Journal of Cranio-Maxillo-Facial Surgery 42 (2014) 1932–1936

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Potential significance of antiestrogen therapy in the development of bisphosphonate related osteonecrosis of the jaw

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ARTICLE INFO

Article history:
Paper received 21 October 2013
Accepted 12 August 2014
Available online 20 August 2014

Keywords:
Bisphosphonate
Jaw
Osteonecrosis
Estrogen deficiency
Antiestrogen therapy
Breast cancer

ABSTRACT

Objectives: There are known risk factors and established treatment protocols for bisphosphonate-related osteonecrosis of the jaw (BRONJ), but it remains a difficult disease to treat, with the risk of relapses. This study investigates whether or not there is a relationship between antiestrogen therapy and BRONJ.
Patients and methods: In our prospective study, we followed up 93 patients with BRONJ who were seen at our clinic between 2006 and 2011.
Results: We found that breast cancer patients had a significantly worse prognosis than patients with other underlying illnesses ($p < 0.01$), which might indicate the role of antiestrogen therapy ($p < 0.001$) as a causative factor.
Conclusion: The dominance of the female gender among BRONJ patients as well as our new findings related to antiestrogen therapy of breast cancer raise the possibility that estrogen deficiency might be a newly discovered risk factor for BRONJ.

1. Introduction

Bisphosphonate induced osteonecrosis of the jaw (BRONJ) due to bisphosphonate therapy has been known since 2003 (Marx, 2003). BRONJ remains a condition difficult to treat (Ruggiero et al., 2009). Its prognosis is uncertain, therefore, prevention is of utmost importance. It is not clear why some people on bisphosphonates develop BRONJ and others do not. Certain risk factors are known: tooth extraction or other invasive dental interventions (Bamias et al., 2005; Dimopoulos et al., 2009), intravenous bisphosphonate treatment (Wessel et al., 2008), smoking, obesity (Reid, 2009), the length of bisphosphonate treatment (Palaska et al., 2009), and the type of drug administered, with special emphasis on zoledronic acid (Hoff et al., 2008), chemotherapy and corticosteroid therapy (Ruggiero et al., 2006). All these factors, however, are not certain initiators of bisphosphonate related ONJ.

Certain underlying conditions are common in BRONJ patients; these include breast cancer, multiple myeloma and prostate cancer. Necrosis of the jaw is not a local manifestation of these illnesses though, but a consequence of the bisphosphonate-induced changes in the jawbone metabolism. The life-span and activity of osteoclasts is reduced as a result of bisphosphonate treatment. Angiogenesis is suppressed, production of endothelial derived growth factor is reduced (Green and Clezardin, 2002) and there is increased apoptosis of osteoblasts (Abe et al., 2000). The number of osteoblast precursors increases (Giuliani et al., 1998), prostaglandin E_2 levels drop (Igarashi et al., 1997), alkaline phosphatase levels rise, IL-6 synthesis decreases, and the apoptosis of tumor cells accelerates (Green and Clezardin, 2002). The therapeutic effect of bisphosphonates is exhibited in a hormonal environment that also has an effect on bone metabolism.

Bone metabolism is a dynamically changing, controlled process that depends on a number of factors. In addition to local mechanical and metabolic effects, its hormonal and metabolic regulation is complicated. Parathormone (PTH), PTH-related protein, vitamin D3, calcitonin, estrogens, progesterone, thyroid hormones, glucocorticoids and androgens as well as insulin have a direct effect on osteoblasts (Caulfield and Rosenblatt, 1990; DeLuca et al., 1990).

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http://dx.doi.org/10.1016/j.jcms.2014.08.002
1010-5182/

The most common endocrine change in women leading to a reduced bone mass is the lack of estrogen.

Estrogen has a direct and an indirect effect on osteoclasts, resulting in inhibition of osteoclast activity (Syed and Khosla, 2005). The indirect action is mediated through the production of IL-1 (Syed and Khosla, 2005). In estrogen deficiency, the increased activity of osteoclasts liberated from inhibition leads to accelerated bone resorption in menopause (Syed and Khosla, 2005). Based on this, it is reasonable to suppose that the hormonal environment is not neutral to the effects and side effects of bisphosphonate therapy.

Therefore, the goal of the present prospective study was to investigate whether or not there is a relationship between antiestrogen therapy and bisphosphonate-related ONJ. It was postulated that antiestrogen therapy, through the local lack of estrogen in the bone, might play a role in the development of BRONJ, thus, we would expect higher numbers of patients to be on antiestrogen therapy and for recurrence to be more common in this group.

2. Material and methods

2.1. Patients

In the present prospective study, clinical parameters of BRONJ patients consecutively referred to and treated at the Department of Oro-maxillofacial Surgery and Stomatology of the Semmelweis University, Budapest between 2006 and 2011, were evaluated. 93 patients were involved in the study with BRONJ. The underlying illnesses of the patients were recorded, they were all treated surgically, underwent sequestrectomy and the local flaps were closed with a single suture line.

2.2. Criteria of BRONJ

The criteria for BRONJ were based on the 2006 American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper as modified in 2009 (Ruggiero et al., 2009). Three criteria had to be present simultaneously: current or previous treatment with a bisphosphonate; exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks; no history of radiation therapy to the jaws.

2.3. Follow-up

The patients were followed up and any recurrence was recorded. A condition was considered to be a recurrence, when the patient had a minimum of 4 weeks with no clinical and radiological signs and symptoms following surgical therapy, and the BRONJ symptoms occurred again. Also, any type or localization of new BRONJ symptoms were handled as a relapse in the study. Patients were checked weekly in the first 4 weeks, then monthly for a minimum of 3 months. They were requested to return immediately in case of any discomfort.

BRONJ and healing were studied, based on the AAOMS classification. The treatment strategy recommended by the Association was followed, except that a surgical solution was chosen in stage 2 disease, and also in stage 1 if 4 weeks of conservative therapy was ineffective. Only patients undergoing surgical therapy were kept in the study.

2.4. Statistical analysis

Fisher's exact test and a chi-square test were applied for the statistical evaluation of the data. Results were considered significant when $p < 0.05$.

3. Results

3.1. Patients, underlying diseases

The majority of the patients in the study were female 74/93 (79.6%), and 19/93 (20.4%) were male. The mean age of the patients was 68.6 (43–88) years.

In 70.9% (66/93) of the patients, a dental intervention preceded the occurrence of necrosis in the same area of the jaw. The necrosis was located in the mandible in 61.3% (57/93) of the cases, the maxilla in 31.2% (29/93), and both jaws in 7.5% (7/93).

The distribution of BRONJ patients according to the underlying disease is shown in Fig. 1. Almost 40% of all patients had breast cancer (39.8%, 37/93). Patients with breast cancer represented 49.3% (37/75) of the total number with malignant disease.

3.2. Breast cancer patients

Eighty percent of the breast cancers showed estrogen receptor positivity; therefore these patients also received antiestrogen therapy. The distribution of different antiestrogen drugs given to the patients was equal. There was no significant difference in recurrence rates between patients receiving intravenous or oral antiestrogens.

The distribution of breast cancer patients on or off antiestrogens is shown according to their AAOMS stage in Fig. 2. Twenty percent of patients were in stage 3, and all of them received antiestrogen therapy (mean stage of breast cancer patients on hormone therapy: 2.04, the rest: 1.71, not significant). The rate of recurrence was studied in the estrogen receptor positive breast cancer and non-breast cancer groups (Fig. 3). The number of recurrences was significantly higher in the breast cancer group ($p < 0.01$). When the number of recurrences in breast cancer patients on antiestrogens was compared with the recurrence rate of all the other BRONJ patients, an even higher significance rate was observed ($p < 0.001$, Fig. 4). Within the breast cancer group, recurrence was much more common among the patients receiving antiestrogen therapy than among those who received no such therapy ($p < 0.05$, RR: 3.72). Recurrence was similar among breast cancer patients who received no antiestrogen therapy compared with those who had BRONJ with a different underlying condition.

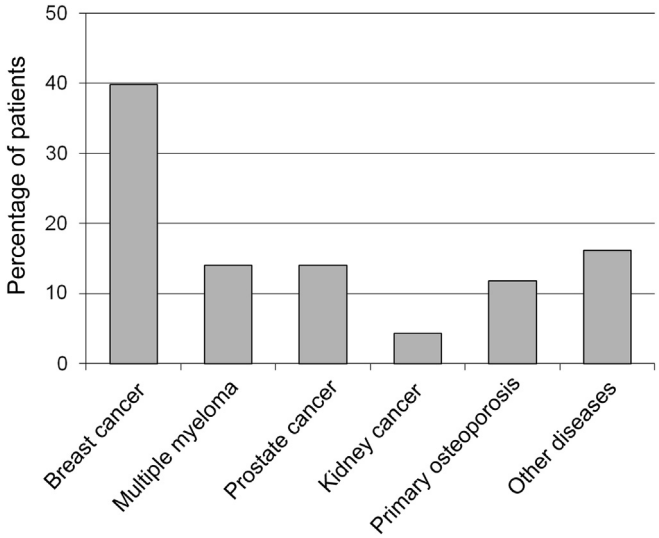

Fig. 1. Distribution of ONJ patients according to the underlying disease.