Osteonecrosis of the jaw secondary to bisphosphonate treatment in multiple myeloma-real world data.

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Introduction:

The working definition of Medicine related osteonecrosis of the jaw (ONJ) has been modified from the 2009 American association of Oral and Maxillofacial surgery position paper. Patients can be considered to have ONJ if all of the following characteristics are present:[1]

- Current or previous treatment with anti-resorptive or antiangiogenic agents
- Exposed bone or bone that can be probed through an intraoral or extra oral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- No history of radiation therapy to the jaw or obvious metastatic disease to the jaws.

The pathophysiology of medicine induced ONJ is not entirely clear. Several potential instigating factors have been implicated in the development of ONJ, such as:

Altered bone remodelling and over suppression of bone resorption-Bisphosphonate is known to inhibit osteoclastic differentiation and induce apoptosis of osteoclasts leading to reduced bone remodelling.

Inhibition of angiogenesis- There is a growing body of literature linking ONJ and anti-angiogenesis factors used in cancer therapy. Studies in patients with cancer treated with zoledronic acid have supported these data by reporting decreased circulating VEGF levels.[2]

Inflammation and infection

Other possible risk factors implicated in development of ONJ are concomitant oral and dental disease, dental extraction, malignancy, corticosteroid, diabetes and tobacco use.

Bisphosphonates form part of current treatment guidelines for active myeloma whether or not lytic bone disease is present. There is widespread variance in local protocol regarding optimal duration of this therapy as there is no clear evidence to support a certain strategy. It is widely agreed appropriate to treat during active disease but management during asymptomatic remission is unclear.

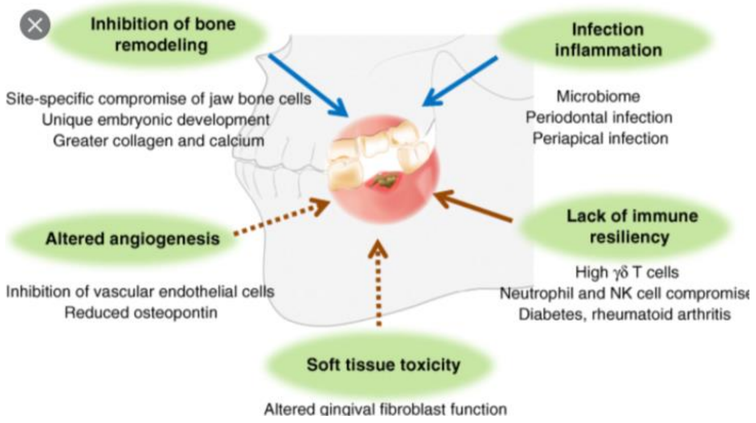

Fig.1 Pathogenesis of ONJ[3]

Objective:

- The main objective of this retrospective data analysis is to create awareness of bisphosphonate induced osteonecrosis of the jaw, which is a rare but well documented adverse effect of intravenous treatment.

Material and Method:

- Data for all myeloma patients who had bisphosphonate therapy was collected retrospectively.
- Data was collected from the hospital patient's record, electronic prescription (ARIA) and hospital PACs (Radiology) system.
- Diagnosis of osteonecrosis of Jaw was confirmed by radiological imaging and specialist clinical input.

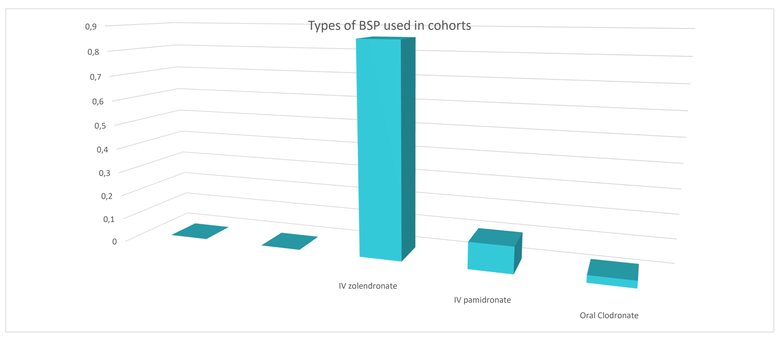

Fig.2 Types of BSP used in cohorts

Results:

- We analysed the data from 77 myeloma patients receiving bisphosphonate therapy.
- The age range of the patients receiving zoledronic acid was between 53 and 89 with a median age of 74 years.
- Forty-seven patients out of 77, had skeletal myeloma deposits.
- Prior to commencing bisphosphonate, 34 out of 77 patients (44%) had formal dental review. Around 43 (56%) patients had dental assessment with untraceable outcome. Of the patients who had a formal dental assessment, one third (33%) required dental procedures prior to commencing bisphosphonates.
- Around 86% of the cohort received zoledronic acid whereas, pamidronate and oral bisphosphonate was given to 11% and 3% of the cases, respectively.
- Duration of bisphosphonate use was variable depending on the time of myeloma diagnosis, ranging between 1 month to 98 months.
- Frequency of infusion varied between 4 to 12 weekly intervals, depending on the status of myeloma treatment, i.e. active myeloma vs. remission. All patients had appropriate renal dose adjusted therapy of zoledronic acid.
- Four out of 77 patients (5%) were found to have bisphosphonate induced osteonecrosis of the jaw.

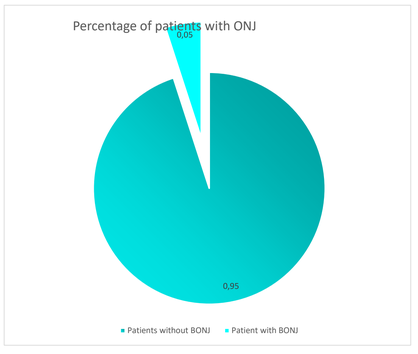

Fig.3 Percentage of ONJ in cohorts

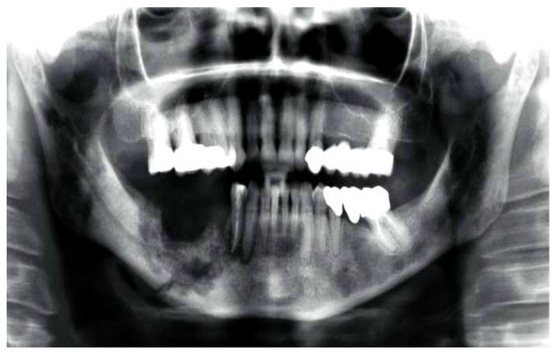

Fig.4 Radiographic appearance of ONJ

Subgroup analysis:

- All 4 patients with ONJ had Zoledronic acid as part of their therapy.
- None of the patients had a traceable dental review prior to commencing bisphosphonate.
- The duration of therapy prior to development of ONJ ranged between 24 months to 56 months with median duration of 30.5 months.
- Three out of four patients (75%) were on a 4 weekly dosing regimen, in a relapsed setting. One patient (25%) was on an 8 weekly dosing regimen, whilst in remission.
- Clinical symptoms of patients presenting with ONJ ranged between, no symptoms, asymptomatic bony spicule, painful ulcer complicated with infection and bony exposure with difficulty in denture fitting.
- Three out of four (75%) patients diagnosed with ONJ required surgical debridement. Only one patient (25%) was managed conservatively.

Conclusion:

- Retrospective data from 77 patient cohort; we identified 4 patients (5%) with ONJ.
- None of the patients who were diagnosed with ONJ had a **prior dental review.**
- All the patients were on IV zoledronate and developed ONJ on long term zoledronate use **(>2 years)**
- ONJ can be asymptomatic, in early stage and early diagnosis and a high degree of clinical suspicion is necessary to identify early stages of ONJ.
- Stage 1 ONJ, can be treated conservatively with excellent outcome. Most patients need surgical debridement if diagnosed late, adding to the chronic morbidity of myeloma patients.

Outcome:

- From our local real-world data, we have implemented and mandated a pathway for hospital based dental assessment prior to bisphosphonate therapy for all newly diagnosed myeloma patients at diagnosis.
- Our evidence supports limiting bisphosphonate administration to 4 weekly while on myeloma treatment and then 2 monthly thereafter to a maximum of 2 years in the absence of active disease.

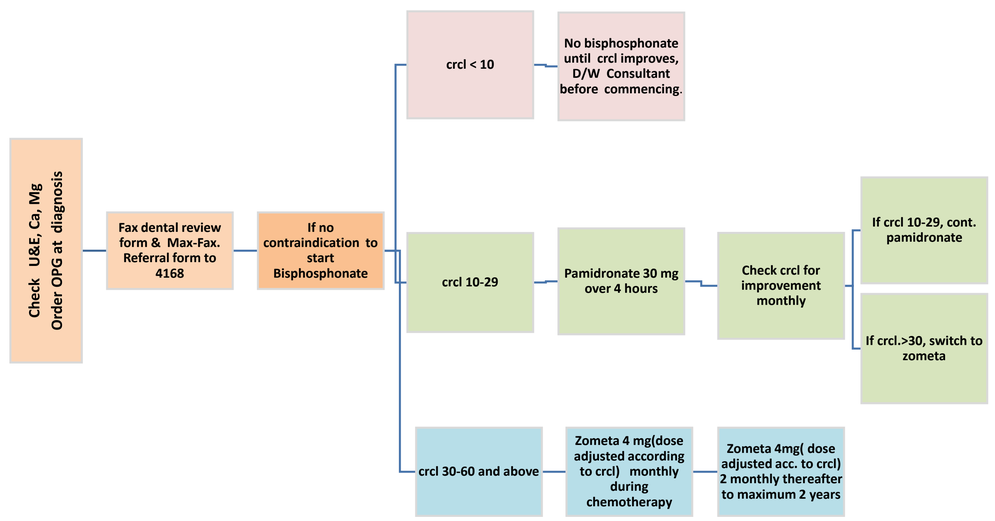

Fig.5 Local pathway implemented for dental review prior to bisphosphonate therapy for all myeloma patients

Acknowledgement:

1.Department of maxillofacial Surgery, Ashford and St. Peter's Hospital NHS Foundation Trust

References:

1.Ruggiero SL, Dodson TB, Fantasia J, et al. (2014). "American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw - 2014 update". *Journal of Oral and Maxillofacial Surgery.* ***72*** *(10): 1938–1956.*

2.Zoledronate sensitizes endothelial cells to tumour necrosis factor-induced programmed cell death: Evidence for the suppression of sustained activation of focal adhesion kinase and protein kinase B/Akt .*J Biol Chem. 2003; 278: 43603*

3. J. Chang, A. E. Hakam, L. K. McCauley. Current Understanding of the Pathophysiology of Osteonecrosis of the Jaw. Epidemiology and Pathophysiology (F Cosman and D Shoback, Section Editors). *Current Osteoporosis Reports*. Volume 16, pages584–595(2018).