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ORIGINAL ARTICLE

Analysis of reasons for osteonecrosis of the jaws

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Abstract
Purpose Osteonecroses of the jaws are caused by several reasons. Bisphosphonate-associated osteonecrosis of the jaws (BP-ONJ) is known since 2003 with an increasing incidence in the first years. Along with more knowledge about the pathophysiology, preventive strategies were implemented trying to reduce the incidence. The aim of this retrospective study was to analyze the frequency and overall proportion of BP-ONJ within the field of osteonecrosis. The data was compared to a similar study performed in 2005.
Methods All patients with osteonecrosis or osteomyelitis treated in the period from April 2005 to July 2012 in the Oral and Maxillofacial Surgery at the University of Mainz, Germany, were analyzed.
Results The reasons for osteonecrosis were bisphosphonates in 45 %, odontogenic or surgically induced osteonecrosis in 32 %, osteoradionecrosis in 17 %, traumas in 1 %, and in 4 % the reason remained unclear. The BP-ONJ became the most important factor for osteonecrosis. Its fraction in the years 2000–2005 was 10 % only.
Conclusions Although preventive strategies are implemented, the number of new cases got bigger. The implemented prevention strategies did not manage to reduce the overall number of new cases. Furthermore, the launch of other medications with a similar side effect on the jawbone as the BP-ONJ for bisphosphonates might influence the overall distribution of osteonecroses.

Keywords Osteonecrosis · Osteomyelitis · Bisphosphonate · Bisphosphonate-associated osteonecrosis of the jaws · Osteoradionecrosis · Prevalence

Introduction

First described in 2003 [1], bisphosphonate-associated osteonecrosis of the jaws (BP-ONJ) was initially denied as an entity [2] and then became a well-known disease afflicting a considerable portion of patients in the oral and maxillofacial surgery [3]. An abundance of research has been performed regarding the epidemiology [4–6], etiology, and pathology of BP-ONJ [7–11]. Latest studies focus on diagnosis and therapy of BP-ONJ such as the use of platelet-rich fibrin [12], piezosurgery [13], or visually enhanced lesion scope [14]. Depending on the nature, stage, and treatment of the primary disease, BP-ONJ prevalences of up to 20 % for special subgroups have been described [5]. Theories currently discussed regarding BP-ONJ onset describe reduced bone remodeling, the antiangiogenic effect of bisphosphonates, a negative impact on the bone-covering soft tissues, and the relative ease of jaw bone contamination with oral bacteria that might contribute to the development of BP-ONJ. In most BP-ONJ cases, a further BP-ONJ factor trigger is also present. These trigger factors have an oral wound in common, for example due to tooth extractions, pressure denture sores, periodontal diseases, or surgical procedures such as implant placements [3–6, 11]. Therefore, several organizations and guidelines propose a prevention regime for patients prior to, during, and after bisphosphonate treatment [15–17]. Some authors have shown the positive effect of these regimes; the perioperative antibiotic treatment of patients undergoing dental surgical

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procedures during ongoing bisphosphonate therapy has shown a decrease in new BP-ONJ cases [18], as did consulting a dentist before the first administration of any bisphosphonate in order to treat sites that might have triggered a BP-ONJ prior to the initial administration of a bisphosphonate [19]. Due to the demographic shift resulting inpatients being older and suffering from typical diseases such as osteoporosis and malignant diseases, the clientele in medicine will change. Many of these diseases require special medical treatment; therefore, the use of bisphosphonates in patients might increase, especially since bisphosphonates are more often used in a preventive manner in patients with malignomas to avoid the development of metastases [20, 21].

The question arising is whether more BP-ONJs are being observed, since more physicians know about the disease and because more patients are receiving bisphosphonates, or if the number of new necroses is decreasing due to the preventive strategies for patients with bisphosphonate treatment. An analysis of all patients with an osteonecrosis of the jaws treated from January 2000 until March 2005 performed at the oral and maxillofacial surgery at the University Medical Center in Mainz, Germany, revealed that 40 % had an osteonecrosis due to some kind of odontogenic or surgical procedure; 28 % suffered from osteoradionecrosis, 10 % had a BP-ONJ, and 8 % had an osteomyelitis or sequester due to a trauma, and in 14 %, no obvious reason was detected [3]. An identical analysis was conducted to obtain data on the prevalence of the different kinds of osteonecrosis with special attention on the BP-ONJ. The question to be answered is as follows: Has the distribution of reasons for the different kinds of osteonecrosis changed since preventive strategies were proposed?

Material and methods

All patients with any kind of osteonecrosis treated from April 2005 to July 2012 in the oral and maxillofacial surgery from the University Medical Center were comprised. The inclusion criteria were clinical or histopathological diagnosis of either osteonecrosis, sequester or bone infection of the mandible, the maxilla, or both.

A PC-based search was performed with all possible diagnoses and treatment procedures, and the results were completed with existing internal data bases existing for most of the entities. All together, 505 patients were included in the analysis.

The patients were separated into five groups [3]:

(1) Bisphosphonate-associated osteonecrosis of the jaws: Patients with osteonecrosis, sequester, or bone infection, and a previous or ongoing bisphosphonate treatment but no head and neck radiation. Diagnosis was clinical, radiological, and histopathological.
(2) Osteoradionecrosis: Patients with head and neck radiation were included in this group. Diagnosis was clinical, radiological, and histopathological.
(3) Trauma-induced osteonecrosis: Patients with a previous trauma and fracture were included in this group. Exclusion criteria were bisphosphonate anamnesis or head and neck radiation. Diagnosis was clinical and radiological.
(4) Surgical and odontogenic infections: Patients with a prior dental surgical procedure or dental infections with an osteomyelitis or sequester that could not be assigned to one of the other groups.
(5) Unknown origin: Patients that did not meet any of the above mentioned criteria.

Epidemiological data was collected for all patients (age, gender, localization, and chronological appearance). Further data analyzed were trigger factors for the different groups and the treatment for the different groups.

The groups were compared regarding the number of patients, the demographics, and the localization of the osteonecrosis in the jaws.

Those data were compared to a similar retrospective study conducted in the same department which included all patients from the year 2000 to April 2005 with the same diseases.

For statistical analysis, SPSS 17.0 (Chicago, USA) was used. To detect any differences between the groups, ANOVA with the post hoc test Tukey was used for parameters with normal distribution. To compare the frequency of events in between the different groups, a chi-square test was performed or Fisher's exact test in cases with counts of less than five. P values of less than 0.05 were considered statistically significant.

Results

A total of 504 patients were included, among them 258 men and 246 women. The demographic data are summarized in Table 1. By far, most patients (45.04 %) had a BP-ONJ. The second biggest group comprised those with odontogenic or surgically induced osteomyelitis, with 32.14 %. The third biggest group is the osteoradionecrosis, with 17.46 %, followed by the group with an osteonecrosis without any obvious reasons (3.97 %) and the trauma group (1.39 %).

Patients with BP-ONJ were older (Fig. 1) than all other patient groups ($p<0.007$). The second oldest group is the osteoradionecrosis group ($p<0.036$). There were no significant differences between the other groups. There were no statistically significant differences for the trauma group in comparison with any other group at all ($p>0.214$), although

Table 1 Epidemiologic data of previously published study [3] and current study

Group	Patient number	Age and SD (year)	Gender ratio Male: female	Localization (*n*/%)		
				Mandible	Maxilla	Both
April 2005 until July 2012 (87 months)						
Bisphosphonate	227 (45 %)	69±10	0.66:1 (0.452)	149/66	43/19	35/15
Osteoradionecrosis	88 (17 %)	63±10	2.38:1 (0.237)	84/95	2/2	2/2
Trauma	7 (1 %)	57±13	1.33:1 (0.651)	7/100	0/0	0/0
Odontogenic/surgical	162 (32 %)	50±19	1.35:1 (0.363)	135	23	4
Unknown origin	20 (4 %)	52±20	0.82:1 (0,494)	17	1	1
Total	504 (100 %)	61±16	1.04:1	390	69	42
January 2000 until March 2005 (63 months)						
Bisphosphonate	17 (10 %)	64±13	0.42:1	12	4	1
Osteoradionecrosis	45 (28 %)	58±10	4.00:1	43	1	1
Trauma	13 (8 %)	44±14	2.25:1	13	0	0
Odontogenic/surgical	65 (40 %)	51±15	1.03:1	53	12	0
Unknown origin	23 (14 %)	46±26	0.53:1	22	0	1
Total	163 (100 %)	53±17	1.26:1	143	17	3

Distribution of all patients with the different kinds of osteomyelitis in this study in comparison with the previous study. Due to rounding, the percentages do not add up to 100 % in the recent study. The numbers in the brackets describe the *p* value for the direct comparison between the two studies, e.g., the difference in the gender distribution of 0.66:1 in the present study compared to the old study with 0.42:1 is not significant ($p=0.452$)

it should be noted that the trauma group was very small for statistical purposes ($n=7$).

Regarding the gender, there are statistically significant differences in the distribution between the groups that are displayed in Table 1 and Fig. 1. In the trauma and odontogenic/surgical group, slightly more men do have an osteonecrosis. More men are affected by osteoradionecrosis, and more women are affected by BP-ONJ or an osteonecrosis of unknown origin.

Of the BP-ONJ cases ($n=227$), the primary diseases leading to a bisphosphonate therapy were breast cancer ($n=57$; 25 %), multiple myeloma ($n=54$; 24 %), prostate cancer ($n=44$; 19 %), lung cancer ($n=4$; 2 %), renal cell carcinoma ($n=4$; 2 %), non-Hodgkin lymphoma ($n=3$; 1 %), mastocytoma

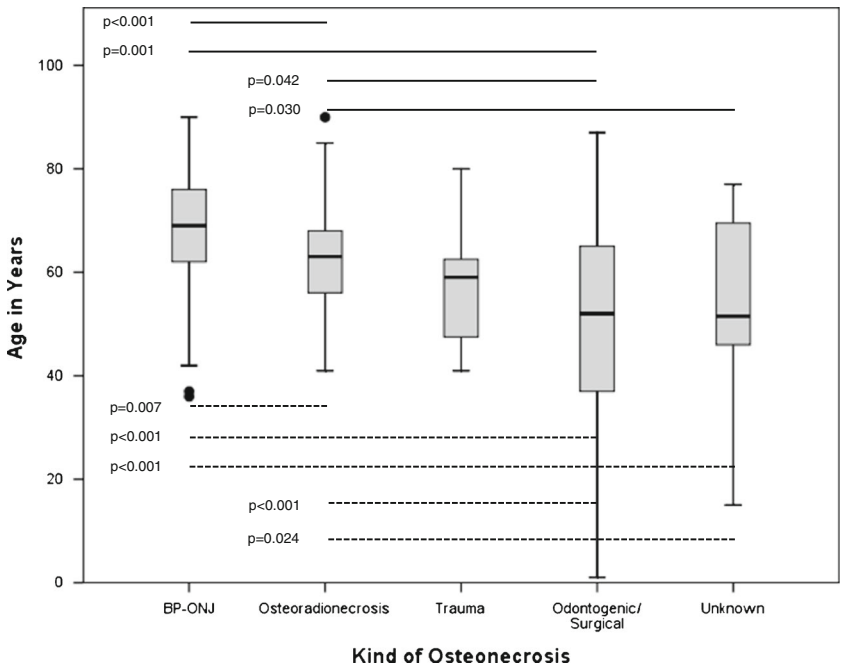

Fig. 1 Age distribution. The *boxplots* describe the age distribution of each group. The *box* represents all values in between the 1st and 3rd quartile. The *line* inside the box represents the median. The *whiskers* show all values not being interpreted as outliers. The *dots* are outliers still being in a range that is 1.5 times of the box length above/below the 25th, respectively, 75th quartile. The *p* values on the *top* of the graph explain statistically significant differences regarding the differences in the gender distribution (*solid line*). The *p* values on the *bottom* of the graph explain statistically significant differences regarding the age distribution (*dotted line*)

(n=1), ovarian cancer (n=1), cervical cancer (n=1), leukemia (n=1), myelodysplastic syndrome (n=1), stomach cancer (n=1), osteoporosis (n=48; 21 %), rheumatism (n=3, 1 %), fibrous dysplasia (n=1), loosened hip joint replacement (n=1), and there is no reason documented in 2 patients. The most commonly used bisphosphonate was zoledronate (n=140), followed by alendronate (n=42), pamidronate (n=34), ibandronate (n=15), risedronate (n=5), and clodronate (n=1). Twenty-three patients had different sequels of bisphosphonates. With the exception of one patient, all received zoledronate. The most common combination was pamidronate with zoledronate (n=12). In 14 patients, the exact sequel of bisphosphonates is unknown. The bisphosphonates were taken for 46.3 months±38.7 months (standard deviation) with a range of minimum 1 and a maximum of 265 months. The trigger factors for the development of BP-ONJ were a previous tooth extraction (n=124; 55 %), dental focus (n=32, 14 %), pressure denture sores (n=21; 9 %), implant surgery (n=7; 3 %), other surgical procedures (n=5; 2 %), periodontal disease (n=5; 2 %), infected bone cyst (n=3; 1 %), endodontic treatment (n=2; 1 %), and no obvious reason in 16 cases (7 %), and in 12 cases (5 %), the BP-ONJ developed at the mylohyoid ridge. The therapy most often performed in these patients was necroses removal (n=90; 40 %), sequestrectomy (n=57; 25 %), partial removal of the mandible (n=46; 20 %), decortication (n=11; 5 %), resection of the mandible with loss of continuity (n=5; 2 %); no surgical procedure was performed in 40 cases (n=18 %) due to several reasons. The numbers do not add up to 227 because some patients had several necroses with different kinds of therapy, and in some cases, there was sequestrum with further necrotic parts of the bone. Seventy out of the 227 patients (30.8 %) either developed a recurrent osteonecrosis or developed a new necrosis at a different site in the oral cavity.

Comparison of the studies is as follows: Patients with BP-ONJ used to make up 10 % of the patient population in this department in the years 2000 until March 2005, but it has increased to a portion of 45 % in the following years. Not taking BP-ONJ into account, there are only minor changes in the distribution of the other diseases: osteoradionecrosis changed from 31 to 32 %, trauma from 9 to 3 %, odontogenic/surgical from 45 to 58 %, and the osteonecrosis of unknown origin from 16 to 7 %. Zoledronate was the predominating bisphosphonate in the first study as well, but 55 % used to have pamidronate as a bisphosphonate. This has changed and amounts to only 14 % in the recent years. The average time of bisphosphonate intake until a BP-ONJ developed was 35.25 months±15.55 months standard deviation in the old study compared to 46.30 months±38.70 months standard deviation for the present study (p=0.258).

Discussion

The most impressive fact in this study is the continuously increasing number of new BP-ONJ cases since its first appearance. BP-ONJ turned out to be the most common reason for osteonecrosis of the jaws and is responsible for half of all osteonecroses, thereby replacing odontogenic and surgically induced osteonecroses and osteoradionecrosis as being more frequent. The portion of BP-ONJ cases was 10 % during the years 2000 until the beginning of 2005 and increased to 45 % in the following years.

The highest increase of cases can be observed in the years 2005 to 2007, which is after the vast majority of dentists learned about the disease and nearly all patients were referred to medical care centers with an attached oral and maxillofacial surgery. In 2008, the number of new patients decreased for the first time. A possible explanation might be that BP-ONJ was more often treated by practitioners so that fewer new cases were introduced to our department. In addition, the implementation of preventive measures that were proclaimed by various medical societies in the previous years [15, 22] might have reduced the overall number of new BP-ONJ cases [18, 19]. In the following years, there was a slight increase in cases again, perhaps due to the increasing frequency of bisphosphonate prescriptions, so that the prevention measures are competing with the continuously increasing use of bisphosphonates in terms of the number of new BP-ONJ cases (Fig. 3). One might keep in mind that usually a cumulative dose of bisphosphonates is necessary to develop BP-ONJ so that increased intake of bisphosphonates in earlier years might explain the increase in new BP-ONJ cases.

Most of the other reasons for which an osteonecrosis might occur had only little changes in their frequency (Fig. 2). Only osteoradionecrosis seemed to occur more frequently; however, not taking BP-ONJ into account, the fraction of osteoradionecrosis from 2000 to 2005 was 31 % and then 32 % for the following years (p=0.885). Regarding the epidemiologic data, no differences could be detected between the already published study and the present study.

Compared to the first study, pamidronate had been used less frequently in patients with BP-ONJ; however, the overall prescription rate of pamidronate (Aredia) has decreased in Germany. The last time it was listed in the annual report analyzing the vast majority of all prescriptions written in Germany in 1 year was for the year 2006, with 0.03×10^6 defined daily doses (Fig. 3), whereas Zometa is listed with 0.2×10^6 in the year 2006 [23] and 0.3×10^6 defined daily doses in the year 2011 [24].

In most patients, the primary disease indicating the bisphosphonate treatment is a malignant disease, as it was previously described.

In addition to this, in the near future the distribution of osteonecrosis due to other medications might change the

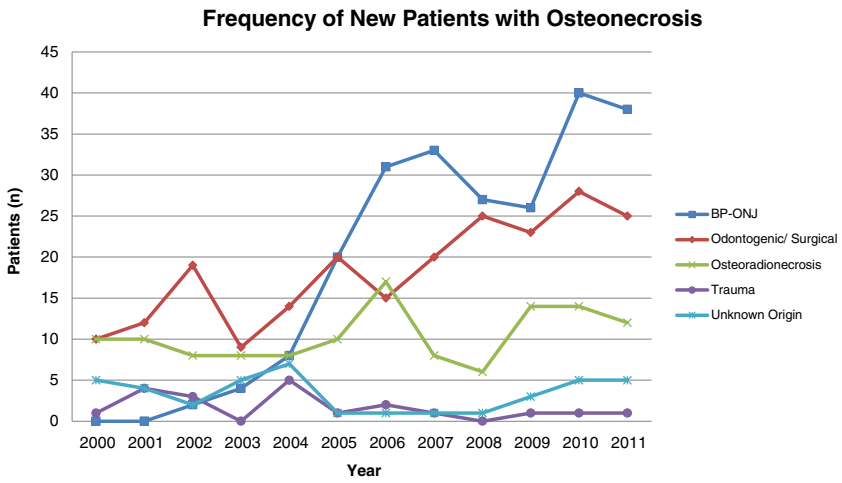

Fig. 2 All new patients with an osteonecrosis due to the various reasons are displayed

composition of different osteonecroses. These agents are denosumab [25], bevacizumab [26], and sunitinib [27]. All of them are antibodies against either RANKL, VEGF, or a tyrosin kinase receptor. In 2010, the defined daily dose for denosumab was approximately 1.543×10^6 in Germany. In 2011, it increased to 9.0×10^6, which amounts to an increase of 483.1 % in 1 year [24]. In the approval study, osteonecroses occurred just as often in patients with bisphosphonates as in patients receiving denosumab [25]. Assuming a similar dynamic as for BP-ONJ development where the average time of intake before BP-ONJ develops is 46 months, the possible wave of patients developing an osteonecrosis due to denosumab is still to come, since it has only been approved for use in Germany since June 2010.

Therefore, the distribution of reasons for osteonecrosis in the jaws might change in the near future. Due to the shorter half-life of those antibodies, it might be easier to influence the bone remodeling. The antibody treatment (drug holiday) could be paused for any necessary dental surgical procedure. The bone physiology might recover faster, and the risk of triggering an osteonecrosis by any procedure that would produce an oral wound might be considerably lower compared to patients receiving bisphosphonates.

Due to the vast number of osteonecroses, further more effective prevention strategies are needed in these patients. One possibility might be a drug holiday for drugs with a short half-life and the implementation of active agents antagonizing the effect of the medication used for the primary disease. One possibility might be geranylgeraniol, which has been recently described [28].

Future studies will analyze the incidences for the different reasons of osteonecrosis and the effectiveness of the different preventive strategies.

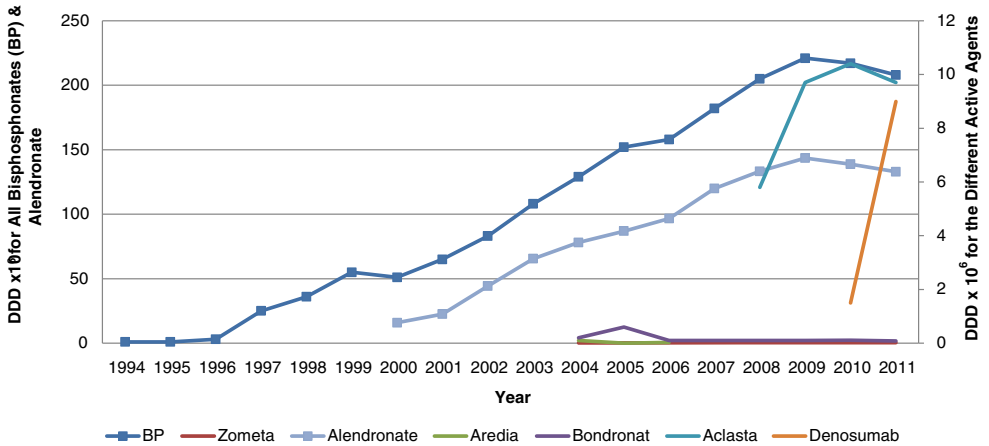

Fig. 3 Bisphosphonate application in Germany. Display of the defined daily dose for the different bisphosphonates. The *y*-axis on the *left-hand side* is valid for the lines with the additional squares, which are the overall numbers for bisphosphonates and alendronate. The other bisphosphonates and denosumab are displayed without additional squares, and the valid *y*-axis is placed on the *right-hand side*. The values for zoledronate are hidden behind Bondronat. Data were taken from the Arzneiveror dnungs-Report 2012 [24] and its previous editions from the years 2000 to 2011

Conflict of interest The authors declare no conflict of interest. The study was not funded by anyone. We have full control of all primary data, and we allow the journal to review our data if requested.

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