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Determinants of outcome in cancer patients with medication-related osteonecrosis of the jaw: A 19-year retrospective study

Jenna Ward[a,1], **Annu Singh**[a,1], **Charlie White**[b], **Elyn Riedel**[b], **Roxanne Lewis**[a], **SaeHee K. Yom**[a], **Jerry Halpern**[a], **Joseph D. Randazzo**[a], **Kenneth L. Kronstadt**[a], **Joseph M. Huryn**[a], **Cherry L. Estilo**[a,*]

[a]Dental Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA

[b]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA

1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) continues to be a rare but challenging complication for cancer patients treated with antiresorptive medications. Bisphosphonates and the fully human monoclonal antibody, denosumab are two common antiresorptive medications used both in the management of metastatic disease to the bone and in multiple myeloma [1,2]. While both target osteoclasts and results in decreased bone resorption, the mechanism of action differs between the two. Bisphosphonates such as zoledronic acid and pamidronate are structural analogs of pyrophosphates which bind to an incorporate into the bone matrix. They are then ingested by mature osteoclasts, which leads to osteoclast apoptosis [3]. Denosumab is a fully human monoclonal antibody that binds to the cytokine RANKL and prevents it from binding to RANK, a receptor on osteoclasts. This inhibits proper maturation, function, and survival of osteoclasts [4]. As a result, bone resorption is reduced. Intravenous bisphosphonate therapy and subcutaneous denosumab injections

*Corresponding author. estiloc@mskcc.org (C.L. Estilo).

[1]JM and AS contributed equally to this work.

Presentation

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CRediT authorship contribution statement

Jenna Ward: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Annu Singh:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Charlie White:** Writing – review & editing, Methodology, Formal analysis. **Elyn Riedel:** Writing – review & editing, Methodology, Formal analysis. **Roxanne Lewis:** Writing – review & editing, Data curation. **SaeHee K. Yom:** Writing – review & editing. **Jerry Halpern:** Writing – review & editing, Supervision. **Joseph D. Randazzo:** Writing – review & editing. **Kenneth L. Kronstadt:** Writing – review & editing, Supervision. **Joseph M. Huryn:** Writing – review & editing, Supervision, Project administration. **Cherry L. Estilo:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization.

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have been effective in their use to prevent skeletal related events such as pathologic bone fractures, spinal cord compression, orthopedic surgery interventions, and palliative radiation to the bone [5–7]. Despite the significant benefits of antiresorptive agents in the oncologic setting, MRONJ is an untoward complication in a subset of patients [1,8,9] (see Fig. 1).

The current literature shows that the risk of developing MRONJ in cancer patients treated with zoledronic acid is believed to be less than 5 %, with some studies showing a range from 0 to 18 % [1]. Similarly, in cancer patients treated with denosumab, the risk of MRONJ ranges from 0 % to 6.9 %, with most studies reporting rates less than 5 % [1]. It is accepted that the risk for developing MRONJ is comparable between those treated with zoledronic acid and those treated with denosumab [1,10,11].

While there are established data examining factors associated with the onset of MRONJ, there is limited information evaluating the relationship between risk factors associated with MRONJ and its resolution. Several risk factors established in the most recent literature as well as within the currently accepted model of MRONJ are associated with its onset [1,12–14]. These factors include duration of antiresorptive therapy [15], dentoalveolar procedures such as extractions [16,17] and implant insertion [18], preexisting dental inflammation such as periodontitis [19] or periapical abscess [20], denture use [21] and corticosteroid use [1,22]. There are variable data regarding the significance of other factors such as smoking, comorbid conditions, chemotherapy and cancer type and their relationship with the onset or precipitation of MRONJ [1].

The most recent treatment algorithm guidelines have been developed by the Academy of Oral and Maxillofacial Surgeons (AAOMS) to include both conservative and surgical therapies for management of MRONJ [1]. Conservative management generally consists of antimicrobial rinses, oral hygiene maintenance and antibiotics as needed [1,23]. Surgical treatment may include sequestrectomy, alveolectomy or resection [1,24]. However, regardless of current management approaches, resolution is not predictable. Often, the course of MRONJ can be prolonged, which can significantly impact quality of life. The purpose of this study was to identify factors that are associated with healing in cancer patients with MRONJ.

2. Materials and methods

This retrospective study was approved by the Memorial Sloan Kettering Cancer Center (MSKCC) Institutional Review Board. To meet the objective of our study, we reviewed the medical and dental records of patients diagnosed with MRONJ in the Dental Service of MSKCC between 2003 and 2022.

The medical records of 433 patients diagnosed with MRONJ were reviewed. Inclusion criteria included (1) cancer patients with history of antiresorptive agents, namely denosumab, pamidronate, or zoledronic acid, (2) with a minimum follow up of 1 month after initial MRONJ diagnosis, and (3) without any history of head and neck radiation or metastatic disease to the jaws. Demographic data included age, gender and primary cancer diagnosis (multiple myeloma, prostate cancer, breast cancer and all other types of

cancer). Staging of MRONJ at initial diagnosis was defined by the clinical team of MSKCC Dental Service based on AAOMS guidelines to include both nonexposed bone variant with radiographic findings only and clinical exposed bone variant (Stage 1,2,3) [1]. Patients with no clinical evidence of exposed necrotic bone and with intact mucosa who presented with nonspecific symptoms such as tooth mobility not explained by chronic periodontal disease or intraoral/extraoral swelling and other clinical and radiographic features as described in the AAOMS guidelines received Stage 0 designation. All patients diagnosed with MRONJ underwent radiographic evaluation using panoramic radiograph and intraoral radiograph, when indicated. Relevant clinical information associated with MRONJ diagnosis included medication type (denosumab, pamidronate, zoledronic acid), total number of antiresorptive doses before MRONJ onset, size of exposed bone area at initial MRONJ diagnosis and MRONJ location (mandible, maxilla or both arches). MRONJ etiology was described as non-spontaneous or spontaneous. Non-spontaneous MRONJ was preceeded by dentoalveolar procedures (eg. dental extraction or implant placement) whereas spontaneous MRONJ occurred without prior dentoalveolar trauma. Concurrent use of corticosteroid, comorbidity such as diabetes and social history such as alcohol use and tobacco use were also reviewed. For the purpose of our study, oral hygiene condition was graded as “optimal” (minimal or no interproximal plaque accumulation and overall healthy gingiva in the absence of gingival inflammation) or “suboptimal” (moderate or heavy interproximal plaque accumulation with either localized or generalized gingival inflammation).

Patients diagnosed with MRONJ were generally treated using a conservative approach with close monitoring, prescription of chlorhexidine gluconate 0.12 % oral rinse, antibiotic (amoxicillin, amoxicillin with clavulanic acid, clindamycin and/or metronidazole) therapy in the presence of symptoms or soft tissue swelling. In selected patients, pentoxifylline and tocopherol regimen and gentle debridement of mobile sequestrum were prescribed. Surgical management including resection was employed when conservative management has failed, or there was progression of MRONJ such as recurrent infection or pathological fracture. Surgical intervention was also considered based on patients’ general systemic condition with bone metastasis, prognosis, and the stage of the underlying disease. The clinical outcome evaluated in this study was “time to resolution” of MRONJ. For the sake of this study, “resolution” was defined as complete mucosal coverage without persistence of any stage of MRONJ according to the AAOMS classification system [1]. A competing risk framework was used to analyze time to MRONJ resolution, which was defined as time from initial MRONJ diagnosis to resolution, with death within 6 months of the last follow-up treated as the competing event. Gray’s test was used to examine the association between each factor and the cumulative incidence of MRONJ resolution. Variables that were significant at the 0.1 level in univariable analysis were entered into a multivariable model. Variables were removed if they were not significant at the 0.05 level in the multivariable model.

3. Results

A total of 300 cancer patients with MRONJ were included in the analysis. The majority were female (n = 190; 63 %) with a median age of 64 years (IQR, 56-70). The most common primary cancer diagnosis was breast cancer (n = 152; 51 %), followed by multiple myeloma (n = 72; 24 %), and prostate cancer (n = 44; 15 %). The majority of patients received

zoledronic acid only (n = 130; 43 %) as the primary medication. Denosumab only and pamidronate only was administered in 72 (24 %) and 14 (4.7 %) patients, respectively. There were 84 (28 %) patients who received a combination of these antiresorptive medications before their MRONJ diagnosis. The median number of doses administered before the diagnosis of MRONJ was 19 (IQR, 10–32). The stage of MRONJ at initial diagnosis according to the AAOMS classification was most frequently recorded as either stage 1 (n = 138; 46 %) or stage 2 (n = 139; 46 %). Thirteen patients (4.3 %) presented with stage 0 at the time of diagnosis and 10 patients presented with stage 3 (3.3 %). The size of exposed bone was usually less than 1 cm at initial presentation (n = 153; 62 %) and predominantly localized to the mandible (n = 194; 65 %). There was equal proportion of spontaneous (n = 142; 47 %) and non-spontaneous (n = 158; 53 %) MRONJ cases. Other characteristics included: concurrent corticosteroid use (n = 100; 33 %), chemotherapy administration (n = 260; 87 %), presence of diabetes (n = 45; 15 %), history of alcohol use (n = 166; 55 %), history of smoking (n = 125; 42 %) and suboptimal oral hygiene (n = 176; 62 %). Patient characteristics are summarized in Table 1.

The median follow-up time was 94.9 months (95 % CI 63 %,177 %). The primary outcome was time to resolution of MRONJ with death within 6 months of last follow up as a competing event. As a result, 121 patients were excluded. 105 patients achieved MRONJ resolution, and 74 patients died without resolution within 6 months of the last follow up. Several factors were significantly associated with time to MRONJ resolution univariately (Table 2). Primary cancer diagnosis was associated with time to MRONJ resolution (P = 0.047), with breast cancer having the lowest rate of resolution among cancer type at both 3 and 5 years (34 % and 40 %, respectively) (Fig. 4A). A higher rate of resolution was seen in male patients (P = 0.014) with 3-year and 5-year rates of 48 % and 55 %, respectively. Patients who were not on concurrent corticosteroid also showed a higher rate of resolution (P = 0.004) at both 3 and 5 years, calculated as 46 % and 55 %, respectively. The 3-year and 5-year rate of resolution in patients who were on concurrent corticosteroid were 28 % and 32 %, respectively (Fig. 4B). The size and location of bone exposure at diagnosis were borderline significant (P = 0.051 and P = 0.061, respectively). The remaining factors were not significantly associated with rate of MRONJ resolution. Since the site of primary diagnosis and the patients' gender were highly associated with each other, only primary cancer diagnosis was examined in a multivariate model along with total number of doses, concurrent corticosteroid use, and size and location of bone exposure. Primary cancer diagnosis, total number of doses, and concurrent corticosteroid use remained independently associated with rate of MRONJ resolution in the final model (Table 3) (see Fig. 2).

4. Discussion

This is the largest single institution cohort study to evaluate factors associated with MRONJ resolution in cancer patients treated with antiresorptive agents over a 19-year period. Overall, the rate of MRONJ resolution at 3-years and 5-years were 39 % (95 % CI 33 %, 46 %) and 47 % (95 % CI 39 %, 54 %), respectively (Fig. 3). Our study found several significant factors independently associated with the rate of MRONJ resolution: primary cancer diagnosis (P = 0.012), concurrent steroid use (P = 0.003), and total number of doses (P = 0.013).

The majority of our study cohort was female (n = 190; 63 %) and the most common primary cancer diagnosis was breast cancer (n = 152, 51 %). Females and breast cancer patients both had significantly lower rates of resolution in a univariable analysis. Given the high correlation between gender and primary cancer diagnosis, only primary cancer diagnosis was chosen to be entered into a multivariable model. Primary cancer diagnosis remains significant in a multivariable analysis adjusting for concurrent corticosteroid use and total number of doses.

It has been established that the duration of antiresorptive therapy is a risk factor for developing MRONJ [1]. Henry et al. found that for cancer patients treated with zoledronic acid or denosumab, there was a 0.5 % chance of developing MRONJ after 1 year, a 1.3 % chance after 2 years and a 1.8 % chance after 3 years [25]. A systematic review by Ng et al. found an increased incidence of MRONJ in patients taking zoledronic acid or denosumab after treatment duration of 24 months compared to a duration of less than 24 months [26]. In this study, the median number of doses before MRONJ diagnosis was 18 (range, 1–112). We found that increased number of doses was significantly associated with a lower rate of MRONJ resolution. Our data show that for every increase in 6 doses, the rate of resolution decreases by 8 % (HR = 0.92; 95 % CI (0.85, 0.99); P = 0.023).

Studies have investigated the association of primary medication with MRONJ resolution [11,15]. In a large phase III trial in patients with metastatic bone disease receiving antiresorptive medications, the MRONJ resolution rate was found to be greater in the denosumab group (21/52; 40.4 %) than the zoledronic acid group (11/37; 29.7 %) [15]. Another study showed that the time to resolution of MRONJ was significantly shorter for patients who received denosumab than for those who received zoledronic acid (P = 0.024) [11]. While denosumab's effects on bone remodeling are mostly diminished after 6 months of treatment cessation [27], the half-life of bisphosphonates is significantly longer [28]. This likely plays a role in reduced capacity of the bone to heal with increased dose of primary medication. The difference in the resolution rates could also be related to the different mechanisms of action of these medications [3,4]. However, in our study, primary medication was not found to be significantly associated with MRONJ resolution on a univariate analysis (P = 0.4). The rate of MRONJ resolution in the first 2–3 years was overlapping between patients on denosumab and zoledronic acid (Fig. 4C). We did see that the 3-year and 5-year rate of resolution was highest among patients on denosumab only (48 % and 52 %, respectively), although there was no clear benefit. Additionally, our study did not examine the cessation or continuation of antiresorptive therapy after MRONJ onset, and therefore continued treatment may have also impacted bone healing in such cases. This is an important consideration when recommending dental treatment and approaches to the management of MRONJ when it occurs.

Patients taking corticosteroids at the time of MRONJ diagnosis had significantly lower rates of resolution at both 3 and 5 years following MRONJ diagnosis (p = 0.003). This correlates with the literature that has shown an increased risk of the development of MRONJ in patients treated with concurrent corticosteroids [15]. It has been theorized that immunosuppressive effects of corticosteroids increase the risk of oral infection and osteonecrosis of the jaw secondary to delayed wound healing and alteration of the oral

microflora [29]. The addition of corticosteroids to an already immunocompromised cancer patient can prolong healing.

The current literature has demonstrated that dentoalveloar procedures such as extractions in patients on antiresorptive medications are a well-known risk factor associated with development of MRONJ [30]. However, there was no significant association between dentoalveloar procedures and resolution of MRONJ. The literature estimates that the risk of developing MRONJ after an extraction in cancer patients treated with bisphosphonates is usually in the range of 1–5% [1,31]. The rate of resolution at 3-years and 5-years post MRONJ onset was 38 % and 45 %, respectively for non-spontaneous cases. The rate of resolution at 3-years and 5-years post MRONJ onset was 41 % and 48 %, respectively for spontaneous cases. From these findings, we conclude that while dentoalveolar procedures may precipitate the onset of MRONJ, once it develops it does not appear to play a role in healing outcome.

The size of the exposed bone area at the initial diagnosis of MRONJ diagnosis was of borderline significance in univariate analysis. A smaller size of bony exposure was marginally associated with a higher rate of resolution ($p = 0.051$). Additionally, the stage of MRONJ at onset did not show a statistically significant difference in rate of resolution (Table 2). A larger cohort may shed light on the true impact of size and stage on MRONJ resolution.

It is well established that MRONJ is more common in the mandible than maxilla (75 % vs 25 %) [15,32]. This was also reflected in our patient population in which 65 % of MRONJ cases were localized to the mandible. Patients that had MRONJ localized to a single arch tended to resolve more often than MRONJ cases involving both arches, but this association was of borderline significance univariately. Only 7 % cases involved MRONJ in both the maxilla and the mandible, but the rate of resolution was 14 % at 3 and 5 years, below the overall resolution rate for single arch involvement. The presence of MRONJ in both arches may be reflective of advanced primary disease or compromised immune function of the patient. Additional studies and larger sample sizes would be important to confirm these findings.

Several factors not included in this study that would be useful in future investigation would be the association between MRONJ resolution and cessation or continuation of antiresorptive doses after MRONJ diagnosis as well as treatment intervention comparing conservative versus surgical approach. In our institution, the management of MRONJ is largely limited to symptom management. This includes the use of antiseptic mouth rinses, maintaining excellent oral hygiene and administration of antibiotics when indicated. Furthermore, additional non-surgical interventions such as a regimen of pentoxifylline and vitamin E are also gaining attention and have shown to have potential benefit in MRONJ resolution [33,34]. Given the lack of a definitive treatment for MRONJ, additional studies that examine the efficacy of newer and alternative therapies will enhance our understanding of MRONJ resolution.

Our data indicates that independent and statistically significant factors associated with MRONJ resolution included the total number of antiresorptive doses prior to MRONJ diagnosis, primary cancer diagnosis, and lack of concurrent corticosteroid use. This information may be beneficial during patient counseling and education.

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References

[1]. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American association of oral and maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaws-2022 update. J Oral Maxillofac Surg 2022 May;80(5):920–43. 10.1016/j.joms.2022.02.008. Epub 2022 Feb 21. [PubMed: 35300956]

[2]. Migliorati CA. Oral complications in cancer patients-medication-related osteonecrosis of the jaw (MRONJ). Front Oral Health 2022 Apr 26;3:866871. 10.3389/froh.2022.866871. [PubMed: 35558547]

[3]. Clézardin P. Mechanisms of action of bisphosphonates in oncology: a scientific concept evolving from antiresorptive to anticancer activities. BoneKEy Rep 2013 Feb 6;2:267. 10.1038/bonekey.2013.1. [PubMed: 24422040]

[4]. Hanley DA, Adachi JD, Bell A, Brown V. Denosumab: mechanism of action and clinical outcomes. Int J Clin Pract 2012 Dec;66(l2):1139–46. 10.1111/ijcp.12022. Epub 2012 Sep 12. [PubMed: 22967310]

[5]. So A, Chin J, Fleshner N, Saad F. Management of skeletal-related events in patients with advanced prostate cancer and bone metastases: incorporating new agents into clinical practice. Can Urol Assoc J 2012 Dec;6(6):465–70. 10.5489/cuaj.12149. [PubMed: 23282666]

[6]. Rachner TD, Coleman R, Hadji P, Hofbauer LC. Individualized bone-protective management in long-term cancer survivors with bone metastases. J Bone Miner Res 2021 Oct;36(10):l906–13. 10.1002/jbmr.4391. Epub 2021 Jun 24.

[7]. Zhang Z, Pu F, Shao Z. The skeletal-related events of denosumab versus zoledronic acid in patients with bone metastases: a meta-analysis of randomized controlled trials. J Bone Oncol 2017 Oct 3;9:21–4. 10.1016/j.jbo.2017.09.003. [PubMed: 29123990]

[8]. Bullock G, Miller CA, McKechnie A, Hearnden V. A review into the effects of pamidronic acid and zoledronic acid on the oral mucosa in medication-related osteonecrosis of the jaw. Front Oral Health 2022 Feb 9;2:822411. 10.3389/froh.2021.822411. [PubMed: 35224540]

[9]. Boquete-Castro A, Gómez-Moreno G, Calvo-Guirado JL, Aguilar-Salvatierra A, Delgado-Ruiz RA. Denosumab and osteonecrosis of the jaw. A systematic analysis of events reported in clinical trials. Clin Oral Implants Res 2016;27:367–75. 10.1111/clr.12556. [PubMed: 25639776]

[10]. Limones A, Sáez-Alcaide LM, Díaz-Parreño SA, Helm A, Bornstein MM, Molinero-Mourelle P. Medication-related osteonecrosis of the jaws (MRONJ) in cancer patients treated with denosumab VS. zoledronic acid: a systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal 2020 May 1;25(3):e326–36. 10.4317/medoral.23324. [PubMed: 32271321]

[11]. Ikesue H, Doi K, Morimoto M, Hirabatake M, Muroi N, Yamamoto S, Takenobu T, Hashida T. Risk evaluation of denosumab and zoledronic acid for medication-related osteonecrosis of the jaw in patients with bone metastases: a propensity score-matched analysis. Support Care Cancer 2022 Mar;30(3):2341–8. 10.1007/s00520-021-06634-7. Epub 2021 Nov 5. [PubMed: 34738163]

[12]. AlRowis R, Aldawood A, AlOtaibi M, Alnasser E, AlSaif I, Aljaber A, Natto Z. Medication-related osteonecrosis of the jaw (MRONJ): a review of pathophysiology, risk factors, preventive measures and treatment strategies. Saudi Dent J 2022 Mar;34(3):202–10. 10.1016/j.sdentj.2022.01.003. Epub 2022 Jan 19. [PubMed: 35935720]

[13]. Van Poznak C, Reynolds EL, Estilo CL, Hu M, Schneider BP, Hertz DL, Gersch C, Thibert J, Thomas D, Banerjee M, Rae JM, Hayes DF. Osteonecrosis of the jaw risk factors in

bisphosphonate-treated patients with metastatic cancer. Oral Dis 2022 Jan;28(1):193–201. 10.1111/odi.13746. Epub 2020 Dec 14. [PubMed: 33274559]

[14]. Wick A, Bankosegger P, Otto S, Hohlweg-Majert B, Steiner T, Probst F, Ristow O, Pautke C. Risk factors associated with onset of medication-related osteonecrosis of the jaw in patients treated with denosumab. Clin Oral Invest 2022 Mar;26(3):2839–52. 10.1007/s00784-021-04261-4. Epub 2021 Nov 23.

[15]. Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT, Diel IJ, Takahashi S, Shore N, Henry DH, Barrios CH, Facon T, Senecal F, Fizazi K, Zhou L, Daniels A, Carriére P, Dansey R. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 2012 May;23(5):1341–7. 10.1093/annonc/mdr435. Epub 2011 Oct 10. [PubMed: 21986094]

[16]. Schwech N, Nilsson J, Gabre P. Incidence and risk factors for medication-related osteonecrosis after tooth extraction in cancer patients-A systematic review. Clin Exp Dent Res 2023 Feb;9(1):55–65. 10.1002/cre2.698. Epub 2022 Dec 4 [PubMed: 36464958]

[17]. McGowan K, McGowan T, Ivanovski S. Risk factors for medication-related osteonecrosis of the jaws: a systematic review. Oral Dis 2018 May;24(4):527–36. 10.1111/odi.12708. Epub 2017 Aug 2. [PubMed: 28656643]

[18]. Pichardo SEC, van der Hee JG, Fiocco M, Appelman-Dijkstra NM, van Merkesteyn JPR. Dental implants as risk factors for patients with medication-related osteonecrosis of the jaws (MRONJ). Br J Oral Maxillofac Surg 2020 Sep;58(7):771–6. 10.1016/j.bjoms.2020.03.022. Epub 2020 Jul 3. [PubMed: 32631756]

[19]. Lorenzo-Pouso AI, Pérez-Sayáns M, Chamorro-Petronacci C, Gándara-Vila P, López-Jornet P, Carballo J, García-García A. Association between periodontitis and medication-related osteonecrosis of the jaw: a systematic review and meta-analysis. J Oral Pathol Med 2020 Mar;49(3):190–200. 10.1111/jop.12963. Epub 2019 Nov 3. [PubMed: 31605632]

[20]. Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, Nooka A, Sayegh G, Guarneri V, Desrouleaux K, Cui J, Adamus A, Gagel RF, Hortobagyi GN. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res 2008 Jun;23(6):826–36. 10.1359/jbmr.080205. [PubMed: 18558816]

[21]. Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. discussion 99-102 N Engl J Med 2005 Jul 7;353(1):99–102. 10.1056/NEJM200507073530120.

[22]. McGowan K, McGowan T, Ivanovski S. Risk factors for medication-related osteonecrosis of the jaws: a systematic review. Oral Dis 2018 May;24(4):527–36. 10.1111/odi.12708. Epub 2017 Aug 2. [PubMed: 28656643]

[23]. Hadaya D, Soundia A, Freymiller E, Grogan T, Elashoff D, Tetradis S, Aghaloo TL. Nonsurgical management of medication-related osteonecrosis of the jaws using local wound care. J Oral Maxillofac Surg 2018 Nov;76(ll):2332–9. 10.1016/j.joms.2018.05.025. Epub 2018 May 29. [PubMed: 29932939]

[24]. Carlson ER, Basile JD. The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2009 May;67(5 Suppl):85–95. 10.1016/j.joms.2009.01.006. [PubMed: 19371819]

[25]. Henry D, Vadhan-Raj S, Hirsh V, von Moos R, Hungria V, Costa L, Woll PJ, Scagliotti G, Smith G, Feng A, Jun S, Dansey R, Yeh H. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. Support Care Cancer 2014 Mar;22(3):679–87. 10.1007/s00520-013-2022-1. Epub 2013 Oct 26. [PubMed: 24162260]

[26]. Ng TL, Tu MM, Ibrahim MFK, Basulaiman B, McGee SF, Srikanthan A, Fernandes R, Vandermeer L, Stober C, Sienkiewicz M, Jeong A, Saunders D, Awan AA, Hutton B, Clemons MJ. Long-term impact of bone-modifying agents for the treatment of bone metastases: a systematic review. Support Care Cancer 2021 Feb;29(2):925–43. 10.1007/s00520-020-05556-0. Epub 2020 Jun 13. [PubMed: 32535678]

[27]. Narayanan P. Denosumab: a comprehensive review. South Asian J Cancer 2013 Oct;2(4):272–7. 10.4103/2278-330X.119895. [PubMed: 24455656]

[28]. Lin JH. Bisphosphonates: a review of their pharmacokinetic properties. Bone 1996 Feb;18(2):75–85. 10.1016/8756-3282(95)00445-9. [PubMed: 8833200]

[29]. Tsao C, Darby I, Ebeling PR, Walsh K, O'Brien-Simpson N, Reynolds E, Borromeo G. Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. J Oral Maxillofac Surg 2013 Aug;71(8):1360–6. 10.1016/j.joms.2013.02.016. Epub 2013 Apr 11. [PubMed: 23582590]

[30]. Coropciuc R, Coopman R, Garip M, Gielen E, Politis C, Van den Wyngaert T, Beuselinck B. Risk of medication-related osteonecrosis of the jaw after dental extractions in patients receiving antiresorptive agents - a retrospective study of 240 patients. Bone 2023 May;170:116722. 10.1016/j.bone.2023.116722. Epub 2023 Feb 28. [PubMed: 36858337]

[31]. Gaudin E, Seidel L, Bacevic M, Rompen E, Lambert F. Occurrence and risk indicators of medication-related osteonecrosis of the jaw after dental extraction: a systematic review and meta-analysis. J Clin Periodontol 2015 Oct;42(10):922–32. 10.1111/jcpe.12455. Epub 2015 Nov 3. [PubMed: 26362756]

[32]. Hallmer F, Andersson G, Götrick B, Warfvinge G, Anderud J, Bjørnland T. Prevalence, initiating factor, and treatment outcome of medication-related osteonecrosis of the jaw-a 4-year prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol 2018 Dec;126(6):477–85. 10.1016/j.oooo.2018.08.015. Epub 2018 Aug 31. [PubMed: 30249535]

[33]. Owosho AA, Estilo CL, Huryn JM, Yom SK. Pentoxifylline and tocopherol in the management of cancer patients with medication-related osteonecrosis of the jaw: an observational retrospective study of initial case series. Oral Surg Oral Med Oral Pathol Oral Radiol 2016 Oct;122(4):455–9. 10.1016/j.oooo.2016.06.019. Epub 2016 Jul 13. [PubMed: 27651287]

[34]. Heifetz-Li JJ, Abdelsamie S, Campbell CB, Roth S, Fielding AF, Mulligan JP. Systematic review of the use of pentoxifylline and tocopherol for the treatment of medication-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol 2019 Nov;128(5):491–497.e2. 10.1016/j.oooo.2019.08.004. Epub 2019 Aug 14. [PubMed: 31488389]

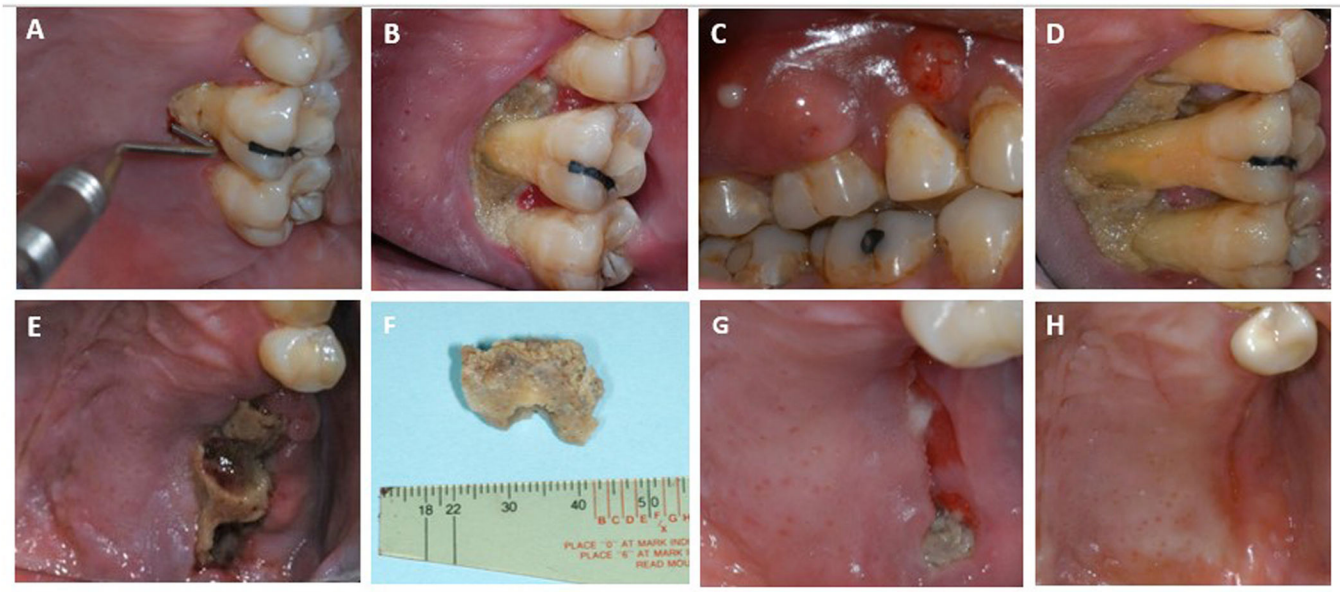

Fig. 1.

A 41-year-old female with history of multiple myeloma s/p autologous stem cell transplant and received 26 doses of intravenous zoledronic acid between October 2012 and April 2015. She underwent deep cleaning of her maxillary and mandibular left quadrants with her local dentist in April 2015. Two weeks later, she reported to our Dental Service with pain while eating. **A:** At the initial dental visit (V1): 5 mm × 8 mm exposed bone area on the palatal aspect of tooth number #14 associated with mild bleeding on probing.

B: V1 + 6 months: Root and bone exposure measuring 15 mm in length and 20 mm in mesiodistal width on the palatal surface of tooth number #14.

C: V1 + 12 months: Swelling involving the buccal gingiva between tooth number #12 and #13 and between tooth number #14 and #15 with purulent drainage. The area of exposed bone seen in the palatal area between #13, 14 and 15 remained unchanged.

D: V1 + 19 months: MRONJ site of the left maxilla noted spanning tooth number #13-#15. The entire palatal root of #14 was fully exposed. There was Grade 3 mobility of tooth number #13-#15.

E: V1 + 21 months: Grade II mobile bony sequestrum measuring 22 mm after gentle removal of tooth number #13-#15.

F: V1 + 21 months: Spontaneous exfoliation of the mobile bony sequestrum.

G: V1 + 23 months: Defect in the maxillary left region with near complete mucosal coverage. Exposed non mobile bone area measuring 5 mm × 5 mm was noted at the distal part of the defect.

H: V1 + 35 months: Complete soft tissue coverage with no bone exposure in the left maxilla. The previous noted area of exposed bone distal to the defect had naturally exfoliated prior to this visit.

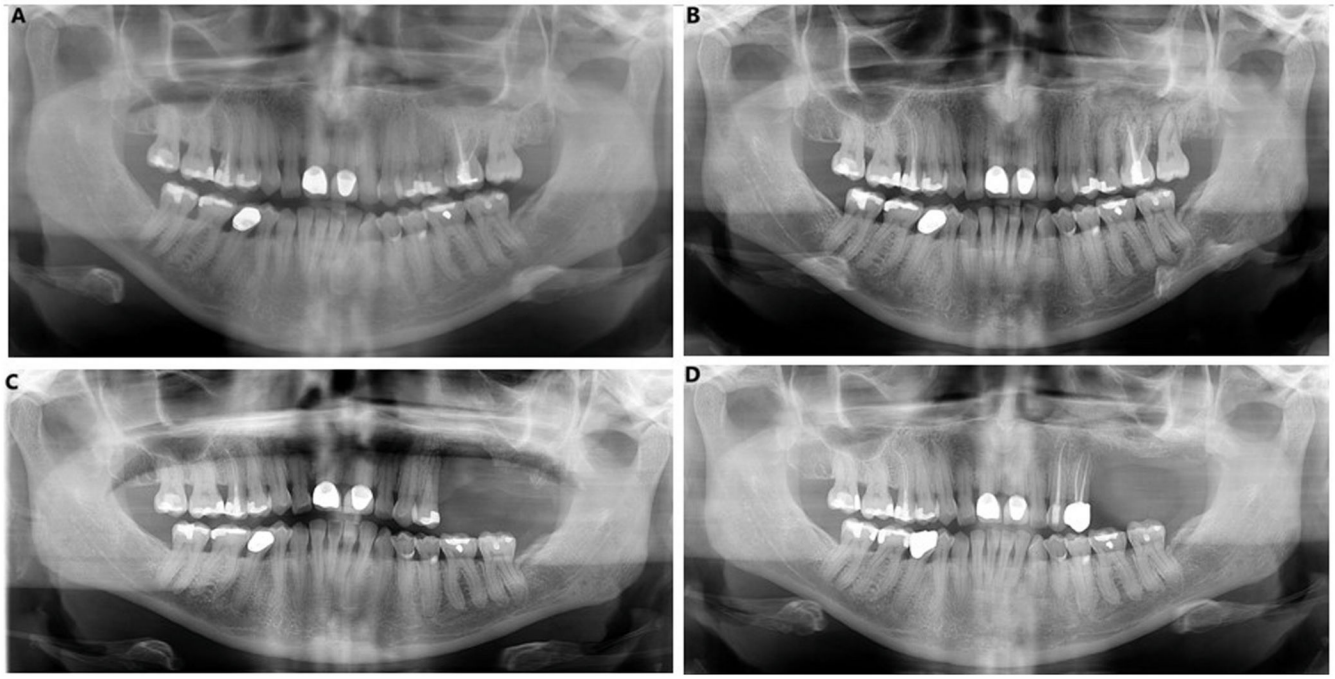

Fig. 2.

Panoramic radiograph. **A:** At the initial dental visit (V1): There were no obvious hard tissue lesions or radiolucent lesions. Normal trabecular patterns are noted throughout the jaws. **B:** V1 + 12 months: There was widening of periodontal ligament of teeth number #14 and #15. There were no obvious radiolucent lesions. **C:** V1 + 21 months from V1 following spontaneous exfoliation of the loose bony sequestrum. **D:** V1 + 35 months: Missing teeth number #13,14,15 and bone loss in the maxillary left posterior teeth.

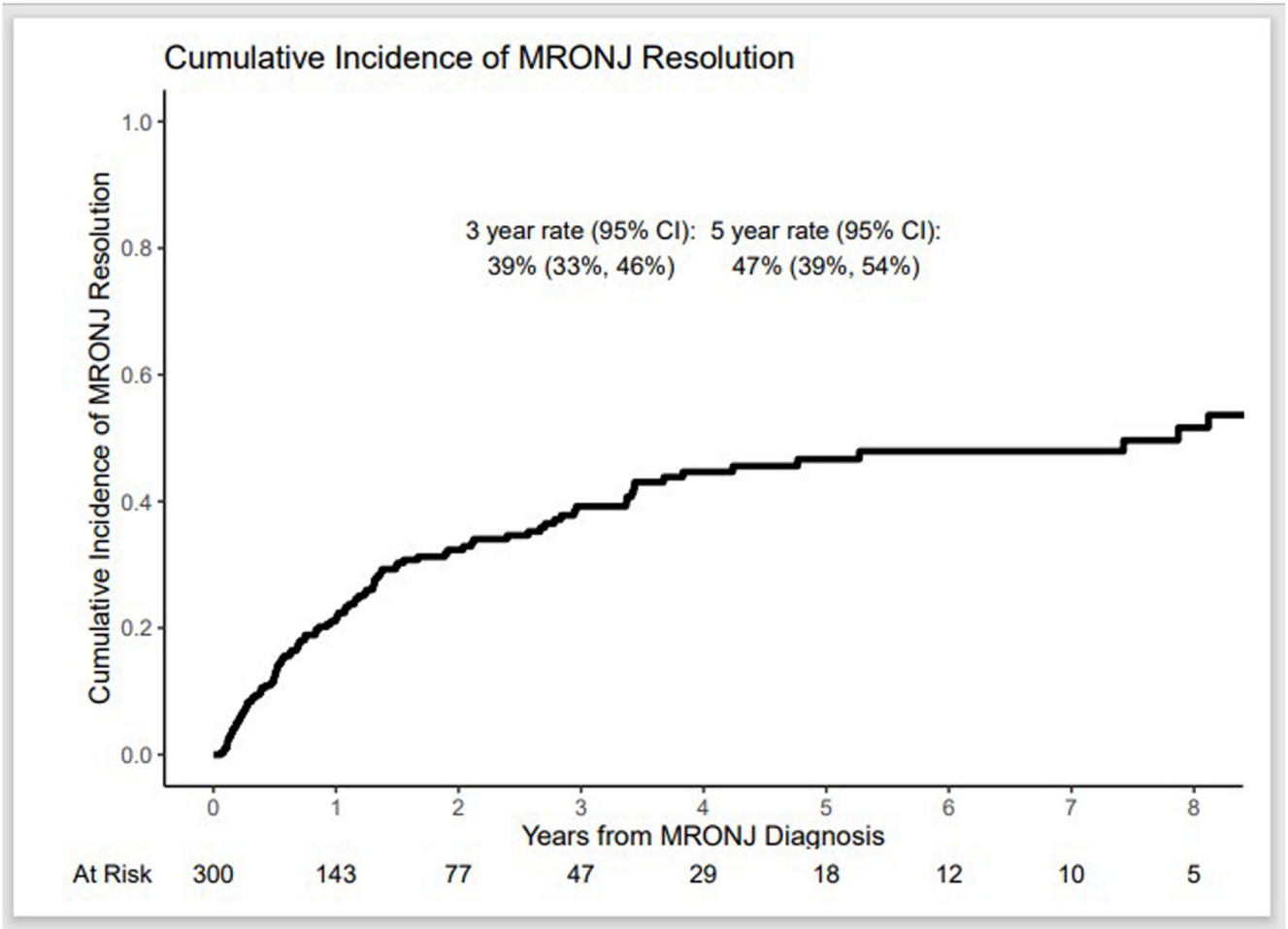

Fig. 3.

Cumulative incidence curve of MRONJ resolution was 39 % (95 % CI 33 %, 46 %) at 3 years and 47 % (95 % CI 39 %, 54 %) at 5 years.

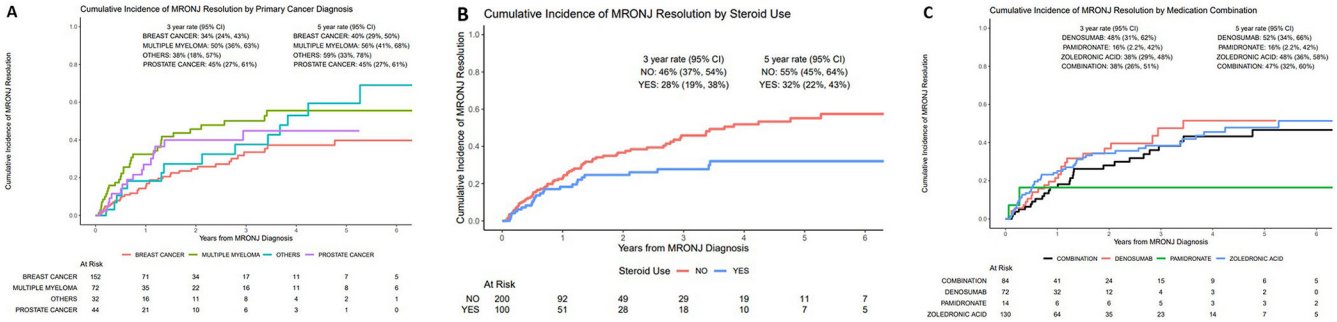

Fig. 4.

Cumulative Incidence (CI) curve of MRONJ resolution. **A:** By primary cancer diagnosis. The 3-year and 5-year rate of MRONJ resolution was lowest in patients with breast cancer (34 % and 40 %, respectively).

B: By concurrent corticosteroid use. The 3-year and 5-year rate of MRONJ resolution in patients without concurrent corticosteroid use was higher than those with concurrent corticosteroid use (46 % and 55 %, respectively).

C: By antiresorptive medication. The rate of MRONJ resolution in the first 2–3 years were overlapping between patients on denosumab and zoledronic acid.

Table 1

Patient characteristics.

Characteristic	Median; n (%)
Age	64 (IQR, 56–70)
Gender	
Female	190 (63)
Male	110 (37)
Primary Cancer Diagnosis	
Breast Cancer	152 (51)
Multiple Myeloma	72 (24)
Prostate Cancer	44 (15)
Others	32 (11)
Antiresorptive medication	
Zoledronic acid only	130 (43)
Denosumab only	72 (24)
Pamidronate only	14 (4.7)
Combination	84 (28)
Total medication doses before MRONJ diagnosis	19 (IQR, 10–32)
Unknown	31
Initial stage of MRONJ	
Stage 0	13 (4.3)
Stage 1	138 (46)
Stage 2	139 (46)
Stage 3	10 (3.3)
Size of exposed bone at time of initial MRONJ diagnosis	
No bone exposure	13 (4)
<1 cm	153 (51)
1–2 cm	50 (17)
>2 cm	42 (14)
Not recorded	42 (14)
MRONJ Location	
Mandible	194 (65)
Maxilla	85 (28)
Both	21 (7)
Etiology	
Non-spontaneous	158 (53)
Spontaneous	142 (47)
Concurrent corticosteroid use	
No	200 (67)
Yes	100 (33)
Chemotherapy	
Yes	260 (87)

Characteristic	Median; n (%)
No	40 (13)
Diabetes	
No	255 (85)
Yes	45 (15)
Alcohol	
Yes	166 (55)
No	134 (45)
Smoking	
Yes	125 (42)
No	175 (58)
Oral Hygiene	
Optimal	106 (38)
Suboptimal	176 (62)
Unknown	18

Table 2

Univariable analysis.

Characteristic	N	Event N	HR[a]	95 % CI[a]	p-value[b]
Gender					
Female	190	56	–	–	
Male	110	49	1.59	1.09, 2.31	**0.014**
Primary diagnosis					**0.047**
Breast cancer	152	42	–	–	
Multiple myeloma	72	33	1.90	1.20, 3.01	
Others	32	14	1.59	0.93, 2.70	
Prostate cancer	44	16	1.39	0.77, 2.50	
Medication					
Denosumab only	72	24	–	–	0.4
Pamidronate only	14	2	0.40	0.08, 1.95	
Zoledronic acid only	130	50	1.05	0.65, 1.71	
Combination	84	29	0.89	0.52, 1.50	
Initial Stage at diagnosis					0.8
0	13	6	–	–	
1	138	50	0.81	0.35, 1.86	
2	139	45	0.68	0.29, 1.58	
3	10	4	0.79	0.21, 2.99	
MRONJ location					0.061
Mandible	194	71	–	–	
Both	21	2	0.23	0.06, 0.93	
Maxilla	85	32	1.10	0.73, 1.66	
MRONJ size					0.051
<1 cm	153	61	–	–	
1–2 cm	50	14	0.75	0.42, 1.34	
>2 cm	42	10	0.46	0.25, 0.85	
Age (10-year increments)	300	105	0.95	0.80, 1.12	0.5
Total doses (6-unit increments)	269	96	0.93	0.86, 1.01	**0.071**
Concurrent corticosteroid use					
No	200	78	–	–	
Yes	100	27	0.55	0.35, 0.86	**0.004**
Diabetes					
No	255	85	–	–	
Yes	45	20	1.12	0.71, 1.77	0.7
Tobacco					
No	175	62	–	–	
Yes	125	43	0.94	0.64, 1.38	0.9
Alcohol use					
No	134	50	–	–	

Characteristic	N	Event N	HR[a]	95 % CI[a]	p-value[b]
Yes	166	55	0.87	0.60, 1.27	0.6
Oral hygiene					
Optimal	106	41	–	–	
Suboptimal	176	57	0.78	0.52, 1.17	0.3
Etiology					
Nonspontaneous	158	54	–	–	
Spontaneous	142	51	1.11	0.76, 1.63	0.5

[a]HR = Hazard Ratio, CI = Confidence Interval.

[b]Gray's Test.

Table 3

Multivariable analysis.

Characteristic	N	Event N	HR[a]	95 % CI[a]	p-Value
Primary Dx					**0.012**
Breast cancer	139	39	–	–	
Multiple Myeloma	63	30	2.27	1.38, 3.74	
Others	28	12	1.63	0.94, 2.83	
Prostate Cancer	39	15	1.57	0.87, 2.81	
Total Doses (6-unit increments)	269	96	0.92	0.85, 0.99	**0.034**
Concurrent corticosteroid use					
No	176	70	–	–	
Yes	93	26	0.49	0.31, 0.78	**0.002**

[a]HR = Hazard Ratio, CI = Confidence Interval.