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Prevalence of Osteonecrosis of the Jaw (ONJ) in Patients Exposed to Bisphosphonates at a University Hospital in Marrakech

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Abstract

Background: Bisphosphonates are compounds similar to inorganic pyrophosphates, with anti-angiogenic, anti-inflammatory, anti-bone resorption, and antitumor effects. They are used to prevent bone metastases in cancer and treat osteoporosis. However, a major side effect is osteonecrosis of the jaw (ONJ), first reported in 2003, which is the exposure of necrotic bone in the mouth, often accompanied by infection. Prevention and treatment of ONJ remain challenging due to a lack of reliable epidemiological data on its incidence and risk factors. The aim of our work is to estimate the prevalence of bisphosphonate-related osteonecrosis of the jaw (BRONJ) and to analyze its correlations with different risk factors reported in the literature. **Methods:** A retrospective observational study was conducted in the Oncology, Rheumatology and Maxillofacial Surgery Department of the Mohamed VI University Hospital; Marrakech, based on complete medical records during the period 2017 to 2022, as well as consultations of patients under bisphosphonates in these departments during July and August 2022. Statistical analysis was performed using IBM SPSS version 16.0. **Results:** Of the 107 patients included in this study, 60.7% were women, and 56.1% were between 40 and 65 years old. 100% of the patients suffered from a general pathology. Regarding treatment with BP, 103 patients were treated with Zoledronate, 4 with Risedronate, and 5 with Ibandronate. 103 patients received this treatment intravenously, while 4 patients received it orally. Regarding Oral health, only 12.1% of patients reported a poor oral health. 99.1% of patients were informed of the need for oral preparation prior to BP treatment, but only 71.02% received dental treatment, mainly tooth extraction. None of the patients were diagnosed with

BRONJ. **Conclusions:** While the global incidence of ONJ ranges from 0.8% to 12%, our finding is zero. Most previous studies are retrospective with limited patient numbers like our study. To accurately assess the prevalence of ONJ, further prospective epidemiological studies with standardized protocols and thorough follow-up over several years are essential.

Keywords

Bisphosphonate-Related Osteonecrosis of the Jaw, Bisphosphonates, Osteonecrosis of the Jaw, Prevalence

1. Introduction

The Bisphosphonates (BPs) are structural analogs of inorganic pyrophosphates, discovered in the 1960s. Their main action is to inhibit bone resorption by inducing cellular apoptosis of osteoclasts, resulting in increased bone mineral density, reduced serum calcium levels, and consequently decreased bone remodeling [1].

Administered intravenously (IV), BPs are indicated for managing multiple myeloma, preventing bone complications in certain advanced malignant tumors, treating malignant hypercalcemia, and treating Paget's disease. BPs also constitute the most widely prescribed low-dose oral treatment for benign diseases, including postmenopausal osteoporosis in women at high risk of fracture, male osteoporosis, and corticoid-induced osteoporosis [2]. Despite the preventive and significant effect these drugs have on the quality of life of cancer patients, the use of BPs can lead to side effects [3]. In 2003, the first case of osteonecrosis of the jaw (ONJ) was reported. Wang *et al.* [4] were the first to describe three cases of breast cancer patients who developed ONJ, while Marx *et al.* [5] reported ONJ in 36 patients treated with BPs. In 2004, Ruggiero *et al.* [6] described 63 complications of this pathology possibly related to BP treatment. Since then, numerous cases of ONJ have continued to be reported in patients treated with BPs.

Only since November 2004, have pharmaceutical companies marketing these molecules issued warning messages to healthcare professionals about the dangers of this treatment. Since then, multiple communications have been sent by health authorities to the concerned practitioners.

These reports have drawn the attention of the medical community to this condition, but they have lacked information on incidence and risk factors.

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS) [2], ONJ is defined by the presence of exposed bone in the maxillofacial region persisting for a minimum of eight weeks in patients receiving BP therapy, without a history of local radiotherapy or maxillary metastases. These diagnostic criteria are currently subject to international consensus [7].

This clinical definition distinguishes BP-associated ONJ from healing delays, osteoradionecrosis, and maxillary metastases or malignant processes. It also

considers the lifespan of BPs in bone tissue, as they have a lingering effect with a long half-life.

BP-related ONJ is a type of osteomyelitis highly resistant to treatment exclusively involving the jaw bones of patients. Powerful BPs containing mainly nitrogen are more often associated with this pathology when administered intravenously [8].

Although research on BP-associated risk factors and the pathogenesis of osteonecrosis remains limited, epidemiological studies have established a circumstantial association. The prevalence of osteonecrosis is difficult to assess and appears to differ depending on the prescribed molecule, dosage, and duration of treatment [2] [9].

However, very little data concerning the frequency of osteonecrosis in the Moroccan population exist, following our initial study at the Casablanca University Hospital [10], which reported a prevalence of 1.9%, we conducted the present study to determine the prevalence of ONJ at the Marrakech University Hospital.

An observational retrospective study was conducted within the Oncology, Rheumatology, and Maxillofacial Surgery department of UHC Mohamed VI in Marrakech, this study was based on complete medical records from 2017 to 2022 as well as consultations of patients undergoing BP treatment in these departments during July and August 2022.

2. Materials and Methods

2.1. Study Design

A retrospective observational study through the analysis of patients' medical records, conducted multicentrically, was carried out at the Mohamed VI University Hospital in Marrakech, Morocco between July 2022 and August 2022.

2.2. Patients and Sampling

The target population consisted of all patients hospitalized or followed up between 2017 and 2022 in the following four departments:

- Oncology Department, Mohamed VI University Hospital, Marrakech.
- Rheumatology Department, Mohamed VI University Hospital, Marrakech.
- Maxillofacial Surgery Department, Ibn Tofail.
- Surgical Odontology Department, Ibn Zohr Hospital.

To create a representative sample, a random survey was conducted using a two-phase sampling method: the principle involves collecting information from an initial sample, followed by the collection of additional information from a smaller sample or sub-sample. This is a multi-level survey approach used when access to the list of individuals in the study population is not available.

In the first phase, patients were divided into two categories:

- Patients treated with bisphosphonates (included).

• Patients not treated with bisphosphonates (excluded).

In the second phase, a simple random sampling of the secondary units including patients treated with BPs was conducted, taking into account the distribution according to the departments. Out of 487 patients across the five departments, 107 patients were selected.

2.3. Inclusion Criteria

Patients on BPs or with a history of BP treatment with complete medical records or present at the consultation.

2.4. Exclusion Criteria

Patients treated with head and neck radiotherapy, and patients with incomplete medical records or absent at the consultation.

2.5. Data Collection

The data collection is hybrid, initially involving the collection of patient data from records using a questionnaire, followed by a clinical examination of the oral cavity and an assessment of oral health.

The questionnaire designed for this study is based on factors and variables identified in the literature, and structured into five sections: 1) socio-demographic data, general health, lifestyle habits, and reason for consultation; 2) medical history, including bisphosphonate use, route and administration regimen, and duration of exposure; 3) dental history and assessment of oral hygiene; 4) history of osteonecrosis of the jaw (ONJ), including onset date and site; 5) clinical and supplementary examinations to establish an accurate diagnosis and determine the appropriate therapeutic approach.

The results analysis was performed using IBM SPSS Statistics version 16.0 software.

It included a descriptive part of the studied population. All variables are described based on their absolute (n) and relative frequency (%).

Before carrying out this study, it was presented and validated by the faculty Thesis Committee which is our institution's ethics committee. All participants were informed that the questionnaire was anonymous, and consent was obtained after explaining the purpose and content of the study.

3. Results

3.1. Population Characteristics

Data were collected and analyzed for 107 patients, 91.6% from the oncology department, 8.4% from the rheumatology department, and 0% from the maxillofacial surgery department of the UHC Mohamed VI de Marrakech. 60.7% were women, and 56.1% were between 40 and 65 years old. 100% of patients suffer from a general pathology (Table 1).

Table 1. Baseline population characteristics.

Population Characteristics		N	Percentage %
Sex	Female	65	60.7
	Male	42	39.3
Interval age (years)	<20	0	0
	20 - 40	11	10.3
	40 - 65	60	56.1
	>65	36	33.6
Residency	Urban	89	83.20
	Rural	18	16.8
Obesity	Yes	18	16.80
	No	89	83.20
Toxic habits	Tobacco	17	15.88
	Cannabis	8	7.48
	Alcohol	17	15.88
	No toxic habits	65	60.76
Family history	Tumor pathology	26	24.3
	ONM	0	0
	Without history	81	75.7
General pathology	Tumor pathologies	91	85
	diabetes	11	10
	HTA	8	7.4
	Chronic renal failure	2	1.8
	Hyercholesterolemia	1	0.9
	hypothyroidism	1	0.9
	Asthma	1	0.9
	Thrombophlebitis	1	0.9
Received treatment for underlying pathologies	Chimiotherapy	95	88.7
	Hormonotherapy	20	18.6
	Immunotherapy	12	11.2
	Corticotherapy	83	77.5
	Oral hypoglycemic	11	10.2
	Antihypertensive	6	5.6
	Anticoagulant	1	0.9

In terms of treatment with BP, 103 patients were treated with Zoledronate, 4 with Risedronate, and 5 with Ibandronate. The most frequent indication is bone metastasis following breast cancer with 51 patients, followed by metastatic adenocarcinoma of the prostate with 30 patients. 103 patients received this treatment

intravenously, while 4 patients received it orally. The administration schedule was divided into 1 time per month for 80 patients and 1 time per week for 4 patients. (Table 2).

Table 2. BPs treatment characteristics.

		N	Percentage %
Molecule administered	Zoledronic acid	103	96.2
	Risedronate	4	3.7
	Ibandronic acid	5	4.6
Route of administration	IV	103	96.3
	Per os	4	3.7
Frequency of administration	1 time per week	4	3.7
	1 time per month	80	74.8
	1 time/3 months	23	21.5
	1 time/6 months	0	0
Indication	Breast cancer	51	47.66
	Prostate cancer	28	26.17
	Postmenopausal osteoporosis	9	8.41
	Lung cancer	7	6.54
	Giant cell bone tumors	2	1.87
	Paget's disease	2	1.87
	Kidney cancer	2	1.87
	Bladder cancer	2	1.87
	Uterus cancer	2	1.87
	Stomach cancer	2	1.87

3.2. Clinical Evaluation

Prevalence:

Osteonecrosis of the jaw (ONJ) was not diagnosed in any patients in the study (Confidence interval at 95%).

Clinically, an average oral state was observed in 77.6% of patients, while 12.1% presented with a poor oral state. 99.1% of patients were informed of the need for oral preparation before treatment with BP, but only 71.02% received dental care, mainly tooth extraction (Table 3).

Table 3. Oral health status and dental care.

		Number of cases	Percentage %
Hygiene frequency	Regular brushing	43	49.5
	Irregular brushing	44	50.5

Continued

Oral health status	Good	11	10.3
	Medium	83	77.6
	Bad	13	12.1
Check-up dentist before BPs treatment	Yes	105	98.1
	No	2	1.9
Dental care carried out before BPs treatment	Dental extractions	53	49.5
	Conservative care	48	44.8
	Prosthetic treatment	4	3.73
	Periodontal care	51	47.6
Occurrence ONJ	YES	0	0
	NO	107	100

4. Discussion

Despite the significant preventive benefits the bisphosphonate offers for cancer patient's quality of life, their use can result in side effects, especially osteonecrosis of the Jaw (ONJ). In 2003, Wang *et al.* [4] described three cases of breast cancer patients who developed ONJ, while Marx *et al.* [5] reported ONJ in 36 patients treated with bisphosphonates.

Patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ) exhibit multiple risk factors, including specific characteristics of BPs (molecule administered, route of administration, dose, duration of exposure), concurrent drug therapies (such as corticosteroids and chemotherapy), and local factors (such as dental infections, invasive dental procedures, and oral health conditions) [11]-[13]. Additional risk factors contributing to the development of BRONJ include demographic characteristics such as sex and age, toxic habits like smoking and excessive alcohol consumption, and underlying general pathologies, such as diabetes, autoimmune diseases, and cancer [2] [14] [15]. Our study aims to investigate the prevalence of BRONJ in a Moroccan population and identify patient profiles associated with its onset.

The 487 patients in our study were selected from the 5 hospital departments. Those with missing or inconsistent data were excluded from the analysis, leaving 107 patients included, all of whom are treated with BP. Overall, we did not diagnose any cases of osteonecrosis of the jaw related to this group of drugs (CI at 95%).

A review of the literature shows much higher incidences and prevalences than those found in our study [1] [2].

However, it is possible to find studies where the statistics are very similar. No cases of ONM were reported in the randomised controlled trial by Gnant *et al.* [16].

Some authors state that it is difficult to define the prevalence broadly or accurately, as it is estimated that undiagnosed pathology in the population is around

25%, mainly in stage 0. It is therefore possible that the true number is higher [17] [18].

Similarly, Salvatore L Ruggiero *et al.* conclude that ONM is difficult to assess and appears to vary according to the drug prescribed, its route of administration, dosage and total duration of administration [2].

Due to the low frequency of the disease, studies with small samples (<500 subjects) should be interpreted with caution, as was the case in our study. It is particularly difficult to obtain good estimates of disease frequency when studying low-frequency events such as BP-induced ONM.

We compared our results with other international studies interested in describing the prevalence of BP-induced ONM.

According to the American Society for Bone and Mineral Research (ASBMR), the global incidence was estimated to be between 1% and 10% in 2007 [19].

In his PubMed-based review, Filleul identified more than 2400 cases of ONM between 2003 and 2009. The majority of these were treated with IV BP [20].

A study by Joan C Lo in the USA reported 9 cases of ONM in a sample of 8572 subjects, giving a prevalence of 0.10% [21].

Another study conducted in Australia between 2004 and 2005 identified 158 cases of ONM. These were mainly patients with bone malignancies (72%) and the main trigger was tooth extraction (73%).

The incidence of ONM in bone malignancies treated mainly with intravenous zoledronate or pamidronate is 1 in 87 to 114 (0.88% to 1.15%). When extractions were performed, the calculated incidence of ONM was 1 in 11 to 15 (6.67% to 9.1%).

The mean time to onset of ONM was 12 months for zoledronate and 24 months for pamidronate and alendronate.

In osteoporotic patients, mainly on weekly oral alendronate, the frequency of ONM is 1 in 2260 to 8470 patients (0.01% to 0.04%). When extractions are performed, the calculated frequency is 1 in 296 to 1130 cases (0.09% to 0.34%).

The frequency of ONM in cases of Paget's disease is 1 in 56 to 380 (0.26% to 1.8%). When extractions are performed, the calculated frequency of ONM is 1 in 7.4 to 48 (2.1% to 13.5%) [22].

A prospective study by Frédéric Hallmer *et al.* reported 55 cases of ONM in Sweden. The prevalence of ONM was estimated to be 0.043% in patients treated with oral BP and 1.03% in patients treated with intravenous BP [23].

A literature search was conducted by Yan-Li Yang *et al.* using the PubMed, EMBASE, Cochrane and Web of Science libraries. They combined the incidence of ONM in 24 retrospective studies to analyse the incidence of ONM caused by BP and to assess the relative risk compared with the control group. The analysis found that the overall incidence of ONM in patients exposed to PB was 2%, which was statistically significant and higher than that observed in the control group [24].

Nationally, in a similar study we conducted at the Ibn Rochd University Hospital in Casablanca, we found 2 cases of ONM due to intravenously administered

BP, with a prevalence of 1.9% [10].

Another retrospective study conducted at the Department of Maxillofacial Surgery and Stomatology at the Mohamed V Military Hospital in Rabat, over an 8-year period from 2009 to 2017, reported an incidence of approximately 9.13% (36 cases out of 394 patients) [25].

In our case, the incidence of ONM during the study period was zero compared to other studies in different countries. This may be explained by several factors:

• The prescribing physician's interest in conditioning the oral cavity before starting BP treatment.

• Prescribers' communication with dentists and monitoring of the oral condition of patients applying for BP.

• The provision of a dental unit within the Ibn Zohr department for the care of patients applying for BP.

• The agreement of the dentist, which is essential for the initiation of BP treatment.

• The patient's commitment to follow the dentist's instructions carefully.

In the majority of departments where our study was carried out, the physicians prescribing BP, *i.e.*, in the oncology, rheumatology and maxillofacial departments, are aware of the significant risk that IV BP treatment poses for the development of osteonecrosis of the jaw. For this reason, physicians urge patients to consult their dentists first, whether in the public or private sector, and to perform a comprehensive and detailed intra-oral assessment before initiating treatment with BP.

Consistent with published reports, tooth extraction is the predominant oral factor associated with the development of ONM. This finding highlights the importance of assessing patients' oral health and, if necessary, providing preventive dental care before initiating treatment [2] [26].

5. Conclusions

Data on ONJ due to BP treatments remain modest. However, the diagnosis and staging of this pathology, the identification of risk factors, and the development of prophylactic approaches have progressed over the last decade. Although rare, ONJ occurs mainly in breast cancer and multiple myeloma patients treated with IV BPs. High cumulative doses of BPs, poor oral health, and dental extractions during treatment are significant risk factors for the development of this pathology.

It is essential to emphasize the importance of prospective studies with significant sampling to identify the risk factors associated with ONJ occurrence and to determine the categories of patients at risk who require adaptation of this therapy.

We conclude that even if the prevalence in our study is null, the risk of developing ONJ in the Moroccan population remains high and requires individualised management and regular monitoring of each patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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