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Osteonecrosis of the jaws by intravenous bisphosphonates and osteoradionecrosis: A comparative study

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Abstract

Aims: We analyze the possible clinical differences between bone jaw exposed areas in ONJ (osteonecrosis of the jaws) and ORN (osteoradionecrosis).

Patients and method: Group 1 was composed with 53 ONJ cases and group 2 with 20 ORN cases. In both groups we analyzed, the major size of the exposed bone areas, the number of exposed areas, the location on the jaws and the presence of others associated and severe complications, such as skin fistulas and jaw fractures. We also investigated the possible local aetiology or trigger factor of the lesions.

Results: The major size of the bone exposed areas was 2.29±2.02(mean ± std.dev) in group 1 and 2.7±2.9 (mean ± std.dev) in group 2 ($p>0.05$). The number of exposed areas was 1.8±1.34 (mean ± std.dev) in group 1 and 1.2±0.55 (mean ± std.dev) in group 2 ($p>0.05$). There were more fractures in the second group (20%) ($p<0.05$), and skin fistulas (35%) ($p<0.05$). We found more patients in group 1 in which the dental extraction was the local aetiology of the bone necrosis (35 cases, 66.03%), while in group 2 there were 8 (40%) ($p<0.05$).

Conclusions: In our study with ONJ there were not differences in the major size of the bone exposed areas, but there were more lesions per patient than in group with ORN. The severity of the complications, such as jaw fractures and skin fistulas were higher in ORN, and in this group it was more frequent the spontaneous lesions than in the ONJ where it is more frequent following dental extractions.

Key words: *Bisphosphonates, osteonecrosis, osteoradionecrosis, jaws.*

Introduction

Bisphosphonate treatment for malignant diseases or osteoporosis is common. In the case of malignant diseases, bisphosphonates are usually given intravenously to manage hypercalcemia and bone metastases, such as in the case of multiple myeloma and metastatic breast cancer (1,2). In the case of osteoporosis these drugs are prescribed orally (3,4).

Marx in 2003 (5) reported some of the first described cases of osteonecrosis (osteochemonecrosis) of the jaws (ONJ) As a severe complication from the use of bisphosphonates. Since then there have been many reports (6-11) and Pubmed contains more than 195 articles on this subject.

In ONJ, the jaw bone is exposed with one or several necrotic areas, some cases arising after surgery such as a tooth extraction, but in other cases the origin is unknown (12-14).

ONJ is similar in clinical appearance to osteoradionecrosis (ORN), where the lesions develop after radiotherapy to the head and neck area, typically for the management of malignant tumours. (15-19). ORN mainly occurs when the radiation dose exceeds 65 Gy. The risk to ORN last for many months after radiation treatment. (15).

Although both conditions, ONJ and ORN have been widely described there are no substantial studies published that compare them in terms of the characteristics of the bone lesions, their aetiology and other clinical aspects. The aim of this study was to determine what are the differences if any between ONJ and ORN.

Material and Methods

We studied two groups. The first (group 1) composed of 53 patients who had developed osteochemonecrosis of the jaws caused by intravenous bisphosphonates for the treatment of malignant diseases (ONJ). We followed the accepted criteria (20) to establish the diagnosis of ONJ. Group 2 was a sample of 20 patients with osteoradionecrosis of the jaws (ORN), the diagnosis being established following the criteria described by Thorn et al. (15).

In both groups we examined the overall size of the exposed bone area, the number of exposed areas, other clinical characteristics such as the location in the jaws and the presence of other severe complications, such as skin fistulas and jaw fractures. We also investigated the possible local aetiology or trigger factors of the lesions. We analyzed the possible association between variables by the x2 test and the Student t test to compare the differences between the means in both groups, when the data follow a normal distribution. We considered a difference statistically significant when p was < 0.05.

Table 1. Tumor and drugs in group on bisphosphonates.

		Number of cases	%
Tumor	Breast	25	47.2
	Multiple myeloma	21	39.6
	Prostate	5	9.4
	Lung	1	1.9
	Kidney	1	1.9
Bisphosphonate	Zoledronic acid (Zometa ®)	51	96.2
	Pamidronate (Aredia ®)	35	66
Other drugs	Corticosteroids	20	41.7
	Talidomide	5	10.4
	Interpheron	7	14.6
	Chemotherapy	46	95.6

Results

Most of the patients in Group 1 (ONJ) had either metastatic breast carcinoma or multiple myeloma (Table 1). In 50 cases the number of months on bisphosphonate treatment was known, the mean being 33.4 ± 17.8 (std. deviation), (range 10 to 84 months). In most instances (51 out of the 53 cases: 96.2%), the patients had been treated with Zoledronic acid (Zometa ®) while there were 18 (34%) cases on Pamidronate (Aredia ®).

In Group 2 (ORN), all the patients had developed at least one ORN area, and most patients (18 cases; 90%) had oral squamous cell carcinoma and the rest had oral lymphomas. The mean radiation dose was 64.85 Gy ± 7.9 (std. deviation), (range 48 Gy to 85 Gy).

The mean ages in both Groups were not statistically different ($p > 0.05$) but there was a significantly higher number of females in Group 1 ($p < 0.05$) (Table 2).

Tobacco and alcohol habits; exposed bone locations, number, and overall size; and other clinical characteristics are shown in table 2.

Discussion

Osteonecrosis caused by bisphosphonates (ONJ) or radiotherapy (ONR) manifest primarily by bone exposure. (5,15) Habits such as tobacco and alcohol have been associated with an increased risk of developing areas of ORN but have not been recorded in ONJ. We found in our studio that 22.6% ONJ patients were smokers, compared with 60% in the ORN group ($p< 0.05$).

Thorn et al. (15) found 92% of patients with ORN were smokers or had been before their radiotherapy. At the time of exposure bone 63 (82%) cases were smokers and 62% of those had a consumption of 10 or more ciga-

Table 2. Comparation of the clinical characteristics in ONJ and ORN.

	Group 1: Bisphosphonates (53 cases)				**Group 2: Osteoradionecrosis (20 cases)**				
Age	63.4				62.2				t=0.42 p>0.05
Gender	Male		Female		Male		Female		χ^2 = 10.37 p<0.05
	20 (37.7%)		33 (62.3%)		16 (80%)		4 (20%)		
Tobacco	12 (22.6%)				12 (60%)				χ^2 = 9.32 p<0.05
Alcohol	10 (19.2%)				8(40%)				χ^2 = 3.23 p=0.06
Location	Mandible								
	44(83.01%)				16(80%)				χ^2 = 3.34 p=0.81
	Upper jaw								
	20(37.7%)				4(20%)				χ^2 = 2.59 p=0.62
Number of the bone exposed areas	1.8±1.34 (mean ± std.dev)				1.2±0.55 (mean ± std.dev)				t=1.79 p=0.07
Major size of the bone exposed areas	2.29±2.02(mean ± std.dev)				2.7±2.9 (mean ± std.dev)				t=-0.62 p>0.05
Jaw fractures	2(1.8%)				4(20%)				χ^2 = 7.14 p<0.05
Skin fistulas	1(3.7%)				7(35%)				χ^2 = 12.53 p<0.05
Etiology	Ext.	Imp.	Prot.	Unk.	Ext.	Imp.	Prot.	Unk.	
	35	1	5	12	8	-	2	10	χ^2 = 12.53 p<0.05

Ext.: Extraction; Imp.: Implant; Prot.: Prosthesis; Unk.: Unknown etiology

rettes a day. With regard to alcohol consumption 54% patients consumed alcohol in varying amounts per day at the time of ORN. Kluth et al. (16) found a relationship between the continuous consumption of alcohol and tobacco and the development of ORN. Marx (12) reported that 83% of his patients with ORN were smokers.

Several studies (5-9) have demonstrated the higher incidence of ONJ in the mandible, both in intravenous and orally prescribed bisphosphonates, and we could not find differences in between ONJ and ORN in the location (p>0.05). ORN lesions are known to have a predilection for the molar area of the mandible (15, 21) though others found in the symphysis to be the most common location (17).

In the present study we analyzed the overall size of bone lesions and did not find a difference between ONJ and ORN (p>0.05), the mean size being 2.29 cm in ONJ and 2.7 cm in ORN. Thorn et al. (15) measured the radiotransparency in the ortopantomograph in patients with ORN and found that almost half of the cases had between 2-5 cm^2 (41%) followed by areas 0-2 cm^2 (34%), 5-10 cm^2 (18%) and greater than 10 cm^2 (8%). In patients with ONJ we found in our previously published study (9) that the average size of the exposed jaw bone areas was 1.96 cm.

We also found in our previous article (9), a mean of 2.3 exposed areas in each patient and a number of authors have reported a greater number of exposed bone areas in ONJ (5-8). In the present study the number of areas was higher in the ONJ group with an average of 1.8±1.34, while in the ORN it was 1.2±0.55 but the difference was not statistically significant.

In the present study fractures were found in 1.8% of our ONJ patients but significantly more frequently in 20% of ORN cases (p<0.05). In the case of ORN the study of Thorn (15) reported that the presence of pain in their ORN cases did not clearly correlate with the size of the lesion, but was always present when there were fractures and fistulas (18).

In the present study extractions were the most important aetiologic factor in ONJ but, in ORN, there were many cases (50%) in whom the lesions appeared spontaneously (Table 2). This is an important and statistically significant distinction between both processes. (p<0.05). Marx et al. (12) also reported that 37.8% of their patients with ONJ were associated with dental extractions, 29% due to periodontal disease and 11% to periodontal surgery.

The present results differ from the comparative study conducted by Walter et al. (21) but with a lower number of cases in the ONJ group than in ours, where dental treatments were the trigger for ONJ in 13 out of 17 cases, but in the ORN group the importance of the dental treatments as a trigger had less importance, being seen in only 14 of 45 cases. This difference is difficult to explain.

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