single-center cohort study. *J Craniomaxillofac Surg*. 2019;47:491-499.
21. Klingelhöffer C, Zeman F, Meier J, Reichert TE, Ettl T. Evaluation of surgical outcome and influencing risk factors in patients with medication-related osteonecrosis of the jaws. *J Craniomaxillofac Surg*. 2016;44:1694-1699.
22. Schiodt M, Otto S, Fedele S, et al. Workshop of European task force on medication-related osteonecrosis of the jaw-Current challenges. *Oral Dis*. 2019;25:1815-1821.
23. Ruggiero SL, Kohn N. Disease stage and mode of therapy are important determinants of treatment outcomes for medication-related osteonecrosis of the jaw. *J Oral Maxillofac Surg*. 2015;73(suppl 12):S94-S100.
24. Shintani T, Hayashido Y, Mukasa H, et al. Comparison of the prognosis of bisphosphonate-related osteonecrosis of the jaw caused by oral and intravenous bisphosphonates. *Int J Oral Maxillofac Surg*. 2015;44:840-844.
25. Petrovic M, Jelovac DB, Antic S, et al. Medication-related osteonecrosis of the jaws: two center retrospective cohort studies. *BioMed Res Int*. 2019;2019:8345309.
26. Kojima Y, Kawaoka Y, Sawada S, et al. Clinical significance of periosteal reaction as a predictive factor for treatment outcome of medication-related osteonecrosis of the jaw. *J Bone Miner Metab*. 2019;37:913-919.
27. Soutome S, Yanamoto S, Sumi M, et al. Effect of periosteal reaction in medication-related osteonecrosis of the jaw on treatment outcome after surgery. *J Bone Miner Metab*. 2021;39:302-310.
28. Whitefield S, Lazarovici TS, Sommer-Umansky M, Friedlander-Barenboim S, Yahalom R, Yarom N. Changing face of medication-related osteonecrosis of the jaw: Sheba Medical Center experience—fifteen years. *J Bone Miner Metab*. 2020;38:819-825.