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Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: a single-center clinical experience

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Background: Osteonecrosis of the jaw (ONJ) is associated with bisphosphonate (BP) therapy and invasive dental care. An Interdisciplinary Care Group (ICG) was created to evaluate dental risk factors and the efficacy of a preventive restorative dental care in the reduction of ONJ risk.

Patients and methods: This prospective single-center study included patients with bone metastases from solid tumors. Patients who received at least one BP infusion between October 2005 and 31 August 2009 underwent one or more ICG evaluation and regular dental examinations. We also retrospectively evaluated patients with bone metastases from solid tumors who did not undergo dental preventive measures.

Results: Of 269 patients, 211 had received at least one infusion of BP therapy: 62% were BP naive and 38% had previous BP exposure. Of these 211 patients followed for 47 months, 6 patients developed ONJ (2.8%). Of 200 patients included in the retrospective analysis, 11 patients developed ONJ (5.5%).

Conclusions: In comparison with published ONJ rates and those extrapolated from the retrospective analysis, the observed ONJ rate in the prospective group was lower, suggesting that implementation of a preventive dental program may reduce the risk of ONJ in metastatic patients treated with i.v. BP therapy.

Key words: bisphosphonate, bone metastases, osteonecrosis of the jaw, solid tumor

introduction

Over the last 20 years, bisphosphonates (BPs) have become an important component in the treatment of bone metastases from solid tumors and in the treatment of multiple myeloma. Their efficacy has been proven in large randomized clinical trials [1, 2] and i.v. BPs, in particular aminobisphosphonates (N-BPs), are the standard of care for the treatment and prevention of skeletal complications associated with bone metastases [2].

There are several available agents with oral and i.v. formulations; i.v. zoledronic acid, i.v. pamidronate, and oral/i.v. ibandronate are commonly used for the treatment of bone metastases from breast cancer [1, 3–7]. Zoledronic acid is the only BP with proven efficacy in the treatment of bone metastases from other solid tumors [8, 9] and is approved, as is pamidronate, in multiple myeloma [6].

Recently, the use of BPs in the oncology setting has been the subject of debate due to their association, in the presence of other risk factors, with the development of osteonecrosis of the jaw (ONJ), a serious adverse event that can negatively affect patient's quality of life [10, 11]. Despite the initial lack of a common and consistent definition characterizing this condition, ONJ has now been identified as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after its manifestation in patients who have not received radiation therapy to the craniofacial region [12]. In accordance with published recommendations, ONJ is diagnosed using a two-step approach consisting of (i) clinical identification of exposed bone in the maxillofacial area, occurring spontaneously or in association with dental surgery without evidence of healing and (ii) differential analysis of these lesions, in order to distinguish them from those derived from metastatic jaw disease or resulting from radiotherapy (osteoradionecrosis) [13].

Since the first case of ONJ was published in 2003 [14], many cases have been reported worldwide; however, most evidence derives from retrospective reviews or small case series in heterogeneous populations, examined mainly in terms of type of malignancy and overall survival. In addition, the use of web-based surveys and retrospective analyses may have introduced potential bias regarding patient selection and data collection

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[15]. Thus, the frequency of ONJ evaluated by many explorative reports varies considerably, ranging from 0.6% to 11% for BP-treated patients with breast cancer or multiple myeloma [15–23]. In the largest retrospective study, based on data collected from 4019 patients treated with i.v. BP between 1996 and 2004, the overall frequency of ONJ was 0.73% (breast cancer 1.2% and multiple myeloma 2.4%) [18].

Despite the risk (albeit low) of developing ONJ with BP therapy, in clinical practice there is a clear awareness that optimal treatment of bone metastases from solid tumors requires BP administration. In view of this, many expert panels have emphasized the importance of a preventive dental program in patients who are candidates to receive BP treatment [11, 13, 24]. Thus, in recent years, there has been increased implementation of preventive dental measures before and during BP treatment in order to minimize ONJ risk associated with dental surgery and to ensure the most appropriate use of BPs in patients with metastatic cancer.

In order to evaluate an interdisciplinary treatment program involving dental and oncological care, an Interdisciplinary Care Group (ICG) was established in the San Giovanni Battista Molinette Hospital (Turin, Italy) in October 2005 to ensure the correct application of preventive dental measures in patients starting BP treatment and to monitor patients for ONJ during therapy. Patients assigned to the ICG program received preventive and restorative dental care as advocated by an expert panel in the recently published guidelines for BP use [2]. After 47 months of ICG activity, this paper describes the impact of this dental strategy on ONJ risk reduction in patients with bone metastases treated with i.v. BP.

methods

patients

The prospective analysis included patients with bone metastases from solid tumors, with at least one ICG evaluation between October 2005 and August 2009. Patients were assigned to one of two evaluation groups according to their previous BP- treatment status:

- Preventive group (PG): for BP-naive patients
- Control group (CG): for patients already treated with i.v. BP at their first ICG visit. This group included any patient who had received at least one infusion of BP before entering the ICG program.

The retrospective analysis included patients with bone metastases from solid tumors, treated with BP i.v. therapy in our cancer center between January 2003 and 30 September 2005. These patients did not receive dental preventive measures or control visits during therapy. These patients were followed until BP therapy was discontinued or until 31 August 2009 for patients who remained on treatment.

We excluded all patients treated with BPs for osteoporosis.

All patients were required to provide consent and all procedures used were in accordance with those advocated by the regional ethical standards committee.

dental care

The principal aim of the dental care program was to search and eliminate all oral ONJ risk factors and to correct dental conditions that were thought to negatively influence oral health during BP therapy [13]. Dental care measures carried out before and during BP treatment are shown in Table 1. At the first ICG visit, all patients underwent a clinical oral examination and radiological assessment using orthopantomography (OPG). Extra- and intraoral examinations were carried out to assess the presence of potential swellings in the head/neck area originating from the oral cavity and the general status of the teeth. In particular, unrecoverable teeth, periodontal disease, totally or partially impacted teeth, peri-implant inflammation, periapical osteolysis, inappropriate endodontic treatments, cysts, jaw diseases, and incorrect dental prostheses were evaluated and corrected in all patients through the procedures shown in Table 1. All conservative dental measures were carried out according to standard operating procedures. Teeth extractions in patients already receiving BP treatment (CG) were carried out in combination with antibiotic therapy (3 g/day of combined amoxicillin + clavulanic acid one day before and for six days after the extraction). We used a technique that demonstrated an evident reduction of ONJ events in postextraction sites. This technique has been designed and applied in our center for several years and its outcomes have been recently published [25]: it involves the use of a sterile field, minimizing surgical trauma (piezosurgery [26]) with platelet precipitates (platelet-rich growth factor) and using the first intention closure on the postextraction alveolus.

In addition to dental assessment and treatment at the first ICG visit, patients were informed about the benefits of BP therapy and the associated risk of developing ONJ and educated about the importance of maintaining optimal oral hygiene during therapy through the daily use of a soft toothbrush and 0.12% chlorhexidine rinses, together with smoking cessation.

At the first ICG visit, patients also received an informative letter addressed to their usual dentist, providing general information about BP treatment and its association, together with other risk factors, with an increased risk of ONJ. The letter described dental procedures to be avoided and dentists were invited to contact the ICG center immediately if further information was needed.

In BP-naive patients (PG), i.v. BP treatment was initiated at least 4 weeks after the last extraction, a reasonable time frame from the oncology point of view before completion of conservative and endodontic treatment and prosthetic fitting. During BP treatment, the following preventive measures were carried out: every 3–4 months, professional oral hygiene avoiding trauma to the parodontal tissues; every 6 months, dental examination and annual OPG and jaw computed tomography assessment. BP therapy was not interrupted before dental avulsion as the scientific and clinical indications supporting this approach are not completely defined.

Table 1. Dental care measures carried out before and during i.v. BP treatment in the PG and CG

Before BP treatment (PG)	During BP treatment (PG and CG)
Orthopantomography	Evaluation of mucosal integrity
Dental extractions	Orthopantomography + jaw computed tomography annually
Conservative interventions	Frequent professional oral hygiene
Adjustment of prosthesis incongruities	Ongoing education on the importance of maintaining oral hygiene
Education on the importance of maintaining oral hygiene	Follow-up visits (every 6 months)
Correction of risk factors (smoking, alcohol intake, and uncontrolled diabetes)	Control of risk factors (smoking, alcohol intake, and uncontrolled diabetes)

BP, bisphosphonate; CG, control group; PG, preventive group.

Based on the evidence that patients already treated with BP (CG) also need specific dental care [23], dental extractions and any invasive oral procedures were limited in this group and conservative procedures were the preferred approach [24]. If dental extractions could not be avoided, patients were referred to our dental clinic for surgical intervention.

BP treatment

All patients (patients in the PG and CG groups in the prospective analysis and those included in the retrospective analysis) were treated with zoledronic acid (Zometa®; Novartis Pharma SpA, Basel, Switzerland) or pamidronate disodium (Aredia®; Novartis Pharma SpA) according to the following standard treatment schedule: zoledronic acid 4 mg or pamidronate 90 mg, by i.v. infusion every 4 weeks.

The first ICG evaluation for CG patients was carried out independently of active dental problems and did not imply BP- treatment interruption.

statistical analysis

Only descriptive statistics were carried out on the data collected: for continuous variables, *t* descriptive statistics for number, mean and standard deviation (SD), and median, minimum, and maximum values were reported; for qualitative/discrete variables, frequencies, and percentages were recorded.

results

patient disposition and characteristics

In the prospective study group, from October 2005 until August 2009, 269 consecutive patients were enrolled into the ICG program and underwent clinical evaluation at least once in the presence of an oral surgeon and a medical oncologist.

Of the 269 patients, 58 were excluded from the subsequent analysis: 10 patients had an osteoporosis diagnosis and 36 patients had not yet received BP treatment by the end of August 2009. Two patients (0.7%) did not start treatment because they did not agree to undergo the prescribed preventive measures and the remaining patients had not yet received clinical indication to start BP therapy.

Among the excluded patients, 11 were not assessable because they were lost to subsequent checks.

Patient clinical characteristics at study entry are shown in Table 2.

In the ICG program, 211 patients received BP therapy [PG: 62% ($n = 129$); CG: 38% ($n = 82$)]. The median age was 65 years (range 33–84 years); 57.8% were female (Table 2). In total, 53.3% of patients had bone metastases from breast cancer, 31.1% from prostate cancer, 9.9% had bone localizations from lung cancer, and 5.72% from other tumors (Table 2).

On 31 August 2009, for the 211 patients receiving BP treatment during the study, the mean follow-up time from first ICG evaluation was 506 days [SD 284.4 days; median 491 days (range 37–1262 days)].

In the retrospective study group, we included 200 consecutive patients who underwent BP therapy in our cancer center between January 2003 and 30 September 2005 without any dental control. Patient clinical characteristics at study entry are shown in Table 3.

The median age was 62 years (range 33–86 years); 58.7% were female (Table 3). In total, 53.2% of patients had bone metastases from breast cancer, 27.4% from prostate cancer, 10% had bone localizations from lung cancer, and 9.5% from other tumors (Table 3).

For the 200 patients receiving BP treatment in the retrospective analysis, the mean follow-up time from the first BP infusion to the last was 522 days [SD 458.4 days; median 393 days (range 22–2134 days)].

Table 2. Patient and clinical characteristics at enrollment into the Interdisciplinary Care Group

	All	Control group	Preventive group
N	211	82	129
Mean age, years (SD)	63.4 (11.23)	60.4 (10.5)	65.3 (11.29)
Male, *n* (%)	89 (42.2)	29 (35.4)	60 (46.5)
Female, *n* (%)	122 (57.8)	53 (64.6)	69 (53.5)
Cancer type, *n* (%)			
Breast	113 (53.3)	48 (58.5)	65 (50.0)
Prostate	66 (31.1)	23 (28)	43 (33.1)
Lung	21 (9.9)	6 (7.3)	15 (11.5)
Other solid tumor[a]	11 (5.2)	4 (4.9)	7 (5.4)
Lung carcinoid	1 (0.5)	1 (1.2)	0

[a]Other solid tumor: four enteric cancers, one esophageal cancer, one gastric cancer, two multiple myelomas, and three kidney cancers.
SD, standard deviation.

Table 3. Patient and clinical characteristics at enrollment into the retrospective study

	All
N	200
Mean age, years (SD)	61.2 (12.02)
Median age, years (range)	62 (33–86)
Male, *n* (%)	82 (40.8)
Female, *n* (%)	118 (58.7)
Cancer type *n* (%)	
Breast	107 (53.2)
Prostate	55 (27.4)
Lung	20 (10.0)
Other solid tumor[a]	19 (9.5)

[a]Other solid tumor type: one esophageal cancer, three gastrointestinal cancers, one multiple myeloma, one neuroendocrine tumor, one cancer of unknown origin, two parotideal cancers, six kidney cancers, and four bladder cancers.
SD, standard deviation.

BP exposure and requirement for dental treatment

In the prospective group, after dental assessment, 48.1% of PG patients initiated BP therapy immediately, while 51.9% required preventive dental care before BP initiation (Table 4). Of the patients requiring dental treatment, 70.1% required one or more extractions in order to achieve optimal oral health.

Among CG patients, following dental evaluation, 25.6% required preventive dental intervention; conservative measures

were carried out in 90.5% of patients, whereas two patients required one or more extractions (9.5%) (Table 4).

Consistent with the risk of ONJ development related to N-BP treatment and zoledronic acid use, we report the mean BP use in the ICG and retrospective groups, in terms of total duration of exposure and number of infusions of i.v. BP (overall and zoledronic acid), as shown in Tables 5 and 6.

In the PG, patients received a mean of 8.3 (SD 5.64) infusions of BP versus a mean of 17.8 (SD 10.97) infusions in the CG. In particular, in patients receiving zoledronic acid, a mean of 16 (SD 9.09) infusions were given in the CG versus a mean of 8.4 (SD 5.64) infusions in the PG.

In the retrospective analysis, patients received a mean of 15.8 (SD 13.63) BP infusions. In patients receiving zoledronic acid, a mean of 13.5 (SD 9.73) infusions were given (Table 6).

The exposure to BPs in the CG was 758 days, 277 days in the PG, and 522 days in the retrospective group (Table 7). The treatment interruption rate was higher in CG patients (45%) than in PG patients (16%). In general, the decision to interrupt treatment was considered based on clinical disease evolution and was not related to dental problems in both the CG and the PG. The only patient who stopped treatment for dental reasons was a patient in the PG group with suspected clinical ONJ.

Table 4. Preventive odontoiatric measures used in the CG and PG

	Patients, *n* (%)	
	CG	PG
Patients requiring preventive measures	21 (25.6)	67 (51.9)
Patients not requiring preventive measures	61 (74.4)	62 (48.1)
Type of preventive measure used		
Conservative	19 (90.5)	15 (22.4)
Extraction	2 (9.5)	47 (70.1)
Conservative + extraction	0	3 (4.5)
Removed implant	0	1 (1.5)

CG, control group; PG, preventive group.

Table 5. Intravenous BP and zoledronic acid exposure in the CG and PG

	CG	PG
BP exposure (zoledronic acid and pamidronate)		
N	82	126
Mean duration of exposure, days (SD)	758 (555.5)	277 (258.7)
Median duration of exposure, days (range)	596 (29–2382)	201 (25–1465)
N	82	124
Mean number of infusions (SD)	17.8 (10.97)	8.3 (5.64)
Median number of infusions (range)	16.0 (1–55)	7.0 (1–28)
Zoledronic acid exposure		
N	70	120
Mean duration of exposure, days (SD)	641 (455.3)	265 (230.6)
Median duration of exposure, days (range)	479 (29–1865)	201 (25–1257)
N	70	123
Mean number of infusions (SD)	16 (9.09)	8.4 (5.64)
Median number of infusions (range)	15.0 (1–51)	7.0 (1–28)

BP, bisphosphonate; CG, control group; PG, preventive group; SD, standard deviation.

ONJ frequency

After 47 months of follow-up, among the 211 patients undergoing comprehensive dental care before and/or during treatment with i.v. BP, 6 patients developed ONJ; this corresponds to a frequency of 2.8%. Among CG patients, who joined the ICG program after already having received at least one infusion of BP treatment, one case of ONJ was observed. Five cases of ONJ were observed in the PG. Table 8 provides a description of the ONJ cases in the ICG program: all these cases underwent specific dental care, with antibiotics and/or a surgical approach, and ONJ resolved. The success of local treatment was due to the early diagnosis of ONJ.

In the retrospective analysis, 11 cases of ONJ were observed (5.5%). Table 9 provides a description of the ONJ cases in the retrospective group.

discussion

Implementing the ICG program of preventive dental care not only ensured that patients were informed of the potential risks and benefits of BP treatment but also minimized ONJ frequency compared with ONJ rates reported in previous

Table 6. Intravenous BP and zoledronic acid exposure in the retrospective group

	Retrospective group
BP exposure (zoledronic acid and pamidronate)	
N	200
Mean duration of exposure, days (SD)	522 (458.4)
Median duration of exposure, days (range)	393 (22–2134)
N	200
Mean number of infusions (SD)	15.8 (13.63)
Median number of infusions (range)	12.0 (1–72)
Zoledronic acid exposure	
N	194
Mean duration of exposure, days (SD)	437 (342.3)
Median duration of exposure, days (range)	348 (22–1631)
N	195
Mean number of infusions (SD)	13.5 (9.73)
Median number of infusions (range)	11 (1–44)

BP, bisphosphonate; SD, standard deviation.

Table 7. Exposition to bisphosphonate in treatment groups

Group	Exposition (days)	95% confidence interval	Osteonecrosis of the jaw (*n*)
Control group	758	665.2–850.9	1
Preventive group	277	202.0–351.8	5
Retrospective	522	461.9–581.6	11

Table 8. ONJ cases in the ICG group

Sex	Primary cancer	ICG first visit	Preventive dental care	Bisphosphonate	*n*	Oral conditions, signs, and symptoms	Therapy prescribed for ONJ
Male	Prostate	PG	Extractions	Zoledronic acid	10	Partial edentulism, poor oral hygiene, nonhospitalized dental extraction during therapy with postextraction infection	Antibiotics
Male	Prostate	PG	Extractions	Zoledronic acid	11	Partial edentulism, prosthesis incongruities without mucosal discontinuity, periodontal disease, spontaneous bone expulsion	None
Female	Breast	CG	None	Zoledronic acid	6	Good oral conditions, nonhospitalized dental extraction during therapy with postextraction infection	Surgery and antibiotics
Female	Lung	PG	Conservative	Zoledronic acid	9	Good oral conditions, nonhospitalized dental extraction during therapy with postextraction infection	Surgery and antibiotics
Female	Breast	PG	Extractions	Pamidronate	8	Poor oral conditions, hospitalized preventive dental extraction with postextraction infection	Surgery and antibiotics
Female	Breast	PG	Extractions	Zoledronic acid	9	Poor oral hygiene and oral conditions, serious periodontal generalized disease, hospitalized preventive dental extraction with postextraction infection	Surgery and antibiotics

CG, control group; ICG, Interdisciplinary Care Group; ONJ, osteonecrosis of the jaw; ICG, PG, preventive group.

studies. In fact, although the development of ONJ was not completely excluded by this strategy, overall our data suggest the strong impact of implementing an interdisciplinary approach for a comprehensive preventive and curative dental care program, and the reduction of ONJ risk in patients with metastatic cancer receiving i.v. BP treatment compared with ONJ rates from previous studies in such patients.

BP treatment has initiated intense debate in recent years, either because of poor knowledge about the etiology and pathogenesis of ONJ or due to the lack of alternative therapeutic options available for patients with metastatic bone disease. The widespread doubts concerning the use of i.v. BPs after the first ONJ cases were reported sparked the initiation of many analyses aimed at investigating incidence, onset mechanisms, risk factors, and also advocating the development of updated clinical guidelines. On the basis of results obtained from these studies, it became clear that invasive dental interventions during BP treatment are one of the main risk factors for ONJ development [27], to the extent that BP treatment is now strongly discouraged if not accompanied by preventive dental monitoring [2, 11]. Based on these recommendations, the first reports on the efficacy of preventive dental care to reduce ONJ incidence have recently become available. In a previous study of 154 consecutive patients receiving preventive dental measures before starting BP treatment, and regular dental control every 6 months during treatment [28], only 2 patients developed ONJ (1.3%); this was a consistent reduction in ONJ frequency compared with data obtained by the same authors from a retrospective analysis carried out on 812 consecutive patients treated with BP without preventive measures, in which 26 cases of ONJ (3.2%) were reported [28]. Similar data were reported in a retrospective study comparing the frequency of ONJ in BP-treated patients with bone metastatic breast ($n = 57$) and prostate ($n = 25$) cancers in the absence of preventive measures, with that observed prospectively in the same type of patients receiving improved dental care and avoiding dental procedures during BP treatment [29]. In patients with prostate carcinoma not undergoing preventive dental measures, 3 of 25 (12%) patients developed ONJ, while two cases of ONJ were observed in patients with breast cancer, one with and one without preventive dental care [29].

We carried out a retrospective analysis of 200 consecutive patients with metastases from solid tumors treated with i.v. BPs followed up at our oncology center from January 2003 to September 2005 (i.e. before the initiation of preventive dental procedures) and found 11 cases (5.5%) of ONJ.

In just over 4 years since the implementation of the ICG dental program, only six cases (2.8%) of ONJ have been reported in 211 patients exposed to BP with a consistent reduction in ONJ frequency compared with data obtained from our retrospective analysis of patients treated with BP without preventive measures.

Table 9. ONJ cases in the retrospective group

Sex	Primary cancer	BP	Number of infusions	Oral conditions, signs, and symptoms	Therapy prescribed for ONJ
Female	Breast	Zoledronic acid	27	Prosthesis incongruities with trauma and mandibular mucosal discontinuation, poor oral hygiene	Antibiotics
Female	Breast	Zoledronic acid	40	Periodontal disease and mandibular infection, pain, poor oral hygiene	Antibiotics
Female	Breast	Pamidronate, zoledronic acid	12, 8	Periodontal generalized disease, multiple root residues, prosthesis incongruities with trauma, mobility on 3.6 (II degree), mandible pain	Antibiotics, curettage, and extractions
Male	Prostate	Pamidronate, zoledronic acid	28, 31	Multiple previous extractions and infections, poor oral hygiene, two root extractions during BP, maxillary pain and left sinus fistula (2.3–2.6)	Antibiotics
Female	Breast	Zoledronic acid	37	Serious periodontal generalized disease, residual roots, superior prosthesis incongruities with trauma and mucosal discontinuities	Antibiotics
Female	Breast	Pamidronate, zoledronic acid	16, 25	Edentulia and prosthesis incongruities with trauma, fistula and mandible pain	Antibiotics
Female	Breast	Pamidronate, zoledronic acid	41, 17	Serious superior periodontal disease, multiple previous extractions and infections, poor oral hygiene. Maxillary pain with oral-sinus fistula, infection and mucosal discontinuity	Surgery and antibiotics
Female	Breast	Pamidronate, zoledronic acid	52, 14	Edentulia, prosthesis incongruities with trauma. Maxillary sinusitis, jaw pain, mucosal discontinuity, poor oral hygiene	Surgery and antibiotics
Female	Breast	Zoledronic acid	44	Periodontal disease with poor oral hygiene	Antibiotics
Male	Prostate	Zoledronic acid	19	Fistula, poor oral hygiene, pain	Antibiotics
Male	Prostate	Zoledronic acid	20	Periodontal disease with poor oral	Antibiotics

BP, bisphosphonate; ONJ, osteonecrosis of the jaw.

It is noteworthy that our study included 80 prospective patients who had previously been treated with BPs before study entry. These patients benefited from a dental check and only one ONJ event (1.3%) was reported during the observation period. In these patients, dental monitoring, conservative intervention, and standard dental hygiene practice were the only preventive tools used; therefore, in patients unable to undertake preventive dental measures before BP treatment, reaching and maintaining a stable oral condition during therapy appears to minimize the risk of developing ONJ. These findings stress the importance of regular dental visits during BP treatment to maintain optimal oral conditions and to ensure patients maintain correct daily oral hygiene. Moreover, as demonstrated in our study, a close radiographic and clinical control of oral conditions allows for easier identification of new early-stage lesions with an improved prognosis.

Our results support the use of such programs to reduce ONJ frequency in similar heterogeneous populations, in terms of BP exposure time and survival.

In this analysis, data appear to be clinically relevant taking into account the standardization of treatment in our institution and the correspondence of our data with those previously reported in the literature. However, it must be acknowledged that some differences between the CG and PG (e.g. a different number of infusions and, therefore, differing lengths of exposure to BP treatment) may limit, at least partially, the robustness of the findings. Moreover, our study is limited by the lack of a statistical analysis, which was not carried out due to the different nature of the prospective ICG and retrospective subgroups and in some cases (e.g. the frequency of ONJ) due to small sample size.

Data available in the literature do not indicate an optimal interval between dental care intervention and the initiation of

BP treatment. However, in cases of surgical invasive intervention, a period of 4 weeks was sufficient to ensure recovery of the mucosa and alveolar healing [24]. Based on our experience, it was practical to optimize oral conditions in advance of BP initiation in most cases; however, in patients who required more urgent BP treatment due to symptoms, number of lesions, and the aggressiveness of the bone metastases, BP therapy could be initiated at least 4 weeks after preventive invasive dental procedures are completed.

Furthermore, there is no definitive evidence supporting the suspension of BP treatment when dental extractions are needed [24]. Considering the prolonged half-life of BP in the bone tissue, in our clinical practice we did not deem it necessary to suspend BP treatment if extractions were needed.

The application and implementation of the above-described preventive dental procedures required a substantial effort in terms of human and organizational resources but, importantly, it allowed the achievement of our primary aim of reducing ONJ frequency among the patients followed by our center. Moreover, the letter provided to all ICG patients for their dentists explaining the risk of ONJ associated with BP treatment has improved physician–patient communication and improved communication with dentists in the local area. This was an inexpensive and effective way to disseminate information and to avoid inappropriate procedures.

Our data show that this interdisciplinary approach is helpful, both for the standardization of treatment type and timing and for logistical practical aspects of care, as demonstrated by the compliance results observed in this study: only 2 of 269 ICG patients refused prophylactic dental care.

Indeed, based on the validated efficacy of BPs in the prevention of skeletal-related events and recent evidence demonstrating the direct antitumor activity of BP [30], the use of these drugs in the oncology setting should be strongly pursued.

In view of the fact that ONJ may also be associated with other antiangiogenic treatments, such as bevacizumab and denosumab [31], this ICG approach could become the model for a more generalized management strategy for patients with neoplastic disease with compromised oral conditions, due to chemotherapy-induced toxicity, immunosuppression, or cancer progression itself.

Thanks to advances in the development of anticancer therapies, life expectancy continues to improve even in metastatic patients with solid tumors; consequently, an increasing proportion of patients with different tumor histologies are eligible for long-term BP treatment. Since the risk of developing ONJ, although low, appears to be correlated with cumulative BP exposure, the need to optimize the safety of this therapy in an ever-increasing number of patients is vital. Thus, in a clinical setting with limited treatment options, reducing the risk of developing ONJ through dental measures represents a promising result.

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disclosure

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