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Onset of MRONJ in Breast Cancer Patients after Switching from Low to High Dose of Bone Modifying Agents Due to Bone Metastases Development: A Single Center Retrospective Cohort Study

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Abstract: Background: Medication-Related Osteonecrosis of the Jaw (MRONJ) is an adverse drug reaction mainly associated to bone modifying agents (BMAs). Breast cancer (BC) is the most frequent cancer worldwide. Its therapy can cause cancer treatment-induced bone loss (CTIBL), commonly treated with BMAs. The aims of this retrospective study are: to describe characteristics of BC patients under BMAs for CTIBL; to record any switch to high-dose BMAs; to assess MRONJ onset and to identify any factors associated with it. Patients: Authors included patients referred for MRONJ prevention to the Unit of Oral Medicine (University Hospital of Palermo). Results: Fourteen female BC patients under low-dose BMAs for CTIBL were eligible (mean age 66.6 years). Four patients switched to high-dose BMAs for bone metastases. In two of the four, MRONJ developed: one case, in the mandible (risedronate for 48 months then Xgeva® for 60 months); the other case, in the maxilla (Prolia® for 20 months then zoledronate for 16 months). Conclusion: It can be theorized that BC patients under BMAs for CTIBL are likely to have MRONJ risk similar to osteo-metabolic patients. These patients need more careful monitoring of oral health since they may switch, for preventing or treating bone metastases, to heavier BMAs therapy, thus increasing their risk of MRONJ.

Keywords: osteonecrosis of the jaw; MRONJ; cancer treatment-induced bone loss; CTIBL; breast cancer; osteoporosis; bone metastases; bisphosphonates; BPs; denosumab

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1. Introduction

Medication-Related Osteonecrosis of the Jaw (MRONJ) can be defined as "adverse drug reaction described as the progressive destruction and death of bone that affects the mandible and maxilla of patients exposed to the treatment with medications known to increase the risk of disease, in the absence of a previous radiation treatment", to be diagnosed and scored by clinics and radiological exams, independently from the presence of exposed necrotic bone or bone probing via sinus/fistula tracts for more than 8 weeks [1,2].

MRONJ is considered a potentially serious complication mainly of bone modifying agents (BMAs) treatment in patients with bone metastases (BM) due to various cancers and with multiple myeloma, as well as osteoporosis [3]. MRONJ may also develop in BMAs-naive patients exposed to a variety of anti-angiogenic agents [4–6].

Breast cancer (BC) is the world's most prevalent cancer. In 2020, there were 2.3 million women diagnosed with BC and 685,000 deaths globally. BC has a prevalence estimated in 2020 (time period 5 years) of 7.8 million women [7,8].

In patients affected by BC, since early menopause is induced by gonadotropin-releasing hormone analogues or chemotherapy and/or aromatase inhibitors reduce estrogen levels, there is the risk of developing Cancer Treatment-Induced Bone Loss (CTIBL), apart from

the further risk of developing BM in advanced stages of BC [8]. The drugs of choice for CTIBL prevention are BMAs, such as bisphosphonates (BPs) or denosumab (DNB) [9,10].

In RCTs on BC patients, treated with low doses of BMAs for CTIBL prevention, the onset of MRONJ was observed between 0% and 10.4%, but data are very scarce and debatable [11–14].

This retrospective cohort study aims to: (i) describe the characteristics of BC patients under BMAs for CTIBL prevention in dental follow-up; (ii) record any switching to high dose BMAs therapy; (iii) assess the onset of MRONJ; and (iv) identify the factors associated with MRONJ.

2. Materials and Methods

2.1. Study Design

The following observational cohort study was approved by the Institutional Local Ethics Committee of the University Hospital "P. Giaccone" of Palermo, Palermo, Italy (approval number 1/2022). The study was conducted according to the Principles of the Declaration of Helsinki on experimentation involving human subjects and a written informed consent was obtained from all participants. The study was performed following the STROBE Statement for Observational Cohort Studies. Authors consecutively included all the BC patients scheduled to receive BMAs therapy or already in BMAs therapy for CTIBL and referred to Unit of Oral Medicine of the University Hospital of Palermo from December 2015 to February 2020. For each patient, demographic data, number and type of BMA therapies, onset of bone metastases, diagnosis of systemic, drug-related and local risk factors (e.g., diabetes, corticosteroids, periodontitis) and smoking habits were recorded. All these patients underwent oral examination and dedicated radiological investigation (e.g., orthopantomography—OPT) and, when necessary, computed tomography (CT) or cone beam CT (CBCT).

2.2. Eligibility Criteria

The patients were selected based on the following inclusion criteria:

- patients suffering from BC commencing, taking or who had taken BMAs for CTIBL
- at least 12 months of dental follow-up.

The exclusion criteria were: patients with different cancer or BC and metastases; patients receiving off-label use of BMAs; patients receiving anti-angiogenic drugs alone or in combination with BMAs; patients who underwent radiant therapy head-neck district or were affected by jaws cancer or metastases.

2.3. Outcome Measures

For each patient, the following data were recorded: demographic data, any systemic, drug-related (i.e., type, duration and formulation of BMAs), and local risk factors (e.g., diabetes, corticosteroids, periodontitis), smoking habits, site of each MRONJ lesion, and clinical-radiological stage by SICMF-SIPMO [2,15].

MRONJ has been diagnosed according to the SICMF-SIPMO recommendation, by means of CT or CBCT [2,15].

2.4. Statistical Analysis

The onset of MRONJ was considered as the primary outcome variable and expressed dichotomously. The type of cancer, reason for BMAs treatment, the type of drug, the duration of therapy as well as drug-suspension were expressed as frequencies and percentages. Age was reported as mean and standard deviation.

3. Results

Characteristics of Patients

Fourteen patients with breast cancer (BC) under low dose of BMAs for CTIBL prevention were eligible. Data have been collected and Table 1 illustrates the characteristics of patients at the baseline.

All patients were female and affected by BC, with a mean age of 66.6 (±11.9 years, range 48–84 years). Seven patients (7/14, 50%) had various comorbidities: five hypertension (35.7%), two arthrosis (14.3%), two diabetes mellitus (14.3%). Twelve patients had local risk factors: poor oral hygiene, periodontal disease, endo-periodontal lesion, and dental prosthesis). Only one patient was a smoker (1/14, 7.1%) (Table 1).

In the first dental visit all patients were assuming low dose BMAs, specifically: alendronate 6/14 (42,9%), clodronate 6/14 (42,9%), risedronate 1/14 (7,1%), Prolia® (DNB 60 mg/biannually) 1/14 (7,1%). Among patients assuming clodronate, one patient had a previous history of alendronate intake. The median number of months of low dose BMAs was 57.9 (+47.1 months) (Table 2).

All patients were subjected to primary and secondary prevention measures for MRONJ.

During the follow-up period (median follow-up period 28.1 ± 19.6 months), out of 14 patients, 4 patients switched from low dose BMAs to high dose BMAs due to the development of bone metastasis (4/14, 28.6%). The mean time from the assumption of low dose to high dose BMAs was 35 months (± 15.1 months). Three patients switched from BPs to Xgeva® (DNB 120 mg/month), one patient switched from Prolia® to zoledronate (e.v.). The median number of months of Xgeva® was 28 (±23.6, 4–60); one patient assumed zoledronate (e.v.) for 16 months (Table 2). Among these four patients, two developed MRONJ (2/4, 50%) (2/14, 14.3%) (Figure 1, Tables 3 and 4).

Seven patients (50%) underwent dental extractions for MRONJ primary prevention (four patients assuming low dose BMAs; three assuming high dose BMAs). Overall, 15 extractions were made: 10 (66.6%) were from the maxilla (2 anterior teeth, 8 posterior teeth) and 5 (33.3%) from the mandible (all posterior teeth). A drug suspension protocol for medications at risk was observed in 85.7% of cases (6/7 patients) when dental surgery was considered necessary. None of these patients developed MRONJ in the post-extraction site. During the follow-up period, one patient changed low dose BMA from alendronate to Prolia®. The two patients that developed MRONJ underwent surgical therapy of MRONJ, both patients healed.

Table 1. Characteristics of enrolled breast cancer patients.

Patient	Age	Systemic Disease	Local Risk Factors	ONJ-Related Drugs	Duration (Months)	Cumulative Doses (mg)	Dental Extractions	N. Teeth Extracted	MRONJ Onset during Follow-Up	Time-Lapse between 1st° Visit and Last Check-Up (Months)
#1	53	Autoimmune thyroiditis	Poor oral hygiene, dental prosthesis	alendronate clodronate	48 12	13,440 2400	No	n.a.	No	12
#2	79	Arthrosis, diabetes	Poor oral hygiene	clodronate	120	24,000	No	n.a.	No	14
#3	73	Hypertension, arthrosis, diabetes, hepatitis C	Poor oral hygiene	clodronate	82	16,400	No	n.a.	No	19
#4	83	n.a.	Poor oral hygiene	clodronate	132	26,400	No	n.a.	No	12
#5	75	n.a.	Dental prosthesis, periodontal disease, poor oral hygiene, endo-periodontal lesion	risedronate Xgeva®	48 60	7200 7200	Yes	2	Yes	84
#6	57	Hypertension, osteomalacia	endo-periodontal lesion	alendronate	12	3360	Yes	2	No	42
#7	70	Hypertension	Dental prosthesis, periodontal disease, poor oral hygiene	alendronate	156	43,680	Yes	1	No	36
#8	48	Thalassaemia carrier	n.a.	alendronate	33	9240	Yes	2	No	40
#9	67	N.a.	n.a.	clodronate	12	2400	No	n.a.	No	12
#10	71	Hepatitis C	Periodontal disease, poor oral hygiene	alendronate Xgeva®	48 4	13,440 480	Yes	4	No	30
#11	51	Hypertension	Dental prosthesis	alendronate Prolia®	20 12	5600 120	Yes	3	No	23
#12	84	Hypertension	Poor oral hygiene	clodronate Xgeva®	24 20	4800 2400	No	n.a.	No	12
#13	56	N.a.	Periodontal disease, poor oral hygiene	Prolia® zoledronate	20 16	180 64	Yes	3	Yes	21
#14	66	N.a.	Dental prosthesis, periodontal disease, poor oral hygiene	alendronate	44	3360	No	n.a.	No	36

Table 2. Details of BMA therapy.

	Number of Patients	Median and Standard Deviation	%
Low dose BMA for CTIBL	14		
alendronate	6	-	42.9%
clodronate	6	-	42.9%
risedronate	1	-	7.1%
Prolia®	1	-	7.1%
Duration of low dose BMAs therapy (mths)		57.9 (±47.1)	-
High dose BMA for BM	4		
zoledronate	1	-	25%
Xgeva®	3	-	75%
Duration of DNB therapy (mths)	3	28 (±23.6)	-
Duration of ZOL therapy (mths)	1	16	-

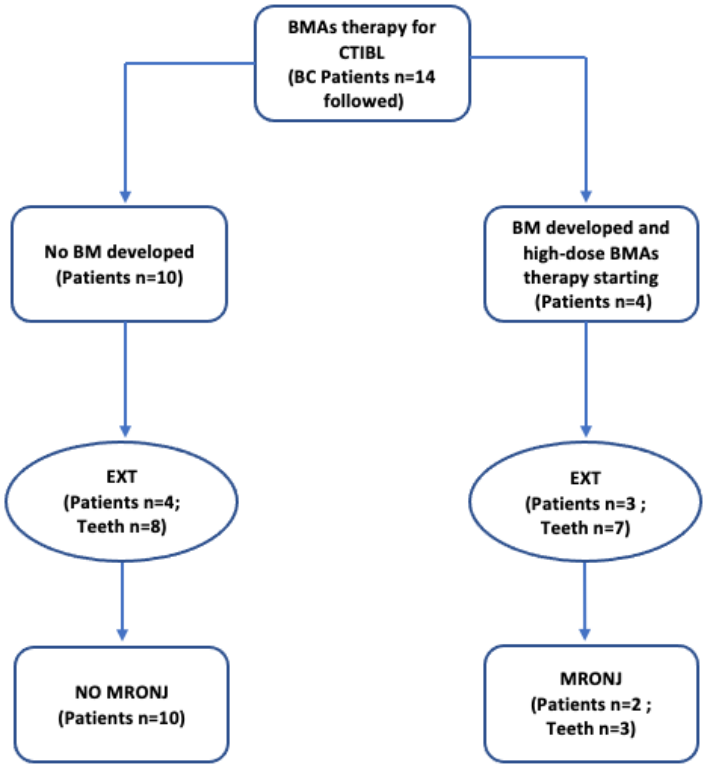

Figure 1. Flow chart of MRONJ occurrence. A relationship between BMAs therapy and MRONJ development after teeth extractions was diagnosed in 14 patients with breast cancer. Four patients developed BM and switched from low dose BMAs to high dose BMAs. Three of these patients underwent dental extractions and two developed MRONJ. Abbreviations: BMAs: Bone Modifying Agents; CTIBL: Cancer Treatment-induced Bone Loss; BM: bone metastases; EXT: extraction.

Table 3. Details of patients affected by breast cancer that switched BMAs therapy due to bone metastases development.

Patient	Age	Sex	MTS	MRONJ after the Pharmaco-logical Switch	ONJ-Related Drgs	Duration (Months)	Cumulative Dosi (mg)	ONJ Localization	ONJ Stage According to SIPMO-SICMF[3]	ONJ Stage According to AAOMS[16]	Clinical Features
#1	75	F	Yes	Yes	risedronate Xgeva®	48 60	7200 7200	Anterior lower jaw	I		Intraoral Fistula, Tooth mobility
#2	56	F	Yes	Yes	Prolia® zoledronate	20 16	180 64	Posterior upper jaw	I		Tooth mobility
#3	71	F	Yes	No	alendronate Xgeva®	48 4	13,440 480	n.a.	n.a.	n.a.	n.a.
#4	84	F	Yes	No	clodronate Xgeva®	24 20	4800 2400	n.a.	n.a.	n.a.	n.a.

Table 4. Differences between BC patients' subgroups.

Characteristics		Patients under Only Low Dose BMAs (No Case of MRONJ)	Patients under Low + High Dose BMAs (No Case of MRONJ)	Patients under Low + High Dose BMAs (Onset of MRONJ)
N patients		10	2	2
Age	Range	48–83	71–84	56–75
	Median	65.5	77.5	65.5
	Standard deviation	11.7	9.2	13.4
Smoking habit		1	0	0
Systemic disease	Hypertension	4	1	0
	Diabetes	2	0	0
	Arthrosis	2	0	0

Table 4. *Cont.*

Characteristics		Patients under Only Low Dose BMAs (No Case of MRONJ)	Patients under Low + High Dose BMAs (No Case of MRONJ)	Patients under Low + High Dose BMAs (Onset of MRONJ)
Local risk factors	Poor oral hygiene	7	2	2
	Dental prosthesis	4	0	1
	Periodontal disease	2	2	1
	Endo-periodontal lesion	1	0	1
Bone MTS		0	2	2
Low dose MRONJ- related drugs durations (months)		67.1 (±52.9)	36 (±17) case #1: 48 mths case#2: 24 mths	34 (±19.8) case #1: 48 mths case#2: 20 mths
Low dose MRONJ- related drugs cumulative dose (mg)		14,788 (±13,286.3)	9120 (±6109.4) case #1: 13,440 mg case #2: 4800 mg	3690 (±4963.9) case #1: 7200 mg case #2: 180 mg
High dose MRONJ- related drugs durations (months)		n.a.	12 (±11.3) Case #1: 4 mths Case#2: 20 mths	38 (±31.1) Case #1: 60 mths Case#2: 16 mths
High dose MRONJ- related drugs cumulative dose (mg)		n.a.	1440 (±1357.6) Case #1: 480 mg Case #2: 2400 mg	3632 (±5045.9) Case #1: 7200 mg Case #2: 64 mg
Dental surgery	N patients	4 (40%)	1 (50%)	2 (100%)
	N extracted teeth	8	4	3
Jaw	Upper	5	3	2
	Lower	3	1	1
Follow-up (months)		24.6 (±12.6)	21 (±12.7)	52.5 (±44.5)

Below detailed cases of MRONJ are presented:

Case 1 (#5 in Table 1 and #1 in Table 3)

In December 2015, A 75-year-old non-smoker woman was referred for primary prevention of MRONJ. In 2011, the patient had been diagnosed with a BC; in September 2015, she developed bone metastases (BM).

From 2011 to 2015 she had been treated with risedronate (48 months, monthly dosing of 75 mg risedronate on 2 consecutive days). After the development of BM and the dental examination, she was switched to Xgeva®. After 60 months of high dose BMA, she developed non-exposed MRONJ in the mandible (Figure 2a). The intra-oral examination revealed a presence of two intraoral fistulas on the 5th sextant, associated with a rapid onset of teeth mobility (3.1, 3.2, 4.2). The CBCT showed cortical erosion, osteosclerotic pattern, periodontal space widening and bone sequestrum formation (Figure 2b–e), confirming to be MRONJ stage I (according to SICMF-SIPMO) [2,3,15]. Moreover, according to the AAOMS staging system, this was Stage I [16]. MRONJ was surgically treated, and there were no signs of recurrencies in the follow-up period.

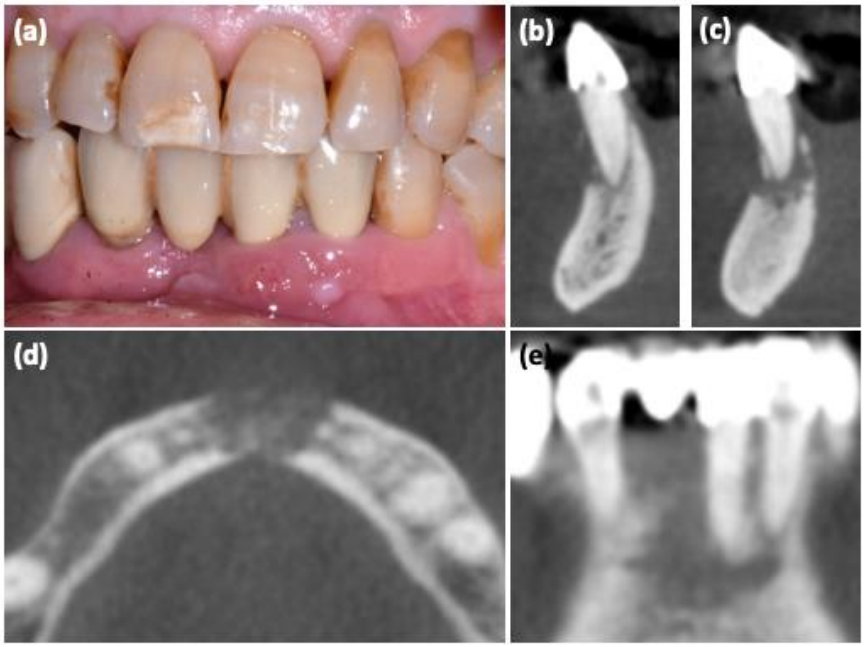

Figure 2. MRONJ stage I, lower jaw: (**a**) clinical view; (**b**–**e**) computed tomography scan sections.

Case 2 (#13 in Table 1 and #2 in Table 3)

In December 2015, a 56-year-old non-smoker woman was referred for primary prevention of MRONJ. In 2004 BC had been diagnosed; in January 2017 she developed BM.

She was treated from 2015 to 2017 with Prolia® (20 months, DNB 60 mg/biannual). After the development of BM, she was switched to zoledronate (e.v.). After 16 months of high dose BMA she developed non-exposed MRONJ in the mandible (Figure 3a). The intra-oral examination highlighted a presence of the rapid onset of tooth mobility (maxillary right third molar) associated with purulent discharge and pain. CBCT showed a slight osteosclerotic pattern, thickening of the alveolar ridge and sinusitis (Figure 3b,d), confirming to be MRONJ stage I (according to SICMF-SIPMO) [2,3,15]. According to AAOMS, this was Stage II [16]. MRONJ was surgically treated, and an alveolar bone specimen was collected from the interradicular septum during the surgical procedures. MRONJ was histologically confirmed (Figure 3e). There were no signs of recurrencies in the follow-up period.

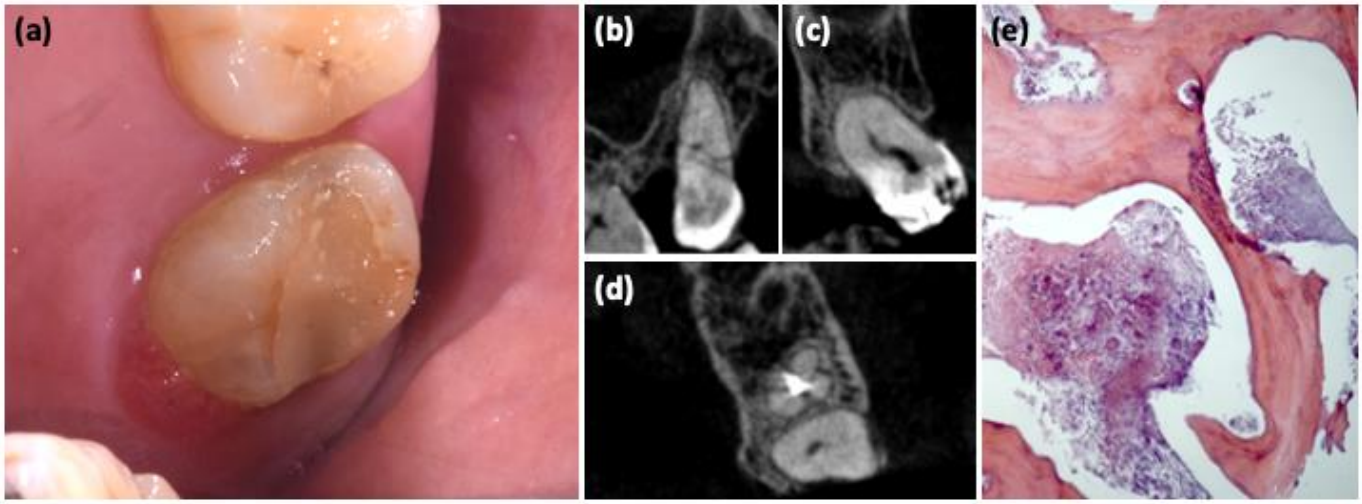

Figure 3. MRONJ stage I, upper jaw: (**a**) clinical view; (**b**–**d**) computed tomography scan sections; (**e**) magnification of histological findings.

4. Discussion

MRONJ is a rare drug adverse reaction that can greatly affect the quality of the life of patients if not promptly diagnosed and treated [2,17,18].

Based on the literature, it is possible to distinguish, at the least, three main common MRONJ patient populations [2,15]:

(1) *cancer patients with BM or myeloma patients*; generally receiving high dose BMAs often associated with other agents (chemotherapy, endocrine therapy, immunotherapy, antiangiogenics and other biological agents) (high MRONJ risk) [19];
(2) *breast cancer (BC) or prostate cancer patients suffering from osteoporosis without bone metastases receiving bisphosphonates or denosumab to limit the risk of non-metastatic bone fractures (due to CTIBL);* this population (assuming the same dosage of BMAs) is considered assumable to those with osteoporosis for what concern their MRONJ risk [20];
(3) *patients suffering from osteoporosis and other non-malignant diseases;* receiving BMAs with different regimens (low MRONJ risk) [21];

As previously stated, the first group has been associated to a higher estimation of MRONJ, that was reported between 1% and more than 20% [22,23].

In the second group, composed by breast or prostate cancer patients, without bone metastases and treated with BMAs for the prevention of CTIBL, the incidence of MRONJ was observed between 0% and 10.4% [11–14]. However, data regarding this group of patients are very scarce. Indeed, this group of patients is still poorly known by many clinicians, especially by dentists; this limited knowledge may lead to the possibility of overestimating the risk of MRONJ onset of these patients, if included in cohorts of cancer patients with BM.

The third group is composed by patients suffering from osteoporosis and other non-malignant diseases receiving low dose BMAs; in this group the MRONJ risk is described between 0.01% and 5.2% [24].

Breast cancer is the most frequent tumor in women worldwide, regardless of age, with a peak of incidence in postmenopausal age. CTIBL has been found to be the most common long-term adverse event experienced by breast cancer patients. BPs and DNB are the two classes of BMAs used in clinical practice with similar efficacy in preventing CTIBL and similar issues to be solved, such as the best time of starting BMAs therapy and its duration [20].

All patients at risk of MRONJ should be subjected to primary preventive measures (even after commencing BMAs), with the aim to maintain and/or reestablish as soon as

possible an acceptable level of oral health. The preventive measures should be done before the administration of ONJ-related medications in cancer patients with BM or multiple myeloma or within the first six months in osteo-metabolic patients. Furthermore, the patients taking BMAs should undergo periodic dental visits for early diagnosis of MRONJ (every four months for cancer patients with BM or multiple myeloma while every six months for osteo-metabolic patients) [2,25].

This study highlights, based on epidemiological data, that breast cancer or prostate cancer patients without BM and treated with low dose BMAs for CTIBL prevention should be considered similar to patients suffering from osteoporosis receiving low dose BMAs (at the same dosage for CTIBL prevention), hence at low risk of MRONJ onset. It is possible to apply them a binary gradient of MRONJ risk, supposed for osteo-metabolic ones [2,25]:

- from the beginning of BMAs administration to within 3 years from the commencing of the treatment, a patient who does not report other MRONJ risk factors (e.g., systemic and/or local) will be classified and considered at low risk of MRONJ.
- if the patient has been in treatment for a period of time longer than 3 years or shorter than 3 years and simultaneously affected by systemic or local risk factors, this patient will bear an incremental and indefinable risk of developing MRONJ, which is linked to one or more additional, reported systemic or local risk factors.

In any case, all non-invasive dental treatments (e.g., restorative dentistry, non-surgical periodontics), as well as surgical procedures which are necessary to eliminate infective outbreaks of MRONJ, are not only considered as *indicated* but also of the utmost importance in reducing the spreading of infectious processes for primary prevention purposes [2,25–27].

If the patient shows a good oral health or after the resolution of inflammatory or infectious process, it is beneficial to plan a six-month follow-up examination in order to maintain the primary prevention program for patients suffering from breast/prostate cancer, treated with low dose BMAs for CTIBL prevention, from osteoporosis or other non-malignant diseases [2,25,28].

It is worthy of note that, if a given cancer patient develops BM before the assumption of high dose BMAs, the oral condition should be re-evaluated by dental examination and when necessary also thanks to a new radiological dental exam. Additionally, cancer patients with BM or multiple myeloma should undergo periodic dental visits every four months.

Among the 14 BC patients included in this study, with a median follow-up period 28.1 ($\pm$19.6) months, only 4 patients developed BM and then they were treated with high dose BMAs. Among the four BC patients with BM, only two developed MRONJ.

One patient, after 48 months of risedronate assumption, had been treated with Xgeva®; 60 months after the switch she developed a non-exposed Stage I MRONJ in the lower jaw. The second patient, after 20 months of Prolia®, had been treated with zoledronate; 17 months after the switch she developed a non-exposed Stage I MRONJ in the upper jaw. Comparing the data of these two patients affected by BM and MRONJ to those with BM without MRONJ, it must be highlighted that the patients with MRONJ took less low-dose BMAs but longer high-dose BMAs (Table 4).

Noteworthy is the fact that both patients developed a non-exposed stage I MRONJ in association with the onset of tooth mobility. This very light and healable condition is probably derived from adequate and continuative primary and secondary prevention measures. The application of periodic follow-up has made it possible to diagnose the disease at the earliest stage, to carry out effective surgical therapies with the following resolution of the disease.

5. Conclusions

The existence at the least of another category of BC patients taking BMAs, for reasons other than contrasting bone metastases, raises the recent need to properly inform principally dentists and to correctly record pharmaceutical data of cancer patients. The aim is to avoid any overestimation of the risk of MRONJ, or worse, an underestimation of the risk in those patients treated with BMAs for bone metastases.

The general aim, in the protection of BC patients' health, is to plan a primary prevention of MRONJ before and while taking BMAs (both low and high doses), as well as secondary prevention (early diagnosis) with the most adequate and effective dental protocols, as being more stringent (e.g., without implants procedures) when the transition to high-dose BMAs is planned and carried out.

The authors suggest that BC patients need more careful and punctual monitoring of oral health since they, due to their frank cancer history, may have to switch, for containing bone metastases, to high dose BMAs therapy, thus increasing their risk of MRONJ.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Local Ethics Committee of the University Hospital "P. Giaccone " of Palermo, Palermo, Italy (approval number 1/2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflict of interest. G.C. declares to have been a scientific expert for Amgen Italia in 2021.

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