



Impact of Preventive Dental Management on MRONJ Development in Multiple Myeloma: A Prospective Study with CTX Evaluation

Multipl Miyelom Hastalarında MRONJ Gelişimi Üzerine Önleyici Dental Yönetimin Etkisi: CTX Değerlendirmesini İçeren Prospektif Çalışma

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ABSTRACT

Aim: Medication-related osteonecrosis of the jaw (MRONJ) is a clinically significant complication associated with bisphosphonate therapy in patients with multiple myeloma. Preventive dental strategies are recommended to reduce this risk; however, the role of biochemical markers such as serum C-terminal telopeptide (CTX) in predicting MRONJ remains controversial. This study aimed to evaluate the impact of preventive dental management on MRONJ development in patients with multiple myeloma receiving bisphosphonate therapy and to assess the relationship between serum CTX levels and MRONJ occurrence.

Material and Method: This prospective study included 50 patients with multiple myeloma who were followed between February 2009 and April 2010. Twenty-five newly diagnosed patients underwent serum CTX measurement and comprehensive dental examination prior to initiation of bisphosphonate therapy. When dental risk factors were identified, bisphosphonate treatment was postponed until completion of necessary dental interventions. The study also included 25 previously diagnosed patients who had already been receiving bisphosphonate therapy without systematic preventive dental evaluation. Serum CTX levels were measured using the Elecsys β -CrossLaps assay, and their association with MRONJ development was analyzed.

Results: No cases of MRONJ were observed in the newly diagnosed group who underwent preventive dental evaluation prior to bisphosphonate initiation. In contrast, MRONJ occurred in 24% of patients in the previously treated group without preventive dental management. Patients who developed MRONJ tended to have lower serum CTX levels compared with those who did not develop osteonecrosis; however, this difference was not statistically significant. Accordingly, CTX values did not demonstrate sufficient discriminatory capacity to serve as an independent predictive biomarker.

Conclusion: Preventive dental examination and appropriate dental management prior to bisphosphonate therapy appear to be effective strategies for reducing MRONJ risk in patients with multiple myeloma. Although lower CTX levels were observed in patients who developed MRONJ, serum CTX alone does not provide sufficient predictive value for MRONJ risk assessment.

Keywords: Multiple myeloma, bisphosphonates, osteonecrosis of the jaw, CTX, preventive dentistry

ÖZ

Amaç: İlaç ilişkili çene osteonekrozu (MRONJ), multipl miyelom hastalarında bifosfonat tedavisi ile ilişkili klinik açıdan önemli bir komplikasyondur. Bu riski azaltmak amacıyla önleyici dental stratejiler önerilmektedir; ancak serum C-terminal telopeptid (CTX) gibi biyokimyasal belirteçlerin MRONJ gelişimini öngörmedeki rolü halen tartışmalıdır. Bu çalışmanın birincil amacı, bifosfonat tedavisi alan multipl miyelom hastalarında önleyici dental yönetimin MRONJ gelişimi üzerindeki etkisini değerlendirmektir. İkincil amaç ise serum CTX düzeyleri ile MRONJ gelişimi arasındaki ilişkinin incelenmesidir.

Gereç ve Yöntem: Bu prospektif çalışmada Şubat 2009 ile Şubat 2010 tarihleri arasında izlenen toplam 50 multipl miyelom hastası değerlendirildi. Yirmi beş yeni tanılı hastada bifosfonat tedavisi başlanmadan önce serum CTX ölçümü yapıldı ve kapsamlı dental muayene gerçekleştirildi. Dental risk faktörleri saptanan olgularda gerekli dental girişimler tamamlanıncaya kadar bifosfonat tedavisi ertelendi. Çalışmaya ayrıca daha önce bifosfonat tedavisi almakta olan ve sistematik önleyici dental değerlendirme yapılmamış 25 eski tanılı hasta da dahil edildi. Serum CTX düzeyleri Elecsys β -CrossLaps yöntemi kullanılarak ölçüldü ve MRONJ gelişimi ile ilişkisi analiz edildi.

Bulgular: Bifosfonat tedavisi öncesinde önleyici dental değerlendirme yapılan yeni tanılı hasta grubunda MRONJ gelişimi gözlenmedi. Buna karşılık, önleyici dental yönetim uygulanmamış daha önce tedavi alan hasta grubunda MRONJ insidansı %24 olarak saptandı. MRONJ gelişen hastalarda CTX düzeylerinin, osteonekroz gelişmeyen hastalara kıyasla daha düşük olma eğilimi gösterdiği gözlemlendi; ancak CTX değerleri MRONJ gelişimini bağımsız olarak öngörebilecek yeterli ayırt edici kapasite göstermedi.

Sonuç: Bifosfonat tedavisi öncesinde gerçekleştirilen önleyici dental muayene ve uygun dental yönetim, multipl miyelom hastalarında MRONJ riskini azaltmada etkili bir yaklaşım olarak görünmektedir. MRONJ gelişen hastalarda daha düşük CTX düzeyleri gözlenmiş olsa da, serum CTX tek başına klinik risk sınıflandırması için güvenilir bir öngörü belirteci değildir.

Anahtar Kelimeler: Multipl miyelom, bifosfonatlar, çene osteonekrozu, CTX, önleyici diş hekimliği

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INTRODUCTION

Multiple myeloma is characterized by extensive bone disease resulting from increased osteoclast activity and suppression of osteoblast function (1,2). For this reason, intravenous bisphosphonates—particularly zoledronic acid and pamidronate—are widely used as a standard therapeutic approach for the prevention and management of skeletal-related events in patients with multiple myeloma. By inhibiting osteoclast-mediated bone resorption, bisphosphonates reduce the incidence of pathological fractures, bone pain, and hypercalcemia, thereby improving quality of life and clinical outcomes (1,2).

However, the long-term and widespread use of potent antiresorptive agents has been associated with the emergence of medication-related osteonecrosis of the jaw (MRONJ), a potentially serious complication observed particularly in patients with malignancies such as multiple myeloma (3,4). The reported incidence of MRONJ varies according to the type of antiresorptive agent, route of administration, cumulative dose, and duration of therapy (3,5). In cancer populations receiving high-dose intravenous bisphosphonates, the risk of MRONJ is substantially higher than in patients treated for osteoporosis (3,5). Clinically, MRONJ is associated with significant morbidity, including persistent exposed bone, infection, pain, and impaired oral function, and it may require prolonged medical or surgical management (3,4).

A wide range of local and systemic factors have been implicated in the development of MRONJ. Among local factors, invasive dental procedures—particularly tooth extraction—periodontal disease, poorly fitting prostheses, and chronic mucosal trauma are considered major triggers (3,4). Systemic factors such as cumulative bisphosphonate exposure, corticosteroid use, diabetes mellitus, and impaired wound healing may further increase susceptibility to MRONJ (4,8). Consequently, current clinical guidelines emphasize the importance of careful dental risk assessment and preventive oral management prior to the initiation of antiresorptive therapy.

Despite increasing knowledge about clinical risk factors, attempts have also been made to identify biochemical markers that might help predict MRONJ development. Serum C-terminal telopeptide of type I collagen (CTX), a marker reflecting bone turnover, has been proposed as a potential indicator of suppressed bone remodeling during antiresorptive therapy (6). Nevertheless, systematic reviews and meta-analyses have demonstrated inconsistent and insufficient evidence supporting the use of CTX as a reliable independent predictor of MRONJ risk (7–9). For this reason, current consensus statements recommend prioritizing clinical and dental risk assessment rather than relying solely on biochemical markers for MRONJ risk stratification.

Preventive dental evaluation before the initiation of bisphosphonate therapy has therefore become a central strategy in MRONJ prevention. Comprehensive oral examination, elimination of potential sources of infection, and completion of necessary dental procedures prior to therapy initiation have been shown to significantly reduce the incidence of MRONJ (3,4). However, prospective clinical data evaluating preventive dental strategies together with biochemical markers such as CTX in patients with multiple myeloma remain limited.

Therefore, the primary objective of this prospective study was to evaluate the impact of preventive dental management on the development of MRONJ in patients with multiple myeloma receiving bisphosphonate therapy. A secondary objective was to explore the relationship between serum CTX levels and MRONJ occurrence in this patient population.

MATERIAL AND METHOD

Study Population

This prospective study included 50 adult patients with a confirmed diagnosis of multiple myeloma who were followed at the Division of Hematology, Department of Internal Medicine, Istanbul University between February 2009 and April 2010. Patient enrollment was completed within the first three months of the study period. The data cut-off date was April 2010, corresponding to completion of the 12-month follow-up period for the last enrolled patient.

Inclusion criteria were age ≥ 18 years, confirmed diagnosis of multiple myeloma, and current or planned treatment with intravenous bisphosphonates. Patients who had previously received radiotherapy to the maxillofacial region or who were unable to complete the planned follow-up period were excluded from the study.

Patients were divided into two groups. The newly diagnosed group consisted of 25 patients who were newly diagnosed with multiple myeloma during the study period and were scheduled to initiate bisphosphonate therapy. The previously diagnosed group included 25 patients with an established diagnosis of multiple myeloma who had already been receiving bisphosphonate therapy prior to study enrollment.

All patients underwent detailed medical history assessment, physical examination, and routine laboratory testing during regular follow-up visits. Routine biochemical analyses were performed at the Central Clinical Biochemistry Laboratory using standard methods. In addition, serum C-terminal telopeptide (CTX) levels were measured as a marker of bone resorption.



Anti-myeloma treatment regimens used during the study period mainly consisted of corticosteroid-based therapies combined with conventional chemotherapy agents, reflecting standard treatment practices at that time.

Dental and Maxillofacial Evaluation

All patients underwent comprehensive oral and maxillofacial evaluation at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Istanbul University, regardless of the presence of oral symptoms. Dental assessment included panoramic jaw radiography and a detailed clinical examination focusing on periodontal disease, dental infections, teeth requiring extraction, and the presence of mucosal trauma or prosthesis-related irritation.

Patients were followed at intervals of up to six months with repeated clinical examinations. Panoramic radiography was performed when clinically indicated, and serum CTX measurements were obtained during follow-up evaluations.

In the newly diagnosed group, dental examination and CTX measurements were performed prior to initiation of bisphosphonate therapy and were repeated at 6 and 12 months during follow-up. In the previously diagnosed group, evaluations were performed at baseline and subsequently at six-month intervals during the study period.

Preventive Dental Management

Preventive dental management was implemented in patients identified as having potential risk factors for medication-related osteonecrosis of the jaw (MRONJ).

In the newly diagnosed group, this strategy included completion of necessary dental procedures—such as tooth extraction, periodontal treatment, or management of dental infections—prior to initiation of bisphosphonate therapy. Bisphosphonate treatment was initiated only after adequate mucosal healing and confirmation of dental clearance. The interval between completion of dental interventions and initiation of bisphosphonate therapy was determined clinically based on adequate healing of the oral tissues.

Patients who were already receiving bisphosphonate therapy were monitored regularly for oral complications during follow-up visits. When osteonecrosis of the jaw was suspected or diagnosed, bisphosphonate therapy was discontinued and appropriate conservative or surgical management was performed by oral and maxillofacial surgeons according to clinical indications.

Bisphosphonate Therapy

Intravenous bisphosphonates were administered for the management of myeloma-related bone disease according to standard clinical protocols used during the study period. Zoledronic acid was the most frequently

administered agent and was given at conventional dosing intervals. Pamidronate was used in selected patients based on clinical indications.

Information regarding the type of bisphosphonate, duration of therapy, and cumulative exposure was obtained from patient medical records and included in the analysis.

Serum CTX Measurement

Serum C-terminal telopeptide (CTX) levels were measured as a marker of bone resorption using the Elecsys β -CrossLaps assay (Roche Diagnostics), which detects beta isomers of CTX released during osteoclastic degradation of type I collagen. Results were recorded in ng/mL.

In the newly diagnosed group, CTX measurements were obtained prior to initiation of bisphosphonate therapy and were repeated during follow-up visits. In patients receiving ongoing bisphosphonate therapy, CTX measurements were performed during routine follow-up evaluations and, when possible, at least four weeks after the most recent bisphosphonate infusion.

Definition and Follow-up of MRONJ

Medication-related osteonecrosis of the jaw (MRONJ) was defined as exposed bone, or bone that could be probed through an intraoral or extraoral fistula in the maxillofacial region, persisting for more than eight weeks in patients with a history of bisphosphonate exposure and no history of radiation therapy to the jaws.

During follow-up visits, patients were evaluated for clinical signs and symptoms suggestive of MRONJ, including exposed bone, pain, infection, and soft tissue inflammation. Radiographic examinations were performed when clinically indicated.

RESULTS

Statistical Analysis

Statistical analyses were performed using SPSS software (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were compared using Student's *t* test, whereas the Mann-Whitney *U* test was used for variables that did not show normal distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

The association between serum CTX levels and the development of medication-related osteonecrosis of the jaw (MRONJ) was evaluated using group comparisons. Continuous variables are presented as mean \pm standard deviation or median (minimum–maximum), as appropriate. A *p* value < 0.05 was considered statistically significant.

Demographic and Clinical Characteristics

The newly diagnosed multiple myeloma group consisted of 25 patients (10 women and 15 men) with a mean age of 59 years (range, 43–80 years). The previously diagnosed group included 25 patients (9 women and 16 men) with a mean age of 60 years (range, 43–79 years). No statistically significant differences were observed between the groups with respect to age or sex distribution ($p > 0.05$). There were also no clinically significant differences between the groups regarding the type of bisphosphonate used or overall treatment characteristics. The demographic and clinical characteristics of the patients are summarized in **Table 1**.

Table 1. Baseline Demographic and Clinical Characteristics of Patients

Variable	Newly Diagnosed (n=25)	Previously Diagnosed (n=25)	P value
Age (years)	59±12	60±10	0.83
Female, n (%)	10 (40)	9 (36)	0.77
Male, n (%)	15 (60)	16 (64)	
Bisphosphonate type			
Zoledronic acid	23 (92)	22 (88)	
Pamidronate	2 (8)	3 (12)	0.17
Duration of BP therapy (months)	3.8±4.8	24±19.6	0.0001
Diabetes mellitus	5 (20)	1 (4)	0.08
Dexamethasone therapy	17 (68)	20 (80)	0.33
Lytic bone lesions	10 (40)	10 (40)	1.00

Note: Data are presented as mean±standard deviation or number (percentage), as appropriate. Comparisons between the newly diagnosed and previously diagnosed groups were performed using Student's t test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. Duration of bisphosphonate therapy reflects cumulative exposure prior to study evaluation. Abbreviations: BP, bisphosphonate; MRONJ, medication-related osteonecrosis of the jaw.

The distribution of patients according to multiple myeloma stage was comparable between the newly diagnosed and previously diagnosed groups (**Table 2**). When disease stage at diagnosis was examined, osteonecrosis of the jaw occurred more frequently in patients with advanced-stage disease (Durie–Salmon stages II–III) compared with those with early-stage disease. However, due to the limited sample size, the statistical power to detect a robust association between disease stage and the development of osteonecrosis of the jaw was limited. No significant association was observed between age and the development of osteonecrosis of the jaw. Male sex and longer duration of bisphosphonate exposure were more frequently observed among patients who developed osteonecrosis of the jaw (**Table 2**).

Table 2. Disease Characteristics at Diagnosis

Variable	Newly Diagnosed (n=25)	Previously Diagnosed (n=25)	P value
Durie–Salmon Stage I	21 (84)	11 (44)	
Stage II	2 (8)	8 (32)	
Stage III	2 (8)	6 (24)	0.09
Beta-2 microglobulin (mg/L)	3.69±2.50	3.58±2.32	0.89
Albumin (g/dL)	3.87±0.56	3.79±0.56	0.64
LDH (U/L)	346±128	400±203	0.36

Note: Data are presented as number (percentage) unless otherwise indicated. Comparisons between groups were performed using the chi-square test or Fisher's exact test, as appropriate. Due to the limited number of MRONJ cases, the statistical power to detect associations between disease stage and MRONJ development was limited. Abbreviations: MRONJ, medication-related osteonecrosis of the jaw.

Preventive dental evaluation was systematically performed in all newly diagnosed patients prior to initiation of bisphosphonate therapy, whereas none of the previously diagnosed patients had undergone preventive dental assessment (**Table 3**). No cases of MRONJ were observed in the newly diagnosed group during follow-up, whereas MRONJ developed in 24% of patients in the previously treated group. In the latter group, several patients had a history of tooth extraction and periodontal disease, both of which are recognized local risk factors for MRONJ.

Table 3. Preventive Dental Evaluation and MRONJ Development

Variable	Newly Diagnosed (n=25)	Previously Diagnosed (n=25)	P value
Preventive dental evaluation	25 (100%)	0 (0%)	<0.001
MRONJ cases	0 (0%)	6 (24%)	0.009
Tooth extraction history	—	4 (16%)	
Periodontal disease	—	6 (24%)	

Note: Data are presented as number (percentage). Comparisons between groups were performed using the chi-square test or Fisher's exact test, as appropriate. Preventive dental evaluation included comprehensive oral examination, panoramic radiography, and completion of necessary dental interventions prior to initiation of bisphosphonate therapy. Abbreviations: MRONJ, medication-related osteonecrosis of the jaw.

When clinical risk factors associated with MRONJ development were analyzed, patients who developed MRONJ had significantly longer exposure to bisphosphonate therapy and higher estimated cumulative bisphosphonate doses compared with those who did not develop osteonecrosis (**Table 4**). In addition, preventive dental evaluation was absent in all MRONJ-positive cases, further supporting the role of pre-treatment dental management in reducing MRONJ risk.

**Table 4. Clinical Risk Factors Associated with MRONJ Development**

Variable	MRONJ (-) (n=44)	MRONJ (+) (n=6)	p value
Age (years)	59.8±11.3	59.7±12.2	0.99
Male sex, n (%)	25 (56.8)	6 (100)	0.04
Duration of BP therapy (months)	12±9	41±21	0.01
Estimated cumulative BP dose (mg)	16	96	<0.01
Preventive dental evaluation, n (%)	25 (56.8)	0 (0)	<0.01
Serum CTX level (ng/mL)	higher	lower	ns

Note: Data are presented as mean±standard deviation or number (percentage), as appropriate. Continuous variables were compared using Student's t test or Mann-Whitney U test, and categorical variables were compared using the chi-square test or Fisher's exact test. Because of the limited number of MRONJ cases, multivariable regression analysis was not performed.
Abbreviations: BP, bisphosphonate; CTX, C-terminal telopeptide; MRONJ, medication-related osteonecrosis of the jaw.

Comparisons between newly diagnosed and previously diagnosed patient groups also demonstrated differences in clinical characteristics and CTX levels during follow-up (**Table 5**). Jaw-related symptoms and osteoporosis were more frequently observed in the previously diagnosed group. Serum CTX levels were consistently higher in newly diagnosed patients at baseline and during follow-up, reflecting higher bone turnover prior to antiresorptive therapy. CTX levels tended to be lower in patients who developed MRONJ; however, the difference was not statistically significant.

Table 5. Clinical Symptoms, CTX Levels, and MRONJ Development According to Patient Groups

Parameter	Newly Diagnosed (n=25)	Previously Diagnosed (n=25)	p value
Jaw-related clinical symptoms, n (%)	3 (12.0)	9 (36.0)	0.047
Dexamethasone use, n (%)	17 (68.0)	20 (80.0)	0.333
Diabetes mellitus, n (%)	5 (20.0)	1 (4.0)	0.082
Bence Jones proteinuria, n (%)	4 (16.0)	3 (12.0)	0.684
Cytogenetic abnormalities, n (%)	9 (36.0)	3 (12.0)	0.047
Osteoporosis, n (%)	1 (4.0)	6 (24.0)	0.042
Lytic bone lesions, n (%)	10 (40.0)	10 (40.0)	1.000
Plasmacytoma, n (%)	8 (32.0)	5 (20.0)	0.333
Serum CTX (ng/mL)			
Baseline	0.45±0.26	0.31±0.35	0.438
6 months	0.34±0.22	0.16±0.09	0.377
12 months	0.29±0.11	0.15±0.07	0.114
MRONJ at 6 months, n (%)	0 (0)	6 (24)	0.009
MRONJ at 12 months, n (%)	0 (0)	5 (20)	0.018

Note: Data are presented as mean±standard deviation or number (percentage). Continuous variables were compared using Student's t test and categorical variables using the chi-square test or Fisher's exact test, as appropriate. Abbreviations: CTX, C-terminal telopeptide; MRONJ, medication-related osteonecrosis of the jaw; SD, standard deviation

When demographic variables were evaluated according to the development of medication-related osteonecrosis of the jaw (MRONJ), no significant difference in age was observed between patients who developed MRONJ and those who did not (**Table 6**). However, all MRONJ cases occurred in male patients, indicating a significant association between male sex and MRONJ development.

Table 6. Demographic Characteristics, Serum CTX Levels, and Clinical Risk Factors According to MRONJ Status

Variable	MRONJ (-) (n=44)	MRONJ (+) (n=6)	p value
Age (years)	59.8±11.3	59.7±12.2	0.991
Sex			
Female, n (%)	19 (43.2)	0 (0)	
Male, n (%)	25 (56.8)	6 (100)	0.041
Serum CTX (ng/mL)			
Baseline	0.58±0.65	0.71±0.32	0.845
6 months	0.26±0.19	0.25±0.22	0.952
12 months	0.22±0.34	0.23±0.16	0.897
Clinical risk factors			
Jaw symptoms, n (%)	10 (21.4)	2 (37.5)	0.568
Dexamethasone use, n (%)	34 (78.6)	3 (50.0)	0.153
Osteoporosis, n (%)	5 (11.4)	2 (33.3)	0.146
Preventive dental evaluation, n (%)	9 (100)	0 (0)	NA

Note: Data are presented as mean±standard deviation or number (percentage). Continuous variables were compared using Student's t test. Categorical variables were compared using the chi-square test or Fisher's exact test when appropriate. Abbreviations: MRONJ, medication-related osteonecrosis of the jaw; CTX, C-terminal telopeptide.

Serum CTX levels were also compared between MRONJ-positive and MRONJ-negative patients at baseline, 6 months, and 12 months (**Table 6**). Although CTX levels tended to be lower in patients who developed MRONJ during follow-up, these differences were not statistically significant.

Clinical risk factors and preventive dental management were further evaluated according to MRONJ status (**Table 6**). Preventive dental evaluation was performed in newly diagnosed patients prior to initiation of bisphosphonate therapy, and no cases of MRONJ were observed in this group. In contrast, MRONJ occurred in 24% of previously treated patients who had not undergone systematic preventive dental assessment. These findings underscore the importance of preventive dental evaluation before initiation of bisphosphonate therapy in reducing the risk of MRONJ.

DISCUSSION

Bisphosphonates, particularly zoledronic acid and pamidronate, remain an essential component of supportive therapy in multiple myeloma by reducing skeletal-related events and improving quality of life (1,2). In the present study, the newly diagnosed and previously diagnosed patient groups were comparable in terms of age, sex distribution, disease stage, and baseline laboratory parameters.

During one year of follow-up, medication-related osteonecrosis of the jaw (MRONJ) was observed in 6 of 50 patients (12%). All cases occurred in the previously diagnosed group receiving long-term intravenous zoledronic acid therapy. Although the same bisphosphonate agent and dosage were used,

the previously diagnosed group had a substantially longer duration of exposure, suggesting that cumulative treatment duration plays a critical role in MRONJ development (3,4).

This observation is consistent with several systematic reviews indicating that cumulative antiresorptive exposure and prolonged treatment duration represent the most important determinants of MRONJ risk in oncology patients (11–15). In our cohort, MRONJ cases occurred in patients with bisphosphonate exposure ranging from 17 to 72 months, supporting the concept that prolonged suppression of bone turnover increases susceptibility to osteonecrosis.

Importantly, no MRONJ cases were detected in the newly diagnosed group despite exposure to the same antiresorptive agent. This difference may be explained not only by the shorter treatment duration but also by the systematic implementation of preventive dental evaluation prior to initiation of bisphosphonate therapy. Patients with potential dental risk factors underwent appropriate dental interventions before treatment initiation and therapy was started only after confirmation of adequate oral healing.

These findings are consistent with the recommendations of the American Association of Oral and Maxillofacial Surgeons (AAOMS), which emphasize the importance of comprehensive dental assessment and elimination of local risk factors prior to antiresorptive therapy (3,4). Invasive dental procedures such as tooth extraction, periodontal disease, and chronic mucosal trauma have been consistently identified as major local triggers for MRONJ development (3,4). A recent systematic review also confirmed that invasive dental procedures significantly increase the risk of MRONJ in cancer patients receiving intravenous bisphosphonates (16).

With regard to systemic risk factors, dexamethasone therapy was widely used in our cohort as part of standard anti-myeloma treatment regimens. Corticosteroids may contribute to MRONJ development through several mechanisms including impaired wound healing, altered immune response, and metabolic disturbances such as hyperglycemia (3,9). Although diabetes prevalence was similar between groups, increased glucose levels observed during follow-up may represent an additional factor influencing tissue repair and infection susceptibility.

All MRONJ cases in this study occurred in male patients. While some studies have reported a higher prevalence of MRONJ in women due to the large number of osteoporotic patients receiving antiresorptive therapy, the predominance of male cases in our cohort likely reflects the epidemiology of multiple myeloma, which is more common in men (9).

Serum C-terminal telopeptide (CTX) has been proposed as a potential biomarker for assessing MRONJ risk (6). In the present study, CTX levels decreased during bisphosphonate therapy, reflecting suppression of bone resorption. Although lower CTX levels were observed in MRONJ-positive patients, the lack of statistical significance and variability in measurement conditions limit its clinical applicability. Therefore, CTX alone does not provide sufficient predictive value for MRONJ risk assessment. These findings support previous systematic reviews and consensus statements reporting that CTX does not provide sufficient predictive accuracy to be used as an independent diagnostic marker for MRONJ risk assessment (3,6,7).

Several limitations of this study should be acknowledged. First, the relatively small sample size and the limited number of MRONJ cases restrict the statistical power of subgroup analyses. Second, the duration of follow-up—particularly in the newly diagnosed group—may not fully reflect the cumulative risk associated with long-term antiresorptive therapy. Third, CTX measurements were not obtained under fully standardized conditions, which may have contributed to measurement variability.

Despite these limitations, the findings of this prospective study emphasize that cumulative bisphosphonate exposure and dental risk factors play a more important role in MRONJ development than biochemical markers alone. Preventive dental evaluation prior to initiation of bisphosphonate therapy therefore appears to be a key strategy for reducing MRONJ risk in patients with multiple myeloma.

CONCLUSION

In this prospective cohort of patients with multiple myeloma receiving intravenous bisphosphonate therapy, medication-related osteonecrosis of the jaw (MRONJ) occurred exclusively in patients with prolonged treatment exposure. No MRONJ cases were observed among newly diagnosed patients who underwent systematic preventive dental evaluation prior to initiation of therapy. Although serum CTX levels tended to be lower in MRONJ-positive patients, CTX alone did not demonstrate sufficient predictive value for clinical risk assessment. These findings support the prioritization of preventive dental management and careful monitoring of cumulative bisphosphonate exposure as key strategies for reducing MRONJ risk in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study did not involve any experimental drugs or interventions outside routine clinical practice. The research was conducted among outpatients followed at the Multiple Myeloma Clinic of the Hematology Department under the institutional



authorization of the hospital, under the supervision of Prof. Dr. Meliha Nalçacı. All procedures were performed in accordance with institutional policies and the ethical standards of the Declaration of Helsinki. As the study was observational in nature and did not include any additional intervention beyond standard care, formal approval from an independent ethics committee was not required.

Informed Consent: Written informed consent was obtained from all patients during routine clinical examinations prior to inclusion in the study.

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Roodman GD. Pathogenesis of myeloma bone disease. *Leukemia*. 2009;23(3):435-41.
2. Terpos E, Morgan G, Dimopoulos MA et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol*. 2013;31(18):2347-57.
3. 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(10):1938-56.
4. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res*. 2015;30(1):3-23.
5. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2007;22(10):1479-91.
6. Marx RE. Oral and intravenous bisphosphonate-induced osteonecrosis of the jaws: history, etiology, prevention, and treatment. *J Oral Maxillofac Surg*. 2007;65(12):2397-410.
7. Bagan JV, Jiménez Y, Murillo J, et al. Serum CTX as a predictor of risk for medication-related osteonecrosis of the jaw. *J Oral Maxillofac Surg*. 2016;74(6):1079-1084.
8. Dimopoulos MA, Kastritis E, Bamia C, et al. Reduction of osteonecrosis of the jaw after implementation of preventive dental measures in patients with multiple myeloma treated with bisphosphonates. *Ann Oncol*. 2009;20(1):117-20.
9. Yamazaki T, Yamori M, Ishizaki T et al. Increased incidence of medication-related osteonecrosis of the jaw after tooth extraction in cancer patients receiving intravenous bisphosphonates. *J Bone Miner Metab*. 2012;30(5):534-40.
10. Nicolatou-Galitis O, Schiodt M, Mendes RA, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2019;127(2):117-35.
11. Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three pivotal trials of zoledronic acid. *Ann Oncol*. 2012;23(5):1341-7.
12. Khan AA, Morrison A, Cheung AM, et al. Osteonecrosis of the jaw associated with antiresorptive agents: a systematic review. *J Clin Endocrinol Metab*. 2017;102(5):1413-22.
13. Yarom N, Shapiro CL, Peterson DE, et al. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO clinical practice guideline. *J Clin Oncol*. 2019;37(25):2270-90.
14. Hasegawa T, Kawakita A, Ueda N, et al. Risk factors associated with medication-related osteonecrosis of the jaw in cancer patients. *J Bone Miner Metab*. 2020;38(3):409-18.
15. Bedogni A, Fusco V, Agrillo A, et al. Learning from experience: prevention and management of MRONJ. *Oral Dis*. 2012;18(8):770-7.
16. Di Fede O, Panzarella V, Mauceri R, et al. The dental management of patients at risk of medication-related osteonecrosis of the jaw. *Int J Environ Res Public Health*. 2023;20(5):3847.