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RESEARCH

Medication-related osteonecrosis of the jaw primary prevention: multidomain long-term intervention versus pre-bisphosphonate treatment standalone dental intervention. A retrospective multi-center comparative cohort study

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Abstract

Purpose Medication-related osteonecrosis of the jaw (MRONJ) is a serious adverse drug reaction mostly associated to the use of bone-modifying agents.

Preventive dental strategies aim to reduce its risk, but the comparative benefit of structured long-term interventions versus a single pre-treatment dental visit remains unclear. This study assessed the impact of a structured long-term, multidomain dental prevention protocol compared with a single baseline dental assessment in patients receiving an oncological-based, high dose (HD) regime of Zoledronic acid (ZA).

Methods Between 2012 and 2015, two Southern Italian university hospitals enrolled adult cancer and myeloma patients initiating ZA. Participants received either the Standard Protocol (SP), a single pre-treatment dental visit, or the Intensive Protocol (IP), which added scheduled follow-ups and periodontal care. MRONJ was diagnosed using SICMF-SIPMO clinical and radiological criteria.

Results 202 patients (M/F = 83/119; mean age 63.3 years), were stratified into a SP group (n = 115) and an IP group (n = 87). Eighteen patients developed MRONJ (8.9%). The MRONJ frequency was significantly higher in the SP group (13.9%) compared to the IP group (2.3%) (p = 0.004).

MRONJ cases in the SP group showed poorer oral hygiene, a higher rate and severity of periodontitis alongside, and higher post-extraction onset rate.

Conclusion Multidomain dental prevention long-term protocol was found to be effective in reducing the incidence of MRONJ by ZA therapy, compared to a single pre-therapy dental intervention, with a potential change of case characteristics. These findings support integrating routine dental evaluation and periodontal maintenance into cancer and myeloma care pathways to improve patient safety and oral outcomes.

Keywords MRONJ · Periodontal diseases · Dental examination · Osteonecrosis of the jaw · Oral hygiene · Prevention · Bisphosphonate · Removable prostheses

Introduction

Medication-Related Osteonecrosis of the Jaw (MRONJ) has been defined as an "adverse drug reaction resulting in 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" [1].

MRONJ is primarily associated with the use of bone-modifying agents (BMAs), also known as antiresorptive drugs (i.e., bisphosphonates, denosumab), and/or drugs with antiangiogenic activities[1–4].

BMAs can be classified into low-dose (LD) and high-dose (HD) categories. LD BMAs are primarily used in the

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medical management of osteometabolic disorders, whereas HD BMAs are indicated for the treatment of bone metastases from solid tumors and of multiple myeloma (mostly, as monthly administrations of IV bisphosphonates or denosumab), and for hypercalcemia secondary to malignant diseases [1, 5].

In 2003, several case series reported the occurrence of Bisphosphonate-related osteonecrosis of the jaw (BRONJ) following the use of bisphosphonates (BPs), especially due to ZA [6, 7]. Although the association between BMAs and the development of MRONJ is well established, studies are still exploring the triggering and predisposing factors of this condition. Among the main risk factors, tooth extractions were initially considered the primary possible "cause" of MRONJ, but they could be consequence of underlying and unrevealed bone necrosis due to BMA therapy [1]. Furthermore, dental infections (both apical and periodontal) are a common cause of dental extraction and have been associated with an increased risk of MRONJ [1].

Ficarra G. et al. (2005) highlighted that extractions of teeth with periodontitis often preceded the onset of osteonecrosis in patients undergoing BP therapy [8]. Similarly, in 2011, Aghaloo T. et al. demonstrated through an animal model that aggressive periodontal inflammation could induce bone necrosis similar to BRONJ, emphasizing the crucial role of oral health in managing BRONJ risk [9].

The initial published recommendations focused BRONJ prevention in patients treated with HD-BMAs which incoroporated clinical dental examinations prior to therapy and the completion of surgical procedures before the initiation of BP treatment. Notably, they did not advocate for the routine use of orthopantomography (OPT) for the detection of latent odontogenic infections, nor did they incorporate evidence-based preventive strategies for periodontal health, such as regular professional dental prophylaxis, adjustment of removable prostheses, or the specification of intervals for periodic oral health evaluations [10–12].

Recently, these gaps have been addressed in updated position papers adopting a more comprehensive approach to MRONJ prevention. These recommendations reflect an improved understanding of the role of periodontal health in MRONJ pathophysiology and have contributed to more effective preventive strategies and better patient outcomes [5, 13–18].

Nevertheless, robust comparative evidence regarding the effectiveness of traditional single-visit preventive strategies versus structured, multidomain interventions implemented throughout the course of BMA therapy remains limited.

This paper reports findings from a multi-center retrospective comparative cohort study. The study was conducted on cancer patients receiving HD BPs (*i.e.*, ZA) for bone metastases or myeloma, in order to assess the frequency of MRONJ by ZA and to compare the effectiveness of a comprehensive multidomain intervention, implemented both before and during ZA therapy, versus a single pre-therapy visit in reducing the risk of MRONJ development. Data were gathered from two university hospital centers over the period 2012–2015.

Methods

Study design and population

We conducted a retrospective comparative cohort study using the databases of two university hospitals of South of Italy: the Unit of Oral Medicine of the "Paolo Giaccone" University Hospital in Palermo (Italy), and the Unit of Oral Surgery of the "Gaetano Martino" University Hospital in Messina (Italy). MRONJ status was assessed over the period from January 1, 2012, to May 31, 2015. Main exposure, patient clinical characteristics, and potential confounders were retrospectively evaluated beginning on January 1, 2012, which served as the reference date for data extraction from hospital records. However, not all patients had started ZA therapy on that date; some initiated ZA treatment later during the study period.

For each individual, the observation period was reconstructed starting from the first administration of ZA and continued until the earliest occurrence of one of the following events: MRONJ diagnosis, death, loss to follow-up, or the end of the study (on May 31, 2015).

Follow-up duration, therefore varied between patients and between groups. Individuals who did not develop MRONJ were censored at their last available dental or oncological visit or at the end of the study period.

To ensure data completeness and comparability between centres, the same inclusion and exclusion criteria, variable definitions and data extraction form were used, and data were collected by calibrated investigators at both sites. When key variables were missing or inconsistent in the electronic medical records, the information was verified by consulting the original clinical records.

Ethics statement

The study protocol conformed to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards; it was also approved by the University Hospital of Palermo review board (approval n.01/2022) and by the University Hospital of Messina Review Board (6311/2017).

Eligibility criteria

This retrospective analysis, reviewed the medical and dental records of all the patients scheduled to receive an oncological-based HD ZA regime, and observed in the two cited oral care units.

The following inclusion criteria were applied:

1. Cancer patients with bone metastases and myeloma patients scheduled to HD ZA treatment;
2. Age ≥ 18 years.

Exclusion criteria included:

1. Previous head and neck radiotherapy;
2. Previous history of administration of BPs or denosumab;
3. Metastatic involvement of the jaws.

Data collection

The study retrospectively analyzed the age and sex of patients, the type of cancer, comorbidities, clinical history, doses and duration of BP treatment (when available), and the presence or absence of MRONJ up to the end of the study. Before analysis, datasets from the two centers were merged after harmonization of variable coding and checked for internal consistency and outliers, further supporting the completeness and comparability of the final analytical cohort.

Patient selection

The study population consisted of consecutive and unselected patients scheduled to receive HD monthly ZA therapy for bone metastases or myeloma.

All patients underwent clinical inspection, assessment of their oral hygiene status and any relevant dental procedures, and an OPT examination prior to the first administration of ZA. Only patients which developed MORNJ had their periodontal status evaluated and not recorded as a base line for every patient.

Oral hygiene status was evaluated using the Simplified Oral Hygiene Index (OHI-S) by Greene and Vermillion (1964) [19], calculated by summing the Debris Index and Calculus Index scores. Six representative teeth (16, 11, 26, 36, 31, 46) were examined on the buccal surfaces of the upper molars and central incisors, and the lingual surfaces of the lower molars and central incisors. For each of the six index teeth, the buccal or lingual surface was scored from 0 to 3 for soft debris and from 0 to 3 for calculus, according to Greene and Vermillion. The Debris Index-Simplified (DI-S) and Calculus Index-Simplified (CI-S) were calculated by dividing the total debris and calculus scores by the number of examined teeth, respectively. The OHI-S (range 0–6) was obtained as the sum of DI-S and CI-S and was classified as good (0.0–1.2), moderate (1.3–3.0) or poor (3.1–6.0), with higher scores indicating poorer oral hygiene.

In the presence of teeth with poor or hopeless prognosis, including teeth with advanced periodontal attachment loss and deep periodontal pockets, marked mobility (≥ grade 2–3), severe furcation involvement, non-restorable crown or root fractures, persistent or extensive periapical pathology, or extensive carious destruction precluding predictable restoration, a standardized protocol for dental extractions was applied [1, 20]. Patients did not receive ZA until 4–6 weeks post-dental extraction, once clinical healing was achieved.

Patients were subsequently enrolled in a structured multidomain preventive protocol and follow-up program for early MRONJ diagnosis, with visits scheduled every 4 months.

To assess the impact of structured multidomain preventive protocol and follow-up diagnosis in relation to the risk of MRONJ, patients were retrospectively stratified into two groups based on the timing and frequency of their dental evaluations.

Intensive protocol group (IP) Patients in the IP group were assessed for the dental status both before and during ZA administration. Dental extractions, when necessary, were carried out at least 1 month before ZA therapy starting. Follow-up visits were scheduled every four months and patients received further targeted dental care aimed at minimizing the risk of onset of MRONJ. This latter included: treatment for periodontal diseases, as well as oral hygiene session, tailored to each patient's periodontal conditions; an annual OPT examination; and an inspection of dentures to identify and solve any eventual areas of mucosal trauma.

Standard protocol group (SP) Patients in the SP group were also offered the same structured dental management and follow-up program with scheduled visits every four months; however, all declined to adhere to these planned appointments, mainly due to logistical reasons (e.g., travel difficulties, advanced age, or the perceived burden of additional visits beyond oncology care). Re-evaluation visits in the SP group were carried out only in the presence of signs and symptoms suggestive of MRONJ (on proposal of the personal oncologist, or of a dental practitioner, or as personal request of the patient).

Each patient with a clinical suspicion underwent a diagnostic workup based on a combined clinical and radiological assessment, through a clinical-radiological approach combining clinical examination and computed tomography (CT) or cone beam CT (CBCT) [21]. Clinical and radiological findings were evaluated by oral medicine specialists with specific expertise in MRONJ, using the same diagnostic protocol in accordance with the SICMF–SIPMO criteria. Radiographic examinations were interpreted as

part of routine clinical practice and were therefore not formally blinded to clinical information or to protocol group allocation.

Periodontal status was evaluated exclusively in MRONJ patients at the point of MRONJ diagnosis. Examination was performed at six sites per tooth (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, disto-lingual) using a UNC-15 manual periodontal probe (Hu-Friedy, Chicago, IL, USA). The diagnosis and classification of periodontitis severity followed the 1999 American Academy of Periodontology case definitions, based on probing depth, clinical attachment loss (CAL) and bleeding on probing. Periodontitis was classified as slight (1–2 mm CAL), moderate (3–4 mm CAL) or severe (≥ 5 mm CAL) [22].

Statistical methods

Continuous variables were summarized with mean and standard deviations (SD) together with median and range, while categorical variables were expressed as counts and percentages. Associations between categorical variables were analysed through Fisher's exact test. Multivariate analysis was planned to account for potential confounding factors. Statistical analysis was performed with R software (version 4.4.1), and a *p-value* < 0.05 was considered statistically significant.

Results

A total of 202 patients (M/F = 83/119, overall mean age 63.3 years) were included and stratified into the IP group (n = 87) and the SP group (n = 115) based on adherence to the clinical follow-up protocol.

Female patients represented 49.4% of the IP group and 66.1% of the SP group. The mean age was 62.9 years (standard deviation + 9.6) in the IP group and 63.2 years (standard deviation + 11.0) in the SD group. Smoking habits were similar, with 14.9% of current smokers in the IP group and 9.6% in the SP group. Corticosteroid use was reported in 33.3% of IP patients and 49.6% of SP patients, while chemotherapy was administered to 62.1% and 61.7% of patients in IP and SP groups, respectively, considering only cycles delivered before the initiation of bone-modifying agent therapy and prior to the baseline dental examination. Hypertension and diabetes were present in 44.8% and 6.9% of IP patients, compared to 24.3% and 7.0% in the SP group.

In the **SP group** (115 patients), at the time of the first visit, good oral hygiene was observed in 15 patients (13.0%), moderate hygiene in 64 patients (55.7%), and poor hygiene in 36 patients (31.3%).

In the **IP group** (87 patients), good oral hygiene was recorded in 28 patients (32.1%), whereas moderate hygiene was found in 11 patients (12.6%) and poor hygiene in 48 patients (55.1%).

Table 1 presents the demographic and clinical characteristics of the study population, further subdivided by MRONJ status within each group.

Overall, MRONJ developed in 18 patients (8.9%; 95% CI 5.4–13.7). Sixteen cases occurred in the SP group (16/115; 13.9%; 95% CI 8.2–21.6) and two cases in the IP group (2/87; 2.3%; 95% CI 0.3–8.1) (Fig. 1). There was a statistically significant association between adherence to the clinical dental management and follow-up protocol (SP *vs.* IP) and the lowest frequency of MRONJ onset (OR = 6.87; 95% CI 1.53–30.73; Fisher's $p = 0.004$).

Among the 18 patients diagnosed with MRONJ, 9 out of 76 females (11.8%) and 7 out of 39 males (17.9%) belonged to the SP group, while in the IP group MRONJ was diagnosed in 1 out of 43 females (2.3%) and 1 out of 44 males (2.3%). No statistically significant difference in MRONJ incidence by gender was observed in either group.

The mean age at MRONJ diagnosis was 67.3 years (SD = 8.93) for SP MRONJ cases compared to 54.5 years (SD = 10.6) for IP MRONJ cases (95%CI = −82.19219, 56.56719, *p*-value = 0.3195).

MRONJ was observed mostly among breast cancer patients (8/65 in SP group and 1/30 in the IP group, that is in 12.3% and 3.3% of the treated patients), and prostate cancer patients (respectively: 7/23 and 1/28, i.e. 30.4% and 5.5%); globally, only one myeloma patient (out of 47) developed MRONJ.

The median cumulative ZA dose was 68.5 mg (IQR 43–87; range 32–120) in the SP MRONJ cases and 46 mg (IQR 41–51; range 36–56) in the IP MRONJ patients (*p*-value = 0.203).

To note, the median ZA cumulative dose of the whole IP group was 84 mg (range 20–372 mg), whereas the data was not available for the whole SP group.

The mean time from the start of ZA therapy to MRONJ diagnosis was 17.1 months (SD 7.6) in the SP MRONJ cases and 11.5 months (SD 3.5) in the IP MRONJ cases. The median time from the start of ZA therapy to MRONJ diagnosis was 17 months (range 8–30) in the SP MRONJ cases and 11.5 months (range 9–14) in the IP MRONJ cases.

Among patients receiving antiangiogenic therapy, MRONJ occurred in all three treated individuals in the SP group (3/3), whereas only one out of five patients in the IP group developed the disease.

At the time of diagnosis, the distribution of MRONJ cases, according to SICMF-SIPMO staging system [12, 23], is reported in Table 2.

Concerning risk factors for MRONJ onset (as shown in Table 3), 62.5% of SP MRONJ patients had undergone dental

Table 1 Detailed characteristics of patients included according to adherence to the clinical follow-up protocol

	Standard Protocol Group (SP)		Intensive Protocol Group (IP)	
	MRONJ free (N = 99)	MRONJ cases (N = 16)	MRONJ free (N = 85)	MRONJ cases (N = 2)
GENDER				
F	67 (67.7%)	9 (56.3%)	42 (49.4%)	1 (50.0%)
M	32 (32.3%)	7 (43.8%)	43 (50.6%)	1 (50.0%)
AGE				
Mean (SD)	63.2 (11.0)	67.3 (8.93)	62.9 (9.64)	54.5 (10.6)
Median [Min, Max]	65.0 [35.0, 84.0]	66.0 [53.0, 82.0]	63.0 [41.0, 83.0]	54.5 [47.0, 62.0]
PRIMARY DISEASES				
MM	18 (18.2%)	1(6.3%)	24 (28.2%)	0 (0%)
MTS/BC	57 (57.6%)	8 (50.0%)	29 (34.1%)	1 (50.0%)
MTS/PC	16 (16.2%)	7 (43.9%)	27 (31.8%)	1 (50.0%)
MTS/LC	5 (5.1%)	0 (0%)	5 (5.9%)	0
MTS/KC	3 (3.0%)	0 (0%)	0 (0%)	0 (0%)
CUMULATIVE ZA DOSE (mg)				
Mean (SD)	N.A	68.5 mg (30.3)	95.0 mg (53.6)	46.0 mg (14.1)
Median [Min, Max]	N.A	68.0 mg (range: 32–120)	84 mg (range: 20–372)	46 mg (range: 36–56)
TIME FROM ZA START TO MRONJ ONSET (MONTHS)				
Mean (SD)	N.A	17.1 (7.6)	N.A	11.5 (3.5)
Median [Min, Max]	N.A	17 (8–30)	N.A	11.5 (9–14)
SMOKE				
EX	5 (5.1%)	1 (6.3%)	0 (0%)	0 (0%)
NO	87 (87.9%)	11 (68.8%)	72 (84.7%)	2 (100%)
YES	7 (7.1%)	4 (25.0%)	13 (15.3%)	0 (0%)
ANTIANGIOGENIC AGENTS				
NO	99 (100%)	13 (81.3%)	81 (95.3%)	1 (50.0%)
YES	0 (0%)	3 (18.8%)	4 (4.7%)	1 (50.0%)
CORTICOSTEROID USE				
NO	49 (49.5%)	9 (56.3%)	57 (67.1%)	1 (50.0%)
YES	50 (50.5%)	7 (43.8%)	28 (32.9%)	1 (50.0%)
CHEMOTHERAPY				
NO	37 (37.4%)	7 (43.8%)	33 (38.8%)	0 (0%)
YES	62 (62.6%)	9 (56.3%)	52 (61.2%)	2 (100%)
HYPERTENSION				
NO	75 (75.8%)	12 (75.0%)	46 (54.1%)	2 (100%)
YES	24 (24.2%)	4 (25.0%)	39 (45.9%)	0 (0%)
DIABETES				
NO	93 (93.9%)	14 (87.5%)	79 (92.9%)	2 (100%)
YES	6 (6.1%)	2 (12.5%)	6 (7.1%)	0 (0%)
OSTEOARTHRITIS				
NO	97 (97.9%)	16 (100%)	84 (98.8%)	2 (100%)
YES	2 (2.0%)	0 (0%)	1 (1.1%)	0 (0%)
RHEUMATOID-ARTHRITIS				
NO	97 (97.9%)	13 (81.3%)	85 (100%)	1 (50.0%)
YES	2 (2.0%)	3 (18.8%)	0 (0%)	1 (50.0%)
HEPATITIS C				
NO	97 (97.9%)	16 (100%)	84 (98.8%)	2 (100%)
YES	2 (2.0%)	0 (0%)	1 (1.1%)	0 (0%)
OSTEOMALACIA/VITAMIN D DEFICIENCY				
NO	98 (98.9%)	16 (100%)	85 (100%)	2 (100%)
YES	1 (1.0%)	0 (0%)	0 (0%)	0 (0%)

Legend: MM = multiple myeloma; MTS/BC = metastasis from breast cancer; MTS/PC = metastasis from prostate cancer; MTS/LC = metastasis from lung cancer; MTS/KC metastasis from kidney cancer; N.A. = Not Applicable

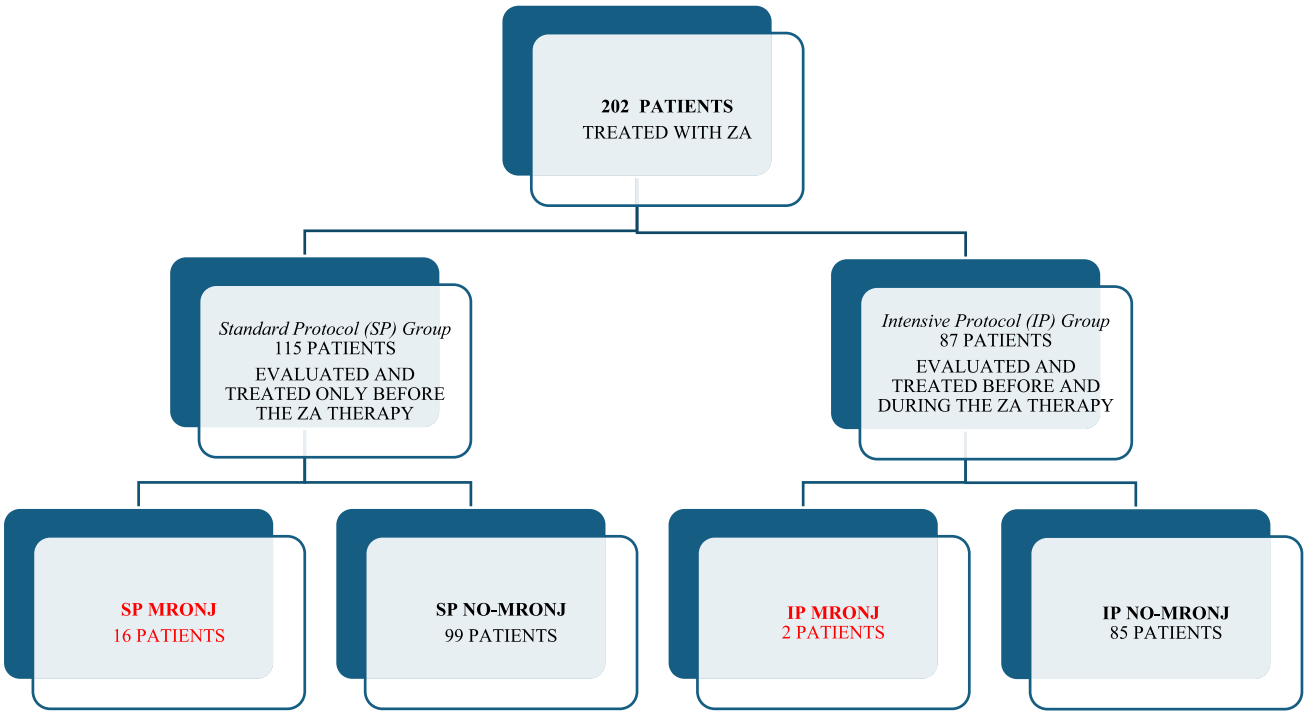

Fig. 1 Stratification of patients based on adherence to the dental clinical protocol and MRONJ onset

extraction (*i.e.*, performed during ZA therapy, outside the referral center), and 31.3% presented with ill-fitting prostheses, both of which could have contributed to the onset of MRONJ.

In the IP MRONJ cases, both patients presented MRONJ at sites of trauma caused by ill-fitting prostheses and none had undergone intercurrent tooth extraction at sites of MRONJ.

In all patients with MRONJ, full-mouth periodontal charting was performed at the time of diagnosis; comparable charting was not systematically recorded for MRONJ-free patients.

The frequency of periodontitis (according to the 1999 classification of periodontal disease [22]) was notably high in SP MRONJ cases, with 10 out of 16 of patients affected (62.5%): among these, 4 (25%) were classified as moderate periodontitis and 6 (37.5%) as severe periodontitis at the point of MRONJ diagnosis. The two patients in the IP group with MRONJ did not suffer from periodontal disease.

According to OHI-S categories, the majority of SP MRONJ patients (15/16; 93.8%) were classified as having poor oral hygiene (OHI-S $\geq$ 3.1), while one patient (6.3%) had moderate oral hygiene (OHI-S 1.3–3.0). In contrast, among IP MRONJ patients, one had good oral hygiene (OHI-S $\leq$ 1.2) and the other had moderate oral hygiene (OHI-S 1.3–3.0) ($p = 0.013$).

The other clinical characteristics, such as comorbidities, smoking habits, corticosteroid or chemotherapy use, were not significantly associated with MRONJ onset among the eighteen affected patients. Therefore, multivariate analysis was not conducted, given the limited number of MRONJ events relative to the number of potential covariates, which would have resulted in an underpowered and statistically unstable model.

Table 2 Distribution of MRONJ cases according to SICMF-SIPMO staging at the time of diagnosis

SICMF-SIPMO Stage	IP MRONJ (N = 2)	SP MRONJ (N = 16)	*p*-value
Stage IA	2	3	
Stage IB	-	6	
Stage IIA	-	2	
Stage IIB	-	4	
Stage IIIA	-	1	
Total	2	16	0.065

Discussion

To the best of our knowledge, this is the first multicentre retrospective cohort study conducted in Italy to assess the effectiveness in MRONJ prevention of a multilevel, multi-step dental protocol and to compare it with one-shot pre-therapy dental visit in patients scheduled to receive HD BPs for bone metastases.

Table 3 Risk factors for MRONJ ONSET in the included patients by adherence to clinical follow-up

RISK FACTORS FOR MRONJ ONSET[1]	SP MRONJ group **(N = 16)**	IP MRONJ group **(N = 2)**	*p*-value
EXTRACTION			0.183
NO	6 (37.5%)	2 (100%)	
YES	10 (62.5%)	0 (0%)	
PROSTHESES			0.137
NO	10 (62.5%)	0 (0%)	
YES	1 (6.3%)	0 (0%)	
YES (ILL-FITTING)	5 (31.3%)	2 (100%)	
PERIODONTITIS			0.183
Slight	0 (0%)	0 (0%)	
Moderate	6 (37.5%)	2 (100%)	
Severe	10 (62.5%)	0 (0%)	
ORAL HYGIENE			0.013
Good	0 (0%)	1 (50%)	
Moderate	1 (6.3%)	1 (50%)	
Poor	15 (93.8%)	0 (0%)	

Conducted in two university hospitals in Southern Italy between 2012 and 2015, it involved 202 cancer patients over four years, providing, at least in our cohorts, a comprehensive understanding of MRONJ by ZA cumulative dose and the role of preventive strategies.

MRONJ incidence varies widely in literature, ranging from 0.01% in patients on low-dose BPs to 5%−15% (or more) in those receiving HD BMA therapy [24–26], but recently higher values have been reported (especially with longer follow-up and with HD denosumab) [1, 27].

In our study, the overall MRONJ incidence after HD monthly ZA was 8.9% (18 out of 202 patients) over four years. Notably, the incidence varied significantly between the two groups: 13.9% in the SP group compared to only 2.3% in the IP group. Even if out of a randomized study, this marked difference (Fisher's $p = 0.004$) underscores the potential protective effect of structured, protocol-based dental care and follow-up in reducing MRONJ onset risk, as also claimed by other studies [28–30].

In the IP-MRONJ group, the two cases were diagnosed at an initial stage and in the absence of clinical signs of infection (Stage IA, according to the SICMF–SIPMO staging) [23]. This pattern is compatible with earlier detection in the context of structured follow-up, but, given the very small number of events and the retrospective design, it should be regarded as hypothesis-generating rather than as evidence of a definitive mechanistic effect.

The time interval between the initiation of therapy and MRONJ diagnosis was highly variable, particularly within the SP-MRONJ cases. It is important to note that this time interval does not reflect an actual clinical follow-up in the SP group, as these patients did not adhere to the scheduled monitoring visits and returned to clinical attention only after the onset of symptoms. This discontinuity in observation may have contributed to a delay in diagnosis and a more advanced clinical-radiological stage of MRONJ at diagnosis time.

The cumulative dose of ZA (reflecting the number of monthly administrations of ZA at 4 mg doses) was higher in MRONJ cases from the SP cases (median 68 mg; range 32–120) compared with those of the two IP cases (median 46 mg; range 36–56).

The cumulative dose data were available for MRONJ cases in both groups and for MRONJ-free patients in the IP group, but not for the full SP cohort. Therefore, direct comparison of cumulative doses at the whole-group level was not feasible. However, these findings suggest that cumulative exposure alone is insufficient to account for the observed differences in MRONJ incidence between the two groups. Given the high potency of ZA and the considerable interindividual variability in drug metabolism and bone remodeling, potentially influenced by genetic polymorphisms affecting pharmacokinetics and pharmacodynamics, a structured multidomain dental management protocol appears to be a critical factor in mitigating the risk of MRONJ [31–33].

Actually, the median received dose of ZA in the IP group (84 mg, with range 20–372) shows that patients were treated in median for almost two years, with a wide range (from 5 months to 7 years), but the 2 only MRONJ cases were registered after 9 and 14 months: earlier than the MRONJ diagnosis time of cases in the SP group (median 17 months, range 8–30 months). The authors could propose a hypothesis; that both cohesive primary intervention and early second prevention plays an important role particularly in at risk cases of MRONJ are anticipated.

Traditionally, MRONJ has been strongly associated with tooth extractions. However, growing evidence indicates that severe periodontal diseases and ill-fitting prostheses, significantly increase risk of MRONJ [30, 34].

In our study, 62.5% of MRONJ cases related to ZA in the SP group occurred in the context of severe periodontal infections (while the other 37.5% showed moderate periodontitis), often followed by tooth extractions (reported in 10 out of 16 cases) that were likely performed without adherence to standardized protocols or by clinicians lacking specific expertise in the management of at-risk patients. Severe periodontal disease has been identified as the most critical risk factor for MRONJ, a finding consistently emphasized in expert position papers [35]. These findings, supported by recent large-scale cohort studies [36], emphasize the critical need for periodontal care in MRONJ prevention.

Epidemiological data in general population indicate that the prevalence of periodontitis reaches approximately 79% in adults aged ≥ 65 years, and increases to 94.9% [37]; in a cross-sectional study of Filipino older adults, periodontitis was diagnosed in nearly all participants, with severe forms affecting 93.1% of those aged 60–69 years, 94.1% of those aged 70–79 years, and 100% of those aged ≥ 80 years [38].

In our cohort, 62.5% of MRONJ cases in the SP group were associated with periodontitis; however, the striking finding was the extremely high prevalence of poor oral hygiene (93.8%) among MRONJ SP cases, while none of the two IP MRONJ cases presented with poor oral hygiene, both instead showing good or moderate conditions.

This finding aligns with growing evidence supporting the role of inadequate oral hygiene as a key modifiable risk factor for MRONJ onset, likely through its contribution to the persistence of chronic inflammatory and the progression of periodontal disease [34].

Among the local risk factors of MRONJ identified, the presence of ill-fitting removable prostheses emerged as particularly relevant. In SP MRONJ, poorly adapted or unstable prostheses were documented in 5 out of 16 cases (31.3%) a proportion that appears higher than that reported in several other case series, where the prevalence typically ranges between approximately 10% and 20% in MRONJ patients [39, 40].

These devices are a potential source of chronic mucosal trauma, which, in the absence of regular dental monitoring, may contribute to persistent local inflammation and disruption of mucosal integrity, thereby promoting osteonecrosis in patients receiving potent antiresorptive therapy [39]. As such, regular assessment and adjustment of removable prostheses should be considered a fundamental component of MRONJ prevention protocols, particularly in cancer patients undergoing HD BMA therapy [1].

In the literature, several studies have identified additional risk factors for MRONJ, including systemic corticosteroid therapy, particularly when combined with chemotherapy and antiresorptive agents [41–44]. Despite this evidence, in our cohort neither corticosteroid use nor chemotherapy showed a statistically significant association with MRONJ onset. However, it should be noted that data on these treatments were collected only at the time of the first dental visit and therefore reflect therapies ongoing at that single time point, without accounting for subsequent changes or cumulative exposure over the follow-up period.

In the IP group, the structured multidomain dental protocol included periodontal disease treatment, professional oral hygiene, follow-up for early MRONJ diagnosis every four months, and annual panoramic radiographs. Additionally, extractions were limited to teeth with poor prognosis, and denture inspections were performed to prevent mucosal trauma [35].

Overall, although the comparison is limited by the small number of MRONJ cases in our study (2 in IP group and 16 in the SP group), all the evaluated characteristics are consistent with the hypothesis that the multidomain protocol may modify both the risk and the clinical course of MRONJ in patients receiving long-term treatment with BMAs. These observations should be interpreted as hypothesis-generating and need confirmation in future prospective studies.

The concept of preventive dental assessment prior to the initiation of bone-modifying agents (BMAs) has its roots in the early years of bisphosphonate-related osteonecrosis of the jaws (BRONJ) research. A landmark case series by Marx et al. (2005) systematically described 119 patients and empirically highlighted the need to eliminate dental infections and optimise oral health before starting BP therapy [45]. Shortly thereafter, Weitzman et al. (2007) reinforced these empirical recommendations in an expert consensus, underscoring the importance of dental monitoring and multidisciplinary preventive strategies in high-risk cancer populations [11].

The first observational studies validating these preventive measures were published in 2009. Ripamonti et al. reported that a preventive dental protocol implemented before BP administration in cancer patients led to a marked reduction in MRONJ cases compared with historical controls [46]. In the same year, Dimopoulos et al. confirmed these findings in a prospective cohort, showing that pre-therapy dental assessment, elimination of oral infection, and patient education could significantly lower MRONJ occurrence [47]. These pioneering studies laid the foundation for a paradigm shift in MRONJ prevention, catalyzing the development of institutional guidelines and the inclusion of dental screening recommendations in major oncology and maxillofacial societies' position papers.

Further evidence was subsequently provided by multicenter studies with larger cohorts. In particular, Vandone et al. (2012) demonstrated that systematic preventive dental protocols significantly reduced the incidence of MRONJ in cancer patients treated with BPs [48]. This single-centre experience adopted a before–after design in which the introduction of an interdisciplinary preventive programme was compared with historical controls. In our multicentre Italian cohort, by contrast, we directly compare an intensive, multidomain long-term protocol with a standard single pre-treatment visit in patients uniformly exposed to HD ZA, thus quantifying the additional benefit of a more complex prevention strategy within the same time frame.

At the Dental Service of the Memorial Sloan Kettering Cancer Center, during the period 2006–2015, Owosho et alreported a 0.9% MRONJ incidence (adopting the AAOMS definition of osteonecrosis) [29, 49] in patients who received pre-medication dental evaluation (PMDE)

before therapy, compared to 10.5% in those referred after prior exposure to the medications [29].

Over the following decade, the evidence base continued to expand, and multidisciplinary recommendations evolved to incorporate not only baseline dental assessment but also structured follow-up, periodontal maintenance, and patient-tailored preventive strategies as integral components of cancer care [1, 17, 20, 29].

Our findings reinforce the importance of structured long-term prevention programs combined with regular follow-ups to mitigate MRONJ risk while preserving optimal oral health. Proactive interventions at every stage of treatment are essential in integrating oral health strategies with cancer care, ultimately improving patient safety and outcomes.

The exact aetiopathogenic mechanism of MRONJ remains unclear, so preventive measures are mainly limited to controlling known risk factors [34, 50–53]. The goal of primary prevention of MRONJ is to reduce the onset of MRONJ by identifying and treating all known oral conditions that can trigger MRONJ and restore good oral health, and not only before starting BMA but also during and after the drug therapy [1].

In our model, both components of the dental pathway are conceived as primary prevention, as all interventions are delivered before MRONJ onset. First, all patients receive primary prevention before starting BMA, through a pre-therapy dental evaluation. In the IP group, primary prevention is further implemented during BMA therapy. No secondary prevention, understood as management after MRONJ onset, was evaluated in this study.

Only recently, the literature has explicitly supported the pivotal role of a structured dental long-term management and follow-up in reducing the risk of MRONJ onset (i.e., primary prevention-together with secondary prevention during BMA therapy) probably due to the logistic difficulties of the cancer patients to adhere it or due to the organization multidisciplinary issues within the cancer centers, as well as objective difficulties for cancer patients followed out of large institutions.

Byrne et al. (2024) advocates the operational integration of oncology and dental services through coordinated preventive regimes, including pre-therapy dental assessment, elimination of infection foci, prosthesis adjustments, patient education, and periodic follow-ups, to improve outcomes and reduce the risk of both MRONJ and osteoradionecrosis [54]. However, their study mainly describes service implementation and does not formally compare alternative preventive pathways. Our work complements this organizational perspective by providing comparative data on MRONJ occurrence under two different levels of dental integration in routine hospital practice.

Alblazi et al. (2024) further reported that the absence of a comprehensive dental care program was associated with an approximately eight-fold increase in MRONJ risk (OR 8.64; 95% CI 1.27–58.62), while tooth extractions were not an independent predictor [55].

Incidentally, in a cohort of cancer patients treated only with denosumab, Beaudouin et al. (2021) reported an MRONJ incidence of 5.1 per 100 person-years under a structured preventive protocol [56]. Notably, periodontal disease was identified as the predominant triggering factor, accounting for nearly 90% of cases and underscoring the central role of periodontal management in MRONJ prevention. Unlike our cohort, which focuses on HD ZA and contrasts an intensive long-term protocol with a single pre-therapy dental visit, this French study evaluates a single structured preventive schedule in denosumab-treated patients and does not include an internal control group with a different level of dental prevention [56]. Our findings, therefore, extend these international data by exploring how the intensity of preventive periodontal and prosthetic management translates into MRONJ risk in real-world oncology settings.

Our retrospective findings in the IP group provide empirical support to the recommendations outlined in the recent position paper by Italian experts for dental hygienists [43], which emphasizes the importance of periodontal assessment and structured oral management and follow-up in MRONJ prevention. Unlike the position paper, which did not present original data, our study contributes clinical evidence indicating that a multidisciplinary strategy—including infection control, prosthesis adjustment, and periodontal care—can effectively reduce MRONJ risk and improve long-term patient outcomes [35].

Our study shows some limits.

The study is not a randomized trial, but a retrospective comparative cohort study of patients observed in two institutions, in a limited range of years (2012–2015): there could be an indeterminate selection bias potentially invalidating the comparison between the IP and the SP group.

Moreover, follow-up was protocol-driven in the IP group but irregular and mainly triggered by MRONJ onset or related oral symptoms of MRONJ in the SP group. As a result, the duration and intensity of observation could not be precisely quantified, particularly for SP patients, and asymptomatic or early MRONJ cases may have been underascertained in this group. Our findings should therefore be interpreted as crude cumulative proportions over the study period rather than as time-standardized incidence rates.

Therefore, unmeasured socioeconomic or organizational factors may have influenced adherence to the intensive preventive protocol and contributed to selection bias between the IP and SP groups, representing additional potential sources of bias [57]. This limitation should be considered when interpreting the effect of the intensive protocol and extrapolating the findings to other settings.

The unbalanced sample size between the IP and SP groups, baseline differences in oral health status (including

periodontal conditions and oral hygiene), and the lack of detailed, standardized pre-treatment periodontal data for all MRONJ-free patients may have introduced residual confounding; therefore, the observed associations should be interpreted with caution.

The sample included only cancer patients receiving HD ZA, which limits the generalizability of the findings to other patient populations, including those treated with different antiresorptive agents, such as denosumab.

Periodontal status was assessed using the 1999 classification, as the updated 2018 system became available after the database was established. As a result, more recent diagnostic criteria could not be applied.

Given the limited number of MRONJ events and the lack of statistically significant associations in univariate analyses, we did not perform multivariable modelling to avoid unstable and underpowered estimates.

Our findings, which are consistent with MASCC/ISOO recommendations on integrated oral care, also prompt reflection on the feasibility of implementing such multidisciplinary preventive pathways in routine oncology settings [58]. Establishing structured collaboration between oncology and oral health teams requires coordination, protected time, and clear referral pathways. Logistical barriers may include limited access to specialised oral medicine clinics, constrained outpatient capacity, and the need to avoid delays in cancer treatment. Resource constraints, especially in smaller or resource-limited centres, may limit the availability of trained staff and the sustainability of repeated preventive visits.

Conclusion

Our findings support the hypothesis that a multidomain and multistep intervention might significantly reduce MRONJ incidence compared to a single pre-therapy dental intervention.

The maintenance and assessment of periodontal health should be considered a fundamental component of MRONJ preventive strategies. Oral health professionals must collaborate closely with oncology teams to ensure thorough pre-treatment assessments and continuous monitoring.

Future research should focus on expanding sample sizes and exploring additional preventive strategies tailored to different patient populations.

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Declarations

Institutional review board statement The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of University Hospital of Palermo "P. Giaccone" (approval number n. 01/2022), and by the University Hospital of Messina "G. Martino" (6311/2017).

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