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Infections in cancer patients with medication-related osteonecrosis of the jaws

Abstract

Introduction: The association between bisphosphonates and osteonecrosis of the jaws has been widely reported in the literature. Despite the higher incidence and the poor prognosis in cancer patients, there is still little understanding of risk factors for infectious complications in these patients.

Objective: Evaluate the factors associated with infectious events related to osteonecrosis induced by zoledronic acid (ZA) in oncological patients.

Methods: It was a retrospective, longitudinal and observational study that included 21 patients and collected the following variables: age; oncological disease; classification of necrosis; affected bone; triggering factor; frequency of ZA use; the number of ZA doses at the time of necrosis; smoking; cancer activity at the time of necrosis; use of corticosteroids; previous or current treatment with chemotherapy, immunosuppressive and antiangiogenics drugs. The outcome of interest was the number of new infection episodes.

Results: 33% of patients showed only one infectious event after MRONJ diagnosis, 28.6% of the cases had two, 19% - four, 9.5% - three, one patient had six and another seven infection episodes. Among all the studied variables only the classification of osteonecrosis, Class.2 + 3: 2.06 (±2.08) vs. Class. 1: 0.00 (±0.54)-p: 0.05 and the frequency of ZA use, Monthly: 2.09 (±1.64) vs. Quarterly: 0.25 (±0.46)-p: 0.002 showed highest incidence of infectious events. In the binary logistic regression, monthly use of bisphosphonate (OR:15; 1.34-16.64) and necrosis in the mandible (OR:10.8; 1.0-11.7) were associated with infection.

Conclusion: MRONJ in cancer patients can be associated with recurrent infections and mandibular involvement, and monthly ZA use is potential risk factor for poor prognosis.

Keywords: Bisphosphonate-Associated Osteonecrosis of the Jaw, infections, neoplasms

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Introduction

Bisphosphonates are used in the treatment of systemic conditions that increase bone resorption, such as osteoporosis, Paget's disease and tumour bone metastases, either to reduce the risk of pathological fracture and pain or to treat secondary hypercalcemia.[1,2] Since the 2000s, cases of bisphosphonate-associated osteonecrosis of jaw have been reported. Since then, little progress has been made regarding the aetiology, pathophysiology and treatment of these complications.[3,4]

Some aspects seem to be directly or indirectly involved in the development and progress of medication-related osteonecrosis of the jaw (MRONJ): (1) inhibition of osteoclastic activity and consequently inhibition of bone remodelling; (2) presence of inflammation and infection; (3) alteration in collagen and fibroblasts metabolism; (4) immune system suppression; and (5) alteration in angiogenesis.[5] The most common risk factors associated with the incidence of MRONJ are: (1) via intravenous administration; (2) number of doses; (3) time; and (4) frequency of medication use.[1–6]

MRONJ can be classified as spontaneous or, more often, associated with a triggering factor (approximately 90% of cases).[7] The most common triggering factors are associated with direct trauma, or bone exposure, such as (1) dental extractions; (2) installation of implants; (3) prosthetic trauma; (4) infectious/inflammatory conditions such as periodontal disease, periapical lesions and osteomyelitis.[8,9] Some systemic conditions related to the immune and degenerative condition, such as diabetes mellitus, active cancer disease, chronic use of corticosteroids, immunosuppressant drugs and use of cigarettes seem to be related toMRONJ development and progression.[10,11]

Recently, animal study models have suggested that the presence of infection and inflammation are sufficient for the development of MRONJ.[12,13] In addition, the role of bacterial infection in the pathogenesis has been suggested from the evidence of a reduction in MRONJ incidence after the improvement in oral hygiene in cancer patients.[14,15] Authors have suggested that immuno-compromised state due to disease and to the treatment, such as steroids and chemotherapy, could also increase MRONJ prevalence and severity.[7]

MRONJ is associated with morbidity and increased mortality in cancer patients, and little is known about the factors associated with its prognosis. Most studies have included different necrosis-inducing drugs and underlying diseases. This study aimed to evaluate infectious events in a cohort of oncological patients with MRONJ induced by zoledronic acid (ZA) injection.

Methods

This retrospective study was conducted developed at the Tertiary Clinical Hospital, approved by the research ethics committee (CAAE 96418618.4.0000.5440) and included a cohort of cancer patients diagnosed with MRONJ associated with the intravenous use of zoledronic acid (ZA).The AAOMS criteria were used for the diagnosis and classification of MIRONJ. All patients were evaluated at the Dentistry and Stomatology Service between January 2014 to May 2019. Exclusion criteria were previous use of other drugs that control bone metabolism (anti-resorptives), previous radiotherapy in the head and neck region, necrosis in other bones, less than six months of follow-up after MRONJ diagnosis, medical records with insufficient or inadequate information, and patients who did not adhere to the treatments proposed.

Through the evaluation of medical records and imaging examinations, the following data were collected: age, oncological disease, classification of necrosis (Ruggiero et al., 2014[7]), affected bone; triggering factor, frequency of ZA use, total number of ZA doses at the time of necrosis diagnosis, smoking, cancer activity at the time of necrosis diagnosis (active or controlled), chronic use of corticosteroids (continuous use for more than 6 months of a 10mg/kg/day dose of prednisolone or prednisone counterpart), use of chemotherapy (previous and current), use of immunosuppressants (previous and current), use of antiangiogenics (previous and current), results of cultures collected,and number of new infectious events (active infection) up to the minimum period of 6 months without infectious complications.

The criteria used to define new infections related to MRONJ were the occurrence of active suppuration associated with the necrotic area, accompanied by a local inflammatory process, with or without pain. Cases of infection less than 2 weeks after the last treatment were considered as therapy failure and were not included as a new infectious event. Culture collections were preferably performed using aspirates, intra-fistula swabs or soft- and hard-tissue collection. We classified the immunosuppressive drugs used for tumor control, as non-chemotherapy and non-hormonal drugs, which have a known effect on activity or counting in white blood cells.

The collected data were tabulated, and descriptive evaluations of the studied variables were performed. Non-parametric statistics were used for inferential analysis. The presence and number of infectious events were treated as the outcome of interest, and their relationship with the other variables was tested. As only one patient presented with necrosis classification 3, two groups were created for this variable (classification 1 and classification 2 + 3). The combination of classifications 2 and 3 was used because both had active infection at the time of diagnosis. Additionally, binary logistic regression was performed using the categorization of infection as absent or present, and odds ratios were estimated. The level of significance used was ≤ 0.05 for all analysis (SPSS® version 23).

Results

Twenty-one cancer patients with MRONJ were included in the study of a mean age of 67 years, with11 cases in the mandible, 8 in the maxilla and 2 in both bones. Eighty-five percent of the cases were associated with triggering factors and only 15% were classified as spontaneous. Most patients (52.38%) used the drug monthly, 38% quarterly and 9% twice a year. The average of cumulative ZA was 17.4. Infections ranged from one to seven episodes throughout the follow-up period. Table 1 shows the main data.

Table 2 shows the variables studied; 42% of the patients (valid percentage) were smokers, 70% had active cancer, 55% used chronic corticosteroids, 42.9% were on chemotherapy, 25% used immunosuppressants and 5% used antiangiogenic agents at the time of necrosis onset. During the entire evaluation period, 46 cultures from necrotic areas were performed, with growth observed in 28 of them (61%). The microorganisms identified varied, but *Actinomyces* ssp., *Enterobacter* ssp., *Streptococcus* ssp. *and Raoltella* ssp. were the most frequent (Table 3).

Among the studied variables, monthly ZA use, maxilla as the affected bone and osteonecrosis classification (2 and 3) were more frequent in patients with a higher number of infections in the necrotic area. In the binary logistic regression, monthly use of bisphosphonates and necrosis in the maxilla and/or maxilla+ mandible were associated with infection (Table 4).

Table 2 Descriptive analysis of the studied variables

Variables		Valid Percent (%) (n=21)
Smoker		42.1
Active Disease		70
Chronic Corticosteroid Use		55
Chemotherapy	Pre-necrosis	71.4
	In necrosis	42.9
Immunosuppressant	Pre-necrosis	30
	In necrosis	25
Antiangiogenic	Pre-necrosis	10
	In necrosis	5

Table 3 Microorganisms identified in positive cultures

Microorganisms	Number of cultures with positive result	Percentage of culture positive for each microorganism
Actinomyces ssp	4	14.29
Enterobacter ssp	3	10.71
Streptococcus ssp	3	10.71
Raoltella ssp	3	10.71
Staphylococcus ssp	2	7.14
Moraxellla ssp	2	7.14
Enterococcus ssp	2	7.14
Bacillus ssp	2	7.14
Klebsiella ssp	2	7.14
Citrobacter ssp	2	7.14
Candida albicans	1	3.57
Rhizobium ssp	1	3.57
Peptostreptococcus ssp	1	3.57

Table 4 Results of statistical evaluations for risk factors *versus* infections

Risk Factors	Risk factor versus number of infections	P value	OR (C.I-95%)
Age	r:-0.52	0.82#	0.96 (0.87-1.06) p=0.42
Number of doses	r:0.36	0.11#	1.04 (0.94-1.16) p=0.41
Frequency of use of bisphosphonate	Monthly: 2.09 (±1.64)* Quarterly: 0.25 (±0.46)☐ Semiannual: 5.0 (±2.82)*☐	0.002$	15.00 (1.34-16.64) p=0.03
Affected bone	Maxilla: 0.64 (±0.92)* Mandíbule+Maxilla: 3.5 (±4.9)*☐ Mandibule: 2.5 (±1.59) ☐	0.002$	10.80 (1.00-11.7) p=0.05
Classification	Class.1: 0.00 (±0.54) Class. 2+3: 2.06 (±2.08)	0.05¥	4.50 (0.54-37.38) p=0.14
Chronic corticosteroid	No: 2.0 (±2.18) Yes: 1.27 (±1.85)	0.29¥	0.34 (0.05-2.46) p=0.28

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Table Continued...

Risk Factors	Risk factor versus number of infections	P value	OR (C.I-95%)
Previous immunosuppressant	No: 1.43 (±1.91) Yes: 2.00 (±2.28)	0.61¥	1.11 (0.15-8.37) p=0.92
Current immunosuppressant	No: 1.93 (±2.15) Yes: 0.6 (±0.89)	0.16¥	0.24 (0.03-2.03) p=0.18
Previous Antiangiogenic	-	-	3.26 (0.14-77.90) p=0.27
Current Antiangiogenic	-	-	1.80 (0.06-50.14) p=0.45
Previous chemotherapy	No: 1.67 (±2.733) Yes: 1.67 (±1.676)	0.52¥	2.75 (0.39-19.67) p=0.31
Current chemotherapy	No: 1.75 (±2.34) Yes: 1.56 (±1.42)	0.76¥	1.00 (0.16-6.26) p=1.00
Active smoker	No: 2.09 (±1.76) Yes: 1.13 (±2.41)	0.07¥	0.13 (0.02-1.09) p=0.052
Active oncological disease	No: 2.33 (±3.26) Yes: 1.43 (±1,22)	0.86¥	2.50 (0.35-18.04) p=0.36

#Spearman; $ Kruskal–Wallis + post hocde Dunn; ¥ Mann–Whitney; OR, odds ratio; CI, confidence interval

In the Kruskal–Wallis tests, variation factors with different symbols indicate statistically different results and equal symbols indicate statistically equivalent results for the studied sample; the values presented indicate medical and standard deviation (±). Bold numbers are statistically significant.

Discussion

This study aimed to evaluate the risk factors for the occurrence of infectious complications in cancer patients affected with MRONJ associated with the administration of intravenous zoledronic acid. The selection of the underlying disease was based on the importance of infectious complications in the context of cancer patients, especially those with active disease and in immunosuppressive treatment.[16,17,18] The exclusion of necrosis caused by other drugs that control bone metabolism was done to reduce bias and prioritize the medication most used in this patient group and most often associated with MRONJ.[7,10]

The number of cases in this study (21) may seem to be an important limitation a priori. However, the restrictions and criteria that we used made it possible to homogenize the groups and make our results more reliable. Studies assessing the risk of developing MRONJ are common. However, there is a heterogeneous population regarding the type of medication, route of administration, underlying disease, and comorbidities. Intravenous administration, longer use time, mandibular bone and severity of the underlying disease are among the most relevant factors for MRONJ development risk. Recently, some studies have suggested a relationship between systemic conditions, such as anemia, diabetes, leukocytosis and smoking, and the development of MRONJ.[18–23]

The mean age (67.57 ± 10.4) and the type of cancer found in our study are in accordance with the literature regarding tumor type and frequency of bisphosphonate use in MRONJ.[24] The factors considered as triggers varied, with a special predilection for surgical interventions and periodontal disease. Only 15% of cases were considered spontaneous events. These findings corroborate most topic.[7,8,11,12,18,25,26-28] However, Mânea et al.,[22] in a retrospective evaluation of 38 patients, classified 32 cases as spontaneous.

The difficulty in recovering microorganisms and the possibility of growth of a contaminating agent have long been discussed in MRONJ cultures.[26,29] These difficulties are registered at a rate of 40% of non-growth in conditions of installed clinical infections. Despite the difficulties, the variety and prevalence of the found microorganisms are in accordance with those found in MRONJ patients.[26,29]

Even though, a greater number of studies have evaluated risk factors and pathophysiology, there is a lack of studies evaluating the prognostic criteria for MRONJ. Most studies compared wound healing events between clinical and surgical procedures. Regardless of the controversial results, surgeries in less extensive necrotic areas, associated with shorter use of the necrosis-inducing drug, seem to be good prognostic criteria.[12,28] All of these studies included patients with different diseases, medications and administration routes of the medication related to necrosis.

Ruggiero and Khohn[30] retrospectively evaluated the prognostic factors for MRONJ in 337 patients and identified non-cancer diseases, MRONJ class 1 and 2 and the surgical treatment as good prognostic factors. Martins et al.,[17] also in a retrospective evaluation of 77 patients, found MRONJ in the mandible and the use of intravenous medications as factors of poor prognosis. All intravenous presentations studied by Martins were bisphosphonates and the MRONJ classification was not associated with the outcome. Unlike in our study, both involved several pathologies and necrosis-inducing medications.

Our study is unprecedented in evaluating the criteria associated with infectious complications exclusively in cancer patients using intravenous ZA. In a study by Ruggiero,[30] 61.5% of patients were oncological and 76% were users of IV bisphosphonates. In Martins' study[17] 67.5% of the patients were oncological and only 48% were users of IV bisphosphonates. Martins[17] showed a similar incidence of class 3 necrosis in our study. This may be due to the fact that these studies had enrolled fewer patients than Ruggiero's. While Ruggiero[30] found a better prognosis for classification 1 and 2, we found the same for classification 1, but our group formed by class 2 + 3 showed worst results (0.00±0.54 versus 2.06±2.08) in individual analysis using the number of infections. The odds ratio analysis did not show classification as a risk factor. This divergence may have been caused by the infection categorization in the two groups (absence *versus* presence) which could have reduced the impact of the number of infections in the first analysis. The lack of significance of the classification in Martins' study may have been due to the smaller relative number of oncological cases of under bisphosphonate use.

While other studies evaluated the time of use as a prognostic definer, we chose to assess the total number of doses and the frequency of drug use, as they are important risk factors for the development of MRONJ.[17,18,20,23,28] The median number of total doses in our study was 17, with significant variation (3-37 doses); possibly a larger sample

could show a different result for this analysis, which in our study was not significant in determining the infectious events.

Monthly use was associated with infection recurrence (table 4). Although the average number of recurrences in twice a year users was numerically higher (5.0±2.82), the small number of patients in this regimen of use (9.52%), and the presence of an atypical case with seven recurrent infections, were the probable cause for this group not presenting a significant difference compared to monthly and quarterly users. A larger sample size, may highlight the difference between monthly and half-yearly users. Our study is unprecedented in its assessment of the frequency of use as a risk factor for prognosis. However, several others showed that the shortest interval between doses is a critical factor for MRONJ development.[18,22,23]

Despite the higher incidence and worse prognosis for MRONJ being associated with cancer patients, little is known about the relationship between systemic conditions and the complications associated with necrosis. In our cohort, 70% of the patients had active disease, 71.4% had already undergone chemotherapy, and 42.9% were still undergoing treatment at the time of necrosis diagnosis. All patients who had not previously undergone chemotherapy had prostate adenocarcinomas. All immunosuppressants used by 30% of the patients in our study were monoclonal antibodies. Only two patients in our study had previously used antiangiogenics and one of them was still using it at the time of necrosis, which made statistical evaluation of this variable unfeasible. This low frequency was also found by Ruggiero,[30] who reported that only 7% of patients had used this type of medication.

This study results of this study showed that MRONJ induced by intravenous ZA in patients with cancer can be associated with recurrent infections and indicate that mandibular involvement, and monthly ZA use are potential risk factors for poor prognosis. Longitudinal controlled studies are mostly performed to confirm the prognostic factor of MRONJ in oncological patients.

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Conflicts of interest

None.

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