Importance of Professional Oral Hygiene in Preventing Medication-related Osteonecrosis of the Jaw

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Abstract

It has been reported that bisphosphonate treatment induces medication-related osteonecrosis of the jaw (MRONJ). Although dental extraction, periodontal disease and systemic disease are noted as risk factors for MRONJ, there are few reports examining the relationship between oral hygiene and MRONJ. The purpose of this retrospective study was to determine risk factors for MRONJ occurrence, and to assess whether MRONJ occurrence is suppressed by professional oral hygiene management or not.

The participants were patients undergoing zoledronate treatment. Dental examination was undertaken by dentists or dental hygienists every six months during the consultation period. The participants were divided into intervention and non-intervention groups. The former underwent professional oral hygiene management by a dental hygienist every three or four weeks, whereas the latter group did not desire professional oral hygiene management.

Two participants in the intervention group (n=40) and four participants in the non-intervention group (n=11) developed MRONJ. The incidence of MRONJ was significantly reduced in the intervention group when compared with the non-intervention group (p = 0.015). The onset of MRONJ in the intervention group was significantly prolonged (p = 0.003). In addition, proportional hazards analysis indicated that the only significant factor in the development of MRONJ was the delivery of oral hygiene management (p<0.05), and the hazard ratio was 0.109.

It is suggested that oral hygiene management suppressed the development of MRONJ. There is a possibility that MRONJ could be suppressed by regular oral hygiene management performed by a dental hygienist.

Keywords: bisphosphonate, MRONJ, oral hygiene, risk factor

Introduction

Bisphosphonates (BPs) are widely used in the treatment of osteoporosis and malignant tumors with bone metastasis as a first-choice medicine. Furthermore, BPs are effective in managing hypercalcemia secondary to malignancy and multiple myeloma. However, intractable necrosis of the jaw was reported as an adverse effect after BP treatment (1–6), and this was subsequently termed bisphosphonate-related osteonecrosis of the jaw (BRONJ). A position paper was then released by the American Association of Oral and Maxillofacial Surgeons, which described the definition, diagnosis and risk factors of BRONJ (1). This position paper was further updated in 2014, whereby the term medication-related osteonecrosis of the jaw (MRONJ) was recommended in place of BRONJ (2).

The occurrence of MRONJ is higher with intravenous than oral administration of BPs. The average period of onset
of MRONJ by intravenous zoledronate, which is most potent BP, is between 12 and 18 months (3,4). Because oral mucosal infection spreads easily to the jaws (5), delayed healing following dental extraction may contribute to the occurrence of MRONJ (6). In addition, periodontal disease, systemic disease, lifestyle factors, medications and poor oral hygiene have also been noted as possible risk factors for the development of MRONJ (7–12). In a previous study, 84% of MRONJ patients demonstrated periodontal disease (13); therefore, we hypothesized that professional oral hygiene management may be suppressed MRONJ. However, there are few intervention studies examining the relationship between professional oral hygiene and MRONJ (13,14).

The purpose of this study was to determine risk factors for the development of MRONJ, and to assess whether MRONJ occurrence is suppressed by professional oral hygiene management in zoledronate treatment patients.

Materials and Methods

Participants

A total of 108 patients (33 men, 75 women, 62.0 ± 11.7 years old) were referred to our dental department from the breast surgery, gynecology, urology, hematology, otolaryngology and respiratory surgery departments of Kansai Rosai Hospital in Japan, from April 2007 to March 2012, before starting intravenous zoledronate treatment. The exclusion criteria were as follows; patients who used other BPs concomitantly, participants who dropped out within the first six months, and edentulous patients. The maximum follow-up duration was set at 24 months.

Study protocol

This study was performed retrospectively. The data recorded at the first visit were as follows: age, sex, systemic disease, medications, smoking habits, body mass index, menstruation status and the primary carcinoma site. Dental examination was carried out by a dentist every six months. The following factors were evaluated: number of teeth, probing pocket depths (P PDs), bleeding on probing ( BOP), history of dental extraction before and during zoledronate treatment, total dose of zoledronate, and the presence and stage of MRONJ. Teeth with PPDs greater than 4 mm were regarded as having deep periodontal pockets (deep PDs). MRONJ was diagnosed by a dentist according to the definition of MRONJ (2). If required, dental extractions and adjustment of participants’ removable partial dentures were undertaken before the commencement of zoledronate treatment. The number of days between the extractions and initiation of zoledronate treatment was also recorded.

At the first visit, all participants were divided into two groups: the intervention group, who received professional oral hygiene management by a dental hygienist every three or four weeks; and the non-intervention group, who did not wish to undergo professional oral hygiene management. In the latter group, only a dental examination was performed by a dentist every six months. In the intervention group, toothbrushing instructions and professional teeth cleaning including dental scaling and polishing and periodontal cleaning were performed by dental hygienists every three or four weeks. The participants in the intervention group were also asked to check the status of their teeth, gingiva and tongue with their hand mirror at least once a day, to lift up their motivation for oral hygiene management and to improve their brushing technique. If the participants in the intervention group complained of floating feeling of the teeth and/or bleeding while brushing, and if the dental hygienist observed gingival inflammation and/or mobility of the teeth, professional management was recommended under the instruction of a dentist. Scaling, root planing and curettage of the periodontal pockets were only performed at the first visit, as these treatments were invasive. If periodontal treatment was needed, scaling was performed only in areas that did not require infiltration anesthesia.

The Ethics Committee of the Kansai Rosai Hospital approved all study protocols (22/10/2012).

Statistical analysis

The relationship between oral hygiene management and MRONJ was examined using the chi-square test, and the relationship between the period of MRONJ onset and oral hygiene management was assessed by log-rank test. In addition, proportional hazards analysis was conducted to examine for factors influencing the development of MRONJ, using a stepwise method. The variables showing univariate association in the chi-square test and Mann–Whitney U test (p<0.25) were used as explanatory variables.

All analyses were performed using the SPSS version 16.0 statistical software (SPSS, Tokyo, IBM, JAPAN). Statistical significance was set at p<0.05.
Results

Participants

Of 108 patients, 51 (11 men, 40 women; average age: 60.1 ± 12.1 years old) were participated in this study. The reasons for exclusion of patients were as follows: concomitant use of other BPs (n=3), failure to attend the 6-month evaluation (n=20), edentulism (n=5), transfer to a different hospital (n=4), death (n=12), non-delivery of BPs despite BP treatment being planned at the time of reference (n=5) and the desire to switch to the intervention group from the non-intervention group (n=8).

Thirty two out of 51 participants expired 24 months during this survey period, however, only 19 out of 32 participants completed all evaluations. Out of the other 13 participants, eight died, four were transferred to another hospital, and one dropped out from the study.

Zoledronate was administered to the participants to treat bone metastases (n=50) and hypercalcemia (n=1). The most prevalent primary carcinoma sites were the mammary gland (n=27; 67.5%) and the digestive organs (n=4; 10.0%) in the intervention group, and the mammary gland (n=5; 45.5%), digestive organs (n=3; 27.3%) and prostate (n=3; 27.3%) in the non-intervention group (Table 1).

The systemic diseases noted in the intervention group were diabetes mellitus (n=3; 7.5%), osteoporosis (n=2; 5.0%) and hypertension (n=1; 2.5%), and in the non-intervention group only diabetes mellitus (9.1%) was noted. Thirty-seven (92.5%) and 11 (100.0%) participants took anti-cancer drugs in the intervention and non-intervention groups, respectively (Table 1). There were no significant differences between the two groups for the items shown in Table 1.

Baseline oral status

Oral status of the participants before zoledronate administration is shown in Table 2. The number of teeth with deep PDs was 7.4 ± 6.8 and 3.2 ± 3.8 in the intervention and non-intervention groups, respectively (p = 0.046). The number of participants who underwent dental extraction before the administration of zoledronate was 11 and four in the intervention and non-intervention groups, respectively. There was no significant difference between the two groups for the items shown in Table 2, except for teeth with deep PDs.

MRONJ and oral hygiene management

Two participants in the intervention group and four participants in the non-intervention group developed MRONJ (Table 3). The rate of occurrence of MRONJ was significantly reduced in the intervention group when compared with the non-intervention group (p=0.015). The onset of MRONJ in the intervention group was significantly prolonged when compared with the non-intervention group by log-rank test (p=0.003, Fig. 1). The onset of MRONJ occurred after 18 months following the delivery of zoledronate in the intervention group, compared with 6 months in the non-intervention group. Moreover, in the intervention group, stages 0 (n=1) and 1 (n=1) of MRONJ were seen, whereas in the non-intervention group, stages 2 (n=3) and 3 (n=1) of MRONJ were observed.

Two of 15 participants who underwent dental extraction before starting zoledronate treatment developed MRONJ. Both participants were in the non-intervention group and the number of days between dental extraction and the initiation of zoledronate treatment was 21 and 28 days.

Risk factors for the development of MRONJ

To investigate the factors related to the development of MRONJ, univariate analysis was conducted (Table 4). Only professional oral hygiene management was a significant factor for the development of MRONJ. Proportional hazards analysis was performed to consider the duration of onset of MRONJ. The factors from the univariate analysis where the p-value was greater than 0.25 were used as independent variables, i.e.: sex, smoking, professional oral hygiene management, number of days between dental extraction and zoledronate administration, and the number of teeth with deep PPDs or BOP at 6-month evaluation. As a result, professional oral hygiene management was the only significant factor in the development of MRONJ (p<0.05), and the hazard ratio was 0.109 (Table 5). The model chi-square test was statistically significant (p<0.001).

Discussion

It has been suggested that the onset of MRONJ may be affected by oral hygiene management (15,16). However, there are few reports investigating the effect of oral hygiene intervention on the risk of MRONJ (17). The current results also suggested that professional oral hygiene management in the intervention group suppressed the development of MRONJ when compared with the non-intervention group.
## Table 1. Participant characteristics

| Characteristic                  | Intervention group | Non-intervention group |
|---------------------------------|--------------------|------------------------|
| Number of participants          |                    |                        |
| Male                            | 7 (17.5)           | 4 (36.4)               |
| Female                          | 33 (82.5)          | 7 (63.6)               |
| Average age                     |                    |                        |
|                                 | 61.0 ± 12.0        | 60.0 ± 11.6            |
| Reason for BP treatment         |                    |                        |
| Bone metastasis                 | 39 (97.5)          | 11 (100.0)             |
| Hypercalcemia                   | 1 (2.5)            | 0 (0.0)                |
| Primary carcinoma site          |                    |                        |
| Mammary gland                   | 27 (67.5)          | 5 (45.5)               |
| Digestive organs                | 4 (10.0)           | 3 (27.3)               |
| Prostate                        | 2 (5.0)            | 3 (27.3)               |
| Lung                            | 2 (5.0)            | 0 (0.0)                |
| Ovary                           | 2 (5.0)            | 0 (0.0)                |
| Uterus                          | 2 (5.0)            | 0 (0.0)                |
| Pharynx                         | 1 (2.5)            | 0 (0.0)                |
| Systemic disease                |                    |                        |
| No systemic disease             | 34 (85.0)          | 10 (90.9)              |
| Hypertension                    | 1 (2.5)            | 0 (0.0)                |
| Diabetes mellitus               | 3 (7.5)            | 1 (9.1)                |
| Osteoporosis                    | 2 (5.0)            | 0 (0.0)                |
| Medication                      |                    |                        |
| No medication                   | 1 (2.5)            | 0 (0.0)                |
| Anticancer drugs                | 37 (92.5)          | 11 (100.0)             |
| Hormone drugs                   | 2 (5.0)            | 0 (0.0)                |
| Smoking                         |                    |                        |
| No                              | 35 (87.5)          | 9 (81.8)               |
| Yes                             | 5 (12.5)           | 2 (18.2)               |
| Menstruation (n=40)             |                    |                        |
| Yes                             | 11 (27.5)          | 2 (18.2)               |
| No                              | 22 (55.0)          | 5 (45.5)               |
| Obesity                         |                    |                        |
| BMI < 25                        | 29 (72.5)          | 11 (100.0)             |
| BMI ≥ 25                        | 11 (27.5)          | 0 (0.0)                |
and poor oral hygiene may be a risk factor for MRONJ. The possibility was also suggested that oral hygiene management by a dental hygienist may suppress MRONJ. In other words, intervention by a dental hygienist may be important for patients undergoing zoledronate treatment.

It has been reported that the main risk factors for MRONJ, aside from periodontal disease, are dental extraction, a high BP dose (9,18), prolonged duration of BP administration (9) and denture use (18). In our study, we could not investigate whether dental extraction is a risk factor or not, because none of the participants received dental extractions during zoledronate treatment. For the number of days between dental extraction and commencement of zoledronate treatment, the duration was longer in the non-intervention group than the intervention group. However, two out of the three participants who underwent dental extraction developed MRONJ in the non-intervention group, whereas none developed MRONJ in the intervention group. A Japanese position paper on MRONJ recommended that BP treatment should be commenced at least 2–3 weeks after dental extraction (16). In our study, the dental extractions were performed 21 and 28 days before the initiation of BP treatment in the two participants who developed MRONJ, and this followed the recommended

Table 2. Oral status before zoledronate administration

|                               | Intervention group | Non-intervention group | P-value | Statistical analysis |
|-------------------------------|--------------------|------------------------|---------|----------------------|
|                               | n=40               | n=11                   |         |                      |
| Number of teeth               | 24.2 ± 4.4         | 22.6 ± 8.0             | 0.873   | a                    |
| Number of participants who underwent dental extraction before ZOL administration | 11 | 4 | 0.234 | b |
| Number of teeth extracted before ZOL administration | 0.87 ± 1.6 | 0.09 ± 0.3 | 0.528 | a |
| Days between dental extraction and ZOL administration | 17.4 ± 5.4 | 21.0 ± 7.0 | 0.080 | a |
| Number of teeth with deep periodontal pockets | 7.4 ± 6.8 | 3.2 ± 3.8 | 0.046 | a |
| Number of teeth with BOP       | 8.1 ± 7.2          | 3.6 ± 5.7              | 0.724   | a                    |
| Number of participants wearing dentures | 12 | 2 | 0.439 | b |

ZOL: zoledronate

a: Mann–Whitney U test

b: chi-square test

Table 3. Professional oral hygiene management and MRONJ

| Oral hygiene management | MRONJ (%) | Total (%) |
|-------------------------|-----------|-----------|
|                         | No        | Yes       |          |
| Intervention group      | 38 (95.0) | 2 (5.0)   | 40 (100.0)|
| Non-intervention group  | 7 (63.6)  | 4 (36.4)  | 11 (100.0)|

p = 0.015 (chi-square test)

Fig. 1. Onset of MRONJ and professional oral hygiene management
Table 4. Factors related to the development of MRONJ (univariate analysis)

|                                    | Non-MRONJ | MRONJ | P-value | Statistical analysis |
|------------------------------------|-----------|-------|---------|-----------------------|
|                                    | n=45      | n=6   |         |                       |
| Sex (male)                         | 8         | 3     | 0.106   | b                     |
| Age (median)                       | 62        | 65    | 0.763   | a                     |
| Primary carcinoma site             |           |       | 0.784   | b                     |
| Mammary gland                      | 29        | 3     |         |                       |
| Digestive organs                   | 7         | 0     |         |                       |
| Prostate                           | 2         | 3     |         |                       |
| Lung                               | 2         | 0     |         |                       |
| Ovary                              | 2         | 0     |         |                       |
| Uterus                             | 2         | 0     |         |                       |
| Pharynx                            | 1         | 0     |         |                       |
| Anticancer drugs                   | 43        | 6     | 0.776   | b                     |
| Smoking                            | 5         | 2     | 0.186   | b                     |
| BMI > 25                           | 10        | 1     | 0.615   | b                     |
| Menstruation (n=40)                | 12        | 1     | 0.704   | b                     |
| Denture use                        | 12        | 2     | 0.433   | b                     |
| Oral hygiene management (intervention group) | 38     | 2     | 0.015   | b                     |
| Number of teeth present before ZOL administration (median) | 25 | 2 | 0.873 | a |
| Number of teeth extracted before ZOL administration (median) | 0 | 0 | 0.528 | a |
| Number of days between dental extraction and ZOL administration (median) | 14 | 24.5 | 0.124 | a |
| Number of teeth with deep periodontal pockets before ZOL administration (median) | 4 | 8 | 0.268 | a |
| Number of teeth with BOP before ZOL administration (median) | 5 | 7 | 0.724 | a |
| Number of teeth present after 6 months (median) | 25 | 24 | 0.988 | a |
| Number of teeth with deep periodontal pockets after 6 months (median) | 3 | 7 | 0.220 | a |
| Number of teeth with BOP after 6 months (median) | 2 | 8 | 0.158 | a |
| ZOL dose for first 6 months (mg) (median) | 24 | 24 | 0.504 | a |

a: Mann-Whitney U test  
b: chi-square test  
BMI: body mass index  
ZOL: zoledronate
Table 5. Factors related to the development of MRONJ (proportional hazards analysis)

| Oral hygiene management | P-value | Exp (B) | 95% Confidence interval |
|-------------------------|---------|---------|------------------------|
|                         | 0.011   | 0.109   | 0.020 - 0.599          |

timeframe. In addition, epithelialization of the extraction sockets was confirmed by a dentist prior to commencement of zoledronate treatment. These cases may suggest that dental extraction before zoledronate treatment was not a significant factor in the development of MRONJ.

The dosage of zoledronate was not a significant risk factor for MRONJ in our study, because approximately the same dose was delivered to all participants. Similarly, denture use was not a significant factor. In the present study, denture adjustment was undertaken before zoledronate administration, as optimal dental treatment may prevent the onset of MRONJ. Our results are consistent with previous reports which indicated that antinecancer medications (9) and smoking (18) were not significant risk factors for MRONJ, confirming our results. However, the number of intervention studies available is insufficient to definitively clarify the risk factors for MRONJ. In the future, a large intervention study across multiple medical institutions should be conducted.

It has been reported that the clinical attachment level in MRONJ patients was significantly higher than in non-MRONJ patients, although the PPDs, BOP, gingival index and plaque index did not differ significantly (19). A large study by Vahtsevanos et al. (18) also showed no significant difference in PPDs between the two groups. In the present study, proportional hazards analysis found that PPD and BOP were not risk factors for MRONJ. Thus, it was unclear why oral hygiene management by dental hygienists was found to be a risk factor for MRONJ whereas PPD and BOP did not appear to contribute. Ximenez et al. reported that weekly professional supragingival plaque removal profoundly diminished counts of both supra- and subgingival bacterial species, including Porphyromonas gingivalis, Tannerella forsythensis and Treponema denticolii (20). Unfortunately, we did not investigate bacterial counts because our study was retrospective in design, and therefore bacterial incubation was not undertaken. A possibility exists that bacteria aside from periodontal pathogens, e.g., bacteria in tongue coating, also affects the occurrence of MRONJ. In addition, salivary volume may contribute to the oral condition, because saliva plays important roles for physical cleansing, mucosal protection and microbial control. A future intervention study that also evaluates these factors is needed.

The incidence of MRONJ following BPs treatment in this study was higher than previous reports (9). In our hospital, the duration between introduction from other clinical departments and initiation of zoledronate administration was sometimes quite short. In these cases, sufficient dental treatment could not be served before initiation of zoledronate administration. Thus, insufficient dental treatments and professional oral hygiene managements might be the reason of why the incidence of MRONJ in this report was higher than other studies. If the condition of patients permits, sufficient time for dental management is desired before commencing BP treatment.

In the present study, 20 patients did not participate up to the 6-month evaluation. Previous reports indicated that although 84% of participants understood the purpose of receiving BP therapy, 82% could not recall if they had been informed about the risk of experiencing adverse reactions including MRONJ (21). The use of leaflets as an educational tool for patients may contribute to increased oral self-checking and may motivate patients to return for dental examination, subsequently reducing the incidence of MRONJ, as well as professional oral hygiene management.

In conclusion, present study indicates that oral hygiene managements by dental hygienists prolong the onset of MRONJ and suppress the development of MRONJ. Thus, professional oral hygiene management could prevent MRONJ.

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