



The effect of drug holiday before tooth extraction on the development of medication-related osteonecrosis of the jaw in cancer patients receiving intravenous bisphosphonates

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Abstract (J Korean Assoc Oral Maxillofac Surg 2023;49:68-74)

Objectives: Drug holidays are suggested to reduce the formation of osteonecrosis in patients under intravenous (IV) bisphosphonates (BPs) therapy. The objectives of this study are to evaluate the incidence of medication-related osteonecrosis of the jaw (MRONJ) following tooth extraction in cancer patients using IV BP, and to assess the effect of drug holiday on the development of MRONJ.

Patients and Methods: A manual search of the patient folders of Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Hacettepe University was undertaken to identify cancer patients who used IV BPs and had at least one tooth extraction between 2012 and 2022. Patients' age, sex, systemic condition, the type of BP used, duration of BP used, number of tooth extraction, duration of drug holiday, localization of tooth extraction and incidence of MRONJ were recorded.

Results: One hundred nine teeth were removed from 57 jaws in 51 patients. All tooth extractions were performed under perioperative antibiotic prophylaxis and with primary wound closure. The incidence of MRONJ was 5.3%. Stage 1 MRONJ developed in 3 patients (only one had a drug holiday). The median duration of drug holiday was 2 months. No significant difference between the patients with and without a drug holiday and MRONJ development was found ($P=0.315$). The mean age of patients developed MRONJ was 40.33 ± 8.08 years. A statistically significant difference was found between age and MRONJ development ($P=0.002$).

Conclusion: The effect of a short-term drug holiday on the development of MRONJ may be limited because BPs remain in bone tissue for a long time. Drug holidays should be applied with the approval of an oncologist with other preventive measurements.

Key words: Bisphosphonate, Bisphosphonate-associated osteonecrosis of the jaw, Cessation of treatment, Osteonecrosis, Tooth extraction

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I. Introduction

Bisphosphonates (BPs) have antiresorptive, antiangiogenic and antitumoral effects and have been widely used to manage osteoporosis, metastatic bone diseases and lytic lesions in multiple myeloma¹⁻⁴. From the first use of BPs to date, many adverse effects such as acute inflammatory reactions, ocular, renal and nephrotic problems, electrolyte imbalance,

osteonecrosis of the jaws and atypical femoral fracture have been reported, especially following the long-term use of these drugs^{5,6}. BP-related osteonecrosis of the jaw (BRONJ) is a common published adverse event that decreases the quality of life. The American Association of Oral and Maxillofacial Surgeons (AAOMS) changed the nomenclature of BRONJ after the increase in osteonecrosis cases due to the other antiresorptive and antiangiogenic drugs and recommended use of the term medication-related osteonecrosis of the jaw (MRONJ)⁷.

The pathogenesis of MRONJ depends on a multifactorial process, including suppression of bone remodeling, inhibition of angiogenesis, local trauma, and infection, so the incidence of MRONJ is significantly variable by country⁸. The incidence is higher in cancer patients administered intravenous (IV) zoledronate and was reported to be between 0.3% and 5% in a recent systematic review⁹. Moreover, the updated

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AAOMS guideline reported that the incidence of MRONJ may increase up to 18% among cancer patients¹⁰. The higher incidence is associated with higher bone affinity⁵, potency¹¹, and cumulative dose of zoledronate in cancer patients. In a clinical study, the mean IV BP injections per year was found to be almost four times higher in cancer patients compared to osteoporotic patients, revealing that the cumulative dose is higher in cancer patients¹². In addition, the use of additional immunosuppressive drugs such as corticosteroids in cancer patients increases the risk of developing MRONJ by affecting wound healing^{12,13}. However, MRONJ does not develop in every cancer patient using IV BPs. When Marx first reported BP-related osteonecrosis in the jaw, it was stated that most cases developed after the removal of painful teeth¹⁴. The current studies have also emphasized that leaving an infected tooth in the oral cavity for a long time rather than extracting it induces the development of MRONJ^{8,14,15}.

Some preventive treatment strategies have been recommended to minimize the risk of developing MRONJ following tooth extraction since tooth extraction can be sometimes necessary in patients receiving IV BPs. Antibiotic prophylaxis, atraumatic dental extraction, removal of bony edges, and primary closure are the most common methods that are routinely performed as preventive approaches. Drug holidays are controversial according to the current guideline¹⁰ but are still recommended to reduce the incidence of MRONJ in various studies. The concept of a drug holiday is based on the decrease in serum level of free BP and, accordingly, its effect on wound healing after BP cessation. The objective of this study is to evaluate the incidence of MRONJ after tooth extraction in cancer patients using IV BP and to assess the effect of drug holiday on the development of MRONJ. The hypothesis is that drug holiday does not affect the incidence of MRONJ in cancer patients receiving IV BP.

II. Patients and Methods

This retrospective study was conducted in the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry at Hacettepe University and approved by the Ethics Committee of Hacettepe University (No. GO 22/605). Informed consent was obtained from all participants.

A search of the database was undertaken to identify patients who applied for tooth extraction and had a history of IV BP use between January 2012 and June 2022. Patients receiving radiotherapy from the head and neck region, significant malignancy and/or metastasis to the jaws and receiving oral BPs and denosumab were excluded from the study. Fifty-one cancer patients over 18 years old using IV BPs were included in this study. The detailed demographic data including age, sex, primary disease, presence of diabetes, use of corticosteroid or other immunosuppressive drugs, IV BP type, duration of BP use, duration of drug holiday, number of extracted teeth and extraction area, whether MRONJ developed after tooth extraction and follow-up duration were recorded.

All tooth extractions were performed with an atraumatic extraction technique under local anesthesia. Perioperative antibiotic prophylaxis (Amoxicillin clavulanic acid, 1 g, 2×1; if the patient is allergic to penicillin, clindamycin 150 mg, 4×1) was administered to all patients, starting 2 days before the procedure and continuing for 3 days postoperatively. Primary wound closure was provided using a resorbable suture in all extraction areas. Sutures were removed 7-10 days later following tooth extraction. Patients were followed for at least 8 weeks postoperatively to assess whether MRONJ developed after tooth extraction. The diagnosis of MRONJ was determined according to the criteria of the AAOMS⁷ and the necrotic bone was confirmed by histopathological examination. (Table 1)

The statistical analysis was accomplished using IBM SPSS

Table 1. Tooth extraction protocol for patients using intravenous bisphosphonates

Full medical and dental history
<ul style="list-style-type: none"> • Consultation phase • Pre-extraction phase: Oral amoxicillin and clavulanic acid (1,000 mg, 2×1) 2 days preoperatively. If allergic to penicillin, use clindamycin (150 mg, 4×1). • Extraction phase: Atraumatic extraction with primary wound closure. • Postoperative phase: Keep on antibiotic therapy for 3 days, anti-inflammatory drug and chlorhexidine gluconate (0.12%) mouthwash 3 times daily for 7 days postoperatively. • Follow-up period: Remove the sutures on day 10 and follow-up at 8 weeks postoperatively. • Diagnosis of MRONJ: AAOMS criteria and histopathological examination.

(MRONJ: medication-related osteonecrosis of the jaw, AAOMS: American Association of Oral and Maxillofacial Surgeons)

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Statistics (ver. 24.0; IBM) in the Department of Biostatistics at Hacettepe University. Descriptive statistics were used to express the medians, the minimum and maximum values and percentage distributions in the groups. The quantitative differences between the test group and the control group were analyzed using Mann-Whitney U test; the qualitative differences between the test group and the control group were examined using Fischer's exact chi-square test. The level of significance was set at $P < 0.05$.

III. Results

Fifty-seven jaws in fifty-one (37 female and 14 male) patients who ranged in age from 33 to 74 years (mean age, 57.21 ± 10.21 years) were evaluated in this study. Stage 1 MRONJ developed in 3 patients. The incidence of MRONJ was 5.3% in 57 jaws. The mean age of patients who developed MRONJ was 40.33 ± 8.08 years. A statistically significant difference was found between patient age and MRONJ development ($P = 0.002$). MRONJ developed in 4.8% of all female patients and 6.7% of male patients ($P > 0.999$).

Breast cancer (CA) was the most common primary disease (49.1%), followed by multiple myeloma (21.1%) and prostate CA (10.5%). The distribution of the diseases that resulted in IV BP use is presented in Fig. 1. The median duration of IV BP use was 24 months (range, 3-96 months) in all patients. While 61.4% of all patients were using IV BP for ≥ 24 months, the remaining 38.6% were using IV BP for < 24 months. MRONJ was detected in 2 of the patients who used IV BP for < 24 months and one patient who used IV BP for ≥ 24 months. No statistical difference was found between the duration of IV BP use and development of

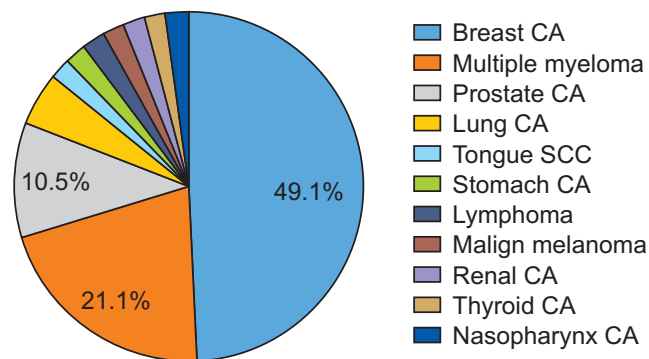


Fig. 1. The distribution of the diseases shows that the most common reason resulted in intravenous bisphosphonate use was breast CA. (CA: cancer, SCC: squamous cell carcinoma)
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MRONJ ($P = 0.553$). Zoledronate was the most widely used IV BP (96.1%), followed by ibandronate (3.9%). However, there was no statistical difference between IV BP type and MRONJ development ($P > 0.999$).

One hundred nine teeth were removed in 51 patients (33.3% of all patients from only the maxilla, 54.9% of them from only the mandible, and 11.7% from both maxilla and mandible). Multiple tooth extractions were performed in 47.1% of all patients, and only one tooth was removed in 52.9% of all patients. The median number of tooth extractions in patients who developed MRONJ was one tooth (minimum 1-maximum 1 tooth extraction), and in those who did not develop MRONJ it was 2 teeth (minimum 1-maximum 10 teeth extraction). No statistical difference was found between the number of teeth extracted and development of MRONJ ($P = 0.117$). Tooth extractions were performed in 31 patients after a drug holiday, while in 20 patients, they were performed without a drug holiday.

The median duration of drug holiday was 2 months (range, 0-96 months) in all patients. While 59.1% of the patients who used IV BP for < 24 months had a drug holiday, 65.7%

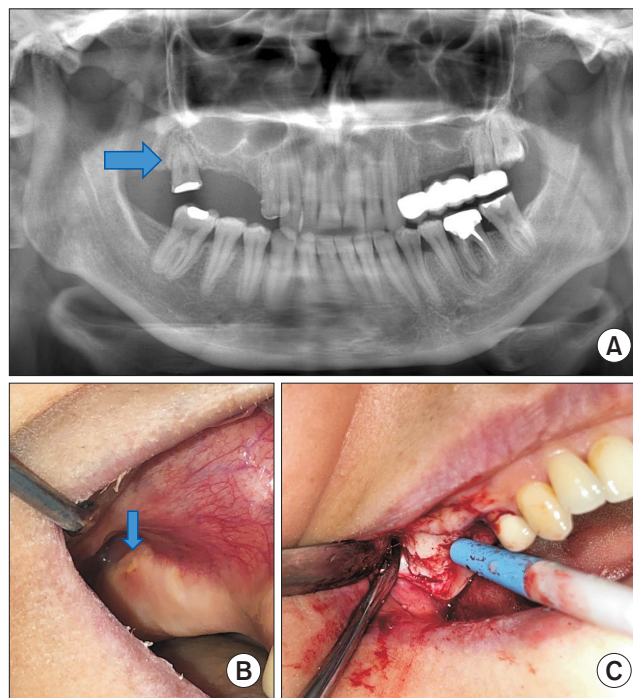


Fig. 2. A. The preoperative panoramic radiograph shows the extracted third molar in the right maxilla (arrow). B. The exposed necrotic bone was determined on the buccal aspect 1 year after tooth extraction (arrow). C. Surgical treatment was performed to remove the necrotic bone and bony edges.
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Table 2. Characteristic of the patients developed MRONJ

Patient No.	Sex	Age (yr)	Primary disease	Type of BP	Use of duration (mo)	Frequency	Drug holiday	Additional immunosuppressive	Extraction area
1	F	33	Breast CA	Zoledronate	24	Monthly	None	None	Maxilla
2	M	49	Multiple myeloma	Zoledronate	6	Monthly	None	Dexamethasone and Bortezomib	Mandible
3	F	39	Breast CA	Zoledronate	19	Once every 3 mo	2 mo	Ribociclib (kinase inhibitor)	Maxilla

(MRONJ: medication-related osteonecrosis of the jaw, F: female, M: male, CA: cancer, BP: bisphosphonate)

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of those who used IV BP for ≥ 24 months had a drug holiday. There was no statistically significant difference between the duration of IV BP use and drug holiday ($P=0.614$). Only one of the 3 patients who developed MRONJ had a drug holiday for 2 months. This patient had used IV BP for <24 months, and MRONJ developed 1 year after right maxillary third molar extraction (Fig. 2). Among these 3 patients, no significant difference between the patients with and without a drug holiday and MRONJ development was found ($P=0.315$). Also, 50% of the patients without a drug holiday developed MRONJ in the maxilla. There was no statistical significance between drug holiday and MRONJ localization ($P>0.999$). Table 2 shows the characteristics of the patients who developed MRONJ. In all MRONJ patients, surgical treatment was performed to remove the necrotic bone areas, and complete healing was achieved after the surgical treatments.

IV. Discussion

Osteonecrosis is defined as the death of bone cells and is histopathologically diagnosed as empty lacunae without osteocytes in the bone. BPs cause osteoclast-mediated bone necrosis that is identified by tissue dehiscence, hypocellularity, hypovascularity, and lytic radiographic features¹⁶. In clinical practice, various preventive measures are implemented to reduce the risk of MRONJ. One of them is drug holiday, although there is limited data on the effectiveness and appropriate duration. Theoretically, the cessation of BP is supposed to enhance osteoclast function, bone remodeling and bone healing^{5,17}. Damm and Jones¹⁸ suggested that a 2-month drug holiday before an invasive dental procedure would be sufficient to reduce the level of free oral BP within the serum. However, pharmacological differences among most oral and IV BPs cause them to be metabolized by various pathways of the drug¹⁹, and the half-life of each BP is thought to change due to the pathway. In addition, BPs bind to mineral surfaces

of bone, and their affinity levels to bone are different from each other. It is thought that when BPs release during bone resorption, they recirculate and bind again to the bone, or they are internalized by osteoclasts, causing apoptosis of osteoclasts⁵. Thus, they maintain their biological effects for a long time.

In animal studies, the importance of drug holidays has been revealed to reduce the risk of developing MRONJ^{17,20}. Although the philosophy of drug holidays is correct, it is still controversial in clinical practice whether or for how long a drug holiday will be implemented due to the mechanisms of BPs. In a multicenter retrospective study, the efficacy of drug holiday and primary wound closure on the development of MRONJ was investigated in patients using oral BPs. The duration of the holiday in the patients included in the study varied from 1 to 246 months. The results revealed that there was no association between drug holiday and development of MRONJ; also, MRONJ did not develop in patients who performed primary wound closure after tooth extraction²¹. In a different clinical study, the incidence of MRONJ in patients who used IV BP was found to be 13.1% after tooth extraction. The duration of the drug holiday ranged from 1 to 63 months (mean, 17.6 months). The authors reported that the percentage of MRONJ was superior to patients undergoing IV BP than in those who had a drug holiday or completed their IV BP therapy. However, they did not find any statistical significance between the two groups²².

In our study, cancer patients using IV BPs were evaluated to determine the incidence of MRONJ and the efficacy of a drug holiday. The incidence of MRONJ was found to be 5.9% in all patients. The duration of IV BP use is accepted as a risk factor for development of MRONJ and it is stated that the duration of IV BP use for more than 2 years increases the risk of MRONJ development^{7,10}. Therefore, the patients were divided into two groups according to their IV BP use duration in our study. Although 61.4% of all patients were using IV BPs

for ≥ 24 months, no statistical difference was found between the duration of IV BP use and development of MRONJ. The duration of drug holiday varied between 1 and 96 months and no significant difference was found between drug holiday and wound healing. In our study, 1 of 3 patients who developed MRONJ had a drug holiday, but this period was only 2 months. In addition, the regimen of IV BP was administered once every 3 months for 48 months in this patient. The tooth extraction was performed 2 months after the last dose of BP administration and the patient restarted the drug schedule 1 month after complete mucosal healing was detected. However, exposed necrotic bone was found in the right maxillary buccal area 1 year after tooth extraction, and Stage 1 MRONJ was diagnosed following clinical and radiological examination. Jung et al.¹² evaluated 1,569 patients with MRONJ to determine the contributory risk factors to formation of MRONJ. As a result, they stated that MRONJ occurred most commonly within 2-3 years after the discontinuation of BPs, and even 4 years later, there were patients who developed MRONJ¹². The current opinion regarding drug holidays for patients before invasive dental procedures is that a short-term drug holiday does not have a positive effect on the treatment results^{12,23,24}. Black et al.²⁵ compared the bone mineral density in osteoporotic patients using zoledronate for 9 years to those with a 3-year drug holiday after using zoledronate for 6 years in a multicenter, randomized, double-blind study. They suggested that patients who used zoledronate annually for 6 years can have a drug holiday for up to 3 years with similar benefits²⁵. Similarly, Adler et al.²⁶ recommended 2-3 years of drug cessation following 3-5 years of BP therapy for osteoporotic women that were not at high fracture risk. It is clearly understood that the long-term use of BPs can preserve their effectiveness for a long period. The AAOMS guideline has emphasized the importance of awareness and maintenance of oral hygiene in patients using IV BPs and reported that drug holidays are still controversial. For this reason, it is recommended to avoid invasive dental procedures if possible and consider root retention techniques rather than tooth extraction¹⁰. A different position paper suggested a drug holiday following 1-2 years of BP therapy in multiple myeloma patients with a low risk of skeletal-related events²⁷. However, BPs not only have antiresorptive effects but also have antiangiogenic activity and inhibition of proliferation and migration of epithelial cells. For this reason, although its effect on bone tissue lasts for a long time, it is believed that a drug holiday increases the healing capacity of the overlying mucosa^{21,28}. In our study, tooth extractions were performed in 2 patients

who developed MRONJ without a drug holiday. One of them was also using bortezomib, an antiangiogenic drug, and dexamethasone, which affects wound healing. The use of additional immunosuppressive drugs with BPs is a strong risk factor for development of MRONJ. Therefore, it is difficult to say that the development of MRONJ in this patient was caused by the use of BP alone.

Invasive dental procedures are sometimes inevitable in cancer patients using IV BPs despite the importance of oral hygiene maintenance. As a consequence, all preventive measures should be taken to decrease the risk of developing MRONJ in these patients. The drug holiday can be challenging in patients with progressing bone metastases; therefore, it should be taken into consideration for patients whose cancer progresses relatively slowly and whose general condition is better with the approval of an oncologist. The tooth extraction protocol was standardized for each patient included in this study, but the cumulative dose of BPs and additional immunosuppressive drugs taken by the patients and the duration of the drug holiday differed from each other. The other limitation of this study is the small number of participants. Standardized multicenter clinical studies with a large sample size are needed to confirm the efficacy of drug holidays because the drug-related risk factors are important in the development of MRONJ.

V. Conclusion

Invasive dental procedures are sometimes inevitable in cancer patients using IV BPs despite the importance of oral hygiene maintenance. As a consequence, all preventive measures should be taken to reduce the risk of developing MRONJ in these patients. The long duration of action of BPs may not be effective on bone healing during a short-term drug holiday. However, drug holidays may be a precaution especially in mucosal healing and may be considered for patients receiving IV BPs with the approval of an oncologist.

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Authors' Contributions

G.T.Y., S.A., and E.U. participated in data collection. Ç.K. and G.T.Y. participated in the study design. Ç.K. wrote the manuscript. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

This study approved by the Ethics Committee of Hacettepe University (No. GO 22/605). Informed consent was obtained from all participants.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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