

A RETROSPECTIVE STUDY OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW IN MULTIPLE MYELOMA PATIENTS

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ABSTRACT

Background: Multiple myeloma is a malignant hematological neoplasm, whose treatment involves the use of bisphosphonates and monoclonal antibodies, which may be related to medication-related osteonecrosis.

Objective: The present study aims to verify the presence of medication-related osteonecrosis of the jaws in patients undergoing treatment for multiple myeloma who used chemotherapy associated or not with bisphosphonates and/or monoclonal antibodies. Beyond this, to trace the epidemiological profile of patients who developed medication-related osteonecrosis.

Methods: This 15-year retrospective observational study consisted of evaluating 461 medical records of patients diagnosed with multiple myeloma from the oncology referral hospital in Paraná state, Erasto Gaertner Hospital.

Results: It was observed in that both groups, which s (the one in which patients developed and did not developed osteonecrosis), had no statistically significant difference when evaluated separately regarding sex, bone marrow transplant and ethnicity. However, the group with osteonecrosis showed a higher frequency in the use of bisphosphonates, did not progress to death, were non-smokers, the jaw was the most affected anatomical site, and the type of bone exposure spontaneously was the most observed.

Conclusions: The combined use of pentoxifylline and tocopherol was responsible for the successful resolution of cases of medication-related osteonecrosis. Isolating the underlying disease allowed for greater control and knowledge regarding the medications used for the treatment of medication-related osteonecrosis.

Keywords: Osteonecrosis; Hematologic neoplasms; Multiple myeloma; Pentoxifylline; Tocopherols.

INTRODUCTION

In Brazil, approximately seven thousand patients are diagnosed with multiple myeloma per year¹. This disease represents 10% of hematological malignancies, in addition to being considered the second most common type of blood-related cancer, followed by

leukemias^{2, 3}. With a prevalence in males, it affects twice as many melanoderma and its diagnosis occurs, in most cases, around the sixth decade of life³. In myeloma multiple, there is an uncontrolled proliferation of type B cells in the bone marrow, which

is responsible for the increase in the production of plasma paraproteins and immunoglobulins, mainly IgG, IgA and, more discreetly, IgM⁴. The abnormal proliferation of plasma cells results in suppression of the bone marrow and can cause bone resorption due to the high level of calcium in the blood, resulting in hypercalcemia⁵. Estimated as one of the most effective forms of treatment, autogenous bone marrow transplantation (BMT) can assist in the treatment of this neoplasm, as well as the inclusion of drugs such as bisphosphonates and monoclonal antibodies, which also help in the patient's survival⁶.

Bisphosphonates are also prescribed for patients with hypercalcemia, osteoporosis and, also in Paget's disease of bone⁷. They are classified according to their side chain to the carbon atom and can be considered as nitrogenous (alendronate, ibandronate, pamidronate, risedronate and zoledronate) and non-nitrogen (clodronate and etidronate)⁸.

One of the most observed adverse effects in the use of bisphosphonates is bone necrosis, since this medication has a high affinity for binding with hydroxyapatite, which makes it difficult for osteoclasts adhesion to the bone surface, in addition to promoting their cell death⁹. These drugs are synthetic analogues of pyrophosphates, whose mechanism of action occurs through the inhibition of bone resorption, being released locally and absorbed by osteoclasts, which inhibit their maturation and lead to apoptosis¹⁰.

Monoclonal antibodies have been used, associated or not with bisphosphonates, for the treatment of multiple myeloma and can also cause bone necrosis¹¹. Monoclonal antibodies are developed in the laboratory, present a specific antigen as a specific target¹² and are classified as anti-resorptive and anti-angiogenic⁷. Anti-resorptive monoclonal antibodies can cause bone necrosis because they act against the receptor activator of nuclear factor kappa-B (RANKL), which prevents the osteoclasts differentiation, promoting apoptosis and resulting in bone resorption inhibition, by depletion of mature osteoclasts¹³. On the other hand, anti-angiogenic monoclonal antibodies are antagonists of vascular endothelial growth factor (VEGF) and can neutralize the biological effects of growth factor activity or block the VEGF receptor and its signaling pathways, thus, there is no vascular neof ormation, which will result in necrosis¹⁴.

As bisphosphonates and monoclonal antibodies can cause osteonecrosis, in 2014 the diagnosis of drug osteonecrosis was established and it is made

when there is current or previous treatment with antiresorptive or antiangiogenic agents; the bone, exposed or not, can be probed through an intraoral or extraoral fistula in the maxillofacial region, which persists for more than eight weeks, and when there is no history of radiotherapy in the head and neck region or obvious metastatic disease in the gnathic bones¹⁵.

The treatment performed for medication-related osteonecrosis consists in a surgical resection associated or not with antimicrobial therapy or with the use of platelet-rich fibrin¹⁶. However, till this moment, few studies have demonstrated the effectiveness of using pentoxifylline and tocopherol (pento protocol) for the treatment of medication-related osteonecrosis^{17,18}.

Previous studies demonstrate the follow-up of medication-related osteonecrosis caused by either bisphosphonate or monoclonal antibody for a period of no more than ten years and the studied population is composed of cancer patients diagnosed with breast cancer, prostate cancer, lung cancer, multiple myeloma, bone metastases and patients with osteoporosis^{17,19}. To our knowledge, there are no studies evaluating only one underlying disease isolated from other malignant neoplasms, as well as an evaluation for a period of 15 years where patients had used bisphosphonates and / or monoclonal antibodies.

Thus, the present study aims to verify the presence of medication-related osteonecrosis in the jaws of patients undergoing treatment for multiple myeloma who used chemotherapy associated or not with bisphosphonates and / or monoclonal antibodies. Beyond this, to trace the epidemiological profile of patients who developed medication-related osteonecrosis in relation to patients who did not develop it, to verify the anatomical site of greatest involvement, the most efficient form of treatment and the type of bone exposure.

METHODS AND MATERIALS

This is a retrospective observational study, with a quantitative basis of secondary data from three sources, which are from the medical records from the Medical and Statistical Archive Service (SAME) of the referral oncology hospital in Brazil (Hospital Erasto Gaertner - HEG, Curitiba-PR), from the book of bone marrow transplant records, from the HEG Hemotherapy Service and from the HEG Oral and Maxillofacial Surgery Service record book, between the years 2004 and 2018, which included patients diagnosed with multiple myeloma as a base disease and who

were not previously submitted to an antineoplastic treatment. The data were collected by an appropriately trained and qualified professional specialized in oral and maxillofacial surgery, since he worked at the present oncological institution working directly in the Service of Oral and Maxillofacial Surgery. This study was approved by the Ethics and Research Committee of HEG under Opinion N°. 3,198,509.

Of the 114,158 patients seen over 15 years, 541 (0,47%) had the diagnosis of multiple myeloma as the underlying disease. After applying the eligibility criteria, there were 461 (0,40%) records that could be included in the study.

The exclusion criteria were in cases when the patient had undergone previous radiotherapy in the head and neck and / or palliative radiotherapy; evolved to death before treatment and / or before confirmation of the anatomopathological result; when the anatomopathological results were inconclusive or absent for multiple myeloma; other tumors; loss of follow-up; abandonment of treatment; chemotherapy performed at another hospital and incomplete information. Eighty patient records were excluded, of which: 7 had undergone prior radiotherapy in the head and neck region; 10 received palliative radiotherapy; 10 died before treatment; 7 passed away before the confirmation of the anatomopathological result; 2 had inconclusive anatomopathological findings; 13 had no anatomopathological evidence of multiple myeloma; 12 had other tumors; 13 cases had loss of follow-up; 1 discontinued treatment; 2 underwent chemotherapy at another hospital, and 3 had incomplete information.

The variables analyzed were: sex, age, smoking, death, type of bone marrow transplant performed, medication used in chemotherapy, presence or absence of bone necrosis, anatomical location (maxilla, mandible or maxilla and mandible affected concomitantly), medication used (bisphosphonates, monoclonal antibody or a combination of both), type of exposure to osteonecrosis (spontaneous or provoked), form of treatment and evolution time for the onset of osteonecrosis, all contained in the data collection form. Bisphosphonates, monoclonal antibody or both were prescribed by doctors at the HEG Hemotherapy Service.

Cases that presented osteonecrosis of the jaws associated with medications were identified in patients undergoing multiple myeloma treatment according to the classification of medication-related osteone-

crosis defined in the Position Paper of the American Association of Oral and Maxillofacial Surgery²⁰, which took into account only the presence or absence of necrosis bone and the site of involvement, without considering its extension.

The data were entered into a database in the Microsoft® Excel 2010 program, being processed and analyzed with the aid of the Statistical Package for the Social Sciences (SPSS), version 25.0.

As the sample size for the group that did not develop medication-related osteonecrosis was greater than 30 ($n = 447$), the sample distribution of means tended to be normal, therefore, parametric tests were chosen. The sample size of the group that developed drug osteonecrosis was less than 30 ($n = 14$) and the Kolmogorov-Smirnov and Shapiro-Wilk normality tests indicated normal distribution for the age variable in this group. Student's parametric t test for independent samples was used to compare the average age of the two groups.

In the Levene homogeneity test of variances, it was shown that the age variable is homogeneous. Pearson's Chi-Square test was performed for the other dichotomous or polytomous nominal variables. When the minimum expected count was less than 1, the value of the Chi-Square test with correction of likelihood ratio was used. After the Chi-Square test indicated dependence between dependent variable and group ($p < 0.05$), the Z-test of difference between two proportions was applied, aiming to identify which categories of dependent variable showed differences between groups.

RESULTS

It was observed that, over the 15 years of study, 3% (14/461) developed medication-related osteonecrosis (MON) and 97% (447/461) did not develop. The mean age of patients without osteonecrosis (58.80 ± 11.181) was similar to the age of patients with osteonecrosis (58.36 ± 6.122), $p = 0.800$.

The percentage of patients who used bisphosphonates was higher in the group with osteonecrosis when compared to the group without osteonecrosis. The Z-test power of difference between two proportions when rejecting H_0 was 94.1%. A higher frequency of chemotherapy not associated with bisphosphonates or monoclonal antibody was found in the group without osteonecrosis when compared to osteonecrosis. For the other variables, there was no statistically significant difference (Table 1).

TABLE 1 - Patients with Multiple Myeloma stratified according to the absence or presence of osteonecrosis.

Z test of differences between two proportions: different lowercase letters on lines indicates differences between groups ($p < 0.05$).

Different capital letters in a column indicates statistically significant differences ($p < 0.05$).

Variable	Patients without osteonecrose	Patients with osteonecrose	Chi-square test P value
SEX			0,928
Man	250 (55,9%)Aa	8 (57,1%)Aa	
Woman	197 (44,1%)Aa	6 (42,9%)Aa	
BMT*			0,197
Autologous	180 (40,3%)Aa	9 (64,3%)Aa	
Allogeneous	1 (0,2%)Aa	0 (0,0%)Aa	
No	266 (59,5%)Aa	5 (35,7%)Aa	
DEATH			0,164
Yes (underlying disease)	212 (47,4%)Aa	4 (28,6%)Aa	
No	235 (52,6%)Aa	10 (71,4%)Ba	
SMOKING			0,143
Yes	183 (40,9%)Aa	3 (21,4%)Aa	
No	264 (59,1%)Aa	11 (78,6%)Ba	
MEDICATION			0,009
Bisphosphonate	259 (57,9%)Aa	12 (85,7%)Ab	
Monoclonal antibody	5 (1,1%)Aa	1 (7,1%)Ba	
Combined	13 (2,9%)Aa	1 (7,1%)Ba	
Chemotherapy not associated with bisphosphonates or monoclonal antibody **	170 (38%)Aa	0 (0,0%)Bb	

differences between groups ($p < 0.05$).

Different capital letters in a column indicate statistically significant differences ($p < 0.05$).

*Bone Marrow Transplantation (BMT).

**Chemotherapy not associated with bisphosphonates or monoclonal antibody: Melphalan, Thalidomide, Vincristine, Doxorubicin, Cyclophosphamide, Cisplatin, Bortezomib, Velcade, Alkeran, Methotrexate and Etoposide.

In the group of patients without osteonecrosis, it was observed that: men and women had the same frequency, there was no statistically significant difference between bone marrow transplantation, deaths and non-deaths, smoking and medications used. For the group of patients with osteonecrosis, there were also no statistically significant differences between sexes and bone marrow transplantation, but a higher frequency was identified in patients who did not progress to death, were non-smokers and used bisphosphonates.

The jaw was the site most affected by medication-related osteonecrosis. Bisphosphonate zoledronic acid, used alone or administered in conjunction with another type of bisphosphonate, pamidronate, were the most frequent treatments for multiple myeloma in cases of MON. A higher frequency of spontaneous bone exposure was observed. Four patients belonging to the group that developed drug osteonecrosis evolved to death due to multiple myeloma. The pento protocol was the most frequent treatment for osteonecrosis, followed by its association with sequestrectomy (Table 2).

TABLE 2. Patients with Multiple Myeloma with osteonecrosis stratified according to the affected anatomical site, the medications responsible for osteonecrosis, the type of osteonecrosis exposure and the form of treatment.

Variable	Frequency
OSTEONECROSIS SITE	
MANDIBLE	09 (64,3%)a
MAXILLA	03 (21,4%)b
BOTH	02 (14,3%)b
TREATMENT OF MULTIPLE MYELOMA	
BISPHOSPHONATE Zoledronic acid	05 (35,7%)a
BISPHOSPHONATE Pamidronate	02 (14,3%)a
BISPHOSPHONATE Zoledronic acid + Pamidronate	05 (35,7%)a
MONOCLONAL ANTIBODY Daratumumab	01 (7,1%)b
COMBINED Bisphosphonate + Monoclonal Antibody	01 (7,1%)b
TYPES OF OSTEONECROSIS EXPOSURE	
SPONTANEOUS	9 (64,3%)a
INDUCED after tooth extraction	2 (14,3%)b
INDUCED after implant installation	1 (7,1%)b
SPONTANEOUS AND INDUCED *	2 (14,3%)b
TREATMENT	
PENTO PROTOCOL	05 (35,7%)a
SEQUESTRECTOMY	01 (7,1%)b
PENTO PROTOCOL + SEQUESTRECTOMY	03 (21,4%)a
PENTO PROTOCOL + HEMIMANDIBULECTOMY	01 (7,1%)b

Z test of difference between two proportions: different lowercase letters indicate differences between groups (p <0.05).

* In one of the dental arches, the exposure was spontaneous and in the other, caused by post-extraction.

Among the patients undergoing the proposed treatment, eight had complete resolution of osteonecrosis exposure, while one patient developed pathological fracture and the other presented resolution of osteonecrosis in the mandible, but the bone exposure remained in the maxilla. These patients who did not resolve remained in treatment after completing this study.

It was observed that, in three isolated cases with the use of bisphosphonates, patients developed drug osteonecrosis in less than one year of administration of the drug. The patient who used a monoclonal antibody developed osteonecrosis 10 years after its administration.

From 461 records included in the study, 96% (443/461) belonged to white patients, 2.4% (11/461) belonged to browns, 0.65% (3/461) belonged to blacks and, in 0, 9% (4/461) had no information regarding ethnicity. The ethnicity variable did not indicate statistically

significant differences when compared to the variables gender, bone marrow transplantation, death, smoking and medication.

DISCUSSION

The present study first isolated an underlying disease in patients who developed drug osteonecrosis and a frequency of 3% was observed. The literature shows that the frequency of MON is 37.6%^{19, 21}. This index is much higher than the one shown in this study, as the patients that make up the other works belong to different oncological areas and, in some cases, multi-center studies have been carried out⁷. However, the present study was carried out only at the oncology referral hospital in the Paraná state. The frequency of medication osteonecrosis in this study proved to be a rare event.

Studies show that groups of patients who used bisphosphonates were higher in the group with os-

teonecrosis when compared to the group without osteonecrosis²¹. The present study corroborates the presented fact. On the other hand, in a study by Wazzan et al (2018)¹⁹, patients who did not develop MON had a higher frequency of use of bisphosphonates compared to the group with osteonecrosis, since patients had a higher quality of oral health¹⁹. In this study, the quality of the patient's oral health was not evaluated, only the presence or absence of medication-related osteonecrosis. Therefore, it cannot be said whether patients who developed medication-related osteonecrosis had a lower oral health condition compared to patients who did not develop osteonecrosis.

The epidemiological profile of the patient without osteonecrosis has a slight predilection for the female gender, non-smokers, with a mean age between 57 and 61 years and with greater frequency in the use of bisphosphonates^{17, 19}. This study showed that there are no statistically significant differences involving the variables gender, smoking and medication used, and the mean age is similar to that reported in the literature (58.8 years). On the other hand, the profile of patients with osteonecrosis is more frequent as: men, jaw as the most affected site, non-smokers, the use of bisphosphonates as medication and the average age is 62 years^{17, 19}. The present study corroborates the literature regarding the variables smoking, bisphosphonates and most affected site. However, there are no statistically significant differences between the sexes and the average age is slightly inferior, being 58.3 years old.

In the present study, it was observed that multiple myeloma was diagnosed in a population composed of 96% of white patients. Perhaps this fact is observed due to the region where the oncological Hospital had the data collected. Since, according to the last census conducted by the Brazilian Institute of Geography and Statistics (IBGE), the southern region is made up of more than 20 million whites, while the rest of the population, together, total almost 6 million people²¹. All patients who developed medication-related osteonecrosis were white.

Pentoxifylline is a phosphodiesterase inhibitor derived from methylxanthine and has an anti-TNF- α effect, increases the flexibility of blood cell membranes, improves microcirculation and peripheral blood flow, in addition to tissue oxygenation^{18, 22}. Tocopherol, also called vitamin E, is an antioxidant agent that protects the phospholipid membrane from oxidative damage and the cell membrane against lipid peroxidation²³. It decreases reactive oxygen species, resulting in the healing of injured

tissue²⁴. When combined, pentoxifylline and tocopherol are effective in reducing radiation-induced fibrosis and decrease the protein expression of the transforming growth factor (TGF- β) molecule more effectively than any medication alone²⁵.

A study carried out by Bohn et. al. (2016)²⁶, involving irradiated patients from the same institution as the present study, demonstrated success in the resolution of osteoradionecrosis (ORN) when the pento protocol was used²⁶. In 2018, Kolokythas et al, published in a systematic and meta-analytical review that the pento protocol showed successful results in advanced cases of ORN²⁷. When the exposure of necrotic bone is caused by the use of drugs such as bisphosphonates, the literature also shows success with the use of the pento protocol^{17, 28}, the present study corroborates this fact.

In 2012, Mcleod et. al.²⁹ demonstrated that the proposed treatment for ORN with the pento protocol consisted of ingesting 400mg of pentoxifylline twice a day and 1000UI of tocopherol once a day²⁹. Thus, based on the conduct in front of the ORN, the HEG Oral and Maxillofacial Surgery Service implemented the pento protocol, using the same dosage, for the treatment of MON, which led to the resolution of clinical cases. As far as is known, the pento protocol is only proposed for the treatment of ORN³⁰. However, the present study sought to demonstrate the effectiveness of the pento protocol for the treatment of MON, as well as the few previous studies²⁸.

The differences found in the resolution of the MON can possibly be attributed to the protocol used, since authors performed control of the local infection through hygiene, antibiotic therapy and, in cases of non-resolution, surgical debridement, bone resection and use of platelet-rich plasma^{31, 32}. In addition, some studies did not have exclusively cancer patients with multiple myeloma and / or who also used monoclonal antibodies as a study population³³. In the present study, patients with MON were submitted to treatment involving the pento protocol with or without sequestrectomy and hemimandibulectomy. It became evident that the use of the pento protocol in the treatment of drug-induced bone necrosis has been successful, as well as in cases of osteoradionecrosis (ORN) in which the same protocol is employed.

Studies suggest that the exact location of MON is in the mandible, and bone exposure occurs more frequently in a provoked way^{17, 30}. In the present study, it was observed that the most affected site was the mandible. However, in three cases the maxilla was

affected, and in two other cases, both the mandible and the maxilla were affected concurrently. It was also analyzed that the spontaneous form of exposure to osteonecrosis was the one with the highest frequency. The use of bisphosphonates alone or the combination of two types of bisphosphonates also resulted in a higher frequency of MON cases, converging with studies where bisphosphonate administered alone was responsible for a higher frequency in the development of MON^{22,34}.

When Marx demonstrated the appearance of bone necrosis caused by the use of bisphosphonates, in 78% of the cases (28 patients), the exposure of necrotic bone occurred after surgical intervention³⁵. In the year following the first report of osteonecrosis caused by drugs, Ruggiero et al (2004)³⁶ identified medical records of patients with various oncological diagnoses (56 patients, 88.9%), including seven cases (11.1%) of treatment for osteoporosis, where everyone used pamidronate and / or zoledronate. In only nine cases, osteonecrosis exposure was spontaneous³⁶. This study differs from the ones mentioned above, since only medical records of patients who had multiple myeloma as the underlying disease were evaluated, where nine cases presented spontaneous bone necrosis.

In the present study, three patients who used only bisphosphonate presented the development of medication-related osteonecrosis in periods of less than one year; they were six, seven and eight months, respectively. Among these cases, two patients presented spontaneous osteonecrosis and one case after extraction of the right upper canine. It was observed in this study that the isolated use of monoclonal antibody (Daratumumab™) was responsible for the spontaneous exposure of necrotic bone after 10 years of use. The case presented by Neuprez et al (2014)³⁷ demonstrated that, in just nine months of using Denosumab™, the region submitted to surgical removal of the third molar did not heal and resulted in the presence of necrotic bone³⁷. It is believed that subsequent multicenter studies involving oncology referral hospitals are necessary to elucidate and increase knowledge about the time of MON emergence due to the use of monoclonal antibodies.

The pathophysiology of MON is still unknown, as it is considered a multifactorial disease^{30, 38}. Hypotheses suggest that there is a change in bone remodeling, inhibition of angiogenesis, soft tissue toxicity, infection, and suppression of immunity³⁸. The diagnosis is based on the patients' medical and medication history, as well as on the clinical and radiographic characteristics of the exposed or not

exposed necrotic bone³⁹. Pharmacogenetic studies are being developed to determine whether genetic differences influence the variability of the patient's response to these drugs⁴⁰. In this study, the diagnosis occurred according to the definition of the American Association of Oral and Maxillofacial Surgeons and further studies may be developed to assess the confirmation or not of the genetic influence of the patient using bisphosphonates and / or monoclonal antibodies⁴⁰.

The literature demonstrates that nicotine has an adverse effect on bone healing and regeneration, since it acts on small blood vessels, producing peripheral vasoconstriction, systemic venoconstriction and increased coronary vascular resistance, in addition to inhibiting the gene expression of bone morphogenetic protein in osteoblasts⁴⁰.

Nicotine results in the accumulation of hypoxia-inducing factors and impairs healing, as it causes a decrease in the proliferation of fibroblasts and a decrease in the production of collagen⁴¹. Benzopyrene, in addition to being a carcinogen found in cigarette smoke, is responsible for decreasing osteoclastic formation, since it inhibits the kappa-B binding factor (RANKL) receptor activator⁴². It was shown that both nicotine and benzopyrene affect, but do not prevent bone healing⁴³. In the present study, only three patients who had MON were smokers, however, it is not known whether bone healing was delayed or not because, once treatment with the pento protocol was proposed, there was complete resolution of the clinical conditions. The association between cigarette components and medications that cause osteonecrosis is a subject that can be analyzed in later studies.

CONCLUSION

It was observed that, even though it is a rare event, osteonecrosis associated with medications in the head and neck region can be observed in patients with multiple myeloma. Obtaining the epidemiological profile of the patient with MON makes it possible, through this retrospective study, to assist in diagnosis and treatment, which will provide greater comfort regarding the quality of oral life.

DISCLOSURE STATEMENT

All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication, as well as have no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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