Factors Influencing Severity of Medication-Related Osteonecrosis of the Jaw: A Retrospective Study

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Purpose: The progression of medication-related osteonecrosis of the jaw (MRONJ) is influenced by many factors. This study aimed to identify the clinical risk factors associated with severe MRONJ (stage 3).

Patients and Methods: The data of patients with MRONJ who were hospitalized between July 2013 and December 2019 were retrospectively analyzed. Demographic and clinical factors were the independent variables, and the clinical stage of MRONJ lesions was the dependent variable. Multivariate logistic regression analysis was performed to identify the risk factors for advanced stage disease (MRONJ stage 3).

Results: A total of 79 patients (with 93 MRONJ lesions) were included. In multivariate regression analysis, the risk factors associated with stage 3 MRONJ were age ≤65 years (odds ratio [OR] = 3.968, 95% confidence interval [CI]: 1.280–12.301; P = .017); chemotherapy (OR = 3.687, 95% CI: 1.048–12.972; P = .042); preoperative MRONJ duration ≥12 months (OR = 7.616, 95% CI: 1.865–31.110; P = .005); lesion location in maxilla (OR = 1.150, 95% CI: 1.006–1.315; P = .041); lesion location in posterior jaw, that is, in molar area (OR = 1.384, 95% CI; 1.118–1.715; P = .003); and serum albumin <40 g/L (OR = 6.257, 95% CI: 1.313–29.815; P = .021).

Conclusions: Age ≤65 years, chemotherapy, preoperative MRONJ duration ≥12 months, lesion location in maxilla, lesion location in the molar area, and serum albumin <40 g/L may increase the risk for severe MRONJ.

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

Not all patients on antiresorptive or antiangiogenic therapies develop MRONJ. Currently recognized risk factors for MRONJ include the type of drug used, the cumulative dose of the drug, and poor oral hygiene.[1] Better awareness of the risk factors can be helpful for prevention and targeted treatment of MRONJ.

The pace of progression of MRONJ lesions varies: some lesions remain in early stages (stages 1 and 2) for relative long periods while others progress rapidly

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to advanced stage (stage 3), even when the treatment is the same. Thus, we hypothesized that there may be risk factors associated with rapid progression of MRONJ to advanced stage. The few studies that have attempted to identify the risk factors associated with MRONJ progression and severity have reported inconsistent conclusions.[2-4]

This retrospective cohort study aimed to identify the risk factors related to the severity of MRONJ. The findings of this study will help clinicians select the appropriate treatment and predict prognosis in individual patients.

Patients and Methods

Patients with MRONJ who were hospitalized in the Department of Maxillofacial Surgery of Peking University Stomatological Hospital between July 2013 and December 2019 were eligible for inclusion in this retrospective study. Diagnosis of MRONJ was based on clinical and radiographic findings, and the criteria recommended in the Association of Oral and Maxillofacial Surgeons (AAOMS) 2014 position paper.[1] Thus, patients were included if *1)* there was exposed necrotic bone or bone that could be probed through an intraoral or extraoral fistula in the maxillofacial region; *2)* lesion had persisted for longer than 8 weeks; *3)* patient was currently receiving or had previously received antiresorptive or antiangiogenic agents; and *4)* there was no history of radiation therapy to the jaw or obvious metastatic disease of the jaw.[1] Disease stage on admission was the primary outcome variable.

Patient-related data were collected from the medical records; these included age and sex; indication for antiresorptive or antiangiogenic therapy; drugs used, duration of use, and mode of administration; drug holiday; preoperative MRONJ duration; anatomic location of lesions; possible etiological factors; receipt of chemotherapy or corticosteroid therapy; history of diabetes mellitus; and hemoglobin and serum albumin and calcium levels.

This study was approved by the local ethics committee (approval No. PKUSSIRB-201949119) and was carried out in accordance with the Principles of the Declaration of Helsinki. The need for informed consent was waived in view of the retrospective nature of the study.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS v24.0 (IBM, Armonk, NY). Descriptive statistics were performed. Data were compared between groups by the t test for continuous variables and the χ^2 test for categorical variables. Multivariate logistic regression analysis was performed to identify the risk factors associated with MRONJ severity (stage 3 disease). Odds ratios (OR) and 95% confidence intervals (CIs) were calculated. Forward selection was used to enter variables that contributed significant information to the model. Statistical significance was set at $P < .05$.

Results

The study population comprised 79 patients—34 (43.0%) men and 45 (57.0%) women—in the age range of 47–85 years (mean age, 65.2 ± 9.0 years). Most patients (71/79, 89.9%) were receiving antiresorptive treatment for primary malignant disease, which included lung cancer (n = 22; 27.8%), breast cancer (n = 22; 27.8%), multiple myeloma (n = 10; 12.7%), prostate cancer (n = 7; 8.9%), renal carcinoma (n = 6; 7.6%), colorectal cancer (n = 2, 2.5%), vaginal cancer (n = 1, 1.3%), and soft tissue sarcoma (n = 1, 1.3%). The remaining 8 of 79 (10.1%) patients were receiving antiresorptive treatment for osteoporosis (n = 3, 3.8%), rheumatoid arthritis (n = 3, 3.8%), or pemphigus (n = 2, 2.5%).

The most commonly used biphosphonates were zoledronic acid (n = 70; 88.6%), followed by pamidronate (n = 8; 10.1%), and alendronate (n = 7; 8.9%). The drugs were administered intravenously in 72 of 79 (91.1%) patients, orally in 6 of 79 (7.6%) patients, and both intravenously and orally in 1/79 (1.3%) patient. Both biphosphonates and antiangiogenic agents were administered to 49 of 79 (62%) patients.

Mean duration of biphosphonate therapy was 33.4 ± 22.0 months, mean preoperative MRONJ duration was 12.0 ± 9.9 months, and the mean duration of drug holiday was 10.8 ± 10.8 months.

While 16 of 79 (20.3%) patients had history of diabetes mellitus, 44 of 79 (55.7%) patients had received corticosteroid therapy and 50 of 79 (63.3%) patients had received chemotherapy.

There were a total of 93 MRONJ lesions in the 79 patients. Although 67 of 79 (84.8%) patients had one lesion each, 10 of 79 (12.7%) patients had 2 lesions each, and 2 of 79 (2.5%) patients had 3 lesions each. Of the 93 lesions, 36 of 93 (38.7%) were stage 2 lesions and 57 of 93 (61.3%) were stage 3 lesions. Only patients with stage 2 or 3 lesions were admitted for surgical treatment at our center, and so there were no patients with stage 1 lesions in this study. While 27 of 93 (29%) lesions were located in the maxilla, 66 of 93 (71%) were located in the mandible. Furthermore, 10 of 93 (10.8%) lesions were located in the anterior portion of the jaw (anterior teeth and premolar area), and 83 of 93 (89.2%) were located in the posterior portion of the jaw (molar area).

The local factors associated with MRONJ lesions included periodontal or peri-implant disease (62/93,

66.7%), previous tooth extractions (26/93, 28.0%), and denture trauma (3/93, 3.2%); no local factor was identified for 2 of 93 (2.2%) lesions.

All operations were performed under general anesthesia. For stage 2 lesions, debridement and saucerization were performed to completely resect the lesions, and the wounds were closed without tension through local mucoperiosteum flaps. For stage 3 and refractory stage 2 mandibular lesions, segmental mandibulectomy was performed to completely resect the lesions. Reconstruction plate fixation and ipsilateral submandibular gland translocation were used to reconstruct the continuity of the mandible.[5] For stage 3 maxillary lesions, the necrotic bone and infected tissue within the maxillary sinus were removed completely, and iodoform gauze was used to pack the maxillary sinus cavity. In some cases, 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 routinely performed in all cases to confirm the diagnosis and to exclude metastatic disease.

The follow-up period ranged from 3 months to 5 years, with an average of 14.5 months. Within the 93 MRONJ lesions, 74 of 93 (79.6%) reached mucosal healing at the last follow-up, whereas wound infection and dehiscence occurred in 19 of 93(20.4%) lesions postoperatively.

Table 1 summarizes the demographic and clinical characteristics of the study sample.

Table 2 presents the descriptive statistics by disease stage. Stage 3 disease was more likely when the lesion was in the maxilla ($P = .037$); in the posterior jaw, that is, molar area ($P = .001$); and when serum albumin was <40 g/L ($P = .021$).

Table 3 presents the results of multivariate analysis. The factors associated with stage 3 MRONJ were aged ≤65 years (OR = 3.968, 95% CI: 1.280–12.301, $P = .017$); chemotherapy (OR = 3.687, 95% CI 1.048–12.972, $P = .042$); preoperative MRONJ duration ≥12 months (OR = 7.616, 95% CI: 1.865–31.110, $P = .005$); lesion location in maxilla (OR = 1.150, 95% CI: 1.006–1.315, $P = .041$); lesion location in posterior jaw, that is, molar area (OR = 1.384, 95% CI: 1.118–1.715, $P = .003$); and serum albumin <40 g/L (OR = 6.257, 95% CI 1.313–29.815; $P = .021$).

Discussion

The etiopathogenesis of MRONJ has not yet been fully elucidated. Genetic factors,[6,7] potency of the drug,[8] cumulative dose of the drug,[9] concurrent administration of antiresorptive and antiangiogenic agents,[10-12] and underlying infection,[13,14] have all been identified as possible risk factors for occurrence

Table 1. CHARACTERISTICS OF THE 79 PATIENTS (WITH 93 MRONJ LESIONS)

Characteristic	Value
Sex	
Female	45 (57.0)
Male	34 (43.0)
Age, yr	65.2 ± 9.0
Primary malignant disease	71 (89.9)
Lung cancer	22 (27.8)
Breast cancer	22 (27.8)
Multiple myeloma	10 (12.7)
Prostate cancer	7 (8.9)
Renal carcinoma	6 (7.6)
Colorectal cancer	2 (2.5)
Vaginal cancer	1 (1.3)
Soft tissue sarcoma	1 (1.3)
Primary benign disease	8 (10.1)
Osteoporosis	3 (3.8)
Rheumatoid arthritis	3 (3.8)
Pemphigus	2 (2.5)
Medication risk factors*	
Zoledronic	70 (88.6)
Pamidronate	8 (10.1)
Alendronate	7 (8.9)
BPs followed by antiangiogenic agents	49 (62)
Mode of delivery	
IV	72 (91.1)
PO	6 (7.6)
PO + IV	1 (1.3)
BP treatment duration, mo	33.4 ± 22.0
Drug holiday, mo	10.8 ± 10.8
Preoperative MRONJ duration, mo	12.0 ± 9.9
Chemotherapy	50 (63.3)
Corticosteroid therapy	44 (55.7)
Diabetes mellitus	16 (20.3)
Stage at diagnosis	
1	0 (0)
2	36 (38.7)
3	57 (61.3)
Site	
Mandible	66 (71)
Maxilla	27 (29)
Anatomic location	
Anterior jaw (anterior teeth and premolar area)	10 (10.8)
Posterior jaw (molar area)	83 (89.2)
Etiology of MRONJ	
Periodontal/peri-implant disease	62 (66.7)
Surgery/trauma	29 (31.2)
Unknown	2 (2.2)

Data are n (%) or mean ± standard deviation.

Abbreviations: BP, bisphosphonate; IV, intravenous; MRONJ, medication-related osteonecrosis of the jaw; PO, oral.

* Sums to >100% because some patients received multiple medications.

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of MRONJ. In addition, there may be other risk factors that influence the progression and severity of MRONJ. Awareness of these risk factors would help the clinician identify those at risk for rapidly progressive disease and implement appropriate therapy or preventive measures.

Nisi et al. found high cumulative dose of bisphosphonate, smoking, corticosteroid intake, and maxillary location of the lesion to be associated with more severe disease.[2] Previous studies also suggest that serum C-terminal cross-linking telopeptide of type I collagen (CTX), serum receptor activator for nuclear factor κ B ligand (RANKL) and osteoprotegerin (OPG) levels, and the RANKL/OPG ratio may be associated with the severity of MRONJ, but this remains controversial.[3,4,15,16] In the present study, we retrospectively analyzed the clinical data of MRONJ patients to identify the factors associated with severe disease (stage 3 MRONJ).

Several previous studies have reported that older patients have increased risk of MRONJ[17-20]; this increased risk was attributed to the longer duration of drug therapy and the altered bone metabolism in the elderly. In this study, however, we found severe MRONJ to be more common in younger patients (≤65 years). There could be several reasons for this contrary finding. First, because primary disease tends to be more aggressive in younger patients, more radical treatment measures are used; this may lead to faster progression of MRONJ. Second, elderly patients usually pay more attention to oral health and seek medical attention at the early stages of the disease, whereas younger patients tend to neglect oral health and therefore have advanced disease at presentation. Third, some elderly patients with advanced MRONJ lesions were probably not admitted to hospital for surgical treatment because of their poor general health, and so a selection bias may be present in our sample.

Chemotherapy has been reported to be a risk factor for MRONJ. Chemotherapeutic agents have immunosuppressive action and also inhibit osteoclast formation. Therefore, when administered in combination with bisphosphonates, there is increased susceptibility for MRONJ.[20-24] It should also be noted that the indications for antiresorptive or antiangiogenic therapy (therapeutic or prophylactic) are similar to those for chemotherapy. Thus, patients with aggressive primary disease are likely to receive chemotherapy in combination with antiresorptive or antiangiogenic therapy. This combination therapy may increase risk for severe MRONJ.[2] Consistent with previous reports, the present study also found chemotherapy to be associated with more advanced MRONJ lesions.

In accordance with the AAOMS 2014 position paper, surgical treatment is not recommended for stage 1 and 2 lesions and should be restricted to

Table 2. STUDY VARIABLES GROUPED BY DISEASE STAGE

Variable	Stage 2, n = 36	Stage 3, n = 57	*P*
Age, yr	66.2 ± 9.1	62.8 ± 9.1	.085*
Sex, male	13 (36.1%)	29 (50.9%)	.163†
Primary disease, malignant	34 (94.4%)	50 (87.7%)	.479†
BP followed by antiangiogenic agent	24 (66.7%)	35 (61.4%)	.608†
Mode of delivery, IV	35 (97.2)	50 (87.7%)	.225†
BP treatment duration, mo	31.8 ± 17.4	35.2 ± 24.8	.468*
Drug holiday, mo	8.5 ± 9.0	12.2 ± 11.7	.106*
Preoperative MRONJ duration, mo	10.1 ± 10.0	13.1 ± 9.7	.156*
Site, maxilla	6 (16.7%)	21 (36.8%)	.037†
Anatomic location, molar area	27 (75.0%)	56 (98.2%)	.001†
Diabetes mellitus	4 (11.1%)	13 (22.8%)	.155†
Chemotherapy	25 (69.4%)	30 (52.6%)	.108†
Corticosteroid therapy	19 (52.8%)	31 (55.4%)	.808†
Hemoglobin, g/L	118.7 ± 16.0	112.0 ± 16.1	.052*
Serum albumin, g/L	37.9 ± 7.3	35.3 ± 3.6	.021*
Serum calcium, mmol/L	2.2 ± 0.4	2.1 ± 0.1	.088*

Data are n (%) or mean ± standard deviation.

Abbreviations: BP, bisphosphonate; IV, intravenous; MRONJ, medication-related osteonecrosis of the jaw.

* Independent-samples *t* test.

† Chi-square test.

Table 3. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF FACTORS ASSOCIATED WITH SEVERE MRONJ (STAGE 3)

Variable	OR	95% CI	*P*
Age			
≤65 yrs	3.968	1.280–12.301	.017
>65 yrs	1 (reference)		
Chemotherapy			
Yes	3.687	1.048–12.972	.042
No	1 (reference)		
Preoperative MRONJ duration			
≥12 mo*	7.616	1.865–31.110	.005
<12 mo	1 (reference)		
Site			
Maxilla	1.150	1.006–1.315	.041
Mandible	1 (reference)		
Anatomic location			
Posterior jaw (molar area)	1.384	1.118–1.715	.003
Anterior jaw (anterior teeth and premolar area)	1 (reference)		
Albumin			
<40 g/L†	6.257	1.313–29.815	.021
≥40 g/L	1 (reference)		

Abbreviations: CI, confidence interval; MRONJ, medication-related osteonecrosis of the jaw; OR, odds ratio.
* Mean preoperative MRONJ duration was 12 months.
† Lower than normal albumin.

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patients with stage 3 lesions or with stage 2 lesions refractory to nonsurgical treatment.[1] However, there is an increasing body of evidence suggesting that surgical removal of necrotic bone might be curative in patients with all MRONJ stages.[25,26] In addition, patients with severe MRONJ lesions are more likely to have negative surgical outcomes.[27,28] Early surgical treatment may prevent progression of the lesions, reduce risk of postoperative recurrence, and improve prognosis.[28-30] In this study, we found preoperative MRONJ duration ≥12 months to be associated with advanced MRONJ stage; this finding supports the view of early surgical treatment for MRONJ.

In our study cohort, MRONJ lesions were more common in the mandible than in the maxilla (2.4:1), and also more common in the posterior portion of the jaw (molar area) than in the anterior portion of the jaw (anterior teeth and premolar area) (8.3:1); this finding is in accordance with previous studies.[31] Multivariate logistic regression analysis revealed that lesions location in the maxilla and in the posterior portion of the jaw (molar area) were both associated with advanced MRONJ stage. This could be because maxillary lesions are more insidious, and therefore likely to be at advanced stage at the initial diagnosis.[2] In addition, the apex of maxillary molar is adjacent to the maxillary sinus floor, and the MRONJ lesions in this region are more likely to involve the sinus early and be classified as stage 3. We also need to reflect on whether the same system can be used for staging of lesions of the upper and lower jaws, given the marked differences in anatomical structure and bone characteristics between the maxilla and the mandible.

Serum albumin is an important plasma protein synthesized mainly by the liver. It participates in the regulation of autoimmunity and the inflammatory response. Decreased serum albumin level has been shown to affect prognosis in many diseases,[32] but so far, there have been no reports of low serum albumin as a risk factor of MRONJ. In the present study, serum albumin <40 g/L was found to be associated with advanced MRONJ stage. It is possible that MRONJ, an inflammatory disease, accelerates the catabolism of the albumin and reduces its synthesis. Low serum albumin may also be an indication of insufficient nutritional intake, which will inevitably affect immunity and wound healing. Clinicians should pay attention to the serum albumin level in patients with MRONJ, as low serum albumin may accelerate the progression of MRONJ and also increase the risk of postoperative infection due to poor wound healing.

The main limitation of the present study was the wide heterogeneity in the antiresorptive or antiangiogenic medications used; the risk of MRONJ varies with the type of drug, but the small sample size made it impossible to carry out subgroup analysis.

In conclusion, this study found age ≤65 years, chemotherapy, preoperative MRONJ duration

≥12 months, lesion location in the maxilla, lesion location in the molar area, and serum albumin <40 g/L may increase the risk for severe MRONJ.

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