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Bisphosphonate induced osteonecrosis of the jaw – A review in cancer patients.

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Abstract

Aim & Objectives

To estimate the incidence of Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ) in cancer patient using C-terminal telopeptide biomarker and OPG and dental evaluation.

To formulate possible protocols to prevent BRONJ and to provide more effective management.

To determine association of BRONJ to therapy, duration of treatment on bisphosphonate modality and efficacy of C-terminal telopeptide biomarker in predicting BRONJ.

Methods

A patient who falls within the inclusion criteria, the following investigation was carried out.

1.C-terminal telopeptide biomarker

2.OPG

3. Dental evaluation.

Patient came with a dental problem requiring dental extraction /oral surgical procedure –

- Duration of bisphosphonate usage was recorded. (dosage for iv remains mostly same 4mg/100ml)
- Drug holiday of 3 months (if possible as a standard protocol reference –Marx et all)
- Before drug holiday CTX done.

After extraction, before initiation of bisphosphonate (probably gap of 2-3 month after extraction depending on the healing of socket and disease), CTX was recorded.

Results

Our statistical analysis showed that BRONJ lesions smaller than 1 cm were associated with better prognosis with respect to treatment outcome (P = 0.0009). Moreover, local treatments combined with long-term antibiotics were also correlated with a better prognosis (P = 0.02).

Keywords: Osteonecrosis, Bisphosphonates, C-Terminal Telopeptide, Cancer

Introduction

Bisphosphonates are a class of drugs that prevent the loss of bone mass. It has been demonstrated that high-potency intravenous bisphosphonates can slow the advancement of malignant bone disease in a wide range of cancer types, particularly breast and frequently prostate cancer and multiple myeloma.

Bisphosphonates bond firmly to the surface of the bone beneath the "osteoclasts," which actively break down bone, after being ingested or administered intravenously. The medications then integrate into the osteoclasts and prevent them from breaking down bone. As a result, bone density is increased, bone loss is minimized, and the risk of fracture is decreased.

Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ) can be described as an area of bone in the jaw that has died and been exposed in the mouth for more than 8 weeks in a person taking any bisphosphonate. BRONJ is thought to be a side effect of bisphosphonate medication, despite the fact that the precise origin is uncertain. The most common way to recognize BRONJ is by the presence of exposed bone in the oral cavity.

BRONJ symptoms include exposed bone, a localized ache, inflammation and gum tissue swelling,

teeth that were once stable loosening.

Objective of the study

To estimate the incidence of Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ) in cancer patient using C-terminal telopeptide biomarker and OPG and dental evaluation.

To formulate possible protocols to prevent BRONJ and to provide more effective management.

To determine association of BRONJ to therapy, duration of treatment on bisphosphonate modality and efficacy of C-terminal telopeptide biomarker in predicting BRONJ.

Justification

This paper will contribute significantly to existing knowledge on the BRONJ and in identification of a better solution to benefit the patient. (1.7% of patient taking bisphosphonate develop BRONJ -0.8-1.2% if IV ,0.01% -0.06% if oral. Value increases if oral surgical intervention. -reference Marx et all -2000, Journal of oral and maxillofacial)

In order to have definitive conclusion on utility of CTX biomarker.

The paper will be useful in assisting clinician to determine a patient's non-surgical treatment response as well as evaluate patients' risk of developing complications during healing following surgical intervention.

Inclusion Criteria

- Cancer patient with skeletal metastasis. (Include breast cancer with skeletal Mets, prostate cancer with skeletal Mets.
- Multiple myeloma

Exclusion Criteria

- Oral cancer patient who has taken radiation therapy.
- Patient not willing for the study.
- Cancer patient taking Denosumab.
- Cancer patient taking sunitinib, bevacizumab, sorafenib.

Methodology

A patient who falls within the inclusion criteria, the following investigation was carried out.

- C-terminal telopeptide biomarker
- OPG
- Dental evaluation.

patient came with a dental problem requiring dental extraction /oral surgical procedure.

- Duration of bisphosphonate usage was recorded. (dosage for iv remains mostly same 4mg/100ml)

- Drug holiday of 3 months (if possible as a standard protocol reference –Marx et all)
- Before drug holiday CTX done.
- After extraction, before initiation of bisphosphonate (probably gap of 2-3 month after extraction depending on the healing of socket and disease), CTX was recorded.

Data was collected for patient visiting hospital from 2012 to December 2020

C-terminal telopeptide cross link biomarker (CTX)

- CTX is a biological marker used to measure rate bone resorption and remodelling. (bone turn over)
- Introduced by Rosen in 2000
- Marx in 2007 gave risk stratification table on BRONJ and Bisphosphonate (ref –journal of oral and maxillofacial surgery)

CTX value (pg/mL)	Assigned risk
<100	High
100-150	Moderate
>150	Minimal

OPG

Sclerosis of laminadura.

Widening of periodontal ligament space (because of this bone remodels in response to occlusal forces).

Since molar area have wider occlusal table and compressive forces are greater on molar, there is higher incidents of Osteonecrosis in the molar region.

Even in edentulous patients the target area remains alveolar bone because of compressive forces from denture wearing on the alveolar crest or round dental implant that are loaded for denture function. (figure 1)

Osteonecrosis

It is a degenerative bone condition characterised by death of cellular components of bone owing to interruption of sub chondral blood supply, resorptive components of repair process results in loss of structural integrity.

These osteonecrosis manifest in the form of:

1. Bone exposure.
2. Recent tooth mobility
3. Swelling and inflammation
4. Occasionally localised pain but they can remain asymptomatic for weeks or even months.

- The prevalence of osteonecrosis in cancer patient with Bisphosphonate could range from 1to 10%.
- Bisphosphonate ae potent inhibitors of osteoclasts.
- They are used in cancer patients with skeletal metastasis, including breasts, prostate or lung cancer and inpatient with multiple myeloma.
- Bisphosphonate are also used to treat hypercalcemia of malignancy.
- Bisphosphonate reduce the risk of fracture and skeletal pain, improving the quality of life of patient with malignant bone disease. (Figure 2)

Bisphosphonate chemistry and pharmacology

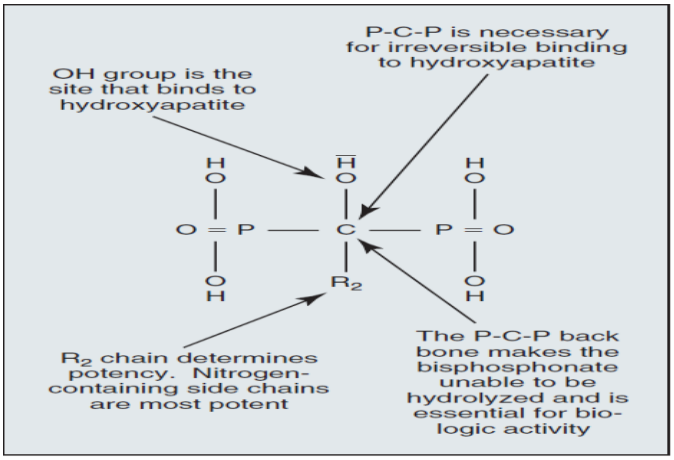
The phosphate components impart an affinity for bone from the systemic circulation – similar to Tc 99m.

The backbone carbon provides strong binding to hydroxyapatite in bone.

Half-life in bone has been found to be longer than 11 years.

Intravenous administration of a bisphosphonate results in renal clearance of 30% to 40% of the drug.

The remaining 60% to 70% becomes bound to bone with a half-life of 11 years



Drugs associated with osteonecrosis

1.Etidronate (didronel) No nitrogen chain Bisphosphonate

2.Tiludronate (skelid)

3.Resedronate (Actonel)

4.Alendronate (Fosamax)

5.Ibandronate(Boniva)

6.Pamidronate

7.Zoledronic acid - Bisphosphonate (antiresorptive)

8.Pamidronate - Bisphosphonate (antiresorptive)

9.Ibandronate- Bisphosphonate (antiresorptive)

10.Alendronate - Bisphosphonate (antiresorptive)

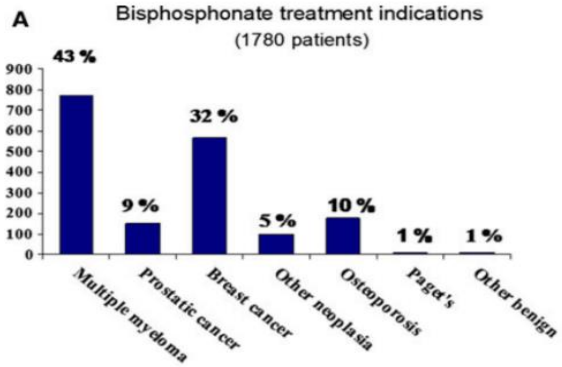
11.Denosumab – Humanized monoclonal antibody (antiresorptive)

12.Bevacizumab – Antiangiogenic

13.Sunitinib – Antiangiogenic

14.Sorafenib – Antiangiogenic

15. Cabozantinib- Antiangiogenic



Result

We retrieved 2,000 cases, 88% of which were associated with intravenous therapy, primarily with zoledronate. Of the total number of cases, 89% were associated with the treatment of a malignant condition, particularly multiple myeloma.

Our patients underwent two treatment schemes; the first scheme comprised medical and surgical treatments, whereas the second was composed of only medical treatments. Of the 2000 patients who underwent dental treatments are 500, dental treatment included simple dental care 400, dental extractions50, root canal treatments50. In this group of patients.

Patients suffered from bronj 14 patients recovered with conservative treatment which included antibiotic prescription Beta-lactam drugs were prescribed most frequently, including the following treatments: aminopenicillins (39% of patients), a combination of aminopenicillins and beta-lactamase inhibitors (28% of patients) and methoxyphenyl penicillin (26% of patients). These treatments were followed by either treatment with clindamycin (33% of patients) or metronidazole (13% of patients) or treatment with other drugs, such as tetracyclines (11%) or fluoroquinolones (1%) 5 patients suffered from persistent BRONJ in which 2 expired 3 are on follow up ,1 patient lost follow up.

In these cases, in which the sex of the patient was reported, more than 60% of patients were women. Reported cases manifested as exposed bone of the mandible (65% of these cases), the maxilla (27%), both jaw 8 %.

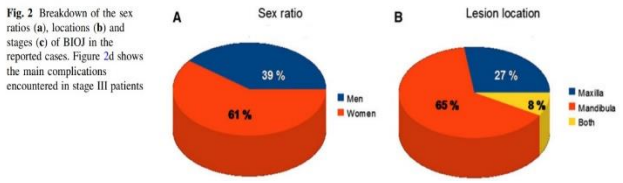
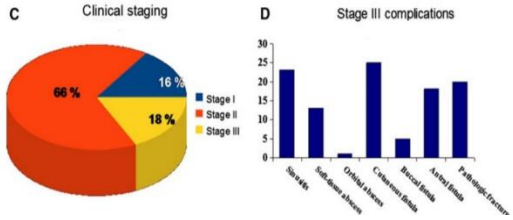
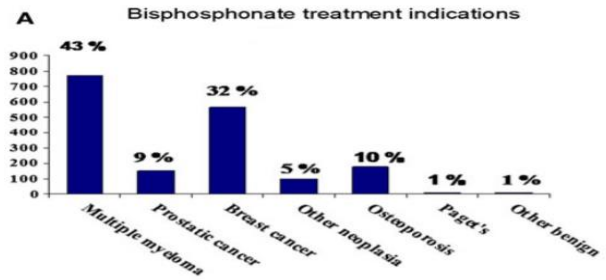


Fig. 2 Breakdown of the sex ratios (a), locations (b) and stages (c) of BIOJ in the reported cases. Figure 2d shows the main complications encountered in stage III patients

Of these patients, 66% were in stage II (painful or infected necrotic bone), whereas in 16 and 18% of patients, the complication was in stage I (asymptomatic necrotic bone) or stage III (extraoral complications, extensive sequestration, or pathological fracture).



Among the malignant conditions, multiple myeloma accounted for the majority of cases, followed by metastatic breast and prostate cancers and other neoplasms; these diseases were observed in 43, 32, 9, and 5% of the cases, respectively.



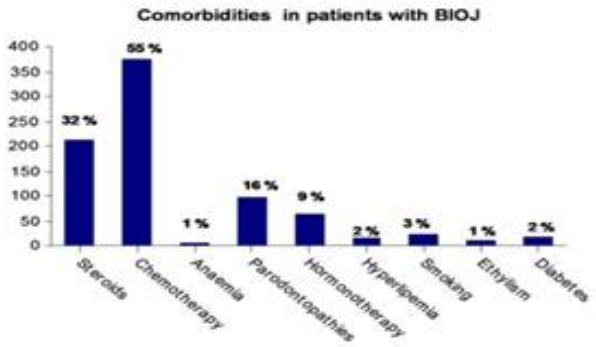
Events that induced BRONJ most cases (67%) were induced by dental extractions. In 7% of the cases, osteonecrosis was caused by a different factor, such as a denture pressure sore or a torus.

Patients who are placed 6-month drug holiday, exhibit marked improvement in their serum CTX value.it showed improvement of 155.5pg/ml over 6 months (a rate of 25.9pg/ml each month) reference Marx et all - 2007.

CTX is not predictive of developing of BRONJ for an individual patient but does identify those in the risk zone which is less than 150pg/ml.

lower CTX results among and concluded that positive correlation does exist.

The sensitivity and specificity of CTX cut off of 150 pg/ml in predicting osteonecrosis were 37.5%and 57.7%respectively.



Conclusion

Prevention is better than treatment, and the establishment of meticulous oral hygiene and surgical procedures prior to commencing BP treatment is important for preventing BRONJ.

Our statistical analysis showed that BRONJ lesions smaller than 1 cm were associated with better prognosis with respect to treatment outcome (P = 0.0009). Moreover, local treatments combined with long-term antibiotics were also correlated with a better prognosis (P = 0.02).

BRONJ is a complication that severely impairs the quality of life. Our review summarized the current clinical knowledge on this complication, although most of the studies reviewed were retrospective and uncontrolled. There is a need for more formal clinical and basic research studies on this subject in order to develop a cure for this painful condition.

Currently, the use of BPs is recommended only until the disease is stabilized for 2 years or until a beneficial response to treatment is observed (Durie 2007; Kyle et al. 2007).

The prolonged skeletal half-life of bisphosphonate may suppress bone turn over markers in BRONJ patients for several years after discontinuation of IV bisphosphonate

therapy suggesting an extended effect on bone homeostasis.

Among inclusion criteria patients, if speaking about 3 year cumulative incidence of osteonecrosis of the jaw ,it was 0.8% in 1st year ,2% at 2nd year and 2.8% in third year .The rate was highest in patients with multiple myeloma -4.3% and lowest with breast cancer 2.4%

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Legend Figure

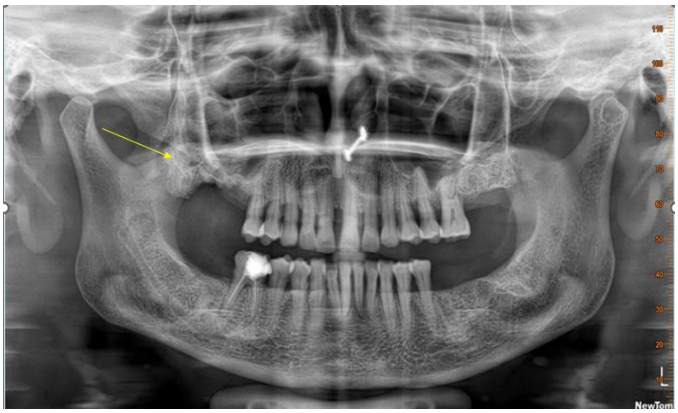

Figure 1

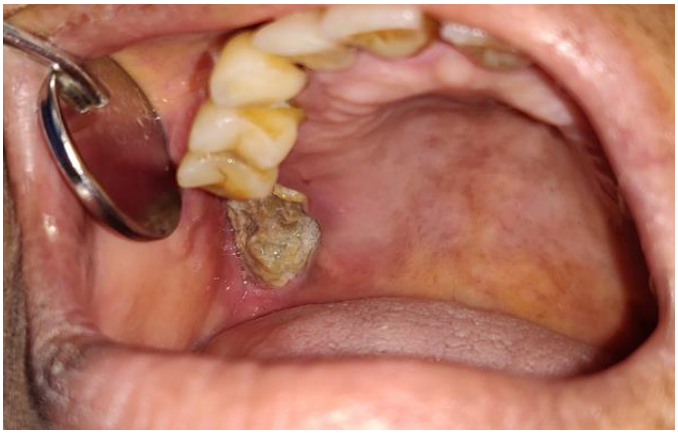

Figure 2