RESEARCH ARTICLE

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Risk Factors for Bisphosphonate-Related Osteonecrosis of the Jaws in Bone Metastatic Breast and Prostate Cancer under Zoledronate Treatment: A Retrospective Analysis from 10 Years of Evaluation

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Abstract

Objective: This study aims to analyze the risk factors for BRONJ in patients taking zoledronic acid (ZA) for metastatic breast and prostate cancer. **Methods:** For this, a retrospective, quantitative, observational cohort study was conducted using data on adverse effects in the oral cavity in patients during chemotherapy for treatment of solid tumors available in the electronic patient record system of the Haroldo Juaçaba Hospital/Ceará Cancer Institute in the period from 2010, to 2019. Data were tabulated in Excel and exported to SPSS v20.0 software for statistical analysis, with 95% confidence. **Results:** Thus, it can be observed that the prevalence of BRONJ in patients under treatment for breast cancer and prostate cancer was <7%, with age <50 years of age (p=0.009), cytotoxic chemotherapy such as methotrexate (p=0.023), paclitaxel (p=0.005), capecitabine (p<0.001), gemcitabine (p=0.007) and bicalutamide (p=0.016), amount of ZA infusions (p<0.001) and hormone therapy (p=0.007), in addition, a slight reduction in survival and increased use of antidepressants (p=0.014) were observed. The reduced overall survival and increased use of antidepressants in patients who developed BRONJ, reinforcing the need for further research to study the mechanisms involved in the unconventional risk factors for BRONJ. **Conclusion:** Thus, increasing the attention to these patients to prevent this condition from compromising the prognosis of these individuals.

Keywords: Osteonecrosis- bisphosphonate- risk factors

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Introduction

Bisphosphonates (BPs) are osteolysis inhibitors commonly employed to treat and prevent bone metastases from multiple myeloma and cancers of the breast, prostate, kidney, and lung (Marinis et al., 2009; Mbase and Aderibigbe, 2021). However, the use of BFs is strongly associated with the development of a change known as Bisphosphonate-related Osteonecrosis of the Jaws (BRONJ) (Nicolatou-galitis et al., 2019).

BRONJ is defined by the World Health Organization as an exposure of the necrotic bone in the maxillofacial region for more than eight weeks in patients with a history of previous or current treatment with BP with no previous history of radiation therapy and is part of a larger class, drug-induced osteonecrosis of the jaws (Ruani et al., 2016). BRONJ can be classified depending on its stage of severity into stage 1 (presence of exposed and necrotic bone or intraoral fistula, without an active infection), stage 2 (presence of exposed and necrotic bone or intraoral fistula, with active infection), and stage 3 (presence of exposed and necrotic bone or intraoral fistula, associated with extensive necrosis, pathological fracture, extraoral fistula) (Thavarajah et al., 2019; Taylor et al., 2013; Barasch et al., 2011; Walter et al., 2008).

Among patients undergoing treatment for bone metastases, breast cancer, and prostate cancer, the most frequent in women and men, respectively, have an incidence of bone metastases of 75% and 65%, respectively (Turner et al., 2008). Breast cancer is a disease that predominantly affects a population over the age of 40. Prostate cancer is the second most common cancer and

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the fifth most common cause of death among men (Azim et al., 2014; Sun et al., 2017; Matsushita et al., 2020). These two tumors have high rates of bone metastasis a negative impact on the survival of these patients (Tahara et al., 2019; Wong et al., 2019).

Given that BRONJ significantly compromises the quality and life expectancy of these patients and may require discontinuation of oncologic treatment, leading to worsening in their prognosis (Ouyang et al., 2018), our study aims to analyze the risk factors for BRONJ in patients using zoledronic acid for metastatic breast and prostate cancer.

Materials and Methods

Study design, site, and ethical precepts

This study is a retrospective, quantitative observational cohort study guided by the STROBE initiative, an international guideline for conducting observational studies (Lababede and Meziane, 2018). This study was conducted using data on oral cavity adverse effects in patients during chemotherapy to treat solid tumors available in the electronic patient record system of the Haroldo Juaçaba Hospital/Ceará Cancer Institute (HHJ/ICC) from January 1, 2010, to December 31, 2019.

The Ethics Committee approved this research of the Haroldo Juaçaba Hospital as part of a project that includes the analysis of risk factors for adverse effects of cancer treatment in the oral cavity, whose protocol number is 4.062.135. All study phases were carried out under law 466/12 of the research ethics legislation, ensuring the confidentiality of information from the patients' medical records and keeping them until the end of the study.

Inclusion and exclusion criteria

The inclusion criterion was patients who had performed at least one zoledronic acid infusion from January 1, 2010, to December 31, 2019, at the HHJ/ICC. All drug infusions in chemotherapy services of the Unified Health System or private health insurance plans are recorded in the Tasy system with the pharmaceutical record of the active ingredient of the drug. Thus, through this system, the services these patients took these administrations were retrieved.

Patients under treatment for solid tumors other than breast or prostate cancer, patients with myeloproliferative diseases or head and neck tumors who received radiotherapy in the region, as well as patients with bone metastases from tumors with unknown primary sites or patients without information about the risk factors for BRONJ (described below) were excluded. Patients with more than one primary tumor were also excluded.

Sociodemographic and clinicopathological data collection

With the service number from the Tasy system, a manual search was performed in the patients' electronic medical records. For patients who appeared more than once in the Tasy search tool, the number of ZA administrations was computed and dated. If necessary, physical medical records were requested to complement the information not available in the digital system.

During manual collection of information from the patients' electronic medical records, the following data were retrieved: gender, age, weight on the day of care, history of surgery for the primary tumor, history of radiation therapy in the region of the primary tumor, history, protocol and intention of chemotherapy (neoadjuvant, adjuvant or palliative), number of chemotherapy treatment lines, clinical stage and location of the primary tumor. The TNM (tumor-nodal-metastasis) system (Lababede and Meziane, 2018) was used to stage the primary tumor. In addition, the history of hormone therapy and any drugs in use were surveyed. Finally, all data were tabulated in a standard spreadsheet in Microsoft Excel (Microsoft Corporation, Windows).

BRONJ prevalence analysis

The toxicity scales encompass analysis of all patients according to toxicity scores suggested by CTCAE v5.0. As per medical history, patients were classified as the following toxicity scores: grade 0, when there is no evidence of osteonecrosis; grade 1, when there is exposed bone, clinically diagnosed asymptomatic; grade 2, when there is exposed bone, with painful symptomatology, limiting self-care; grade 3, when there is exposed bone, with intense painful symptomatology, limiting self-care; grade 4, when there is exposed bone with life-threatening conditions, such as infection, fractures, fistulas, among others; grade 5, when there is death related to bisphosphonate-related osteonecrosis of the jaws (National Cancer Institute, 2018).

Therefore, the evaluations were exported to a standard Microsoft Excel spreadsheet containing the information of number and date of attendance, and degree of severity of the adverse effect.

Statistical Analysis

The data were tabulated in Microsoft Excel and exported to SPSS v20.0 for Windows software, in which the analyses were performed adopting a 95% confidence level.

The absolute and percentage frequencies of BRONJ and other clinical and therapeutic variables were calculated and associated with the prevalence of BRONJ by multinomial logistic regression. Associations with $p<0.200$ were submitted to a multinomial logistic regression model. The Kaplan-Meier curve of overall survival of patients with and without BRONJ was compared using the Mantel-Cox log-rank test.

Results

The sample was composed of 1,925 patients seen during the years 2010 to 2019, of which the majority of the sample was female breast cancer 1,408 (73.1%), and 517 (26.9%) were men with prostate cancer. All patients had metastatic tumors. Data collection was conducted from 2010 until 2019, totaling ten years, and most of the patients were included in the year 2013 (15.7%) (Table 1).

The mean age of the patients was 61.0±13.5 years ranging from 16 to 99 years, and the most prevalent age group was patients aged over 50 years (77.0%). Surgical

treatment of the primary tumor was described in 1,336 (69.4%) patients and radiotherapy in 1,090 (56.6%). However, chemotherapy (n= 1818, 94.4%) was the most frequently used therapeutic modality for these patients (Table 1).

Most patients who had chemotherapy had up to two lines of chemotherapy treatment (n=1,665, 86.5%), 72 (3.7%) patients had one line of treatment, 1486 (77.2%) had two lines of treatment, 170 (8.8%) had three lines of treatment, 52 (2.7%) had four lines of treatment, and 38 (2.0%) went through five lines of chemotherapy treatment. The mean number of ZA infusions was 5.4±6.6, ranging from 1 to 67, with most patients having up to eight ZA infusions (n= 1,396, 72.5%) (Table 1).

Of the 1925 patients evaluated, there were 123 (6.4%) cases of BRONJ. It was observed that the prevalence of BRONJ was not related to tumor location (p=0.091), year of diagnosis (p=0.244), and type of treatment of the primary tumor, whether the tumor was treated with surgery (p=0.496), with radiotherapy (p=0.216) or with chemotherapy (p=0.455). In contrast, BRONJ had a higher prevalence in patients who were younger than 50 years of age (p=0.009) and/or who took more than two lines of chemotherapy treatment (p=0.010) and/or who received more than eight infusions of ZA (p<0.001) (Table 1).

Most of the sample received some type of hormone therapy (n= 1341, 69.7%), with Anastrozole being the most commonly used drug (n= 727, 37.8%), followed by Tamoxifen (n= 360, 18.7%) and Zoladex (n= 225, 11.7%). It was observed that patients who used hormone therapy had a higher prevalence of BRONJ (n= 99, 80.5%) compared to patients who were not treated with this therapy (n= 560, 31.1%) (p=0.007). The hormone therapy leuprorelin was inversely associated with BRONJ (p=0.032) (Table 2).

Regarding the chemotherapeutics used, and Cyclophosphamide (n= 663, 34.4%) was the most frequently used in the therapeutic schemes. Following the most used antineoplastics were Doxorubicin (n= 538, 27.9%), Docetaxel (n= 465, 24.2%), Paclitaxel (n= 417, 21.7%), Capecitabine (n= 215, 11.2%), Gemcitabine (n= 158, 8.2%) and Bicalutamide (n= 82, 4.3%). In our

Table 1. Prevalence and Analysis of Risk Factors for Osteonecrosis of the Jaws (BRONJ) in Patients Undergoing Male Prostate and Female Breast Cancer Treatment from 2010 to 2019. Chemotherapy (QT), Zoledronic Acid (ZA)

		BRONJ		
	Total	No	Yes	p-Value
Total	1925	1802 (93.6%)	123 (6.4%)	-
Location				
Male Prostate	517 (26.9%)	492 (27.3%)	25 (20.3%)	0.091
Female breast	1408 (73.1%)	1310 (72.7%)	98 (79.7%)	
Year of diagnosis				
2010	55 (2.9%)	52 (2.9%)	3 (2.4%)	0.244
2011	142 (7.4%)	133 (7.4%)	9 (7.3%)	
2012	175 (9.1%)	161 (8.9%)	14 (11.4%)	
2013	303 (15.7%)	284 (15.8%)	19 (15.4%)	
2014	298 (15.5%)	270 (15.0%)	28 (22.8%)	
2015	384 (19.9%)	365 (20.3%)	19 (15.4%)	
2016	228 (11.8%)	210 (11.7%)	18 (14.6%)	
2017	167 (8.7%)	160 (8.9%)	7 (5.7%)	
2018	130 (6.8%)	125 (6.9%)	5 (4.1%)	
2019	43 (2.2%)	42 (2.3%)	1 (0.8%)	
Age				
Up to 50	442 (23.0%)	402 (22.3%)	40 (32.5%)*	0.009
>50	1483 (77.0%)	1400 (77.7%)*	83 (67.5%)	
Primary tumor treatment				
Surgery	1336 (69.4%)	1254 (69.6%)	82 (66.7%)	0.496
Radiotherapy	1090 (56.6%)	1012 (56.2%)	78 (63.4%)	0.216
Chemotherapy	1818 (94.4%)	1700 (94.3%)	118 (95.9%)	0.455
QT treatment lines				
Up to 2 lines	1665 (86.5%)	1568 (87.0%)*	97 (78.9%)	0.010
>2	260 (13.5%)	234 (13.0%)	26 (21.1%)*	
ZA infusions quantity				
Up to 8	1396 (72.5%)	1330 (73.8%)*	66 (53.7%)	<0.001
>8	529 (27.5%)	472 (26.2%)	57 (46.3%)*	

*p<0.05, Pearson's chi-square test (n, %)

Table 2. Influence of Hormone Therapy on the Prevalence of Osteonecrosis of the Jaws (BRONJ) in Patients undergoing Treatment for Female Breast Cancer and Male Prostate Cancer

		BRONJ		
	Total	No	Yes	p-Value
Hormone therapy				
No	584 (30.3%)	560 (31.1%)*	24 (19.5%)	0.007
Yes	1341 (69.7%)	1242 (68.9%)	99 (80.5%)*	
Hormone therapy drug				
Anastrozole	727 (37.8%)	673 (37.3%)	54 (43.9%)	0.147
Tamoxifen	360 (18.7%)	329 (18.3%)	31 (25.2%)	0.056
Fulvestrant	116 (6.0%)	104 (5.8%)	12 (9.8%)	0.072
Zoladex	225 (11.7%)	207 (11.5%)	18 (14.6%)	0.293
Exemestane	86 (4.5%)	77 (4.3%)	9 (7.3%)	0.114
Leuprorelin	93 (4.8%)	92 (5.1%)*	1 (0.8%)	0.032
Cyproterone	4 (0.2%)	4 (0.2%)	0 (0.0%)	0.601
Destilbenol	5 (0.3%)	5 (0.3%)	0 (0.0%)	0.559

*p<0.05, Pearson's chi-square test (n, %)

Table 3. Influence of Chemotherapy on the Prevalence of Osteonecrosis of the Jaws (BRONJ) in Patients Undergoing Treatment for Female Breast Cancer and Male Prostate Cancer.

		BRONJ		
	Total	No	Yes	p-Value
Chemotherapy drug				
Methotrexate	22 (1.1%)	18 (1.0%)	4 (3.3%)*	0.023
Doxorubicin	538 (27.9%)	500 (27.7%)	38 (30.9%)	0.452
Cyclophosphamide	663 (34.4%)	614 (34.1%)	49 (39.8%)	0.193
Ifosfamide	3 (0.2%)	2 (0.1%)	1 (0.8%)	0.056
Docetaxel	465 (24.2%)	432 (24.0%)	33 (26.8%)	0.474
Paclitaxel	417 (21.7%)	378 (21.0%)	39 (31.7%)*	0.005
Capecitabine	215 (11.2%)	189 (10.5%)	26 (21.1%)*	<0.001
Cabazitaxel	8 (0.4%)	7 (0.4%)	1 (0.8%)	0.479
Filgrastim	4 (0.2%)	3 (0.2%)	1 (0.8%)	0.128
Cisplatin	155 (8.1%)	143 (7.9%)	12 (9.8%)	0.473
Gemcitabine	158 (8.2%)	140 (7.8%)	18 (14.6%)*	0.007
Enzalutamide	10 (0.5%)	8 (0.4%)	2 (1.6%)	0.078
Carboplatin	61 (3.2%)	54 (3.0%)	7 (5.7%)	0.094
Everolimo	6 (0.3%)	6 (0.3%)	0 (0.0%)	0.522
Bicalutamide	82 (4.3%)	82 (4.6%)*	0 (0.0%)	0.016
Thalidomide	3 (0.2%)	3 (0.2%)	0 (0.0%)	0.651
Pemetrexede	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.794
Eribulin	5 (0.3%)	5 (0.3%)	0 (0.0%)	0.559
Vinflunine	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.794
Epirubicin	53 (2.8%)	50 (2.8%)	3 (2.4%)	0.826
Vimblastine	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.794
Fluorouracil	77 (4.0%)	75 (4.2%)	2 (1.6%)	0.165
Mitoxantrone	6 (0.3%)	5 (0.3%)	1 (0.8%)	0.303
Etoposide	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.794
Vinorelbine	23 (1.2%)	21 (1.2%)	2 (1.6%)	0.649
Oxaliplatin	6 (0.3%)	6 (0.3%)	0 (0.0%)	0.522
Irinotecan	3 (0.2%)	2 (0.1%)	1 (0.8%)	0.056
Carmustine	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.794

*Pearson's chi-square test (n, %).

Table 4. Influence of mAb and Other Chronic Use Medication on the Prevalence of Osteonecrosis of the Jaws (BRONJ) in Patients Undergoing Treatment for Female Breast Cancer and Male Prostate Cancer.

		BRONJ		
	Total	No	Yes	p-Value
mAb				
No	1771 (92.0%)	1659 (92.1%)	112 (91.1%)	0.690
Yes	154 (8.0%)	143 (7.9%)	11 (8.9%)	
mAb				
Gefitinib	2 (0.1%)	2 (0.1%)	0 (0.0%)	0.712
Bevacizumabe	29 (1.5%)	23 (1.3%)	6 (4.9%)	0.002
Denosumabe	9 (0.5%)	9 (0.5%)	0 (0.0%)	0.432
Trastuzumabe	106 (5.5%)	102 (5.7%)	4 (3.3%)	0.257
Abiraterone	9 (0.5%)	8 (0.4%)	1 (0.8%)	0.562
Lapatinib	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.794
Pertuzumabe	8 (0.4%)	8 (0.4%)	0 (0.0%)	0.459
Ipilimumab	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.794
Atezolizumab	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.794
Other drugs of chronic use				
Antihypertensives	402 (20.9%)	386 (21.4%)*	16 (13.0%)	0.026
Antidepressants	317 (16.5%)	287 (15.9%)	30 (24.4%)*	0.014
Anticoagulants	101 (5.2%)	97 (5.4%)	4 (3.3%)	0.305
Opioids	498 (25.9%)	461 (25.6%)	37 (30.1%)	0.270
Antacids	172 (8.9%)	160 (8.9%)	12 (9.8%)	0.741
NSAIDs	219 (11.4%)	204 (11.3%)	15 (12.2%)	0.768
Corticoids	188 (9.8%)	174 (9.7%)	14 (11.4%)	0.533
Hypoglycemic agents	204 (10.6%)	199 (11.0%)*	5 (4.1%)	0.015

*p<0.05, Pearson's chi-square test (n, %).

Table 5. Multivariate Analysis of Risk Factors for Developing of Osteonecrosis of the Jaws (BRONJ) in Patients Undergoing Male Prostate and Female Breast Cancer Treatment.

	p-Value	Adjusted OR (CI95%)
	BRONJ	
Breast tumor vs. Prostate tumor	0.477	1.28 (0.65-2.51)
Age >50 vs. <50	0.236	0.76 (0.48-1.20)
More than 2 lines of chemotherapy treatment	0.791	0.92 (0.49-1.71)
More than 8 ZA infusions	*0.002	1.89 (1.28-2.80)
Hormone therapy	*0.041	1.89 (1.03-3.48)
Anastrozole	0.816	1.06 (0.66-1.69)
Tamoxifen	0.665	0.89 (0.53-1.51)
Fulvestrant	0.945	0.98 (0.47-2.01)
Exemestane	0.967	1.02 (0.45-2.32)
Leuprorelin	0.057	0.14 (0.02-1.06)
Methotrexate	*0.049	3.33 (1.01-11.03)
Cyclophosphamide	0.845	1.05 (0.67-1.63)
Ifosfamide	0.233	5.76 (0.32-102.67)
Paclitaxel	0.521	1.17 (0.72-1.90)
Capecitabine	*0.043	1.76 (1.02-3.03)
Filgrastim	0.863	1.31 (0.06-27.01)
Gemcitabine	0.490	1.26 (0.65-2.44)
Enzalutamide	0.070	5.03 (0.88-28.87)

Table 5. Continued

	p-Value	Adjusted OR (CI95%)
	BRONJ	
Carboplatin	0.454	1.41 (0.58-3.44)
Fluorouracil	0.072	0.26 (0.06-1.13)
Irinotecano	*0.036	20.02 (1.21-331.26)
Bevacizumabe	0.087	2.44 (0.88-6.77)
Antihypertensives	0.093	0.59 (0.32-1.09)
Antidepressants	*0.010	1.85 (1.16-2.96)
Hypoglycemic agents	0.065	0.39 (0.15-1.06)

*p<0.05, multinomial logistic regression; OR, Odds ratio; CI 95%, 95% confidence interval of Adjusted OR.

study it was possible to observe that administration of some types of chemotherapy drugs were associated with increased prevalence of BRONJ, such as methotrexate (p=0.023), paclitaxel (p=0.005), capecitabine (p<0.001) and gemcitabine (p=0.007). However, the chemotherapy Bicalutamide was inversely associated with BRONJ (p=0.016) (Table 3).

Only a small portion of the sample used some type of monoclonal antibody (mAb) (n= 1,771, 92%). The most commonly used mAb was trastuzumab (n= 106, 5.5%) followed by bevacizumab (n= 29, 1.5%). Additionally, most patients were using opioids (n= 498, 25.9%)

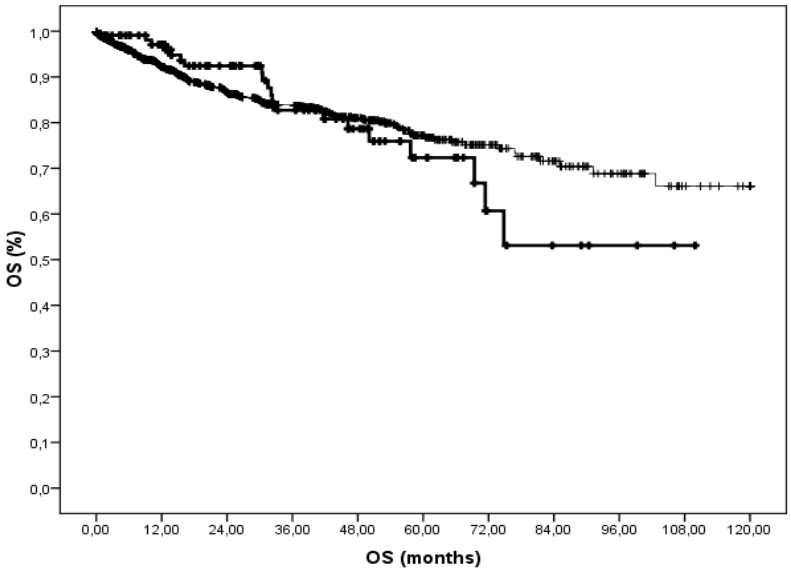

Figure 1. Influence of Osteonecrosis of the Jaws (BRONJ) on Overall Survival of Patients with Metastatic Breast or Prostate Cancer Treated with ZA. Thick line = Kaplan-Meier curve of patients who developed BRONJ; Thin line = Kaplan-Meier curve of patients who did not develop BRONJ.

and antihypertensives (n= 402, 20.9%), followed by antidepressants (n= 317, 16.5%) and NSAIDs (n= 219, 11.4%). Patients who took Ab Bevacizumab had a higher prevalence of BRONJ (p=0.002). Chronic use of antihypertensives (p=0.026) and hypoglycemic agents (p=0.015) were inversely associated with BRONJ, and use of antidepressants was associated with a higher prevalence of BRONJ (24.4%) (p=0.014) (Table 4).

In multivariate analysis it was observed that the use of more than 8 infusions of ZA (adjusted OR = 1.89) (p=0.002), use of hormone therapy (adjusted OR = 1.89) (p= 0.041), Methotrexate (adjusted OR = 3.33) (p=0,049), Capecitabine (adjusted OR = 1.73) (p=0.043), Irinotecan (adjusted OR = 20.02) (p=0.036) and antidepressants (adjusted OR = 1.85) (p=0.010) significantly increased the prevalence for BRONJ (Table 5).

Regarding overall survival, there was no significant difference between the overall survival of patients with BRONJ (n=70/110; 81.40±5.38 [CI 95% = 70.85-91.95] months) and without BRONJ (n=1216/1642; 94.13±1.80 [CI 95% = 90.59-97.66] months) (p=0.769) (Figure 1).

Discussion

This study showed a prevalence of BRONJ of 6.54% in association with age, some chemotherapy drugs, mAbs, hormone therapy, and other chronic use drugs. In similarity to our study, Walter et al. in 2009 obtained a prevalence of BRONJ of 5.3% in breast cancer patients who took bisphosphonate use (Kotán et al., 2019), despite Taylor et al. in 2013 had described a much higher prevalence with 34.8% of patients presenting with a diagnosis of BRONJ and use of venous bisphosphonates and Kotán described a much lower prevalence with only 0.9% of BRONJ (Bamias et al., 2005). This difference in prevalence is related to the different study designs, therapy protocols implemented, and exposure to risk factors. For example, in the study by Taylor et al., (2013) (Taylor et al., 2013) all patients underwent the process of exodontia, which increases the risk of BRONJ.

Regarding the prevalence of BRONJ in female breast cancer and prostate cancer, a discrete prevalence was observed in breast cancer, but without significant difference. Bamias et al., (2005) also demonstrated similar results, but in contrast, Rugani et al., (2016) reported a higher prevalence of BRONJ in prostate cancer (3.8%) compared to breast cancer (2.09%) (Rugani et al., 2016) and Walter et al., (2008) also observed a lower prevalence of BRONJ in breast cancer (Fung et al., 2017).

We could also observe that patients in oncological treatment who use ZA for an extended period had a significant increase in the risk of BRONJ, and this finding was observed even in the multivariate analysis. Studies show that the increased risk of BRONJ is directly proportional to the dose and frequency of ZA use (Grahan et al., 2007; Barasch et al., 2011), since ZA generates a cumulative effect on bone tissue (Basso et al., 2018). Furthermore, ZA has been linked to toxic cellular effects and the production of proinflammatory cytokines in bone tissue (Badel et al., 2013). The administration of chemotherapeutic drugs has been described as a risk factor for the development of BRONJ (Zhou et al., 2020; Shibahara et al., 2019). Chemotherapeutic drugs generate cytotoxic effects on metabolism and vascularization, thus increasing the prevalence of BRONJ (Shibahara et al., 2019), which could be associated with several drugs in use in the patients of this study.

A peculiar finding of our work was that the highest prevalence of BRONJ is related to patients in the less than 50 years age group. This relationship probably occurs due to the predominance of edentulism in the aged 50 years and older. As one of the risk factors for BRONJ is the presence of infectious foci in dental or periodontal tissue, edentulism would reduce this risk significantly (Kyrgidis

et al., 2008). Thus, younger patients who have more teeth in their mouths are more likely to develop BRONJ, although the use of dentures has also been described as a risk factor (Okuma et al., 2020).

There was an increased prevalence of BRONJ in patients who used hormone therapy, including in the multivariate analysis. This may be associated with the modulation of bone metabolism and immunosuppression that this therapy causes, making the individual more susceptible to developing BRONJ (Hoff et al., 2018). In a classic case-control study, Hoff describes risk factors for developing BRONJ in patients with metastatic cancers, and patients with positive estrogen receptor breast tumors demonstrate a higher risk than patients without this receptor (Gnant et al., 2009). After the consolidation of primary therapy, regardless or not of having bone metastases, patients with breast tumors that express positivity for hormone receptors start maintenance treatment with sex hormone synthesis inhibitors, a hormone therapy, apparently increasing this risk (Gnant et al., 2011; Cenci et al., 2000).

Hormones such as estrogen, progesterone, and testosterone have anti-inflammatory activity in the bone tissue (Vural et al., 2006; Michael et al., 2005; Bagan et al., 2014). Hormone suppression has been linked to bone-inflammatory dysregulation, which is the main risk factor for BRONJ (Bagan et al., 2014). However, paradoxically, leuprorelin use is inversely associated with BRONJ.

In 2018 McGowan (McGowan et al., 2018), in a systematic review, described that chemotherapy is the most prevalent factor in BRONJ cases, and in our study, it was no different. Although chemotherapy itself showed no association with increased risk of BRONJ, due to >90% of patients taking QT, in the present study, the use of methotrexate and paclitaxel were directly related to the development of BRONJ in patients on antineoplastic treatment. Methotrexate is an immunosuppressive drug that significantly worsens gingival changes and periodontal disease (Horie et al., 2015; Furukawa et al., 2018), and as periodontal disease is one of the main risk factors for BRONJ (Thumbigere-Math et al., 2014) due to infection (Kilic et al., 2018), periodontal attention should be given to patients on concomitant use of bisphosphonates and methotrexate.

Paclitaxel has also been associated with BRONJ, but the literature lacks clinical studies associating these two drugs. In mice treated with paclitaxel, significant trabecular bone loss, increased marrow adiposity, increased numbers of osteoclasts, and suppression of osteoblast differentiation have been described (Lee et al., 2019), together with the immunosuppression caused by the drug may empower its risk of BRONJ. Whereas irinotecan, which increased the risk of BRONJ in our study, including in multivariate analysis, has been associated with strong suppression of the immune system (Hayashi et al., 2018), dysregulation of the RANK-RANKL-OPG axis (Decaux et al., 2020). which is an axis associated with the development of BRONJ (Cankava et al., 2013). Capecitabine and gemcitabine have also been associated with a higher prevalence of BRONJ. In addition to these chemotherapeutics being potent immunosuppressive agents, they are known to generate delay in the healing process of post-surgical wounds, findings strongly immunosuppression and BRONJ (Badel et al., 2013; Hayashi et al., 2018). On the other hand, bicalutamide was inversely associated with BRONJ, which may be associated with stimulation of testosterone synthesis, which is vital for maintaining bone mineral density (Wadhwan et al., 2010).

The use of monoclonal antibodies showed no significant difference in the prevalence of BRONJ. However, therapy with bevacizumab showed an increased risk of BRONJ in patients under treatment. Bevacizumab is an antiangiogenic drug that acts by blocking vascular proliferation and reducing the concentrations of endothelial growth factors, which is of fundamental importance for bone formation due to the regulation of osteoclastic cells. The inhibition of angiogenesis by bevacizumab or during wound healing plays a key role in the development of BRONJ, where the association with ZA causes an increase in avascularization (Guaneri et al., 2010; Yamaguchi et al., 2018). The use of bevacizumab has been gaining space in the treatment of breast cancer (Hey et al., 2020) and in solid tumors in general (Roviello et al., 2017) in the form of combined therapy with chemotherapies, so in the future, its use may potentiate the incidence of BRONJ.

The use of antihypertensives and hypoglycemic agents was inversely associated with the onset of BRONJ, which may be associated with the prevalence of hypertension and diabetes in patients aged 50 years or older (Jorgensen et al., 2020), a group at lower risk for BRONJ in our sample.

In our study, it was possible to observe a direct association between the use of antidepressants and BRONJ, including in the multivariate analysis. BRONJ significantly decreases patients' quality of life, generating anxiety, discomfort, pain, and depression (Miksad et al., 2011). Studies have shown that the development of BRONJ significantly depresses the quality of life of patients using bisphosphonates (El-rabbany et al., 2021), so we can relate that the increased prevalence of BRONJ was related to the use of antidepressants due to the decline in the quality of life of these individuals (Bausewein et al., 2015).

Although there was no significant difference, it was possible to observe that patients who developed BRONJ had a reduction in overall survival compared to patients who did not develop this condition. These BRONJ has been associated with significantly reduced overall survival in patients with metastatic cancers (Corraine et al., 2017; Nieuwenhuizen et al., 2021) and negatively interferes with the quality of life of these patients (Miksad et al., 2011).

The major limitation of this study is the cross-sectional nature of the evaluations and the lack of a detailed dental history. It was not possible to follow the patients longitudinally or to evaluate intraoral surgical procedures' performance during treatment. Even so, this study found important risk factors for BRONJ in patients with breast and prostate cancers and may serve as a guide for specific patient groups.

Thus, the prevalence of BRONJ in patients being treated for breast cancer and prostate cancer was low (<7%), and the main risk factors were age <50 years,

cytotoxic chemotherapy, amount of ZA infusions, and, interestingly, hormone therapy. Discrete reduction in overall survival of patients and increased use of antidepressants in patients who developed BRONJ are attention-grabbing findings and reinforce the need for prospective studies to study the mechanisms involved in unconventional risk factors for BRONJ.

Author Contribution Statement

Matos Carlos AC, Moreira Caetano Lívia, Malta CN, Magalhães IA data collect and writing of the paper. They read and approved the final version. Borges MF, Junior JS and Silva LG was responsible for the review of the statistical analysis and writing of the paper. They read and approved the final version. Barros Silva PG designed the model, performed statistical analysis, reviewed the text and read and approved the final version.

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Ethics approval

The Ethics Committee approved this research of the Haroldo Juaçaba Hospital as part of a project that includes the analysis of risk factors for adverse effects of cancer treatment in the oral cavity, whose protocol number is 4.062.135. All study phases were carried out under law 466/12 of the research ethics legislation, ensuring the confidentiality of information from the patients' medical records and keeping them until the end of the study.

Conflicts of interest

The authors have no conflicts of interest.

References

Azim HA, Partridge AH (2014). Biology of breast cancer in young women. *Breast Cancer Res*, **16**, 427.

Badel T, Pavicin IS, Carek AJ, Rosin-grget K, Grbesa D (2013). Pathophysiology of osteonecrosis of the jaw in patients treated with bisphosphonate. *Coll Antropol*, **37**, 645-1.

Bagan J, Sáez GT, Tormos MC, et al (2014). Interleukin-6 concentration changes in plasma and saliva in bisphosphonate-related osteonecrosis of the jaws. *Oral Dis*, **20**, 446-2.

Bamias A, Kastritis E, Bamia C et al (2005). Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol*, **23**, 8580-7.

Barasch A, Cunha-cruz J, Curro FA, et al (2011). Risk factors for osteonecrosis of the jaws: a case-control study from the CONDOR dental PBRN. *J Dent Res*, **90**, 439-4.

Basso FG, Pansani TN, Soares DG et al (2018). Influence of bisphosphonates on the adherence and metabolismo of epitelial cells and gingival fibroblasts to titanium surfaces. *Clin Oral Inverstiga*, **22**, 893-0.

Bausewein C, Simon ST, Pralong A et al (2015). Palliative care of adult patients with cancer. *Dtsch Arztebl Int*, **112**, 863-0.

Çankaya M, Senel FC, Duman MK et al (2013). The effects of chronic zoledronate usage on the jaw and long bones evaluated using RANKL and osteoprotegerin levels in an animal model. *Int J Oral Maxillofac Surg*, **42**, 1134-9.

Cenci S, Weitzmann MN, Roggia C et al (2000). Estrogen deficiency induces bone loss by enhancing T-cell production of TNF-α. *J Clin Invest*, **106**, 1229-7.

Corraini P, Heide-jorgensen U, Schiodt M et al (2017). Osteonecrosis of the and survival os patients with cancer: a Nationwide cohort study in Denmark. *Cancer Med*, **6**, 2271-7.

Decaux J, Magremanne M (2020). Medication-related osteonecrosis of the jaw related to epacadostat and pembrolizumab. *J Stomatol Oral Maxillofac Surg*, **121**, 740-2.

El-rabbany M, Blanas N, Sutherland S, et al (2021). Development and evaluation of the clinimetric properties of the Medication-Related Osteonecrosis of the Jaw Quality of Life Questionnaire (MRONJ-QoL). *Int J Oral Maxillofac Surg*, **51**, 768-5.

Fung P, Bedogni G, Bedogni A, et al (2017). Time to onset of bisphosphonate-related osteonecrosis of the jaws: a multicentre retrospective cohort study. *Oral Dis*, **23**, 477-3.

Furukawa S, Oobu K, Moriyama M et al (2018). Oral methotrexate-related lymphoproliferative disease presenting with severe osteonecrosis of the jaw: A case report and literature review. *Intern Med*, **57**, 575-1.

Gnant M, Mlineritsch B, Schippinger W et al (2009). Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med*, **360**, 679-1.

Gnant M, Mlineritsch B, Stoeger H, et al (2011). Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol*, **12**, 631-1.

Guarneri V, Miles D, Robert N, et al (2010). Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. *Breast Cancer Res Treat*, **122**, 181-8.

Hayashi M, Morimoto Y, Lida T, Tanaka Y, Sugiyama S (2018). Risk of delayed healing of tooth extraction wounds and osteonecrosis of the jaw among patients treated with potential immunosuppressive drugs: A retrospective cohort study. *Tohoku J Exp Med*, **246**, 257-4.

Hey SP, Gyawali B, D'andrea E, et al (2020). Systematic review and meta-analysis of bevacizumab in first-line metastatic breast cancer: lessons for research and regulatory enterprises. *J Natl Cancer Inst*, **112**, 335-2.

Hoff AO, Toth BB, Altundag K, et al (2018). Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res*, **23**, 826-6.

Horie N, Kawano R, Kaneko T, Shimoyama T (2015). Methotrexate-related lymphoproliferative disorder arising in the gingiva of a patient with rheumatoid arthritis. *Aust Dent J*, **60**, 408-1.

Jorgensen JMA, Hedt KH, Osmar OM, Davies JI (2020). Hypertension and diabetes in Zanzibar – prevalence and access to care. *BMC Public Health*, **20**, 1352.

Kilic E, Doganay O (2018). Current management concepts for bisphosphonate-related osteonecrosis of the jaw: a review. *Gen Dent*, **66**, e1-e5.

Kotán EV, Lieb TB, Parisek Z, et al (2019). Database analysis of the risk factors of bisphosphonate-related osteonecrosis of the jaw in hungarian patients. *BMJ Open*, **9**, 025600.

Kyrgidis A, Vahtsevanos K, Koloutsos G, et al (2008). Bisphosphonate-related osteonecrosis of the jaws: a case-control study of risk factors in breast cancer patients. *J Clin Oncol*, **26**, 4634-8.

Lababede O, Meziane MA (2018). The eighth edition of TNM

staging of lung cancer: reference chart and diagrams. *Oncologist*, **23**, 844-8.

Lee AMC, Bowen JM, Su YW, et al (2019). Individual or combination treatments with lapatinib and paclitaxel cause potential boné loss and boné marrow adiposity in rats. *J Cell Biochem*, **120**, 4180-1.

Marinis FD, Eberhardt W, Harper PG, et al (2009). Bisphosphonate use in patients with lung cancer bone metastases: recommendations of a European expert panel. *J Thorac Oncol*, **4**, 1280-8.

Matsushita M, Fujita K, Nonomura N (2020). Influence of diet and nutrition on prostate cancer. *Int J Mol Sci*, **21**, 1447.

Mbese Z, Aderibigbe BA (2021) Bisphosphonate-based conjugates and derivatives as potential therapeutic agents in osteoporosis, bone cancer and metastatic bone cancer. *Int J Mol Sci*, **22**, 6869.

Mcgowan K, Mcgowan T, Ivanovski S (2018). Risk factor for medication-related osteonecrosis of the jaws: A systematic review. *Oral Dis*, **24**, 527-6.

Michael H, Harkonem PL, Vaananem HK, Hentunen TA (2005). Estrogen and Testosterone Use Different Cellular Pathways to Inhibit Osteoclastogenesis and Bone Resorption. *J Bone Miner Res*, **20**, 2224-2.

Miksad RA, Lai KC, Dodson TB, et al (2011). Quality of life implications of bisphosphonate- associated osteonecrosis of the jaw. *Oncologist*, **16**, 121-32.

National Cancer Institute. Cammon Toxicity Criteria Version 5.0 de 2017, Acessado em março de 2020, disponivel http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx.

Nicolatou-Galitis O, Schiodt M, Mendes RA, et al (2019). Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. *Oral Surg Oral Med Oral Phatol Oral Radiol*, **127**, 117-5.

Nieuwenhuizen AJV, Buffart LM, Langendijk já, et al (2021). Health-related quality of life and overall survival: a prospective study in patients with and neck cancer treated with radiotherapy. *Qual Life Res*, **30**, 1145-3.

Okuma S, Matsuda Y, Nariai Y, et al (2020). Retrospective observational study of risk factors for denosumab-related osteonecrosis of the jaw in patients with bone metastases from solid cancers. *Cancers (Brasel)*, **12**, 1209.

Ouyang Z, Li H, Zhai Z, et al (2018). Zoledronic acid: pleiotropic anti-tumor mechanism and therapeutic outlook for osteosarcoma. *Curr Drug Targets*, **19**, 409-1.

Roviello G, Bechelot T, Hudis CA, et al (2017). The role of bevacizumab in solitumours: A literature based meta-analysis of randomised trials. *Eur J Cancer*, **75**, 245-8.

Rugani P, Walter C, Kimbauer B, et al (2016). Prevalence of cátiontion-related osteonecrosis of the jaw in patients with breast cancer, prostate cancer, and multiple myeloma. *Dent J*, **4**, 32.

Russell RG, Xia Z, Dunford JE, et al (2007). Bisphosphonates: an update on Mechanisms of action and how these relate to clinical efficacy. *Ann N Y Acad Sci U S A*, **1117**, 209-7.

Shibahara T (2019). Antiresorptive Agent-Related Osteonecrosis of the Jaw (ARONJ) A Twist of Fate in the Bone. *Tohoku J Exp Med*, **247**, 75-6.

Sun YS, Zhao Z, Yang ZN, et al (2017). Risk factors and preventions of breast cancer. *Int J Biol Sci*, **13**, 1387-7.

Tahara RK, Brewer TM, Theriault RL, Ueno NT (2019). Bone metastasis of breast cancer. *Adv Exp Med Biol*, **1152**, 105-9.

Taylor T, Bryant C, Popat S (2013). A study 225 patients on bisphosphonates presenting to the bisphosphonate clinic at king´s college hospital. *Br Dent J*, **214**, E18.

Thavarajah M, Jayaram R (2019). Uncommon presentation of medication-related osteonecrosis of the mandible in a patient with metastatic prostate cancer. *BMJ Case Rep*, **12**, e228238.

Thumbigere-math V, Michalowicz BS, Hodges JS, et al (2014). Periodontal Disease as a Risk Factor for Bisphosphonate-Related Osteonecrosis of the Jaw. *J Periodontal*, **85**, 226-3.

Turner B, Drudge-coates L, Ali S (2016). Osteonecrosis of the jaw in patients receiving boné-targeted therapies: na overview – part I. *Urol Nurs*, **36**, 111-6.

Vural P, Akgul C, Canbaz M (2006). Effects of hormone replacement therapy on plasma pro-inflammatory and anti-inflammatory cytokines and some bone turnover markers in postmenopausal women. *Pharmacol Res*, **54**, 298-2.

Wadhwan VK, Weston R, Parr NJ (2010). Frequency of zoledronic acid to prevent further bone loss in osteoporotic patients undergoing androgen deprivation therapy for prostate cancer. *BJU Int*, **105**, 1082-8.

Walter C, Al-nawas B, Grotz KA, et al (2008). Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate. *Eur Urol*, **54**, 1066-2.

Walter C, Nawas BAL, Bois AD, et al (2009). Incidence of bisphosphonate-associated osteonecrosis of the jaws in breast cancer patients. *Cancer*, **115**, 1631-7.

Walter C, Nawas BAL, Frickhofen N, et al (2010). Prevalence of bisphosphonate associated osteonecrosis of the jaws in multiple myeloma patients. *Head Face Med*, **6**, 11.

Wong SK, Mohamad NV, Giaze TR, Chin KY, Ima-nirwana S (2019). Prostate cancer and boné metástases: the underlying mechanisms. *Int J Mol Sci*, **20**, 2587.

Yamaguchi K, Masuda T, Fujitaka K, et al (2018). Bevacizumab with single-agent chemotherapy in previously treated non-squamous non-small-cell lung cancer: phase II study. *In Vivo*, **32**, 1155-0.

Zhou Y, Yu Y, Shi Y, et al (2020). Combined administration of bisphosphonates, chemothaerapeutic agentes, and/or targeted drugs increases the risk for stage 3 medication-related osteonecrosis of the jaw: A 4-years retrospective study. *Biomed Res Int*, **2020**, 5847429.