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Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan

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Background: Screening of the oral cavity and dental care was suggested as mandatory preventive measures of osteonecrosis of the jaw (ONJ) in patients receiving bisphosphonates (BPs). We investigated the occurrence of ONJ before and after implementation of dental preventive measures when starting BP therapy.

Patients and methods: Since April 2005, 154 consecutive patients treated with BPs (POST-Group) have undergone a baseline mouth assessment (dental visit ± orthopantomography of the jaws) to detect potential dental conditions and dental care if required. A retrospective review was also conducted of all consecutive cancer patients with bone metastases (PRE-Group) and treated for the first time with BPs from January 1999 to April 2005 in our clinic without receiving any preventive measure. Incidence proportion and incidence rate (IR) were used to estimate the incidence of ONJ.

Results: Among the study population (966 patients; male/female = 179/787), 73% had breast cancer. 25% of patients were given zoledronic acid (ZOL), 62% pamidronate (PAM), 8% PAM followed by ZOL and 5% clodronate. ONJ was observed in 28 patients (2.9%); we observed a reduction in the incidence of ONJ from 3.2% to 1.3%, when comparing—pre and post-implementation of preventive measures programme. Considering the patients exposed to ZOL, the performance of a dental examination and the application of preventive measures led to a sustained reduction in ONJ IR (7.8% in the PRE-Group versus 1.7% in the POST-Group; $P = 0.016$), with an IR ratio of 0.30 (95% confidence interval 0.03–1.26).

Conclusions: ONJ is a manageable and preventable condition. Our data confirm that the application of preventive measures can significantly reduce the incidence of ONJ in cancer patients receiving BPs therapy. Dental exams combined to the identification of patients at risk in cooperation with the Dental Team can improve outcomes and increase the number of ONJ-free patients.

Key words: bisphosphonates, bone metastases, dental preventive measures, dental team, ONJ, osteonecrosis of the jaw, osteoporosis

introduction

Bone metastases are the most common event in cancer patients [1–4]. They can cause pain, hypercalcaemia, increased risk of skeletal-related events (SREs) such as pathological fractures, spinal compression, need for orthopaedic surgery and/or radiotherapy to bone. Thus, SREs can significantly modify the clinical course of the disease.

Intravenous bisphosphonates (BPs)—like pamidronate (PAM) and zoledronic acid (ZOL)—have been used for long time for the treatment of bone metastases. BPs have proven to significantly decrease SREs, hypercalcaemia and pain [5–17]. In the light of the clinical data, a number of international scientific associations proposed and developed practical clinical recommendations in relation to the use of these agents in solid tumours and multiple myeloma [18–22].

Osteonecrosis of the jaw (ONJ) is an emerging complication seen in cancer patients receiving BPs [1, 23–26].

Major risk factors for ONJ have been reported in the literature, such as tooth extractions (~60% of cases) [27],

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major dental surgery in the course of BP therapy, duration of administration and type of BP (risk is higher with i.v. aminobisphosphonates and among these is probably higher with ZOL than with PAM). Other risk factors such as concomitant use of corticosteroids, antiangiogenic drugs, poor oral hygiene, diabetes and peripheral vasculopathy still need to be further investigated [27].

On the basis of published recommendations from several dentistry associations, the importance to prevent ONJ is strongly emphasised since an optimal therapy for this rare but serious complication does not exist [28, 29].

Such preventive measures include: (i) careful visual examination of the oral cavity; (ii) proactive management of any possible dental disorder before initiating BP therapy, usage of antibiotic treatment; (iii) avoidance of invasive dental procedures in patients on BP therapy and (iv) identification of risk factors [28, 30–32].

The need for prospective studies has been highlighted by several authors in order to get better clinical evidences concerning the validity of the preventive measures as they were empirical recommendations.

As such, the present study is comparing two populations of cancer patients with bone metastases and/or osteoporosis treated with BPs. One of the two groups was retrospectively assessed and did not undergo any dental prevention programme (PRE-Group). The second group was evaluated prospectively and was part of a dental prevention programme (POST-Group). This study allowed us to verify if the application of preventive measures according to the published recommendations could clinically diminish the incidence of ONJ.

patients and methods

The study was carried out at the Day Hospital and Outpatient Clinic of the Palliative Care Operative Unit in Milan (Italy), where ~80% of BPs prescribed in the hospital are infused and patients are referred directly from the Oncology Department just from the diagnosis of bone metastases from solid tumours and regardless of the presence of pain.

This study included all patients ($n = 966$) treated from 1 January 1999 to 28 February 2007 with at least one infusion of PAM and/or ZOL for bone metastases management and patients treated with clodronate (CLO) for osteoporosis associated with anticancer therapies.

schedule of BP infusion

BPs were administered as follows:

- ZOL: 4 mg was prepared in 250 ml saline solution and infused over 45 min every 28 days.
- PAM: according to our internal scheme consisting of two courses of PAM 60 mg weekly for a 2 h i.v. infusion for 2 weeks with a 3-week interval between courses (six infusions ~7 weeks) followed by one infusion every 3 weeks [33].
- CLO: 300 mg was prepared in 500 ml saline solution and infused over 2 h for three consecutive days every 4 weeks.

All patients treated with ZOL were also received daily calcium supplements.

retrospective group (PRE-Group)

All patients who started their BP treatment from January 1999 to 14 April 2005 were retrospectively evaluated and did not receive any preventive dental care. These patients were followed until patients discontinued their BP or until 28 February 2007 for patients who remained on treatment.

prospective group (POST-Group)

All consecutive patients who started their first BP treatment from 15 April 2005 to 28 February 2007 were prospectively enrolled and were included in the dental prevention programme.

definition of ONJ and data collection

We have considered the 'working diagnosis of ONJ'. It was made when there was no evidence of healing after 6 weeks of appropriate evaluation and dental care and no evidence of metastatic disease in the jaw or osteoradionecrosis [29].

The following data were collected for each patient: demographics, tumour type, type and reasons of BP administration and presence of bone metastases/injury/radiotherapy at the jaws.

Given the partially retrospective nature of the data collection, it was not possible to gather any data on associated conditions or potential risk factors for ONJ.

The patients in the PRE-Group were referred to the hospital dental team (DT) who assessed their dental conditions and provided them with specialised care. The possible presence of ONJ was defined using the following criteria:

- The presence or recurrent dental abscesses or infections, complaints of gum soreness and/or pain, painful parodontopathies, tooth mobility and mastication difficulties due to unstable removable prostheses.
- Patients reporting to be under the care of a private dentist for recurrent dental abscesses.

Several variables were recorded for each patient diagnosed with ONJ—date of diagnosis, presence of symptoms, number of BP infusions received before the diagnosis, prior and/or concomitant oncologic therapies, analgesic treatments and use of corticosteroids.

dental preventive measures in the POST-Group

From 15 April 2005, all patients candidate to BP therapy were referred to the hospital DT in order to evaluate any possible infection or inflammation which could lead to a dental intervention. After clinical inspection and according to the oral status, a decision was made about the need for an orthopantomography (OPT). In addition, other dental aspects were also monitored and recorded (e.g. tooth mobility, parodontopathies, presence of root fragments, decays, granulomas, edentulism and periapical conditions), as well as any concomitant treatments received, or OPTs carried out.

dental care required before BP treatment

- Avulsion of parodontopathic teeth with marked tooth mobility (grades 3–4), which would be likely avulsed within the subsequent 24 months.
- Correction of treatable parodontal conditions.
- Performance of both superficial and deep oral hygiene treatments with professional root scaling.

All pathogenic conditions deserving a conservative or endodontic treatment had to be managed. Preventive interventions were not mandatory, allowing patients to complete these cares even in the course of BP treatment.

If patients needed dental intervention, we carefully considered the need for a rapid BP therapy versus delaying the initiation of BP treatment due to dental procedures.

Patients were given some indications to definitely comply with, along with the specific motivations:

Whenever required, an 'oral sanitation' was the *conditio sine qua non* to start BP treatment. Oral sanitation consists in removing all the pathological conditions which in the 24-month treatment period could likely lead to an odontoiatric approach and in particular to a surgical interventions.

- The preventive oral sanitation could be carried out according to standard dental protocols,
- Any invasive required dental treatment while undergoing BP therapy should be carried out carefully and usage of antibiotic was highly suggested.
- Except in extreme cases, no mucogingival surgery was carried out when patients were receiving BP therapy.
- Prosthetic interventions requiring implant should be avoided on BP therapy.
- Patients were still considered at risk for at least 24 months after stopping BP therapy.

In case of dental interventions, wide-spectrum antibiotics were given from 7 days before, till 7 days after superficial interventions or until the healing of the wound if more complex interventions were carried out. Dental examinations were repeated regularly (every 6 months) from 15 April 2005 onwards and throughout the BP treatment.

statistical analysis

ONJ incidence was estimated in two different ways: the incidence proportion (IP) and incidence rate (IR).

IP is defined as

$$\text{IP} = \frac{\text{Number of patients developing ONJ}}{\text{Number of patients of study sample}} \times 100.$$

This measurement of incidence required all patients to be followed for a similar time period for the risk to be calculated and comparisons to be made between groups. Although this was not true for the study sample (each patient got his/her observation period), IP was anyway calculated because it is the measurement most used in the literature on BP-related ONJ [23, 27, 34].

IR is defined as

$$\text{IR} = \frac{\text{number of patients developing ONJ}}{\text{total observation time of all patients of study sample}}.$$

Since this index implies a measurement of the observation time (each patient contributes to the total observation time only with his/her actual observation time), the incidence is estimated more appropriately in this instance.

Observation time was calculated for each patient as the period in years between the date of first and last BP administration and the last update date. For PRE-Group patients, the update date corresponded with the last infusion date; for patients developing ONJ, the update date was the ONJ diagnosis date.

Comparison between IPs before and after prevention programme was carried out by one-tailed Fisher's exact test ($P < 0.05$ was considered significant), while IRs comparison was carried out by estimating the incidence rate ratio (IRR) and its 95% confidence interval (CI).

Due to the possibility that not all patients undergoing prevention followed the recommendations from the DT, two kinds of analysis were conducted: an intention-to-treat (ITT) analysis where patients were considered undergoing the prevention programme regardless of the actual compliance with the DT's recommendations and a per-protocol (PP) analysis where patients not correctly following the prevention recommendations were moved into the PRE-Group.

Kaplan–Meier curves of failure (trunked at 24 months) are shown by implementation of the prevention programme and by administered BP for descriptive purpose only.

results

Table 1 shows the demographics of 966 patients included in the study receiving at least one BP infusion. The most frequent primary tumour sites were breast (73%), lung and prostate. Nine hundred and three patients (93.5%) had bone metastases, 27 patients (2.8%) had osteoporosis and 3.7% both conditions.

Eight hundred and twelve patients assumed BPs before dental prevention programme (PRE-Group) while 154 patients were enrolled after (POST-Group).

The median follow-up time was 9.3 (range 0.1–94.2) and 11.4 (range 0.1–22.7) months, respectively, in the PRE- and POST-Group.

Given the partially retrospective nature of the data collection, no data on associated conditions or potential risk factors for ONJ were gathered.

Most patients under investigation (601 = 62.2%) had been treated with PAM, though only 34 of them (22.1%) had received PAM in the POST-Group, in comparison with 69.8% in PRE-Group; 76% in the POST-Group versus 15.6% in the PRE-Group received ZOL. In the POST-Group, no patient received ZOL after PAM courses. Only a minority of patients (4.5%) received CLO.

Table 2 shows causes and types of dental treatment undergone by the 154 patients of POST-Group before starting BP treatment. Ninety-nine patients (64.2%) did not require any DT intervention and started immediately after the BP treatment. The avulsion of one or two teeth or root fragments was required in 12 of 154 patients, where the situation was no longer recoverable through conservative or endodontic care. Twelve of the POST-Group patients had severe parodontopathies, prompting for large interventions requiring surgical flaps to be repositioned and sutured at the end of the intervention. Thirty-two OPTs were required to confirm the diagnosis in clinically doubtful cases, among which five were required to plan further sanitation interventions (on multiple root fragments) (data not shown).

Throughout the follow-up, on BP treatment, fifteen POST-Group patients needed some dental care (data not shown).

Table 3 shows the individual data of the 28 patients who developed ONJ. The table shows in detail the numbers of infusions received when oral abscess appeared; these range from 4 to 24 for ZOL, administered as single therapeutic agent, and from 5 to 69 for PAM, administered as single BP. Nine of 26 patients belonging to PRE-Group developed ONJ on treatment with both BPs administered sequentially. No patient treated with CLO developed ONJ.

Lesions were shown to have initially occurred after dental extraction in 22 patients and following infection from gingival lesion caused by unstable prosthesis in three patients; one patient developed infection after failure of mandibular implantation. All 26 patients underwent antibiotic therapy without healing of ONJ, though repeated antibiotic courses seemed to result in symptom control and contained progression of the infectious necrotic process. Three patients

Table 1. Patients' demographics

	Pre-Group[a] (n = 812)	POST-Group[b] (n = 154)	Total (n = 966)
Gender, *N* (%)			
Female	672 (82.8)	115 (74.7)	787 (81.5)
Male	140 (17.2)	39 (25.3)	179 (18.5)
Median age (range)	62.4 (21.4–90.4)	62.9 (29.8–84.3)	62.5 (21.4–90.4)
Primary tumour, *N* (%)			
Breast	590	112	702 (73%)
Lung	61	6	67 (7%)
Prostate	44	24	68 (7%)
Multiple myeloma	3	0	3
Thyroid	6	2	8
Kidney	11	0	11
Endometrium	4	0	4
Gastrointestinal stromal cancer	1	0	1
Bladder	7	3	10
Tongue	2	0	2
Lymphoma	9	1	10
Multiple cancers	9	3	12
Others	65	3	68 (7%)
Type of administered BP, *N* (%)			
Pamidronate	567 (69.8)	34 (22.1)	601(62.2)
Zoledronic acid	127 (15.6)	117 (76.0)	244 (25.3)
Pamidronate followed by zoledronic acid	78 (9.6)	0	78 (8.0)
Clodronate	40 (4.9)	3 (1.9)	43 (4.5)
Reason for BP administration, *N* (%)			
Bone metastases	752 (92.6)	151 (98.0)	903 (93.5)
Osteoporosis	24 (2.3)	3 (1.9)	27 (2.8)
Bone metastases + osteoporosis	36 (4.4)	0	36 (3.7)

[a]Before dental prevention.
[b]After dental prevention.
BP, bisphosphonate.

underwent hyperbaric oxygen therapy and seven underwent surgical curettage, all without success. One patient underwent sequestrectomy and another one underwent mandibular reconstruction, both without success. One patient presented both mandibular osteomyelitis and malignant cells in another area of the jaw, treated with radiotherapy.

In the POST-Group, two patients treated with ZOL developed ONJ after undergoing a dental avulsion before BP treatment. In the retrospective study, it is not possible to grade lesions of the patients according to the classification of Weitzman et al. [29]. In the prospective study, the two patients, who developed the ONJ after dental care and before the BP treatment, were graded, respectively, as 3A (patient 1) and 4A (patient 2) according to the classification of Weitzman et al. [29].

It is worth to point out that patient 1 developed ONJ in spite of an antibiotic therapy assumed as prescribed before and after dental avulsion, while patient 2 did not assume the prescribed antibiotic.

In ONJ cases we observed, we noted the presence of particularly resistant inflammatory pus collections. Even in the most difficult cases, we always obtained the regression of pus collections by using one 500-mg tablet of azithromycin per day for 9 days.

Sixteen patients complained about local pain and gum soreness, while six patients experienced eating difficulties leading to severe weight loss. These patients needed a support therapy with parenteral nutrition (Table 3).

Table 2. Causes and types of dental treatments in the POST-Group patients

Treatment	Cause	n	Subtotal
None			99
Avulsion	Root fragments	3	12
(of 1–2 teeth)	Dental mobility	2	
	Decay	4	
	Abscess	2	
	Granuloma	1	
Sanitation	Parodontopathy	6	12
(avulsion of more than teeth)	Root fragments	5	
	Decay	1	
Scaling/curettage	Poor oral hygiene	22	25
	Parodontopathy	2	
	Dental mobility	1	
Denture reline	Prosthesis instability	2	2
Conservative/endodontic therapy	Decay	6	6
Total[a]			156

[a]Two patients had more than one dental problem.

Table 3. Individual data of 28 patients with osteonecrosis of the jaw

Patients	Age	Primary cancer	Pamidronate (no. of infusions)	Zoledronate (no. of infusions)	No. of infusions before ONJ diagnosis	Oral conditions, signs and symptoms	Therapy prescribed for ONJ
Twenty-six patients not undergoing preventive dental programme (PRE-Group)							
1	68	Breast		19	7	Postextraction mandibular + maxillary infection, external fistula, pain, weight loss	Antibiotics, curettage
2[ab]	66	Endometrium	57		24	Postextraction maxillary infection, pain, weight loss	Antibiotics, curettage
3[bc]	67	Breast	78		15	Postimplant failure mandibular infection, pain	Antibiotics + radiotherapy
4	76	Breast	15		9	Postextraction mandibular + maxillary infection, pain	Antibiotics, curettage,
5[b]	63	Breast	15	18	12 (zoledronate)	Postextraction mandibular infection, external fistula, pain, weight loss	Antibiotics, curettage, sequestrectomy, hyperbaric oxygen therapy
6[b]	53	Breast	20	18	12 (zoledronate)	Postimplant failure mandibular infection, pain, weight loss	Antibiotics, curettage hyperbaric oxygen therapy
7	43	Breast	16	23	12 (zoledronate)	Postimplant failure mandibular infection, pain	Antibiotics
8	62	Breast	19	16	13 (zoledronate)	Postimplant failure maxillary infection	Antibiotics, curettage
9	77	Breast		14	12	Postextraction mandibular infection	Antibiotics
10	53	Breast		4	4	Postextraction maxillary infection, pain	Antibiotics
11	56	Gastrointestinal stromal cancer	14		5	Postextraction maxillary infection (periodontal cyst), pain	Antibiotics
12[a]	57	Bladder	61		53	Postextraction mandibular infection, pain, weight loss	Antibiotics
13	55	Breast	42	23	20 (zoledronate)	Postextraction maxillary infection	Antibiotics
14	63	Breast		21	19	Postextraction mandibular infection, pain	Antibiotics
15	75	Breast	54		53	Postextraction mandibular infection, pain	Antibiotics
16	72	Breast	27		25	Postextraction maxillary infection, bleeding	Antibiotics
17[d]	89	Prostate		18	17	Postextraction maxillary infection, pain	Antibiotics
18	59	Breast	50		50	Postextraction mandibular infection, pain	Antibiotics
19	68	Breast		24	24	Postextraction mandibular infection, pain	Antibiotics
20	64	Breast	2	2	2 (zoledronate)	Postextraction mandibular infection	Antibiotics
21[b]	65	Lung	20		20	Postextraction mandibular infection, pain	Mandible reconstruction, antibiotics
22[bd]	63	Kidney	35	13	12 (zoledronate)	Postextraction mandibular infection	Curettage, hyperbaric oxygen therapy, antibiotics

Table 3. (*Continued*)

Patients	Age	Primary cancer	Pamidronate (no. of infusions)	Zoledronate (no. of infusions)	No. of infusions before ONJ diagnosis	Oral conditions, signs and symptoms	Therapy prescribed for ONJ
23	59	Breast	14	23	23 (zoledronate)	Recurrent postextraction mandibular infection, denture sores	Antibiotics
24	64	Breast	7	8	8 (zoledronate)	Dental infection in patients with instable prostheses, weight loss	Antibiotics
25	71	LNH		15	15	Dental infection in patients with instable prostheses	Antibiotics
26	57	Breast	69		69	Dental infection in patients with prostheses	Antibiotics
Demographics of two patients with ONJ who underwent preventive dental programme (POST-Group)							
1	48	Breast		9	9	Postextraction mandibular infection[e]	Antibiotics
2	60	Breast		13	13	Postextraction mandibular infection[f]	Antibiotics

[a]Osteoporosis.
[b]Patients with histological diagnosis.
[c]Mandibular metastases.
[d]Male gender.
[e]With antibiotic prophylaxis and postextraction therapy.
[f]Patients did not take the antibiotic therapy prescribed.
ONJ, osteonecrosis of the jaw; LNH, non-hodgkin lymphoma.

In all patients, the first clinical sign was a tooth abscess, with an external fistula in two patients. After antibiotic therapy and dental extraction, the most common clinical findings were mucosal ulcerations, mucosal infections and exposed bone. Among 28 patients with ONJ, these were localised in the mandible in 20 patients, in the maxilla in seven patients and in both areas in one patient.

When osteonecrosis was diagnosed, five patients were on chemotherapy and only one on concomitant radiotherapy. Concomitant nononcological treatments were nonsteroidal anti-inflammatory drugs (17.8%), weak or strong opioids (46.4%) and corticosteroids (two patients).

Only six patients had a biopsy diagnostic of osteomyelitis, carried out in another hospital, since our DT considered biopsy as a risk factor [32]. As a precautionary measure, BP therapy was stopped in all patients with suspected or documented ONJ.

Table 4 shows the number of patients with ONJ, the IPs and IRs by implementation of prevention programme and by type of administered BP. Overall, ONJ was observed in 28 patients (2.9%), with a reduction from 3.2% PRE- to 1.3% POST-prevention programme (not statistically significant). Considering the observation time for each patient, the IR was 0.029 cases/year for PRE-Group, decreasing to 0.014 cases/year in the POST-Group, representing a decrease in IR of about 50% (IRR = 0.49). Although not statistically significant in the ITT analysis, the IP reduction proved significant in the PP analysis ($P = 0.048$). Different levels of incidence but similar pattern of reduction were found for different subsample of patients; in particular, the incidence reduction from PRE- to POST-Group is remarkable in those patients assuming ZOL alone or combined with PAM, with values of IP of 7.8% and 1.7% in PRE- and POST-Group, respectively, and a 70% decrease in IR (from 0.67 to 0.20 cases/year; IRR = 0.30). The PP analysis gave stronger results, with an 85% decrease in IR (IRR = 0.14; 95% CI 0.003–0.90).

Figure 1 shows the box plots of number of infusions by BP administered in patients with and without ONJ. It can be observed that, among patients taking PAM, those who developed ONJ received more infusions than those who did not. This did not occur in the other groups. In addition, the figure shows that no patient taking CLO developed ONJ.

Figure 2 shows the time to onset of ONJ by implementation of prevention programme and by administered BP, according to ITT analysis of all patients treated with any BP. Regarding the PP analysis, the patient who underwent a dental avulsion before starting BP treatment but refused to take antibiotics was moved to the PRE-GROUP.

This figure too confirms that the subpopulation with the highest difference between PRE- and POST-prevention programme implementation corresponds to the patients assuming ZOL alone or combined with PAM.

discussion

The results of our study show a reduction in IR of ONJ from 0.029 cases/year in the PRE-Group to 0.014 cases/year in the POST-Group, in all patients treated with any type of BP. The reduction was more remarkable in the subpopulation of

Table 4. Osteonecrosis of the jaw frequencies, IPs and IRs by prevention programme implementation and bisphosphonate administration

	Any bisphosphonate, $N = 966$			Only zoledronate, $N = 244$			Only pamidronate, $N = 601$			Zoledronate or pamidronate + zoledronate, $N = 322$[a]		
	ONJ cases	IP	IR	ONJ cases	IP	IR	ONJ cases	IP	IR	ONJ cases	IP	IR
Intention-to-treat analysis												
PRE	26	3.20	0.029	7	5.51	0.046	10	1.76	0.017	16	7.80	0.067
POST	2	1.30	0.014	2	1.71	0.020	0	0	0	2	1.71	0.020
P[b]		NS			NS			NS			0.016	
IRR (95% CI)		0.49	(0.056–1.96)		0.43	(0.04–2.25)		0	(0–6.93)		0.30	(0.03–1.26)
Per-protocol analysis												
PRE	27	3.32	0.030	8	6.25	0.052	10	1.76	0.017	17	8.25	0.071
POST	1	0.65	0.007	1	0.86	0.010	0	0	0	1	0.86	0.010
P[b]		0.048			0.025			NS			0.003	
IRR (95% CI)		0.24	(0.006–1.45)		0.19	(0.004–1.43)		0	(0–6.93)		0.14	(0.003–0.90)

[a]Subsample consisting of 244 patients assuming zoledronate and 78 patients assuming pamidronate and then zoledronate.
[b]Fisher's exact test.
ONJ, osteonecrosis of the jaw; IP, incidence proportion; IR, incidence rate; NS, not significant; IRR, incidence rate ratio; CI, confidence interval.

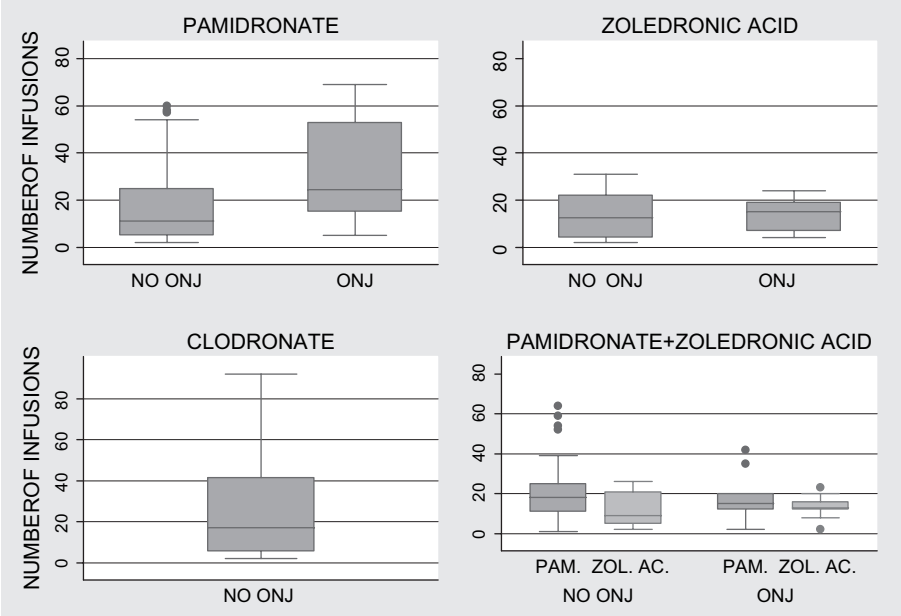

Figure 1. Box plots of the number of infusions by osteonecrosis of the jaw development and bisphosphonate administered. For patients taking pamidronate and then zoledronate, numbers of infusions of each drug are separated.

patients treated with ZOL alone or combined with PAM, with a 70% decrease in IR.

These data reflect mostly breast cancer patients and may probably be extrapolated for the other cancers, specially multiple myeloma which represents one of the most important group of patients with osteonecrosis, but which was underrepresented in this trial.

In agreement with data from the literature, the mean time to onset of this complication after the start of BP therapy is extremely variable (range 1–3 years) [25].

The minimum number of single-agent infusions at the appearance of oral abscess was four for ZOL alone, five for PAM alone and four for PAM and ZOL (i.e. within the first months of therapy and much <1 year).

According to the literature, the frequency of development of ONJ varies with the assumed drug and its dosage, with values ranging from 0.1% to 10% [27]. The percentage of patients treated with BP and developing ONJ is 3%–4% of patients with breast cancer and 7%–10% of patients with multiple myeloma [23, 34]. In the study by Durie et al. [34], ONJ was suspected in 6% of patients with myeloma and 8% of patients with breast cancer.

In agreement with data from the literature [27, 31], a dental extraction was the common denominator in all patients developing ONJ.

In our study, the IR of ONJ was 2.9% in PRE-Group and 1.4% in POST-Group, according to the ITT analysis of all patients treated with any BP. If we consider the PP analysis,

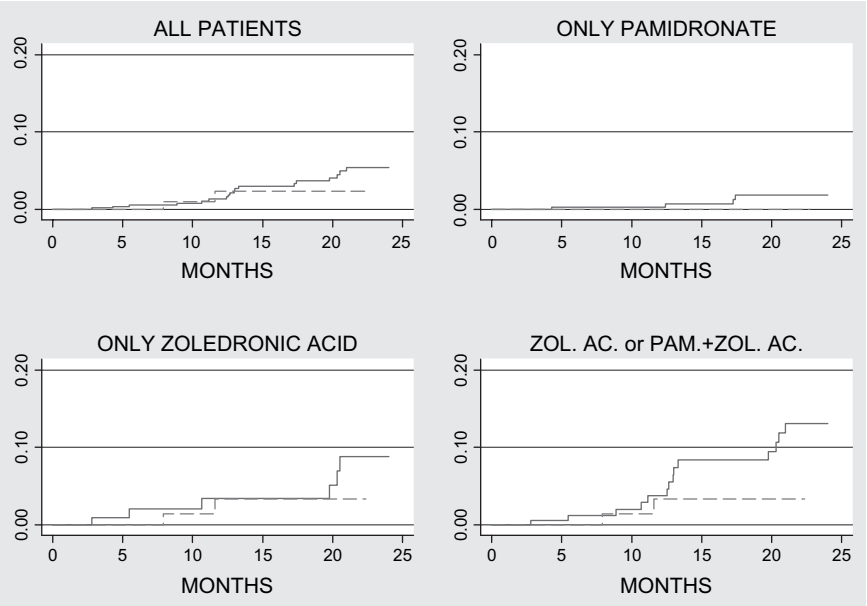

Figure 2. Time to onset of osteonecrosis of the jaw by prevention programme implementation and bisphosphonate administered. Data are censored at 24 months. Intention-to-treat analysis. Solid lines: patients before prevention programme; dashed line: patients after prevention programme.

excluding then the patient of the POST-Group who underwent a dental avulsion before starting BP treatment but refused to take antibiotics, the IR becomes 3.0% in PRE-Group and 0.7% in POST-Group, i.e. significantly decreased. This confirms the guidelines previously published on ONJ prevention [28, 29, 31].

The publication of clinical recommendations about the importance of dental prevention led us to a closer cooperation with the hospital DT, with the purpose of understanding together the relevance of ONJ and starting a preventive treatment. The DT contacts in turn the caring dentists of patients in order to enable the accurate application of the treatment protocol and to set an educational route.

As far as we know, this is the first study carried out to assess if dental preventive measures before BP infusion can play a role in decreasing ONJ incidence, as reported in the published clinical practice recommendations [28, 29, 31].

The design of our study has some limitations:

- The retrospective, nonsystematic gathering of data on ONJ onset in preprevention cases led probably to an underestimation of their number in this subpopulation.
- The short duration of the prospective part of the study (prevention programme application) might have resulted in a decreased power of the carried out tests and in an underestimation of the ONJ incidence in the POST-Group (potentially too short follow-up time for the complication to emerge and lower total dose of BPs assumption).
- This is not a controlled study; though, in view of the role of prevention in decreasing the incidence of ONJ, it can no longer be ethically proposed conducting a controlled study where patients are randomised to receive preventive dental measures or not. Therefore, in spite of the methodological limitations of our study, such a kind of study is the only feasible one that gives the strongest evidence possible.

conclusions

The findings of our study support the published clinical recommendations, showing an important reduction of ONJ occurrence in those patients who receive appropriate dental preventive measures by a DT working in collaboration with the oncologists.

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