

# Osteonecrosis of the Jaw among Patients Receiving Antiresorptive Medication: A 4-year Retrospective Study at a Tertiary Cancer Center, Kerala, India

## Abstract

**Purpose:** Osteonecrosis of the jaw (ONJ) is a rare but complicated side effect of antiresorptive medications. The aim of the study is to evaluate the dental and drug-related factors related to ONJ among patients on these drugs at a tertiary cancer center, India. **Methodology:** A retrospective record review of patients who received antiresorptive medication at our center from 2011 to 2014 was done. The demographic factors, type, dosage, and duration of the medication and dental history were collected, and the data were entered and analyzed using Epidata software. **Results:** A higher incidence of ONJ (8.1%) was noted in our sample ( $n = 183$ ). Dental intervention after zoledronic acid (ZA) administration showed a statistical significance ( $P < 0.001$ ). No significance ( $P$  value) was noted with respect to sex (0.78), age (0.28), median duration (0.9), and median dosage (0.9) of ZA. **Conclusion:** Oro-dental screening and dental monitoring shall reduce the incidence of ONJ. Within the limitations of our study, no significant relation could be pointed toward the dosage and duration of the drug and development of ONJ.

**Keywords:** Bisphosphonates, multiple myeloma, osteonecrosis of the jaw, zoledronic acid

## Introduction

Osteonecrosis of the jaw (ONJ) is a complication associated with antiresorptive medications (bisphosphonates and denosumab) and antiangiogenic drugs.<sup>[1]</sup> Patients with lytic lesions associated with multiple myeloma and solid tumors of the breast, prostate, lungs, kidney, and colon receive these medications.<sup>[2-7]</sup> Although the exact mechanism for the development of ONJ remains unclear, many have hypothesized that this may be secondary to disruption of bony remodeling and angiogenesis inhibition precipitated by excessive local microtrauma in the presence of a microbiologically diverse oral environment, causing impairment of local healing.<sup>[4,8-10]</sup>

Several risk factors of ONJ have been identified which includes drug-related factors, i.e., type of drug, dosage, duration and mode of administration, comorbidities, steroid therapy, genetic factors, tobacco and alcohol use, etc.<sup>[11]</sup> Parenteral administration of bisphosphonates for 3 years or more increases the risk of ONJ incidence 20 times.<sup>[12-14]</sup> Dental intervention/surgery

is one of the strongest risk factors of ONJ. More than half of the patients with ONJ had tooth extraction as a predisposing event.<sup>[14-16]</sup> Periodontal and periapical surgery and dental implants in patients receiving intravenous (IV) bisphosphonate increase the risk of ONJ by 7 fold.<sup>[7,17]</sup> Dental screening and necessary dental care reduce the risk of ONJ by 50%.<sup>[18,19]</sup>

However, there is a lack of scientific literature on ONJ and its risk factors in India. Most studies are confined to case reports only.<sup>[20]</sup> Thus, the present study was carried out to study the factors associated with ONJ and the time taken for onset of ONJ after initiation of antiresorptive medications at a tertiary cancer center in India.

## Methodology

### Study design

This was a retrospective cohort study involving review of patient case records.

### Study setting

Kerala is a state in South India with a population of 33.4 million, spread over 14

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districts. Kannur district is in northern part of the state with a population of 2.5 million.<sup>[21]</sup> The incidence of cancer in Kannur is increasing with a crude incidence rate of 33.8/100,000, and the cancer care is being catered by both public and private health facilities.<sup>[22]</sup>

### *Specific setting*

Malabar Cancer Center (MCC) is an autonomous institution under the Government of Kerala which was established in the year 2001 to provide state-of-the-art oncology care to patients from Kerala and neighboring states such as Karnataka and Tamil Nadu. It caters to around 70,000 cancer patients every year.

Multiple myeloma and solid tumor patients with skeletal metastasis are routinely planned for initiation of antiresorptive medication to reduce pain and skeletal-related events by the medical oncologists. The department of dentistry and rehabilitation is involved in oro-dental screening and necessary dental treatments for all the registered cancer patients.

### **Study period**

This study was conducted from June 2016 to December 2016.

### **Study population**

All multiple myeloma patients and patients with solid tumors who received antiresorptive medication during January 2011 to December 2014 at MCC and were followed up for at least 1 year were included in the study.

### **Exclusion criteria**

Patients who died or were lost to follow up within 1 year of initiation of antiresorptive medication and those with previous history of radiotherapy to head and neck region were excluded from the study.

### **Operational definitions**

#### *Osteonecrosis of the jaw*

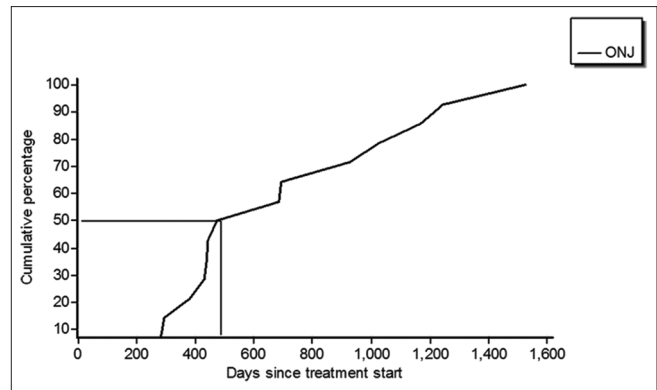
According to the American Academy of Oral and Maxillofacial Surgeons,<sup>[11]</sup> Patients may be considered to have medication-related osteonecrosis of the Jaw (MRONJ) if all of the following three characteristics are present:

1. Current or previous treatment with antiresorptive or antiangiogenic agents
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula (e) in the maxillofacial region that has persisted for more than 8 weeks
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

Figures 1 and 2 represent the clinical and radiographic picture of MRONJ.

#### *Antiresorptive medication*

Medications inhibit bone resorption and/or favor bone mineralization and bone regeneration.



**Figure 1: Time to develop osteonecrosis of the jaw among patients taking zoledronic acid at a tertiary cancer center in Kerala, India, 2011–2015**

### *Oro-dental screening*

Screening included evaluation of intraoral soft-tissue health, dental health status, periodontal condition, and status of the restorations and/or prosthesis.

### *Dental intervention*

Dental care provided by surgical or nonsurgical approaches.

### **Data collection**

Unique Hospital Identification Number (UHID) of all the patients who received antiresorptive medication during the study period was collected from the Medical Oncology Department, MCC, Thalassery. Subsequently, patient case records were retrieved from the medical record division with the help of the UHIDs. Data were extracted from patient case records into data abstraction form. Demographic (age and sex) and clinical (comorbidities, primary disease, any dental intervention, steroid use, cumulative drug dosage, development of ONJ, date of start of treatment, and date of diagnosis of ONJ) variables were collected.

### **Data entry and analysis**

The collected data were double entered and validated using EpiData entry v3.1 and analyzed using EpiData analysis v2.2.2.182 (EpiData Association, Odense, Denmark). Chi-square test and *t*-test wherever applicable were used to study the role of sociodemographic and clinical variables in the development of ONJ. A cumulative plot was drawn to describe the timing of development of ONJ after starting on antiresorptive medication.

### **Ethics approval**

The study was ethically approved by the Institutional Scientific Committee at MCC and The Union Ethics Advisory Group, Paris, France. Data were extracted from routinely filled patient case records without the name or any other personal identifiers.

### **Results**

Among 183 patients on IV zoledronic acid (ZA) and followed up for 1 year, 15 developed ONJ. Only



**Figure 2: Clinical presentation of osteonecrosis of the jaw of right posterior mandible in a 70-year-old patient on zoledronic acid (edited photograph of patient [not included in the study] after getting duly signed consent)**



**Figure 3: Orthopantomograph of a 58-year-old female with osteonecrosis of the jaw or mandible at right posterior mandible in relation to tooth 45. The thickening of lamina dura, a classic feature of osteonecrosis of the jaw, is evident. (Edited OPG of patient not included in the study; retrieved from medical records after administrative approval)**

2 patients underwent dental screening before starting medication (data not tabulated). Dental intervention emerged as a significant risk factor for the onset of ONJ ( $P < 0.001$ ). Median (interquartile range) duration and cumulative dosage of ZA for the onset of ONJ were 14 (10–23) months and 56 (40–92) mg, respectively. Intake of steroids ( $P = 0.12$ ) and comorbid diabetes ( $P = 0.8$ ) failed to show a statistically significant association with the onset of ONJ. The median time of onset time for ONJ was 683 (429–1169) days [Table 1].

Figure 1 shows that 50% of the cases of ONJ developed within 483 days of starting antiresorptive medication.

Table 2 shows the detailed patient-wise clinical profile, treatment, and follow-up status of patients taking ZA who developed ONJ.

Figures 2 and 3 represent the clinical and radiographic pictures of ONJ related to bisphosphonates.

### Discussions

The retrospective study analyzed the drug-related and dental-related factors related to ONJ in patients on ZA therapy. The cumulative drug dosage or drug administration duration was not showing any difference in the two groups. The effect of drug type could not be assessed as all the patients received a single type of drug. More than 50% of the patients who developed ONJ had some form of dental interventions after initiation of the drug.

The higher incidence of ONJ in breast cancer patients (5%) and multiple myeloma patients (8%) is in consensus with the study by Vandone *et al.*<sup>[19]</sup> The primary disease was insignificant as in other studies.<sup>[12]</sup>

Published literature suggests that the risk of ONJ increases with dosage and duration of drug administration.<sup>[2-5,12,13]</sup> All our patients received ZA ranging from 5 to 33 months with a mean onset duration of ONJ at 15 months.

**Table 1: Factors associated with development of osteonecrosis of the jaw among patients on zoledronic acid at Malabar Cancer Center, Thalassery, Kerala, India, from 2011-2014**

Characteristics	ONJ (n=15)	No ONJ (n=168)	P
Median age in years (interquartile range)	54 (50-60)	60 (52-66)	0.28
Sex, n (%)			
Male	5 (33)	62 (37)	0.78
Female	10 (67)	106 (63)	
Primary disease, n (%)			
Breast cancer	5 (33)	70 (42)	0.27
Multiple myeloma	8 (53)	56 (33)	
Others	2 (13)	42 (25)	
Median duration of ZA in months (interquartile range)	14 (10-23)	15 (12-20)	0.9
Median cumulative dosage of ZA in mg (interquartile range)	56 (40-92)	60 (48-79)	0.9
Median time of onset of ONJ in days (interquartile range)	683 (429-1169)	-	
Dental intervention, n (%)	9 (60)	13 (8)	<0.001
Steroid administration, n (%)	8 (53)	57 (34)	0.12
Comorbid diabetes, n (%)	2 (13)	21 (13)	0.8

ONJ: Osteonecrosis of the jaw; ZA: Zoledronic acid

Exclusion of patients who did not complete a minimum 1-year follow-up might be the reason for the statistical insignificance.

Dental screening before initiating antiresorptive medication and regular dental monitoring reduces the risk of ONJ.<sup>[23,24]</sup> The screening and necessary dental treatment would minimize the need for any surgical dental procedures later. Restorative and endodontic treatment and oral prophylaxis can be done safely in patients on antiresorptive medications. Dental extractions, dental implants, periodontal disease, poorly fitting dentures, and bony exostoses are the precipitating risk factors for ONJ.<sup>[12]</sup> Our sample (99%) lacked dental screening which

**Table 2: Clinical profile of patients on zoledronic acid who developed osteonecrosis of the jaw at Malabar Cancer Center, Thalassery, Kerala, India, from 2011-2014**

Patient number	Diagnosis	Age	Sex	ZA dosage (mg)	Onset of ONJ (days)	Dental interventions	Site (s) of ONJ	Treatment of ONJ	Status of ONJ lesion	Follow-up status (as on December 2016)
1	Multiple myeloma	50	Male	132	1525	None	Posterior mandible	Conservative <sup>#</sup>	No progression	On follow-up
2	Multiple myeloma	50	Female	96	1615	Restorative	Posterior mandible	Conservative	No progression	On follow-up
3	Multiple myeloma	77	Male	40	379	Extractions	Posterior mandible	Surgical	Resolution	Lost to follow-up
4	Multiple myeloma	51	Female	96	1026	Surgical	Posterior mandible	Conservative	No progression	On follow-up
5	Multiple myeloma	60	Female	32	429	None	Posterior maxilla and anterior mandible	Conservative	No progression	On follow-up
6	Multiple myeloma	59	Male	80	926	Surgical	Posterior mandible	Conservative	Resolution	On follow-up
7	Multiple myeloma	54	Female	92	475	Extractions	Posterior mandible	Conservative	No progression	Lost to follow-up
8	Multiple myeloma	49	Female	56	1169	Restorative	Posterior mandible	Conservative	No progression	On follow up
9	Breast cancer	71	Female	48	1245	None	Posterior mandible	Conservative	No progression	On follow-up
10	Breast cancer	54	Female	92	691	Extractions	Posterior mandible	Conservative	Resolution	Lost to follow-up
11	Breast cancer	39	Female	60	440	None	Posterior mandible	Conservative	Not available	Lost to follow-up
12	Breast cancer	44	Female	36	283	Conservative	Posterior maxilla and anterior mandible	Conservative	No progression	On follow-up
13	Breast cancer	58	Female	48	441	None	Posterior mandible	Conservative	Progression	On follow-up
14	Prostate cancer	78	Male	32	683	None	Posterior mandible	Conservative	No progression	Lost to follow-up
15	Prostate cancer	52	Male	48	294	Restorative	Posterior mandible	Conservative	Not available	Lost to follow-up

<sup>#</sup>Implies use of antibiotics. ZA: Zoledronic acid; ONJ: Osteonecrosis of the jaw

might have necessitated dental extractions (45%) in due course that resulted in ONJ. A study by Montefusco *et al.* suggested that prophylactic antibiotics before and during dental procedures may reduce the risk of developing ONJ.<sup>[25]</sup>

Our data are also in consensus for site of ONJ.<sup>[12,24]</sup> Less vascularity and dense bone of the mandible might have triggered the onset of ONJ. After any dental surgeries, a minimum healing period of 3 weeks is suggested before starting antiresorptive medication.

The study being a retrospective record review has got its inherent defects in the design. Lack of in-house dental treatment facility than at our center did not provide any oro-dental screening or oral care instructions for the patients. The effect of drug type could not be assessed as all the patients received ZA alone. Missing entries in patient's record might have excluded the patients too.

The greatest strength of the study is that it could be used as a baseline data upon which further prospective trails can be planned. Most of the published studies are related to Western population and our data will provide an insight to the risk factors among Indian population. These data may be extrapolated for initiating a standard protocol for dental care of patients planned for antiresorptive medications at our center. Thus, the incidence of ONJ and the possible need for discontinuation of medications can be certainly avoided. The risk factors and treatment strategies for ONJ need for discontinuation of the medication and overall patients' response to cancer treatment should be put for further study prospectively

## Conclusion

Dental intervention after initiation of antiresorptive medication is a significant risk factor for the onset of ONJ. Duration and dosage of ZA therapy were not related to

the development of ONJ. Dental screening and necessary dental treatment before initiation of the drug should be a mandate.

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### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given consent for images and other clinical information to be reported in the journal. The patients understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

### References

- Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L, Pompa G, *et al.* Medication-related osteonecrosis of the jaw: Clinical and practical guidelines. *J Int Soc Prev Community Dent* 2016;6:97-104.
- Bamias A, Kastritis E, Bamia C, Mouloupoulos LA, Melakopoulos I, Bozas G, *et al.* Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: Incidence and risk factors. *J Clin Oncol* 2005;23:8580-7.
- Dimopoulos MA, Kastritis E, Anagnostopoulos A, Melakopoulos I, Gika D, Mouloupoulos LA, *et al.* Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: Evidence of increased risk after treatment with zoledronic acid. *Haematologica* 2006;91:968-71.
- Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005;353:99-102.
- Zervas K, Verrou E, Teleioudis Z, Vahtsevanos K, Banti A, Mihou D, *et al.* Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: A single-centre experience in 303 patients. *Br J Haematol* 2006;134:620-3.
- Aragon-Ching JB, Ning YM, Chen CC, Latham L, Guadagnini JP, Gulley JL, *et al.* Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents. *Cancer Invest* 2009;27:221-6.
- Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: Bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006;144:753-61.
- Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 2005;63:1567-75.
- Woo SB, Hellstein JW, Kalmar JR. Systematic review: Bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006;144:753.
- Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115-7.
- Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, *et al.* American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg* 2014;72:1938-56.
- Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, *et al.* Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res* 2008;23:826-36.
- Tsao C, Darby I, Ebeling PR, Walsh K, O'Brien-Simpson N, Reynolds E, *et al.* Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. *J Oral Maxillofac Surg* 2013;71:1360-6.
- Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT, *et al.* 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;23:1341-7.
- Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis CG, *et al.* Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. *J Clin Oncol* 2009;27:5356-62.
- Fehm T, Beck V, Banys M, Lipp HP, Hairass M, Reinert S, *et al.* Bisphosphonate-induced osteonecrosis of the jaw (ONJ): Incidence and risk factors in patients with breast cancer and gynecological malignancies. *Gynecol Oncol* 2009;112:605-9.
- Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, *et al.* Osteonecrosis of the jaw in multiple myeloma patients: Clinical features and risk factors. *J Clin Oncol* 2006;24:945-52.
- Bonacina R, Mariani U, Villa F, Villa A. Preventive strategies and clinical implications for bisphosphonate-related osteonecrosis of the jaw: A review of 282 patients. *J Can Dent Assoc* 2011;77:b147.
- Vandone AM, Donadio M, Mozzati M, Ardine M, Polimeni MA, Beatrice S, *et al.* Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: A single-center clinical experience. *Ann Oncol* 2012;23:193-200.
- Rastogi A, Rattan V, Bhadada SK. Osteonecrosis of jaw associated with bisphosphonate use. *Indian J Endocrinol Metab* 2012;16:450-2.
- Kannur (Cannanore) District Population Census. Kerala Literacy Sex Ratio and Density; 2011. Available from: <http://www.census2011.co.in/census/district/272-kannur.html>. [Last accessed on 2017 May 05].
- Nandakumar A, Gupta PC, Gangadharan P, Visweswara RN, Parkin DM. Geographic pathology revisited: Development of an atlas of cancer in India. *Int J Cancer* 2005;116:740-54.
- Dimopoulos MA, Kastritis E, Bamia C, Melakopoulos I, Gika D, Roussou M, *et al.* Reduction of osteonecrosis of the jaw (ONJ)

- after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. *Ann Oncol* 2009;20:117-20.
24. Bramati A, Girelli S, Farina G, Dazzani MC, Torri V, Moretti A, *et al.* Prospective, mono-institutional study of the impact of a systematic prevention program on incidence and outcome of osteonecrosis of the jaw in patients treated with bisphosphonates for bone metastases. *J Bone Miner Metab* 2015;33:119-24.
25. Montefusco V, Gay F, Spina F, Miceli R, Maniezzo M, Teresa Ambrosini M, *et al.* Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates. *Leuk Lymphoma* 2008;49:2156-62.