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Medication-related osteonecrosis of the jaw (MRONJ): An update on the Memorial Sloan Kettering Cancer Center (MSKCC) experience and the role of Pre-medication Dental Evaluation in the prevention of MRONJ

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Abstract

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Objective.—We aim to investigate the relationship between type of antiresorptive medication and MRONJ onset and the role of pre-medication dental evaluation (PMDE) in the prevention of MRONJ.

Study Design.—Our database of MRONJ patients was reviewed. Kruskal-Wallis test was used to analyze the onset dose of the three frequent medication types associated with MRONJ. To evaluate the role of PMDE in the prevention of MRONJ, all patients on anti-resorptive and/or anti-angiogenic medications (A/A) seen in the Dental Service of MSKCC during a 10-year period were sub-classified into two groups. Group I, patients seen for PMDE before the commencement of A/A and Group II, patients seen after prior exposure to A/A. Fischer's exact test was used to compare the incidence of MRONJ in both groups.

Results.—Patients on denosumab developed MRONJ earlier compared to zoledronate and pamidronate (p=0.003). Group I had a significantly reduced incidence of MRONJ (0.9%) compared to Group II (10.5%) (p<0.0001). Dentoalveolar trauma as a precipitating factor between Groups I and II was not statistically significant.

Conclusions.—Denosumab was associated with an earlier occurrence of MRONJ compared to zoledronate and pamidronate. The role of PMDE may be an effective preventive strategy in reducing the incidence of MRONJ.

Keywords

MRONJ; ONJ; Dental screening; Pre-medication dental evaluation; Bevacizumab; Denosumab

Introduction

We previously reported our institution's experience with intravenous bisphosphonate-related osteonecrosis of the jaw with an analysis of long-term follow up of 109 patients treated between 1998 – 2009 [1]. Since then, other classes of medication have been implicated in the development of osteonecrosis of the jaw (ONJ), including denosumab (humanized monoclonal antibody that inhibits the activation of receptors for nuclear factor kappa β ligand), anti-angiogenic medications such as sunitinib (tyrosine kinase inhibitor) and bevacizumab (humanized monoclonal antibody) [2–9]. Additionally, case reports have indicated possible association between ONJ and azacitidine, imatinib, everolimus, ipilimumab and ziv-aflibercept [10–15]. With the advent of these new classes of medications, the condition is now more aptly known as medication-related osteonecrosis of the jaw (MRONJ). Although possible pathogenesis and associated risk-factors have been previously suggested, additional studies are needed to fully define them. This report presents an update on our institution's experience, using an expanded cohort of 273 cancer patients who developed MRONJ and were managed in the Dental Service of Memorial Sloan Kettering Cancer Center between March 1998 and September 2016. This report also investigates the onset of MRONJ for different medication classes and combinations thereof, as well as the role of pre-medication dental evaluation (PMDE) in the prevention of MRONJ during a 10-year period, 2006–2015.

Patients and Methods

This retrospective study was approved by the Memorial Sloan Kettering Cancer Center (MSKCC) Institutional Review Board. To answer the objectives of our study we investigated two data sets.

First data set:

We reviewed the medical and dental records of patients diagnosed with medication-related osteonecrosis of the jaw (MRONJ) in the Dental Service of MSKCC between March 1998 and September 2016. A total of 273 MRONJ patients were diagnosed during this period.

Demographic and clinical variables assessed in our analysis included: gender; primary cancer diagnosis; medication types (anti-resorptive, anti-angiogenic and others); precipitating factors (invasive dentoalveolar trauma or other traumatic causes versus spontaneous); MRONJ stage at diagnosis, as defined by the American Association of Oral and Maxillofacial Surgeons [16]; number of MRONJ cases diagnosed by years; number of doses of medication before the onset of MRONJ; and the clinical outcome of MRONJ at last follow-up. This data set is used to present an update on our experience with MRONJ and to investigate the onset of MRONJ for different medication classes and combinations thereof.

Second data set:

In order to determine the role of PMDE in the prevention of MRONJ, a second data set of patients who were treated with anti-resorptive and/or anti-angiogenic medications at MSKCC and referred to the Dental Service during the period 2006–2015. The MRONJ status was assessed for two groups of patients. The two groups included patients who were treated with anti-resorptive and/or anti-angiogenic medications at MSKCC and referred to the Dental Service during the period 2006–2015 at the following time points: (1) Prior to commencement of the medications (Group I); and (2) after prior exposure to the medications (Group II).

PMDE is currently implemented in the Dental Service of MSKCC, New York. PMDE consists of: (1) Patient education; (2) Comprehensive oral and dental evaluation; and (3) Completion of recommended pre-medication dental treatment. During this visit, patients are fully informed of the potential oral risk associated with these medications. Oral and dental examination is performed including panoramic and bitewing radiographs (and selected periapical radiographs as needed). Extraction of non-restorable teeth and those with poor prognosis is completed at least 2–3 weeks prior to commencement of antiresorptive treatment.

Descriptive analyses were performed to: (1) Identify the medication type with the earliest MRONJ onset between the 3 common medication types associated with MRONJ; (2) compare the incidence and precipitating factor (dentoalveolar procedure or spontaneous) of MRONJ in patients who had a PMDE (Group I) versus patients who did not receive a PMDE (Group II). Statistical analyses were performed using Kruskal-Wallis and Fisher’s exact (2-sided) tests on an SPSS V. 24 platform.

Results

First data set:

A total of 273 (153 female, 120 male) patients were diagnosed with MRONJ between March 1998 and September 2016. Their primary cancer diagnoses were breast cancer (n = 118), multiple myeloma (n = 65), prostate cancer (n = 48), renal and lung cancers (n = 12 each), and others (n = 18) (Table 1). The distribution of patients according to medication type includes patients treated with zoledronic acid (Z) alone (n=105), denosumab (D) alone (n=28), pamidronate (P) alone (n=19), bevacizumab (B) alone (n=7), ipilimumab alone (n=1) and a combination of these medications in 113 patients (Table 2). 157 (58%) MRONJ patients reported a history of an invasive dentoalveolar trauma as the precipitating factor. The MRONJ stages at diagnosis were: 0 (8%), 1 (50%), 2 (37%) and 3 (5%). The median follow-up period was 10 months (range: 0 – 141 months). There was an increase in the number of patients diagnosed with MRONJ in 2004 from an average annual diagnosis of 2.3 (0–6) patients before 2004 to 24 patients diagnosed in 2004. The year 2015 marked the highest number of patients (n=31) diagnosed with MRONJ. The median number of doses at onset of MRONJ based on medication type was 14 (Z, 1–112), 11.5 (D, 1–46), 33.5 (P, 2–84) and 14 (B, 8–18). Only two patients on Z had a single dose prior to the onset of MRONJ and only one patient on D had a single dose prior to the onset of MRONJ. The median onset of MRONJ in doses for patients on a combination of Z+P, Z+D and Z+B was 36, 26 and 25 doses, respectively. As at last follow-up, resolution of the MRONJ was noted in 29% (n = 79) of patients, progressed in 27% (n = 74), was unchanged in 23% (n = 63) and partially resolved in 21% (n = 57).

Seven patients developed MRONJ related to bevacizumab alone. The two index patients of osteonecrosis of the jaw related to bevacizumab in the literature previously described by Estilo et al.[8] are included. There were 4 females and 3 males with ages ranging from 33 to 77 years. Their primary cancer diagnoses were breast cancer (n = 2), lung cancer (n = 2), colorectal cancer (n = 1), anaplastic astrocytoma (n = 1), and glioblastoma multiforme (n = 1). Only one patient reported a history of dentoalveolar trauma as a precipitating factor others were spontaneous. The number of doses at onset of MRONJ range from 8 to 18 (mean: 14). The follow-up period ranged from 1 to 9 months. As at last follow-up, resolution of the MRONJ was noted in three patients, partially resolved in two patients, unchanged in one patient, and one patient was lost to follow-up.

Second data set:

A total of 2216 MSKCC patients on anti-resorptive and/or anti-angiogenic medications were evaluated in the Dental Service during a 10-year period (2006 – 2015). 872 patients underwent PMDE before the commencement of anti-resorptive and/or anti-angiogenic medications (Group I), while the remaining 1344 patients were seen after prior exposure to anti-resorptive and/or anti-angiogenic medications (Group II). Of the patients seen for PMDE (Group I), eight (0.9%) developed MRONJ, and for patients who did not receive a PMDE (Group II), 141 (10.5%) developed MRONJ (Fig. 1). MRONJ was precipitated by invasive dentoalveolar trauma in 37.5% (n = 3) of patients in Group I compared to 58.2% (n = 82) of patients in Group II. No patient presented with Stage 3 MRONJ in Group I while,

5.7% (n = 8) presented with Stage 3 MRONJ in Group II. Notably, 57% (n = 80) of MRONJ patients in Group II were diagnosed with MRONJ at their first dental visit to the Dental Service.

The three frequent medication types associated with MRONJ were Z, D and P. When comparing the number of doses of these medication types prior to the onset of MRONJ, there was a significant difference between Z, D and P (p=0.003; Kruskal-Wallis), with D requiring the fewest doses prior to the appearance of MRONJ (Table 3). There was a significant difference (p<0.0001; Fischer's exact test) when comparing the incidence of MRONJ between Group I and Group II (Table 4). The role of invasive dentoalveolar trauma as a precipitating factor between Group I and Group II was not significant (p=0.290; Fischer's exact test).

Discussion

In this study, we report our institution's 18-year (March 1998 to September 2016) experience of medication-related osteonecrosis of the jaw (MRONJ) in 273 patients. Since our last report on intravenous bisphosphonate-related osteonecrosis of the jaw in 109 patients diagnosed between 1998 – 2009 [1], other classes of medications have been implicated in the etiology of MRONJ. These medications include denosumab, bevacizumab, sunitinib, ipilimumab, azacitidine and ziv-aflibercept [6, 8, 9, 11, 13, 14]. With these new classes of medications implicated in the etiology of MRONJ and the increasing rate of emergence of new oncologic therapies, we expect to see an increase in the number of MRONJ cases in the oncologic setting. The review of our database showed an increase in the average annual diagnosis of MRONJ from 2.3 patients before the year 2004 to twenty-four patients in the year 2004 with a continuous trend upwards. This is most likely attributed to the FDA approval of zoledronic acid in the year 2001, which is commonly used for the management of patients with multiple myeloma and bone metastases of solid tumors. In the seven years since our last review [1], we saw a rise in the number of patients diagnosed with MRONJ from 109 to 273.

Invasive dentoalveolar trauma, such as dental extraction, periodontal surgery, or implant placement are considered major precipitating factors for the initiation of MRONJ in patients who have been exposed to these classes of medications [1, 17–19]. Over half of the patients that develop MRONJ have a history of invasive dentoalveolar trauma [1, 17–19]. In our MRONJ cohort, 58% (n = 157) of the patients developed MRONJ following dentoalveolar procedures (e.g, dental extraction). One of the aims of this study was to identify the medication type with the earliest MRONJ onset among the 3 common medication types associated with MRONJ. Our study found a significant difference in the number of doses prior to the onset of MRONJ among patients taking zoledronic acid alone, denosumab alone and pamidronate alone. With patients on denosumab alone requiring the fewest doses prior to the development of MRONJ compared to patients taking zoledronic acid or pamidronate. The tendency for MRONJ to develop earlier in patients on denosumab therapy compared to intravenous bisphosphonates has been observed in other reports [5, 6, 20]. Denosumab is a humanized monoclonal antibody that inhibits the activation of receptors for nuclear factor kappa-β ligand (RANKL). It prevents the binding of RANKL to RANK, a receptor that is

expressed on cell membranes of pre-osteoclasts and osteoclasts, and thereby inhibits osteoclast development and activation. Denosumab is cleared by the reticuloendothelial system with a circulatory half-life of 26 days, and does not accumulate in the bones; therefore, the drug should be largely cleared from the body within 6 months after last administration. Because of these pharmacokinetic properties, denosumab discontinuation prior to an invasive dental procedure in patients on this medication may have some utility as a preventive measure against the development of MRONJ [5, 16, 21, 22]. However, there are insufficient clinical data and experience to support whether discontinuation of denosumab prior to an invasive dental procedure is beneficial in preventing MRONJ.

The other aim of this study was to investigate the role of pre-medication dental evaluation (PMDE) in the prevention of MRONJ in our institution during a 10-year period. Our study found a significant difference in the incidence of MRONJ between patients who received a PMDE and those who did not, with patients who received PMDE having an almost 12-fold decrease of MRONJ compared to patients who did not receive PMDE. The use of PMDE has been shown to be very effective in reducing the incidence of MRONJ in patients on these medications. Pioneer studies by Dimopoulos et al. and Ripamonti et al. found a significant ($p = 0.0296$ and 0.048, respectively) reduction in the incidence of MRONJ in patients who received PMDE compared to patients who did not receive a PMDE [23, 24]. Other recent studies by Bonacina et al., Vandone et al., and Bramati et al. have all shown the effectiveness of PMDE in the reduction of the incidence of MRONJ [25–27]. The study by Dimopoulos et al. with 128 patients showed that the incidence of MRONJ in patients that did not receive PMDE was 23%, while, the incidence of MRONJ in patients that did receive PMDE was 7% [23]. The study by Ripamonti et al. with 966 patients showed that the incidence of MRONJ in patients that did not receive PMDE was 3.2%, while, the incidence of MRONJ in patients that did receive PMDE was 1.3% [24]. Similar studies by Bonacina et al. and Bramati et al. with 282 and 212 patients, respectively demonstrated a reduction in the incidence of MRONJ from 10.8% and 8.6%, respectively, to 0% after implementation of PMDE [25, 27]. In this current study with the largest number of patients ($n = 2216$), the incidence of MRONJ in patients that did not receive PMDE was 10.5%, while the incidence in patients who did receive PMDE was 0.9%.

The use of preventive measures such as PMDE is an effective strategy for patients at risk of MRONJ as clinical management of MRONJ remains controversial, with no established treatment guidelines. Different therapeutic approaches or a combination of chlorhexidine gluconate 0.12% or 2% rinse, antibiotic therapy (amoxicillin, amoxicillin with clavulanic acid, clindamycin and/or metronidazole), pentoxifylline and tocopherol, low level laser therapy, hyperbaric oxygen, conservative surgery (sequestrectomy and/or superficial debridement of sequestrum), and extensive surgery (alveoloplasty, resection) with or without fluorescence light or plasma rich protein have been utilized in the management of MRONJ, with variable clinical outcomes [1, 28–36].

As such, at MSKCC, all patients scheduled to start anti-resorptive and/or anti-angiogenic medications are recommended to undergo oral/dental evaluation. PMDE consists of 3 components: (1) Patient education; (2) Comprehensive oral and dental evaluation; and (3) Completion of recommended pre-medication dental treatment. During this visit, patients are

fully informed of the potential oral risk associated with these medications. In addition, patients are provided detailed oral hygiene instructions, nutritional counseling and the need to avoid as much as possible invasive dental procedures after commencement of the medications. A thorough oral and dental examination is performed including panoramic and bitewing radiographs (and selected periapical radiographs as needed). Treatment of dental caries and periodontal disease is initiated. Dental extractions are completed at least 14–21 days prior to commencement of anti-resorptive and/or anti-angiogenic medications. A prescription is issued for high-potency fluoridated toothpaste. The patients are then followed periodically (every 3 months for the first 2 years and biannually, thereafter).

Limitation to this study is its retrospective nature. Moreover, the total number of patients (n=2216) in this study does not represent the total number of patients treated with antiresorptive and/or antiangiogenic medications at MSKCC during the same time period.

Conclusions

Our study shows and emphasizes the need for oral/dental evaluation prior to commencement of anti-resorptive and/or anti-angiogenic therapy. It is important for oral health practitioners to work closely with the patient's medical oncology team to advocate the need for pre-medication evaluation for the prevention of MRONJ and to identify potential risk of MRONJ. MRONJ can occur without a prior history of an invasive dentoalveolar trauma. However, invasive dentoalveolar trauma still remains a major precipitating factor. Also, the use of denosumab may be associated with an earlier occurrence of MRONJ compared to zoledronic acid and pamidronate. Additional studies are needed to validate this finding and to show its clinical significance. A further study to identify potential risk factors of MRONJ in our database is currently underway.

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Statement of Clinical Relevance

Pre-medication dental evaluation may be an effective preventive strategy in reducing the incidence of RONJ, and denosumab may be associated with an earlier occurrence of MRONJ compared to zoledronic acid and pamidronate.

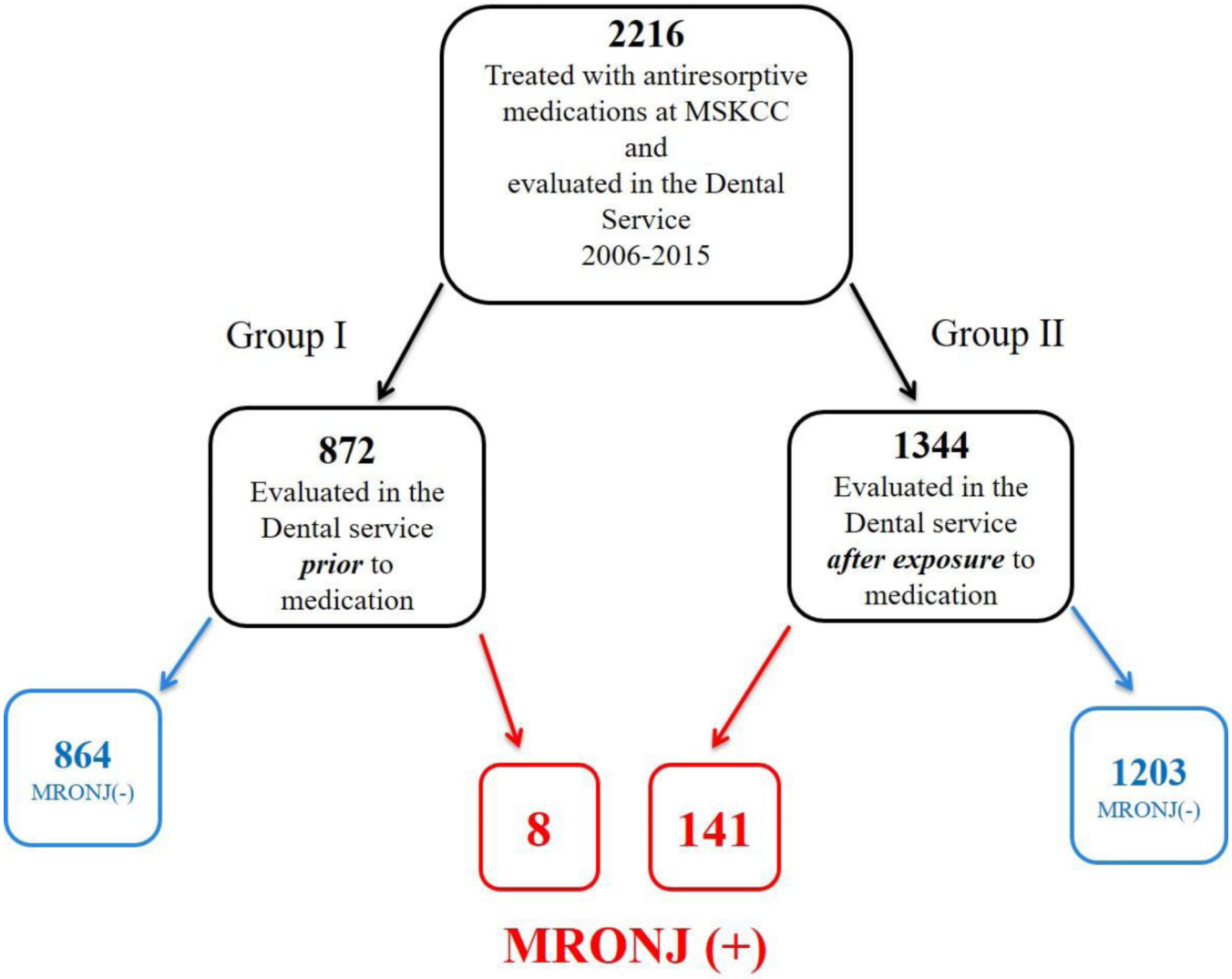

Figure 1.
Patients flowchart.

Table 1.

Clinical features of MRONJ patients

	All patients (%)
n	**273**
Gender	
Male	120 (44%)
Female	153 (56%)
Primary diagnosis	
Breast cancer	118 (43%)
Multiple myeloma	65 (24%)
Prostate cancer	48 (17.6%)
Renal cancer	12 (4.4%)
Lung cancer	12 (4.4%)
Others	18 (6.6%)
Precipitating factors	
Dentoalveolar trauma	157 (57.5%)
Spontaneous	116 (42.5%)
MRONJ stage at diagnosis	
0	22 (8%)
1	136 (50%)
2	101 (37%)
3	14 (5%)

Table 2.

The distribution of MRONJ patients according to medication types

Type of medications	Number of patients
Z	105
D	28
P	19
B	7
I	1
Z + P	48
Z + B	28
Z + D	21
D + B	4
Z + S	2
D + S	1
D + I	1
Z + D + B	3
Z + P + B	2
Z + P + D	1
Z + B + S	1
Z + P + D + B + S	1

Z – Zoledronic acid; D – Denosumab; P – Pamidronate; B – Bevacizumab; I – Ipilimumab; S – Sunitinib

Table 3.

Comparison of the doses of the 3 common medication types to onset of MRONJ

	Z (n = 105)	D (n = 28)	P (n = 19)	P-value
Median (range) doses to onset	14 (1–112)	11.5 (1–46)	33.5 (2–84)	0.003

Table 4.

Comparison of the incidence of MRONJ between Group I and Group II

	Number of patients (%)			
Characteristics	**Total (%) (n = 2216)**	**No MRONJ (n = 2067)**	**MRONJ (n = 149)**	**P-value**
Pre-medication dental visit				
Group I (Yes)	872 (39.4%)	864 (99.1%)	8 (0.9%)	<0.0001
Group II (No)	1344 (60.6%)	1203 (89.5%)	141 (10.5%)	