Effect of the cumulative dose of zoledronic acid on the pathogenesis of osteonecrosis of the jaws

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Abstract. Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is a severe bone disease for which the pathogenetic mechanisms and risk factors are not fully understood. The present study evaluated the data of 652 patients with bone metastasis that had undergone treatment with biphosphonates. Subsequently, 24 patients with BRONJ and 20 control patients without BRONJ that were treated with zoledronic acid were enrolled. It was found that BRONJ occurred in 3.6% of patients. The mean age and the administration of dental treatment were found to be significantly associated with BRONJ development (P=0.049 and P=0.013, respectively). The cumulative dose median in the BRONJ group was found to be significantly higher compared with the cumulative dose average in the control group (P=0.037). In addition, at the time of BRONJ development, improvement in the disease was determined to be better in the BRONJ group than in the control group (P=0.031). The present study determined that age, the existence of dental extraction and the cumulative dose of zoledronate were all important risk factors in BRONJ development.

Introduction

Bisphosphonates (BPs) are synthetic drugs used in the treatment of osteolytic bone disorders, including osteoporosis, Paget's disease, bone metastasis and multiple myeloma (MM) (1,2). BPs are pyrophosphate analogues with a high affinity for hydroxyapatite crystals (3,4). Once bound to hydroxyapatite crystals, BPs are slowly released during bone resorption and are subsequently internalised by osteoclasts. BPs inhibit osteoclastic bone resorption by interfering with osteoclast recruitment, differentiation and activity, and by promoting apoptosis (5-8). In addition, BPs are reported to exert direct antiproliferative and proapoptotic effects on cancer cells, thereby reducing bone metastases (9,10). Furthermore, BPs alter angiogenesis (11) and signal transduction between osteoclasts and osteoblasts (12). Depending on the presence or absence of a nitrogen atom, nitrogen-containing and non-nitrogen-containing BPs differ in the mechanism of action exerted on osteoclasts (13,14). Various BPs demonstrate different relative potencies and affinities for bone. The more recent nitrogen-containing BPs, such as zolendronic acid (ZA), are the most potent inhibitors of bone resorption (13,15). ZA is an agent that is administered intravenously, and patients receiving BPs intravenously are at a high risk of developing BP-related osteonecrosis of the jaws (BRONJ) (16).

Different definitions make it challenging to reach conclusions on the incidence of BRONJ, which has been reported to be <10% in various studies, and the associated risk factors (17-19). The present study reports a single-centre retrospective study that was performed to determine the frequency, risk factors and clinical presentation of BRONJ, and to also determine the progression of malignancy in patients with cancer treated by ZA once BRONJ develops.

Materials and methods

Study design. The present study reports a cross-sectional retrospective analysis of all individuals that were treated with a ZA and were diagnosed with BRONJ at Cukurova University Medical School (Adana, Turkey) between January 2008 and December 2012. The control group was randomly selected from the hemato-oncological patients at the same medical centre that were treated with ZA during the same period. All patients in the BRONJ and control groups were examined by the same oral and maxillofacial surgeon, to confirm or reject the diagnosis of BRONJ.

For the patient inclusion criteria, only patients with malignancy that were treated with 4 mg of ZA once every 3 or 6 weeks due to bone metastasis were included. The diagnosis of BRONJ was performed according to the 2009 update of the American Association of Oral and Maxillofacial Surgeons

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position paper (20), specifically exposed bone in the maxillofacial region that had persisted for >8 weeks. Patients with head and neck neoplasms and those who received radiotherapy to the head and neck region were excluded.

From medical records, interviews with patients, and questionnaires completed by patients, data were retrieved regarding the age and gender of patients, BP treatment, indication for treatment, drug administered, cumulative dose of agent, duration of treatment, concomitant steroid use, diabetes status, administration of dental treatment, smoking, use of angiogenic agents and state of disease during the development BRONJ in the patients. Written informed consent was obtained from all patients.

Statistical analysis. Statistical analyses in the present study were performed using the Number Cruncher Statistical System 2007 statistical software (NCSS, LLC, Kaysville, UT, USA). To analyze the data, in addition to the descriptive statistical methods of the mean and standard deviation, the independent *t*-test was used for the comparison of dual groups, and χ^2 and Fisher's exact tests were used for the comparison of qualitative data.

Results

Comparison between patients with and without BRONJ. A total of 24 patients that were administered with ZA were diagnosed with BRONJ between January 2008 and December 2012. Examinations performed by the same oral medicine specialist confirmed the diagnoses of BRONJ in all patients in the BRONJ group, and excluded BRONJ in all 20 patients in the control group. The gender distribution in the patients with BRONJ was 11 males and 13 females, and the control group consisted of 8 males and 12 females. In the patients with BRONJ, 37% (n=9) possessed ONJ of the mandibular, 20% (n=5) possessed ONJ of the maxilla, 20% (n=5) demonstrated multiple location involvement and 6% (n=5) possessed ONJ of unknown location. Out of the 24 patients with BRONJ and the 20 without BRONJ, the indications for ZA treatment consisted of breast cancer in 8 patients (33%), MM in 8 patients (33%), prostate cancer in 6 patients (25%) and other cancers in 2 patients (8%), comprising colon cancer and renal cell carcinoma (Table I). The median usage time of ZA was calculated to be 36 months (range, 12-84 months) in the BRONJ group and 27 months (range, 7-65 months) in the control group. No statistically significant difference was observed in the gender distribution of the BRONJ and control groups (P=0.697) or the diagnosis distribution of the BRONJ and control groups (P=0.0090).

The median age of the patients with BRONJ was significantly higher than that of the control group (P=0.049). The cumulative dose medians of the BRONJ group were found to be significantly higher compared with those of the control group (P=0.037; Table II). The median cumulative dose in the control group was found to be 88 mg (range, 36-120 mg), while in the BRONJ group the median cumulative dose was 126 mg (range, 72-168 mg).

In the BRONJ group, 13 out of 21 patients (61.9%) underwent dental treatment for their recent medical condition compared with 4 out of 18 patients (22.2%) in the control group, which was a statistically significant difference (P=0.013). When the incidences of diabetes mellitus (DM), smoking and steroid use were compared with those of the control group, the difference was not significant (P>0.05).

Table I. Characteristics of patients in the BRONJ and Control groups.

	Group		
	Control, n (%)	BRONJ, n (%)	P-value
Gender			
Female	12 (60.00)	13 (54.17)	0.697
Male	8 (40.00)	11 (45.83)	
Diagnosis			
Prostate	0 (0.00)	6 (25.00)	0.090
Breast	9 (45.00)	8 (33.33)	
MM	7 (35.00)	8 (33.33)	
Other	4 (20.00)	2 (8.33)	
Dental treatment			
No	14 (77.78)	8 (38.10)	0.013
Yes	4 (22.22)	13 (61.90)	
DM			
No	18 (94.74)	19 (95.00)	0.970
Yes	1 (5.26)	1 (5.00)	
Use of steroids			
No	13 (68.42)	17 (70.83)	0.864
Yes	6 (31.58)	7 (29.17)	
Smoker			
No	12 (75.00)	14 (77.78)	0.849
Yes	4 (25.00)	4 (22.22)	
Angiogenesis			
No	14 (73.68)	14 (70.00)	0.798
Yes	5 (26.32)	6 (30.00)	
State of disease			
Bad	11 (64.71)	4 (26.67)	0.031
Good	6 (35.29)	11 (73.33)	

BRONJ, Bisphosphonate-related osteonecrosis of the jaws; MM, multiple myeloma; DM, diabetes mellitus.

The percentage use of anti-angiogenic agents was 25% (n=6) in the BRONJ group, with thalidomide being used by 5 patients and bevacizumab being used by 1 patient, while the percentage use was 25% (n=5/20) in the control group, with thalidomide being used by four patients and bevacizumab being used by one patient. No significant difference was observed between the control group and the patients with BRONJ in the usage of anti-angiogenic agents (P=0.798; Table II).

In terms of the progression of the main malignancy during jaw osteonecrosis (ONJ) development, the results were 11/24 (45.8%) patients with BRONJ, and 6/20 (30%) control individuals, which demonstrated a significant difference (P=0.03).

Table II. BRONJ and control group data according to age and cumulative medication dosage.

Characteristic	Control group	BRONJ group	P-value
Age, years	54.3±7.83	60.17±11.07	
	52 (48.25-60.75)	60.5 (52.5-68.75)	0.049
Z, months	26.37±16.17	35.45±18.69	
	22 (16-40)	36 (22.5-42.5)	0.094
Cumulative dose, mg	94.32±65.31	135.45±76.35	
	88 (36-120)	126 (72-168)	0.037

Data are expressed at the mean ± standard deviation. BRONJ, bisphosphonate-related osteonecrosis of the jaws; Z, time of using zoledronic acid.

Discussion

BRONJ is a side-effect of BP therapy that is a relatively rare complication, but may have a notable impact on the quality of life of the affected patients. At present, the risk factors of BRONJ have been researched in numerous studies (15,21,22).

The present study determined that the frequency of BRONJ reached 3.6% in patients diagnosed with a malignancy that was treated using intravenous administration of ZA. In the literature, the rate of ONJ development in patients with malignancies treated using intravenous BP administration has been reported as 1.2, 3.1 and 5% in different studies (18,21-25). It was hypothesized that other factors such as the usage period of the medication, patient diagnoses, presence of chronic disease and presence of other medication usage may have had an effect on the difference in these rates (23). Also, the differences in ethnicity and particularly in dental hygiene habits affected the risk of BRONJ (15,21-24).

In the present study, 33% of the patients with ONJ were suffering from breast cancer (n=8), 33% (n=8) from MM, 25% (n=6) from prostate cancer and 8% (n=2) from other cancers, consisting of colon cancer and renal cell carcinoma. No significant association was detected between the diagnosed malignancy and the development of BRONJ (P=0.09). In certain previous studies, no association was found between the diagnosis and BRONJ, while in other studies it was identified that BRONJ was encountered at a higher rate in patients with MM in comparison to the patients with breast cancer (15,21-25).

While age was not assessed as a risk factor in the present study, the development of BRONJ occurred in patients with a mean age of 60.5 (range, 52.5-68.75), which was significantly different (P=0.04) from the age of the control individuals. This may be associated with the reduction in the metabolism of the medication and insufficient mouth care and hygiene in patients of advanced age.

The assessment of the association between the development of BRONJ in patients receiving ZA and the cumulative dose revealed that the cumulative dose of ZA was significantly higher in patients with BRONJ (P=0.03). The median cumulative dose was determined to be 88 mg (range, 36-120 mg) in the control group and 126 mg (range, 72-168 mg) in the BRONJ group. The time of exposure to ZA was determined to be 36 months in the BRONJ group and 27 months in the control group. In previous studies, the time of exposure to medication was identified as a risk factor in BRONJ development (15,21-23). However, an optimal treatment time or dose was not clearly suggested with regard to these patients. In another study, no association was determined between the cumulative BP dose and the risk of BRONJ (26).

In the present study, the risk of BRONJ development was found to be significantly higher in patients that underwent tooth extraction while using ZA (P=0.01). Surgical dental procedures have also been researched in previous studies, and the status of surgical dental procedures as an important risk factor for BRONJ development has been demonstrated (27).

The presence of DM and the incidence of smoking were researched in previous studies as risk factors for the development of BRONJ (23,28). In the present study, the association between DM and smoking and the risk of BRONJ was assessed in the BRONJ and control groups, and the results were not significantly different (P=0.09 and P=0.08, respectively). When the previous studies were considered, evaluating DM and smoking according to the time of exposure to smoking and the time since DM diagnosis and the state of DM regulation was considered to be an improved method for the evaluation of their effects in BRONJ development.

It is also critical to identify the involvement of steroid usage in this rare but important complication of ZA, since a notable number of patients using ZA have MM, and steroids constitute a component of the treatment for MM. Previous studies have identified steroid usage as a risk factor in BRONJ development (26,29). However, in the present study, steroid usage was not monitored as a risk factor (P=0.8).

The association between an increased risk of BRONJ and the administration of anti-angiogenic agents or other BPs has been investigated in a number of small scale studies (23,30-32). There is a previous study that specifies the use of sunitinib and ZA as a predisposing factor to the development of BRONJ (30), and there are studies that report bevacizumab to be a risk factor (31-33). However, there are also studies stating that bevacizumab is not a risk factor (23,34). No patients were co-administered with sunitinib and ZA in the present study, but there were patients that used bevacizumab and ZA together. The association of between bevacizumab and ZA and the development of BRONJ was not determined to be statistically significant (P=0.7).

In the present study, the course of disease was also investigated during the period of BRONJ development, as was the association between ONJ development and the state of malignancy. The state of disease in patients with ONJ was monitored, and was found to be improved during ZA usage, with a statistically significant association (P=0.031). The most likely cause of the situation may be associated with the long-term usage of ZA. The antitumour effect of the medication may have slowed or stopped the progress of malignancy, due to the long-term usage of ZA. However, BRONJ was encountered more frequently in these patients.

According to the results of the present study, advanced age, the application of dental treatment application and cumulative dose of ZA (median, 126 mg), were found to be risk factors for BRONJ development. Determination of ZA usage and net

cumulative dosage in BRONJ development may be presented through a joint calculation to be carried out in the light of other studies that need to be performed. Also, the state of malign disease was determined to be improved during BRONJ development when compared with the patients that did not develop BRONJ. BRONJ development may therefore be a factor during ZA usage, particularly for patients with advanced age. In addition, more frequent and regular dental treatment should be administered to patients with ONJ development, and cooperation between patients, doctors and dentists is required for the treatment of these patients.

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