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A population based study of multiple myeloma patients with medication-related osteonecrosis of the jaw

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SUMMARY

Objective. Medication-related osteonecrosis of the jaw (MRONJ) is a rare complication of antiresorptive or antiangiogenetic therapy that manifests as an exposed bone with clinical signs of infection, persisting for more than 8 weeks, without history of radiation therapy or metastases to the jaws. The aim of the study was to describe the incidence, risk factors, staging process and clinical course of MRONJ in patients with multiple myeloma (MM).

Materials and methods. We retrospectively analyzed all (126) newly diagnosed MM patients at Riga East Clinical University Hospital (Riga. Latvia) from June 2014 to June 2017.

Results. Among 88 MM patients treated with bisphosphonates (BP), 6 (6.8%) patients developed MRONJ. All six patients received intravenous nitrogen-containing BPs. The average time until MRONJ manifestation was under two years. For our patients the severity of MRONJ was stage I in two, stage II in three, and stage III in one patient. Five patients had MRONJ of mandibula and one of maxilla. All patients with MRONJ had undergone a dental extraction or a trauma before the development of MRONJ.

Conclusion. We found that MRONJ correlated with the patient's age. The average time until MRONJ manifestation in reserach group is 2 years. One of triggerring MRONJ factors are tooth extraction or trauma.

Key words: medication-related osteonecrosis of the jaw, bisphosphonates, multiple myeloma, osteonecrosis.

INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 10 percent of all hematologic malignancies (1). According to the Centers for Disease Control and Prevention (CDC), the annual incidence in the United States of America (USA) is approximately 4 to 5 per 100.000 (2, 3). In general, worldwide, there are approximately 154.000 cases and 101.000 deaths per year attributed to MM (4). Lytic skeletal lesions are present at the time of diagnosis in approximately 60 percent of patients with MM and almost all patients with MM will have lytic bone lesions at some point in their diseases course (5).

In Latvia treatment of MM includes chemotherapy with cyclophosphamide, bortezomibe, corticosteroids (dexamethasone), erythropoietin, calcium, vitamin-D, autologous stem cell transplantation (ASCT) and bisphosphonates (BPs). BPs are widely used in the management of lytic bone lesions as addition to other therapies directed at the malignant plasma cell clone (6, 7). They do not repair existing bone damage but they prevent the development of new lesions. BPs do not improve overall survival or progression-free survival but have a beneficial impact on pain control, and act as an adjunct to radiation therapy or surgical intervention to stabilize fractures or impending fractures (6, 8-14). The BPs mechanism of action is the inhibition of bone resorption by suppressing osteoclast activation and inducing osteoclast apoptosis. They also have anti-angiogenic properties, activate T-cells and have direct anti-tumor activity (15, 16). The overall effect is decreased bone turnover and inhibition of the bone's reparative ability (17-19). However. BPs usage has side effects. Medication-related osteonecrosis of the jaw (MRONJ) is the main side

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effect of treatment with BPs (20). It is attributed to the fact that alveolar bone of jaws has very high turnover rates therefore BPs accumulate in alveolar bone. Corticosteroids and chemotherapy increase the vulnerability of the oral mucosa and reduce its nutritive supply, posses an anti-angiogenic effect by inhibiting vascular endothelial growth factor and fibroblast growth factor (20).

MRONJ strongly correlates with age because of physiological effects of aging, including inflammatory issues, immune dysfunction, a reduction in blood flow and bone remodelling ability (10).

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS) MRONJ is confirmed if these three points are fulfilled: 1 – current or previous treatment with bisphosphonates, denosumab or antiangiogenic agents; 2 – exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks; 3 – no history of radiation therapy or obvious metastatic disease to the jaws (30). MRONJ is diagnosed by using panoramic radiography, computed tomography (CT) and clinical signs and symptoms. Despite multiple diagnostic methods available, the radiographic features of MRONJ are relatively nonspecific (5, 30).

The management of MRONJ remains controversial and there is no definitive standard of care for this disese. Non-surgical, conservative, and minimally invasive treatment regiments for MRONJ are considered useful to control the disease, leading to predictable good results in cases of lower stages of MRONJ (10).

MATERIAL AND METHODS

We retrospectively analyzed all 126 newly diagnosed MM patients at Riga East Clinical University Hospital (Riga, Latvia) from June 2014 to June 2017. Bone lesions were detected by either radiography. CT, magnetic resonance imaging (MRI), or positron emission tomography (PET/CT). The stage of MRONJ was set according to the staging system proposed by AAOMS (5).

In accordance with International Myeloma Working Group recommendations, all MM patients with bone lesions received bisphosphonates (excluding patients with glomerular filtration rate (GFR) <30 ml/min). The BPs were administered either orally or intravenously (5).

The study design, patient's information and consent forms were approved by the Ethics Committee of Riga Stradins University and in accordance with the Declaration of Helsinki.

Descriptive statistics were used to analyse demographics and clinical characteristics of study population. Continuous variables were described as means (standard deviation (SD)). Data were analysed with *t* tests for independent samples. A two-sided *p*-value <0.05 was considered statistically significant. To understand whether differences were statistically meaningful Cochen's *d* value (<0.5 – small effect size, 0.5-0.8 – medium effect size, >0.8 – large effect size) for *t*-test was used. Statistical analyses were performed using IBM SPSS statistics (version 23 for Windows. IBM Corp.. Somers. NY. USA).

RESULTS

From all 126 MM patients enrolled in this study, 70 (57%) were female and 53 (43%) were male. Patients in our study were aged 35-88 years, average age was 69.68 yrs. Lytic skeletal lesions were present at the time of diagnosis in 88 (69.84%), patients.

All patients with bone disease received treatment with corticosteroids and 71 of them received chemotherapy. Of 88 patients with bone disease 84 (95.45%) received intravenous BPs (zoledronic acid 4 mg every 4 weeks) and 2 patients were treated with oral bisphosphonates and 2 more were treated with denosumab.

Among patients with MM treated with BPs, 6 patients (6.8%) developed MRONJ. Their mean age was 72.8 yrs; SD=9.17 (62-88). Between these 6 patients male to female ratio was 1:5. All six patients received intravenous nitrogen-containing BPs (Zoledronic acid). Average time until manifestation of MRONJ was 23.8 months; SD=5.41 months, range 17-33. For patients with MRONJ the severity of it was stage I in two patients, stage II in three, and stage III in one patient. Five patients had MRONJ of mandibula and one – of the maxilla. All patients with MRONJ had undergone a dental extraction or trauma before the development of this complication. The first patient with MM who developed MRONJ in Latvia was among the patients who were included in this research. The patient was a female, 76 years old, with complaints about facial swelling, bone exposure, and severe pain in the right premolar region of the mandible. These symptoms had developed 2 months following a tooth extraction. Physical examination showed facial swelling, neck lymphadenopathy and cutaneous submandibular fistula with pus discharge. Patient had history of MM, chronic kidney disease, anemia, vertebral fracture at Th12-L1 level and myocardial infarction. In our study from 6 patients with MRONJ 5 had comorbidities:

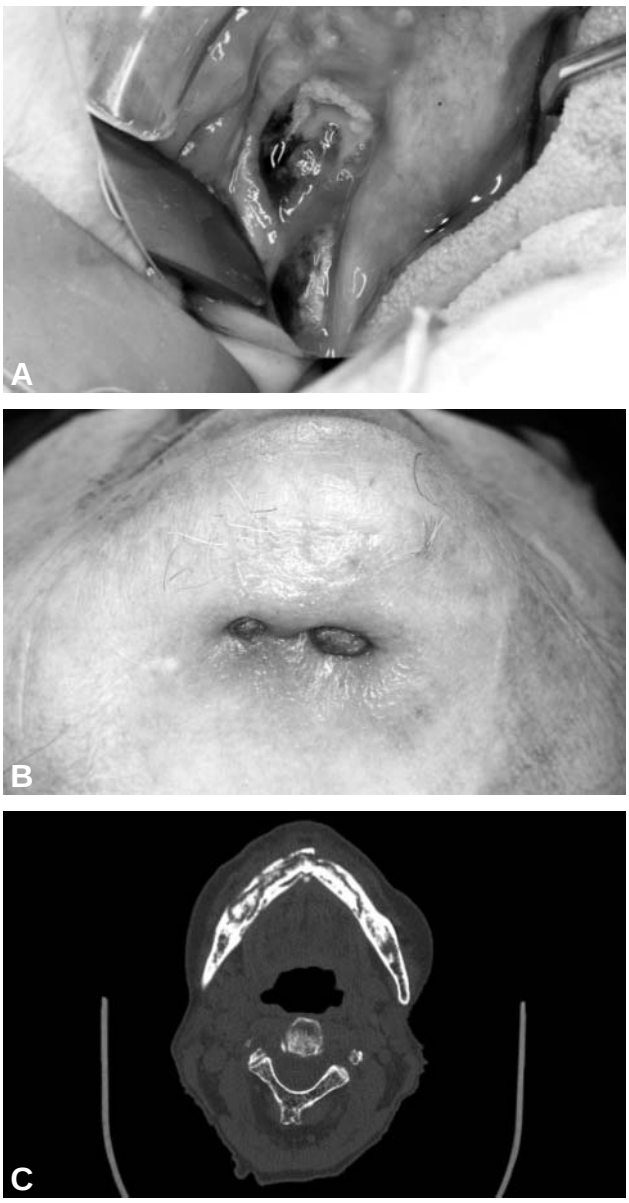

Fig. Bisphonate-related osteonecrosis of the jaw in 76-year old female MM patient under BF therapy, after beeing subjected to a tooth extraction. A – clinical examination shows areas of bone exposure in the right side of mandible. B – fistula in the submandibular skin. C – CT shows diffuse osteolysis with bone sclerosis, bone sequestration and destruction of the bone.

3 – diabetes, 2 – hypertension. Especially diabetes is generally associated with with microvascular ischemia of the bone, endothelial cell dysfunction, decreased bone turnover and remodeling, resulting in a delayed wound healing and proneness to infection. According to Zhang Q *et al.*, it is a established risc factor for MRONJ.

The first patient with MRONJ in Latvia had been diagnosed with MM and received intravenous zoledronic acid for 18 months (total dose was 72 mg). CT scan (Figure) showed diffuse osteolysis with bone sclerosis, bone sequestration and destruction of the bone. Histological examination showed bacterial debris and granulation tissue with infiltration of lymphocytes and histiocytes. Evidence of metastatic bone disease was not detected. The patient received conservative surgical treatment – debridement of the bone seqestrum, pain relief, antibiotic therapy for 10 days, hyperbaric oxygen therapy. Treatment with BPs was discontinued. This therapy stabilised the patient's state. The wound healed without any further complications.

In our study, patients with MRONJ were on average older (mean age 72.83 years) than other MM patients (mean age – 69.68 years). Independent sample t-test showed that patients in osteonecrosis group (M=72.83; SD=9.17 years) were older than other MM patients (M=69.68; SD=10.35 years), although without statistical significance (p=0.46), however, calculating the size of the statistical effect using Cohen's d value, the effect is average (d=0.32). Research group patients data were summerized in Table.

DISCUSSION

We found several factors that could be attributable to the development of MRONJ. Since calculation of the statistical effect of patients' on MRONJ development using Cohen's d value found average

Table. Patient's summary

Patient number	Age* (years)	Sex	Location	Length of antiresorptive therapy	MRONJ stage	Bisphosphonates	Medication prescribed	Diabetes
1.	76	F	R Md	18 months	3	Z i/v.	S. Ch	Yes
2.	72	F	R Md	20 months	2	Z i/v.	S. Ch	No
3.	62	F	R Md	25 months	2	Z i/v.	S. Ch	Yes
4.	65	M	L Md	26 months	2	Z i/v.	S. Ch	No
5.	88	F	L Mx	25 months	1	Z i/v.	S. Ch	No
6.	74	F	R Md	34 months	1	Z i/v.	S. Ch	Yes

F – female. M – male. R – right. L – left. Md – mandible. Mx – maxilla. Z – acidi zoledronici. S – steroids. Ch – chemotherapy.
*At the time of the complication.

effect, our estimation is that the age difference actually exists between the patients who have been diagnosed with MM and who have MRONJ. According to Luis Jungera. Lorena Gallego research, where intravenous BPS usage was associated with MRONJ, we too found that intravenous BPs were much more frequently associated with MRONJ: in our study 100% of MRONJ lesions developed following intravenous use of BPs (10). It was also observed that most patients developed MRONJ after recieving BPs for a period of time exceeding 1 year. Thus, the occurrence of MRONJ appears to be related to the duration of treatment, patients age and the route of administrasion for BPs as described in literature (10). Systematic review of Fliefel R, et al with research group, which included 97 articles, 4879 cases, showed that mean duration of BP administration was 38.2 +/–15.7 months. Similar to the systematic review, we did find a female predilection for developing MRONJ after treatment with BPs.

Cofactors such as diabetes, corticosteroids and chemotherapy, which are often present in MM patients, form an immunosuppressive background and potentiate MRONJ development (28). This was confirmed in our study, as all patients with MRONJ had received steroids and chemotherapy and half had diabetes. Our finding that all patients had undergone a dental extraction or trauma before the development of MRONJ is consistent with the reviews by Badros *et al,* and C. Dannemann *et al.*, which reported an association between the occurrence of MRONJ and a history of dental extraction in MM patients treated with intravenous BPs. (10-15) Similar to Fliefel R, et al with research group, systematic review, we found that MRONJ affected the mandible more often than maxilla. This could be attributed to the decreased vascularity of the mandible and to existing local conditions. (4-10).

CONCLUSIONS

We did find MRONJ to be a rare complication in patients who were being treated with BPs . One of the triggering factors for MRONJ development is dental extraction or trauma.

Only collaboration among hematologists and dentists-jaw surgeons will provide concordant treatment. A more comprehensive understanding of MRONJ will, hopefully, allow haematologists and other specialists to enhance accuracy in risk assessment.

CONFLICT OF INTERESTS

The authors indicate no potential conflicts of interest.

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