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ORIGINAL ARTICLE

Prevalence of bisphosphonate-associated osteonecrosis of the jaw after intravenous zoledronate infusions in patients with early breast cancer

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Abstract
Objectives The definite incidence rate of bisphosphonate-related osteonecrosis of the jaws (BRONJ) is still unknown. The aim of this study was to investigate prevalence of BRONJ in a group of breast cancer patients applying the classification of the Association of Oral and Maxillofacial Surgeons 2009.
Patients and methods Between 2000 and 2008, 63 premenopausal early breast cancer patients who were free of metastases were treated with 4 mg zoledronic acid every 6 months over 3 years as participants of a multicenter, randomized, controlled, adjuvant breast cancer medication trial. Patients were not informed about the risk of jaw necrosis. None reported tooth or jaw complaints during the breast cancer follow-up examinations. In 2010, 48 patients of this cohort were investigated concerning BRONJ by clinical and radiological examinations.
Results No advanced stages (AAOMS 2009)were detected. However, five patients (10.4 %) presented purulent (2) and nonpurulent (3) fistulas and radiological signs correlating to BRONJ stage 0.
Conclusion Although no case of advanced BRONJ was detected, the study revealed a high prevalence of BRONJ stage 0. This supports the need for tight cooperation between dentists and medical specialists prescribing bisphosphonates including dental pre-therapeutic and follow-up examinations. Adaption of the BRONJ classification taking account to bone exposure via fistulas is recommended.
Clinical relevance BRONJ is said to be a complication linked to high-dosage bisphosphonate therapy. The study demonstrates that even after application of zoledronate in a low-dose protocol, early BRONJ occurred. Radiological signs solely are not sufficient to confirm BRONJ; clinical signs are mandatory.

Keywords Bisphosphonates · Osteonecrosis · Osteochemonecrosis · Early breast cancer · Bisphosphonate osteonecrosis of the jaw · BRONJ

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Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a severe adverse side effect of bisphosphonate therapy, potentially resistant to conventional and surgical treatment options. It is primary defined as a condition of exposed, necrotic bone in the maxillofacial region that has persisted

for more than 8 weeks in patients who have received or are receiving treatment with bisphosphonates and have no history of radiation therapy of the jaws [1]. This definition relies on a combination of various symptoms in combination with the patient's anamnesis. The underlying principles of pathogenesis are not clarified yet. Common theories deal with reduced bone remodeling, impairment of local vascularization, and neoangiogenesis [2], accumulation of microcracks in devitalized bone with empty osteocyte lacunae [3], and infection of bone via osteoclast-independent bone resorption [4, 5].

In 2007, the American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed a stage-related treatment. Three stages were specified (Table 1) [6]. In addition, an "at-risk category" was defined for patients who have been treated with either oral or IV bisphosphonates, but show no apparent exposed/necrotic bone.

As experience grew in this condition, clinicians recognized that bisphosphonate-exposed patients can show clinical and radiological signs potentially indicating osteonecrosis lacking the cardinal symptom of exposed bone in the maxillofacial region. Therefore, the AAOMS updated its classification and added a stage 0 category, implying patients who show nonspecific clinical and radiological findings or symptoms that possibly correlate to osteonecrosis (Table 2). These findings must not be explicable by other conditions [1]. As a current study shows that patients who present BRONJ stage 0 are at high risk of developing advanced stages of BRONJ [7], the relevance of an early diagnosis increased.

In contrast to the AAOMS classification, the Deutsch-Österreichisch-Schweizerische Arbeitskreis für Tumoren im Kiefer- und Gesichtsbereich (DÖSAK) already categorizes mucosal lesions like fistulas as stage 1. Stage 0 is equal to the "at-risk" category of the AAOMS classification, and radiological findings are completely left out [8].

The number of published cases of BRONJ is steadily increasing [9–12], but the definite prevalence is still unknown. The incidence rate is higher in patients with intravenous administration of bisphosphonates compared to the oral route of administration. The estimates of BRONJ for intravenous application range from around 1 [13, 14] to 21 % [15].

The main reasons for this lack of knowledge are:

- People suffering from BRONJ have various underlying diseases. They present a heterogeneous group of patients treated by independent medical specialists. A standardized oral investigation of patients at risk has not been implemented to date.
- The condition is influenced by several factors, such as drug potency, type of administration as well as individual local and systemic conditions.
- Many patients are asymptomatic for a long time and, therefore, may not be diagnosed or do not relate their oral symptoms to the bisphosphonate therapy.
- Different classifications are taken into account and most studies investigating the prevalence rate of BRONJ do not consider stage 0 AAOMS 2009.

Objective

The aim of this study was to investigate the prevalence of BRONJ in a homogenous group of premenopausal early breast cancer patients who did not receive dental preventive measures. Cases of BRONJ were classified according to the staging system of AAOMS 2009 additionally considering BRONJ stage 0.

Methods

Patients

From 2000 to 2008, 63 hormone receptor-positive, premenopausal breast cancer patients who were free of metastases were adjuvantly treated with infusions of zoledronic acid in 4 mg doses every 6 months over 3 years at the Department of Gynecology, Medical University of Graz, Austria. All these women participated in a randomized, controlled multicenter clinical trial with 1,803 patients [16].

Each of the 63 patients received seven infusions with 4 mg zoledronic acid, totaling 28 mg. All patients had undergone primary surgery for stage I or II estrogen-receptor–positive breast cancer, progesterone-receptor–positive early breast cancer, or both, and received standard therapy with goserelin (3.6 mg) and either tamoxifen (20 mg) or anastrozole (1 mg). Patients with a history of other neoplasms or preoperative radiotherapy were excluded.

Patients who were recruited until March 2004 were not routinely informed about the risk of jaw necrosis. From April 2004 on this information was integrated in the informed consent. None of the whole collective received a standardized

Table 1 BRONJ classification, AAOMS position paper 2007

Stage 1: exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2: exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3: exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border

Table 2 Nonspecific findings and symptoms categorizing stage 0 by AAOMS

Symptoms
Odontalgia not explained by an odontogenic cause
Dull, aching bone pain in the body of the mandible that may radiate to the temporomandibular joint region
Sinus pain, which could be associated with inflammation and thickening of the maxillary sinus wall
Altered neurosensory function
Clinical findings
Loosening of teeth not explained by chronic periodontal disease
Periapical/periodontal fistula that is not associated with pulpal necrosis due to caries
Radiographic findings
Alveolar bone loss or resorption not attributable to chronic periodontal disease changes to trabecular pattern—dense woven bone and persistence of unremodeled bone in extraction sockets
Thickening/obscuring of periodontal ligament (thickening of the lamina dura and decreased size of the periodontal ligament space)
Inferior alveolar canal narrowing

pre-, peri- or post-therapeutic dental and oral assessment. Nevertheless, over the entire active study or follow-up period, none of the 63 women reported maxillary complaints.

Study design

The actual study addressed the local cohort of 63 patients and was independently conducted at the Department of Oral Surgery and Radiology, Medical University of Graz, Austria, from March to December 2010. Analysis in regard to symptoms of BRONJ was performed by two experienced oral surgeons, who cross-checked their findings.

Patients underwent careful dental and mucosal investigation as well as radiological examination after an average time period of 4 years and 8 months (37 to 74 months) from cessation of bisphosphonate therapy. Radiological examination in each case included orthopantomograms (ORTHOPHOS XG Plus DS/Ceph, Sirona Dental Systems GmbH, Germany) and, if indicated, additional periapical views (Heliodent Plus, Sirona Dental Systems GmbH, Germany) and, in the event of suspicious findings, cone beam computed tomography was performed (ProMax 3D, Planmeca Oy, Finland). Staging followed the AAOMS classification of 2009 [1]. The study protocol was approved by the local ethics committee (ethical board number: EK-20-257 ex 08/09).

To assess the validity of the unspecific signs associated with stage 0, a control group was set up. The 52 women of this group were at comparable age (34–73 years, median 50 years) but none of them had received bisphosphonate therapy or other relevant medication like antiangiogenetics or had local radiation therapy in her history.

Results

Fifteen (23.8 %) of 63 patients dropped out of the actual study, by personal request (12; 19 %), due to alterations in the therapy protocol (1; 1.6 %), or due to death (2; 3.2 %). Forty-eight patients (76.2 %) fulfilled the study criteria.

In the study group, five patients (10.4 %) presented clinical findings as fistulas with (two patients) or without (three patients) purulent drainage. Additional five patients (totaling ten patients, 20.8 %) displayed suspicious radiological signs of BRONJ. In eight patients, these findings were located in the mandible, and in two patients, in both jaws. Radiological signs were alteration of trabecular pattern-like sclerosis, persistence of unremodeled bone in extraction sockets, and thickening of the lamina dura (Table 3).

In the control group, five patients showed unspecific radiological signs that are associated with BRONJ in patients with history of bisphosphonate therapy. No clinical signs were detected. Statistical evaluation revealed no statistically significant difference between groups, although a tendency was visible (Fisher's exact test, $p=0.098$). Comparing the frequency of clinical signs, Fisher's exact test was significant. (Five patients in the study group versus 0 patients in the control group, $p=0.023$).

Discussion

The presented clinical study did not reveal any case of BRONJ stage I–III in a cohort of 48 early breast cancer patients treated with a cumulative dose of 28 mg zoledronic acid. However, according to the classification of AAOMS 2009, 10.4 % (five patients) showed BRONJ stage 0 with clinical and radiological signs, and another five patients (totaling 20.8 %), only radiological signs. Radiological findings without any clinical correlation are not sufficient to confirm BRONJ diagnosis. Clinical signs or symptoms are mandatory.

Table 3 Radiographic and clinical findings

Patient	Age	Age–ST	BP-OE	Clinical findings	Radiographic findings	Possible trigger
D.M.	60	51	65	Fistula, left mandible—first molar region	Sclerosis, left mandible—third molar region; unremodeled alveolar socket with thickening of the lamina dura, left mandible—first molar region	Third molar region: unknown; first molar region: tooth extraction
K.B.	57	50	69	None	Changes of the trabecular pattern, right mandible—third molar region	Unknown
L.G.	43	35	58	None	Unremodeled alveolar socket and changes in trabecular pattern, right mandible—first premolar region	Unknown
R.G.	45	35	66	None	Sclerosis, left mandible—first molar region; density confluence of cortical and cancellous bone, left mandible—third molar region	Unknown
S.R.	57	51	37	Fistulas, right mandible—first and second premolar region	Density confluence of cortical and cancellous bone, right mandible—canine and second premolar and sclerosis, right mandible—second molar region and left mandible premolar region	Pressure mark, tooth extraction, left mandible—first and second premolars
S.E.	48	41	42	Pain; fistula, left mandible—second molar region, and left maxilla—second and third molar regions	Changes in trabecular pattern, right maxilla—third molar region, left and right mandible—second molar region	Tooth extraction
St.E.	51	42	74	Fistula, right mandible—first molar region	Sclerosis, right mandible—first molar region	Implant therapy
S.A.	54	46	48	None	Density confluence of cortical and cancellous bone, right maxilla—second incisor region, and right mandible—first molar region; unremodeled alveolar socket, right maxilla—second premolar region, and right mandible—third molar region	Tooth extraction, maxilla—second premolar
U.M.	59	50	62	None	Persisting alveolar socket and sclerosis, right mandible—second molar; changes in trabecular pattern, left mandible—first molar region	Unknown
VH.W.	54	47	44	Fistula with purulent drainage, right mandible—second molar region; crestal	Persisting alveolar socket, right mandible—second molar	Tooth extraction: right mandible—second molar

BP-OE period from cessation of bisphosphonate therapy to oral examination in months, *Age–ST* age at start of bisphosphonate therapy

BRONJ prevalence

Published incidences and prevalence of BRONJ in patients with malignant diseases range from about 1 [13, 14] to 21 % [15]. In breast cancer patients, prevalence of 1.2 [11], 2.3 [17], 3 [18, 19], 4.3 [7, 20], 5.3 [10], 6 [21, 22], and 11 % [23] are stated. Walter et al. [15] assume that this significant variation may result from a selection bias due to the retrospective design of most studies, in which a thorough oral examination of all, even asymptomatic, patients to detect BRONJ has rarely been performed. Furthermore, none of these studies considered BRONJ stage 0. Taking into account unspecific radiological signs, the actual study shows a rather high prevalence rate compared to earlier published data. The actual results are getting more comparable if only more specific clinical symptoms as evident fistulas are considered as BRONJ.

In general, a very important risk factor for developing BRONJ is length of exposure and cumulative dose. Bamias et al. [18] showed that the incidence rate increased with time to exposure from 1.5 % among patients treated for 4 to 12 months to 7.7 % for treatments of 37 to 48 months. The cumulative risk increased from above 1 % after 12 months of treatment to up to 11 % after 4 years. In their study, the median number of infusions in patients presenting BRONJ was 35. No patient who received fewer than 13 treatments with bisphosphonates developed osteonecrosis.

On the contrary, patients of this study cohort who suffered from early breast cancer received only seven infusions of

prophylactic intravenous zoledronic acid (cumulative dose 28 mg) over a period of 3 years. According to the BRONJ guidelines of the Deutsche GesellschaftfürMund-, Kiefer- und Gesichtschirurgie (DGMKG), this cohort would correlate to a medium risk group and a BRONJ rate of 1 % would be expected [24]. Nevertheless, even after application of this "low-dose protocol," symptoms possibly indicating jaw necrosis and complying with BRONJ stage 0 could be detected in a high proportion of 20.8 % of patients and, out of these, still 10.4 % presented evident clinical symptoms as fistulas.

Fedele et al., on the other hand, investigated 332 preselected symptomatic patients who received intravenous bisphosphonate therapy and developed clinical jawbone abnormalities (jaw pain, jaw bone enlargement, gingival swelling, and sinus tract). Including stage 0, they detected a BRONJ rate of 28.9 % [25].

A very important factor accounting for BRONJ prevalence seems to be the application of routine dental prevention. Two studies showed that the implementation of these measures reduces the BRONJ rate [26, 27]. The evaluation of oral and dental status and preventive measures to eliminate potential sites of infection prior to bisphosphonate treatment as well as the maintenance of good oral hygiene are, therefore, indicated [4].

A possible reason for the rather high prevalence in this study cohort could be the lack of professional dental pre- and peritherapeutic supervision. The foregoing breast cancer study was designed in 1998 and patient enrollment began in 1999. As this took place 4 years before the first reports of jaw necrosis as side effect of bisphosphonate therapy were published, no adequate patient information and preventive measures were conducted. Therefore, the prevalence of jaw necrosis was assessed retrospectively by studying dental records of patients with suspicious symptoms. Appropriate oral investigation was not performed. Walter et al. showed in their study that prevalence of BRONJ is underestimated if thorough inspection of the oral cavity is omitted [15].

BRONJ staging

In the AAOMS classification, the diagnosis BRONJ stage 0 is based just on unspecific clinical and/or radiographic symptoms and findings. Described radiological signs of osteonecrosis are regional or diffuse osteosclerosis, density confluence of cortical and cancellous bone, prominence of the inferior alveolar nerve canal, markedly thickened and sclerotic lamina dura, uniform periradicular radiolucencies, cortical disruption, lack of bone fill after extraction, persisting alveolar sockets [9] as well as mottling, fragmentation/sequestra formation, sinus communication [28], jaw expansion, and periosteal new bone formation [29]

Especially when frank bone exposure is missing diagnosis, determination of dimensions of bony involvement and the differentiation from other diagnoses are relying on radiographic techniques. Computed tomography is more accurate in showing the lesion and its extent than orthopantomography [30].

Radiographic parameters related to BRONJ stage 0 are unspecific and can rely on different pathological and physiological mechanisms. The frequency of nonspecific radiological and clinical signs was not significantly different in the control group. This underlines that the radiological suspected diagnosis of BRONJ, at least, demands essential clinical correlations and/or histological verification. As a consequence, staging of BRONJ has to be considered. Stage 0 only relies on unspecific parameters. Even though a tendency was visible, occurrence was not significantly different to the control group. This is maybe due to the small patient number. Controlled clinical trials to assess the validity of these parameters are urgently needed. A diagnosis of osteonecrosis based only on unspecific radiological findings carries a great risk of "overinterpretation" and may falsely increase the number of reported cases of BRONJ. However, overinterpretation of BRONJ prevalence may not have clinical consequences, as the only treatment intended for stage 0 cases is tight recall, but it contributes to a growing feeling of displeasure towards bisphosphonates among health professionals and can also cause concern to patients treated. Another matter of dispute is staging BRONJ 0 in case of additional clinical presence of sinus tracts. Woo et al. [31] proposed the installation of stage 0_{sa} (sinus tract asymptomatic) and stage 0_{ss} (sinus tract symptomatic), referring to a proposal of Bagan et al. [32] of a staging that considers sinus tracts.

In the authors' opinion, fistulas are already a kind of bone exposure and should be rated as BRONJ stage 1, or in case of present inflammation stage 2. This is in a partial accordance to the classification by the DÖSAK [8]. Each finding implying bone exposure or infection and provoking progression to advanced stages should be treated in an adequate therapeutic manner as early as possible.

The definition of BRONJ basically relies on the clinical symptom of bone exposure. A stringent staging system should be based on secure diagnostics and refer to therapeutic consequences. As long as reliable noninvasive diagnostic tools of osteonecrosis are missing, the authors suggest adapting AAOMS staging by abandoning stage 0 and referring unspecific symptoms to a "symptomatic at risk" stage. As already mentioned above, fistulas should be rated as stage 1, or in case of present inflammation stage 2. Applying this to the presented study cohort who showed radiological signs of nonexposed osteonecrosis would result in a BRONJ prevalence of 10.4 % (three patients with asymptomatic sinus tracts (6.2 %) stage 1, two patients with purulent sinus tracts (4.2 %) stage 2).

Importance of early diagnosis of BRONJ

The knowledge of presence of BRONJ stage 0 of early signs correlating to BRONJ is important for the dental practitioner.

It appears that patients are highly at risk of developing further advanced stages of BRONJ, especially if invasive procedures like tooth extractions are performed or other risk factors for development of necrosis, such as mucosal trauma due to pressure marks, are present. Fedele et al. reported that 53.1 % (51/96) of patients in their study cohort who showed nonexposed osteonecrosis subsequently developed frank bone exposure [26]. Mawardi et al. referred to four of five patients presenting sinus tracts or deep periodontal pockets who developed exposed bone afterwards [33].

Dentists must be aware of the existence of early stages of BRONJ and the importance of proper dental aftercare of bisphosphonate-treated patients. Prevention of the progression of disease and early onset of therapy in case of presence of clinical symptoms is the most promising treatment strategy for this disease pattern. Early intervention allows the use of conservative means like local disinfectant rinsing and oral antibiotics with good chances of success in gaining stable mucosal coverage. Furthermore, conservative treatment does not have to deal with possible impairments in oral function and esthetics due to resective surgery.

In general, according to our experience, the more successful the therapy of BRONJ is, the less advanced the condition is. This was also reported by Nicolatou-Galitis et al., who reached a significantly increased healing probability in the lower stages 0 and I of BRONJ (P=0.003) applying a conservative treatment regime [34]. Additionally, the association of advanced stages of BRONJ with reduced healing rates has been published [35].

We conclude three factors to be essential in dealing with patients who are at risk of developing BRONJ: a close cooperation of medical specialists prescribing bisphosphonates with dentists; periodical dental explorations before, during, and after bisphosphonate therapy; and education of dental practitioners in the diagnosis of possible clinical and radiological signs of necrosis as well as in preventive measures.

Conclusion

Although the presented investigation did not reveal any case of BRONJ stage I–III according to AAOMS 2009 classification, a quite high prevalence of suspicious early BRONJ was detected. As these patients are at risk for progression, proper dental follow-up and patient education are essential. Adaption of the BRONJ classification taking account of bone exposure via fistulas is recommended. Radiological findings are not sufficient to confirm BRONJ diagnosis. Clinical signs or symptoms are mandatory.

Conflict of interest None.

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