



## Research Article

# Can Docetaxel Concomitant Administration with Bisphosphonates be Considered as a Risk Factor for Osteonecrosis of the Jaw in Metastatic Breast Cancer Patients? A Preliminary Study

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### Abstract:

Osteonecrosis of the jaws (ONJ) is rare complication of bisphosphonates use which was described for the first time by Marx in 2004. Bisphosphonates (BP) are stable derived of inorganic pyrophosphate which had an antiresorbant effect in the bone making them very useful in bone metastasis, especially with the third generation of bisphosphonates. Many risk and trigger factors have been described as predisposing to the development of ONJ. The aim of this work is to show if Docetaxel administration can be considered as a predisposing factor to develop ONJ. We report a series of 11 patients treated during 5 years in the maxillofacial surgery department in HU Habib Bourguiba Sfax – Tunisia for ONJ due to BP use for breast cancer bone metastasis. Those patients were divided into two sub-groups: with and without concomitant Docetaxel administration. All patients' data (age and delay of appearance of ONJ, cumulative doses and trigger factors) were collected and analyzed. It was found that patients treated with Docetaxel in association to bisphosphonates developed ONJ in earlier age, with a lower cumulative doses of zoledronic acid within a shorter delay period. ONJ occurred in these patients even in the absence of trigger factor and intrinsic risk factors.

**Keywords:** Bisphosphonates; Osteonecrosis; Jaws; Docetaxel

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## Introduction

Bisphosphonates (BP) are a stable derived of Inorganic Pyrophosphate widely used in medical domain due to its antiresorptive proprieties especially in bone metastasis. Its use was addicted with the appearance of multiple complications such as osteonecrosis of the jaws. Many studies were realized to study its characteristics, its risk factors and its appearance delays. Searching PubMed data base using “bisphosphonates+docetaxel+ONJ” had found only five articles. In this five years retrospective study, we are trying to find if concomitant Docetaxel administration with BP may affect epidemiological characteristics of ONJ.

## Patients and methods

During five years, all women patients' data treated for bisphosphonates related osteonecrosis of the jaws in our maxillofacial surgery department were noted. The following parameters were collected: age, bisphosphonates doses, delay of ONJ appearance, trigger factor. Data analysis and statistic results were realized using XLSTAT program.



**Figure 1** Clinical presentation of oral ulceration and bone exposure in ONJ due to bisphosphonates in a 73 year's old woman.

## Results

During 5 years, eleven patients were treated in our department of maxillofacial surgery for bisphosphonate related osteonecrosis of the jaws (Figure 1). Five of those have a history of concomitant Docetaxel administration during bisphosphonates treatment. All our patients were treated with zoledronic acid with an intravenous administration. The mean age in our patients when ONJ appearance was 63,18 years. It was found that it was lower in patients treated with bisphosphonates in

association with Docetaxel: 59 years versus 68,5 years in those treated only with bisphosphonates (Student tests' p-value = 0,0013 with an alpha equal to 0,05). Cumulative doses of zoledronic acid were about 70,36 mg in average for all patients (40 to 104 mg). They were more important to lead to the development of ONJ in patients treated with bisphosphonates only: 86 mg versus 59,5 mg in those treated by both molecules (p = 0,0196).

The delay of appearance of ONJ after the beginning of bisphosphonates treatment was about 24,81 months in average. It was shorter in patients treated with concomitant administration of bisphosphonates and Docetaxel (22,5 months in average) than those treated only with bisphosphonates (31 months) (p = 0,0251). It was found that ONJ appeared in 2 cases (40%) even in the absence of triggers factors in the first patients group. However, in the second group, a trigger factor was always present.

In this study, we found that patients treated with bisphosphonates in association to Docetaxel developed ONJ in earlier age, with a lower cumulative doses of zoledronic acid within a shorter delay period. ONJ occurred in these patients even in the absence of trigger factor and intrinsic risk factors.

The following table contains the summary of our patients' observations (Table 1):

Table 1 All observations' data (\* Patients treated with concomitant BP and TXT administration, \*\* Patients treated with BP only).

	Age (years)	BP Cumulative doses (mg)	ONJ Apparition delay (months)	Associated risk factors	Trigger factor
Case 1*	48	44	14	None	Tooth extraction
Case 2*	49	40	10	None	None
Case 3*	58	40	31	Obesity	Tooth extraction
Case 4*	73	95	32	Diabetes	None
Case 5*	56	63	17	Diabetes	Infection
Case 6**	66	100	29	Diabetes Obesity	Tooth extraction
Case 7**	76	72	34	Diabetes Obesity	Infection
Case 8**	83	92	24	Diabetes Obesity	Tooth extraction
Case 9**	56	104	43	None	Infection
Case 10**	59	76	23	Obesity	Tooth extraction
Case 11**	71	48	17	None	Tooth extraction

## Discussion

Bisphosphonates related osteonecrosis of the jaws can be defined by the association of 4 elements: an ulcer of the oral mucosa persistent for more than 8 weeks in patients treated with bisphosphonates who don't have a history of facial radiotherapy and no maxillary bone metastasis [1]. Its prevalence seems to be difficult to assess [2]. It differ according to the prescribed molecule, its administration route, the dosage and the total administration period. Woo and col. revealed that ONJ prevalence vary from 6 to 10% in patients treated for malignant tumors with intravenous bisphosphonates [3]. It was also

described after oral route bisphosphonates with lower rates (from 1case/20000 patients to 1case/110000 patients per year of bisphosphonates treatment) [4]. Aragon-Ching and col. showed a relatively high incidence of occurrence of ONJ in patients with metastatic prostate tumors treated with zoledronic acid in association with Docetaxel compared with patients who received only zoledronic acid [5].

Generally, ONJ affects both sexes. However, its occurrence is more frequent in females [6, 7]. It primarily affects the elderly population with reduced capacity of bone turnover. In literature, median age was about sixty years (Table 2):

Table 2 Literature review of median age for ONJ appearance

Author	Year	Patients	Median age	Extremes
Merigo [8]	2006	29	69 years	45 – 83 years
Kos [9]	2010	34	65 years	42 - 80 years
Pichardo [10]	2013	51	66 years	45 – 84 years

The risk to develop ONJ is more important with zoledronic acid than other molecules (pamidronic, alendronic, risedronic and ibandronic acid) and this is due to his very important antiresorbant capacity [11, 12].

The cumulative dose is the total dose of bisphosphonates administered to the patient before the onset of ONJ. It is probably the most important predisposing factor for the occurrence and development of this complication. A prospective study by Bamias et al. [13] evaluated this relationship: it clearly showed that the impact of ONJ was correlated with the cumulative dose of bisphosphonates: the higher cumulative dose was, the greater the risk of appearance of ONJ increases.

According to Woo et al. study in 2006 [3], ONJ had occurred four months on average after the end of treatment with BP, with a range from 22 to 39 months. However, it may appear in varying timescales ranging from one month to several years[6, 14]. A study conducted in 2012 by Miyazaki et al. of 111 patients treated with both zoledronic acid and Docetaxel found that 8.1% of patients developed ONJ within a shorter delay (14.5 months in average)[15].

Other risk factors have been described as predisposing to ONJ such as diabetes (a study conducted between 2004 and 2006 found that 58% of patients suffered from ONJ were diabetics against 14% of diabetics in the general population) [16]. Obesity has also been associated with the risk of ONJ in Wessel et al. study [17].

Tooth extraction was reported as the most important trigger factor in more than half the cases of ONJ [18]. Other trigger factors can be found with variable frequencies such as a local infectious episode [19] or an oral surgery [20]. Note that ONJ can occur spontaneously [10, 21].

## Conclusion

Bisphosphonates related osteonecrosis of the jaws may occur earlier in patients treated with bisphosphonates in association with Docetaxel, with lower cumulative doses even in the absence of trigger factor and intrinsic risk factors. Larger series will be needed to establish a more significant relationship.

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