Incidence of and risk factors for medication-related osteonecrosis of the jaw in women with breast cancer with bone metastasis: a population-based study

Fredrik Hallmer, DDS, PhD,[a] Olof Bjarnadottir, MD, PhD,[b] Bengt Götrick, DDS, PhD,[c] Per Malmström, MD, PhD,[d] and Gunilla Andersson, DDS, PhD[e]

Objective. The aim of this study was to prospectively determine the incidence of medication-related osteonecrosis of the jaw (MRONJ) and define risk factors in patients with metastatic breast cancer treated with zoledronic acid and/or denosumab.
Study Design. In a prospective cohort study performed in Region Skåne, Sweden, from January 1, 2012, until December 31, 2015, all patients with breast cancer who had radiographic evidence of bone metastases and were treated with zoledronic acid or denosumab were included and followed up until May 31, 2018.
Results. Of the 242 patients, MRONJ developed in 16 (6.6%) during the 77 months of study. The incidence of MRONJ in patients treated with zoledronic acid was 4.1%, and in patients treated with denosumab, it was 13.6%. The risk of MRONJ was higher in patients on denosumab than in those treated with zoledronic acid ($P = .011$). Corticosteroid use was associated with a decreased risk of MRONJ ($P = .008$), and diabetes was associated with an increased risk of MRONJ ($P = .02$).
Conclusions. The incidence of MRONJ is 13.6% (>3 times higher) in denosumab-treated patients with breast cancer compared with that in patients treated with zoledronic acid (4.1%). Corticosteroid use decreased the risk of MRONJ. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:252−257)

Breast cancer is the most common cancer among women worldwide and the second most common cause of cancer-related death.[1,2] In Sweden, the 5-year survival rate for patients with breast cancer is 90%, but breast cancer survivors remain at risk for late recurrence several years after the primary diagnosis.[3] To reduce the risk of local and distant recurrences, endocrine treatment, with or without chemotherapy, is administered. Bone is the most common and often the first location for metastases.[4] Antiresorptive medications, that is, intravenous (IV) bisphosphonate and/or subcutaneous denosumab, are frequently used to reduce skeletal-related events (SREs) associated with bone metastases and to treat cancer-related conditions in metastatic settings, such as hypercalcemia.[5-7] In a randomized study, patients treated with denosumab had a better quality of life and fewer SREs compared with patients treated with zoledronic acid.[8]

Several studies have shown that in postmenopausal women with early breast cancer, treatment with bisphosphonate decreases recurrence in bone and visceral sites as well as breast cancer mortality.[9,10] Thus, bisphosphonate treatment was recently recommended as adjuvant treatment for postmenopausal patients with breast cancer.[11]

Medication-related osteonecrosis of the jaw (MRONJ), earlier known as *bisphosphonate-related osteonecrosis of the jaw*, was first described in 2003, when avascular necrosis of the jaw was detected in patients treated with the IV bisphosphonates pamidronate or zoledronic acid.[12,13] The American Association of Oral and Maxillofacial Surgeons has defined MRONJ as a condition in which patients treated with antiresorptive and/or antiangiogenic agents develop exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region.[14] This condition should have persisted for longer than 8 weeks, and there should be a history neither of metastatic disease in the jaw nor of radiation therapy of the region.[14] The pathophysiology of MRONJ is still debated. Inflammation and infection, decreased angio-

Statement of Clinical Relevance

The incidence of medication-related osteonecrosis of the jaw (MRONJ) in patients with metastatic breast cancer was 4.1% in those treated with zoledronic acid and 13.6% on those treated with denosumab. Corticosteroid use was associated with a decreased risk of MRONJ and diabetes with an increased risk of MRONJ.

[a]Consultant, Department of Oral and Maxillofacial Surgery, Malmö University, Faculty of Odontology, Malmö, Sweden and Department of Oral and Maxillofacial Surgery, Skåne University Hospital, Lund, Sweden.
[b]Consultant, Division of Oncology and Pathology, Department of Clinical Sciences, Lund University, Lund, Sweden.
[c]Associate Professor and Head, Department of Oral Diagnostics, Malmö University, Faculty of Odontology, Malmö, Sweden.
[d]Professor, Department of Haematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden.
[e]Associate Professor, Department of Oral and Maxillofacial Surgery, Malmö University, Faculty of Odontology, Malmö, Sweden.
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genesis, and inhibition of osteoclastic bone resorption and remodeling have been suggested as causes.[14,15] Described risk factors for developing MRONJ are duration of antiresorptive treatment and local risk factors, such as dentoalveolar surgery, tooth extraction, and periodontitis.[14,16-18] The estimated prevalence of MRONJ varies widely.[14,19] In an earlier study from southern Sweden (Skåne), the prevalence of MRONJ with IV bisphosphonate was estimated to be 2.8%.[20] Previous incidence studies of MRONJ have mainly been retrospective. As the indications for antiresorptive treatment have expanded and as denosumab treatment has been introduced, it has become increasingly important to estimate the incidence of and define the risk factors for MRONJ.

The aim of this study was to prospectively determine the incidence of MRONJ and define systemic risk factors in patients with metastatic breast cancer treated with zoledronic acid and/or denosumab.

MATERIALS AND METHODS

Women older than 17 years of age with histologically or cytologically confirmed breast cancer and radiographic evidence of 1 or several bone metastases were eligible for inclusion in the study.

The catchment area was Region Skåne with a population of 1.3 million and 4 departments of oncology responsible for the treatment of breast cancer and 4 oral and maxillofacial surgery clinics responsible for the treatment of patients with MRONJ.

Patients receiving zoledronic acid or denosumab during the study period were identified in the treatment registries and the medical records at the 4 departments of oncology.

Exclusion criteria were prior exposure to oral or IV bisphosphonates and/or denosumab for treatment of advanced cancer; prior treatment with oral bisphosphonates or denosumab for other bone loss conditions (e.g., osteoporosis); and a history of evidence of MRONJ or osteomyelitis of the jaw as well as radiation therapy to the head and neck region.

To ensure a certain amount of exposure to antiresorptive medications, we excluded patients who received less than 4 infusions of zoledronic acid or less than 4 injections of denosumab. Patients were enrolled from January 1, 2012, to December 31, 2015, and followed up until May 31, 2018. Treatment consisted of 4 mg of zoledronic acid administered intravenously for 15 minutes every 4 to 6 weeks or 120 mg of denosumab (Xgeva; Amgen Inc., Thousand Oaks, CA) subcutaneously every 4 weeks.

Data collected from patient medical records included age, bisphosphonate or denosumab use, treatment time, chemotherapy or corticosteroid use, diabetes, and smoking habit.

The cohort included 263 patients. Of these 21 patients were excluded: 15 treated with only 1 infusion with zoledronic acid, 3 treated with only one treatment with denosumab, and 3 treated with oral bisphosphonates for osteoporosis before the study. The studied cohort consisted of 242 patients (mean age 64 years; range 31−90 years). All cases of MRONJ were recorded and the patients referred to one of the oral and maxillofacial surgery departments in Skåne.

The study was conducted in compliance with the tenets of the Helsinki Declaration. Ethical approval was given by the Ethical Review Board in Lund, Sweden (Dnr 2011/274) and (Dnr 2018/344).

Statistical analysis

The relationship between MRONJ and different background variables (treatment time, corticosteroid treatment, chemotherapy, diabetes mellitus, and smoking) were investigated by using odds ratios (OR) with 95% confidence intervals (CIs). The OR was tested by using χ^2 tests with the significance level set at 5%.

The relationship between time to MRONJ and different background variables (corticosteroid treatment, chemotherapy, diabetes mellitus, and smoking) were investigated by using the log-rank test. The data were analyzed by using the Kaplan-Meier method.

All calculations were performed in SPSS version 25 (SPSS Inc., Chicago, IL).

RESULTS

Incidence

In 16 (6.6%) of the 242 patients, MRONJ developed during the study period. Mean age was 64.6 years (range 41−84 years). The incidence of MRONJ in patients treated with zoledronic acid was 4.1%, and in patients treated with denosumab, it was 13.6%. Among patients initially treated with zoledronic acid and subsequently switched to denosumab, the incidence was 8.3% (Table I). The risk of MRONJ in patients on denosumab was higher compared with zoledronic acid (OR 3.7; 95% CI 1.3−10.6; $P = .011$). The cumulative incidence of MRONJ in patients with metastatic breast cancer treated with zoledronic acid and denosumab is presented in Figure 1.

Risk factors

Mean antiresorptive treatment time for all patients was 27.5 months. Among patients with MRONJ, mean treatment time was 35.3 months (range 8−70 months) and among patients without MRONJ, it was 27 months (range 2−77 months). The mean treatment time for zoledronic acid was 26.1 ± 17.0 months: 25.4 ± 16.7 months for patients without MRONJ and 40.9 ± 18.8 months for those with MRONJ. The mean treatment time for denosumab

Table I. Incidence of medication-related osteonecrosis of the jaw (MRONJ) in women with disseminated breast cancer, according to antiresorptive treatment, zoledronic acid, denosumab, or zoledronic acid followed by denosumab

Antiresorptive treatment	Number of patients	*Patients without MRONJ*	*Patients with MRONJ*	*Incidence %*
Zoledronic acid	171	164	7	4.1*
Denosumab	59	51	8	13.6*
Zoledronic acid followed by denosumab	12	11	1	8.3
All patients	242	226	16	6.6

**P* value zoledronic acid versus denosumab = .039.

was 30.8 ± 17.5 months: 31.3 ± 17.5 months for patients without MRONJ and 27.8 ± 18.5 months for those with MRONJ.

Corticosteroid treatment was administered to 163 of the 242 patients (Table II). Of these 163, 6 were diagnosed with MRONJ compared with 10 of the 79 not receiving corticosteroids. Corticosteroid use was associated with a decreased risk of MRONJ (OR 0.3; 95% CI 0.1−0.8; P = .008). The mean treatment time with antiresorptives was 25.1 ± 17.0 months with corticosteroid treatment and 31.9 ± 16.4 months without corticosteroid treatment.

Chemotherapy was administered to 145 of the 242 patients (see Table II). Of the 145 chemotherapy-treated patients, 12 were diagnosed with MRONJ compared with 4 of the 97 not receiving chemotherapy. Chemotherapy was not associated with an increased risk of MRONJ (OR 2.1; 95% CI 0.7−6.7; P = .2). Mean antiresorptive treatment time was 26.1 ± 16.9 months with chemotherapy and 29.6 ± 17.6 months without chemotherapy.

In the cohort, 14 of the 242 patients had diabetes mellitus (see Table II). Three patients with diabetes mellitus had MRONJ of a total of 16 patients with MRONJ. Diabetes was associated with an increased risk of MRONJ (OR 4.5; 95% CI 1.1−18.1; P = .02). Mean treatment time of antiresorptive treatment was 20.5 ± 17.7 months in patients with diabetes and 28.0 ± 17.2 months without diabetes.

In total, 27 of the 242 study patients were regular smokers, including 4 of the 16 in the group with MRONJ (see Table II). Smoking was not associated with an increased risk of MRONJ (OR 2.9; 95% CI 0.9−9.9; P = .07). Mean time of antiresorptive treatment was 30.7 ± 18.8 months in smokers and 27.1 ± 17.1 months in nonsmokers.

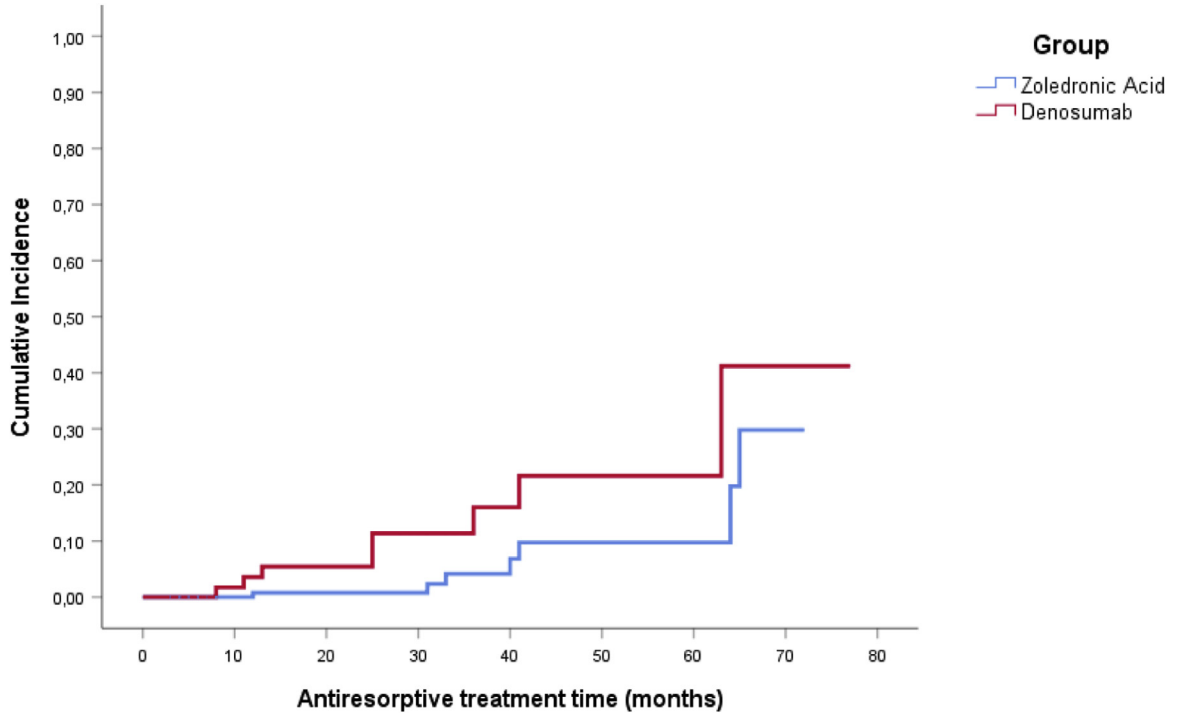

Fig. 1. Cumulative incidence of medication-related osteonecrosis of the jaw (MRONJ) in patients with metastatic breast cancer treated with zoledronic acid *(blue line)* and denosumab *(red line)*.

Table II. Risk factors of for medication-related osteonecrosis of the jaw (MRONJ) in 226 women with disseminated breast cancer, according to corticosteroid treatment, chemotherapy, diabetes, or smoking

Risk factor	*Number of patients*	*No MRONJ*	*MRONJ*	*Incidence (%)*	*Odds ratio; 95% CI*	*P value*
Corticosteroid treatment						
Yes	163	157	6	3.7	0.3; 0.1−0.8	.008
No	79	69	10	12.7		
Chemotherapy						
Yes	145	133	12	8.3	2.1; 0.7−6.7	.2
No	97	93	4	4.1		
Diabetes						
Yes	14	11	3	21.4	4.5; 1.1−18.1	.02
No	228	215	13	5.7		
Smoking						
Yes	27	23	4	14.8	2.9; 0.9−9.9	.07
No	215	203	12	5.6		

CI, confidence interval.

DISCUSSION

The strength of this study is its design as a prospective, population-based cohort study. All patients with disseminated breast cancer were treated at 1 of the 4 departments of oncology in the region, and these cases were recorded in the database in this study. Because there are no private departments of oncology in the region, it is estimated that very few patients receiving antiresorptive treatment were omitted. Awareness of MRONJ is also high, and patients with symptoms in their teeth or jaws during antiresorptive treatment are regularly referred to the departments of oral and maxillofacial surgery. Most patients in the study received treatment when MRONJ developed. Therefore, it is unlikely that any cases of MRONJ were missed. The few cases not identified might have been of patients who did not seek health care because of asymptomatic MRONJ lesions. A shortcoming of the study was that the numbers of patients and events were not sufficient for multivariable analyses of risk factors.

With regard to treatment with zoledronic acid, the incidence rate of MRONJ (4.1%) found in our study is in accordance with that reported by Bamias et al., who found an incidence rate of 2.9% of MRONJ in patients with breast cancer treated with bisphosphonates,[16] whereas the incidence rate of MRONJ in the total population is higher (6.6%). The explanation for this is the greater than three times high risk for MRONJ with denosumab compared with zoledronic acid. In patients on denosumab, MRONJ had developed after 28 months, whereas in patients on zoledronic acid mean time to MRONJ was 41 months. Plausible explanations for the higher incidence (13.6%) and earlier onset of MRONJ in patients treated with denosumab may be the different mechanisms of the medications and their effects on patients. Stopeck et al. demonstrated reduced bone turnover and delayed SREs with denosumab compared with zoledronic acid.[5] In a study comparing denosumab and zoledronic acid in several cancer types, bone turnover markers were significantly lower, and hypocalcemia was more common in the denosumab group, which may suggest stronger bone affinity.[21]

Although MRONJ is a serious complication of antiresorptive treatment, the benefits of these medications with reduction of SRE and a better quality of life predominate. Furthermore, if MRONJ develops, most patients can be treated surgically with sequestrectomy, block, or segmental resection, with complete healing achieved in the majority of cases.[22-26]

The decreased risk of MRONJ in patients receiving corticosteroid treatment is in contrast to the findings in other studies which reported corticosteroid intake as a systemic risk factor for MRONJ.[14,19] Corticosteroids have several indications in the treatment of breast cancer, including as antiemetic agents and to treat pain and inflammation.[27] Our findings could be explained by the positive anti-inflammatory effect of corticosteroids reducing periodontitis, which, in most patients, is a strong local risk factor for MRONJ.[22,28] In addition, MRONJ often starts as an osteomyelitis with periosteal bone formation, as seen in stage 0 lesions, probably caused by inflammatory response to an oral infection, such as marginal or apical periodontitis, and might, thus, be reduced by corticosteroid treatment. The risk of MRONJ in patients on chemotherapy was not significantly increased, probably because the study groups were too small. The increased risk of MRONJ recorded in patients with diabetes might be explained by the fact that periodontitis is more common in patients with diabetes[29]; however, the medical risks (microangiopathy) with diabetes probably are predominant factors in the development of MRONJ in this group of patients.

To further reduce the risk of MRONJ, local risk factors, such as periodontitis, ought to be identified and treated. Dental and periodontal examination should be performed before commencement of antiresorptive

therapy, if possible. If invasive dental procedures involving the jaws are necessary, initial healing, evidenced by mucosal coverage of bone, should occur before antiresorptive therapy is initiated, as suggest by Yarom et al.[30]

Kyrgidis et al.[31] reported smoking as a risk factor for MRONJ in patients with cancer, although it was not statistically significant. Those authors concluded that smoking does not seem to be an independent risk factor. In our study, there was no increase in risk (OR 2.94; 95% CI 0.88−9.88). This might be explained by a small number of smokers in the cohort.

CONCLUSIONS

In this prospective, population-based cohort study, MRONJ incidence and risk factors in patients with disseminated breast cancer on zoledronic acid and/or denosumab were assessed. A striking finding not previously reported is the greater than 3 times higher risk of MRONJ in patients treated with denosumab compared with those treated with zoledronic acid. Furthermore, the study demonstrated that diabetes is associated with an increased risk of MRONJ and that corticosteroids decrease the risk of MRONJ. The risk of MRONJ, as reported in this study, does not outweigh the benefits of the antiresorptive treatment, especially because MRONJ lesions can be successfully treated.

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Reprint requests:

Fredrik Hallmer
Department of Oral and Maxillofacial Surgery
Faculty of Odontology
Malmö University
205 06 Malmö-SE
Sweden
Fredrik.hallmer@mau.se