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Critical Reviews in Oncology/Hematology 71 (2009) 12–21

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

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Physiopathology and management of osteonecrosis of the jaws related to bisphosphonate therapy for malignant bone lesions. A French expert panel analysis

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Accepted 14 October 2008

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Abstract

Bisphosphonates (BP) are the current standard of care for preventing malignant skeletal related-events. Recent reports have documented the relationship between osteonecrosis of the jaws (ONJ) and the use of BPs. Based on the opinion of experts, the purpose of our analysis was to summarize current knowledge, to propose therapeutic options, and to define areas of research. Identified risk factors were long-lasting

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1040-8428/$ – see front matter
doi:10.1016/j.critrevonc.2008.10.009

exposure to BPs, intravenous nitrogen-containing BPs, and poor dental status. Three major hypotheses could explain the genesis of ONJ: excess of bone turnover inhibition, antiangiogenic effect, and local infection. Before the onset of therapy, the dental status must be controlled, and followed during treatment. Dental procedures could worsen the risk of ONJ, and indications must be well evaluated. When an ONJ occurs, the management should be adapted according to its extent. Thereby, a customization of BP therapy should be applied taking into account the aggressiveness of the underlying disease.

Keywords: Bisphosphonates; Osteonecrosis of the jaws; Physiopathology; Risk factors; Treatment of necrotic bone

1. Introduction

Bisphosphonates (BP) are the current standard of care for the management of skeletal related-events (SRE) associated with bone lesions in patients with breast cancer and multiple myeloma [1]. According to their molecular characteristics, BPs currently used in oncology have been classified in two groups: non-nitrogen-containing BPs (clodronate), and nitrogen-containing BPs (ibandronate, pamidronate, zoledronate). Although differences in bone resorption potencies have been described experimentally [2], prospective randomized trials have shown a significant benefit in favor of BPs regardless of their structure [1,3–9]. Two large overviews have confirmed advantages provided by both oral and intravenous BPs in malignant bone diseases [1,10].

Noteworthy, none of clinical trials demonstrated a benefit in terms of survival, enhancing quality of life and safety as crucial decision-making tools. Despite being a standard supportive care for malignant bone diseases, BPs are associated with a number of toxicities that can limit their clinical benefit. The majority of these toxicities were described for a long time. More recently, a new unrecognized potential complication has been described, consisting of osteonecrosis of the jaws (ONJ). Recent reports have documented that ONJ were associated with the use of BPs, predominantly when administered intravenously on a long-term basis, and few cases have been reported subsequently to a short delivery [11,12]. Between 2003 and 2005, a first review has registered 180 cases of ONJ described in the literature [13]. In 2006, a new review reported 368 cases, excluding those described in abstracts of Ref. [14]. In 1 year, the number of reported BP-related ONJ doubled. Since 2003, the number of publications has dramatically increased.

This complication has been described predominantly after exposure to nitrogen-containing BPs [15,16]. Exact mechanisms of BP-related ONJ are not fully elucidated. The risk factor prevailing to develop an ONJ associated with the treatment by BP seems to be a poor dental status. Although numerous case series reports have been published, and despite the position paper provided by the American Association of Oral and Maxillofacial Surgeons (AAOMS) [17], there have been no documented uniform treatment strategies that would yield consistent resolution and healing of ONJ. Many cases have poor outcomes in spite of therapy, evolving to extensive dehiscence and exposure of bone. However, in the absence of treatment, the natural history of ONJ is always poor, evolving more or less rapidly towards spontaneous sequestration or fractures, and/or infections of surrounding soft tissues or adjacent maxillary sinus.

The purpose of the present analysis was based on the consideration of an expert panel including oncologists, rheumatologists, and stomatologists. They analyzed the literature in order to summarize current knowledge, to propose preventive and therapeutic measures limiting the deleterious effects of ONJ, to establish a treatment algorithm with BPs according to the clinical setting, and to define areas of research.

2. Definition and diagnosis

A BP-related ONJ is defined as an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider in patients receiving or having received BPs, without maxillofacial radiotherapy [18]. The exposed bone process, treated with standard techniques, persists even after proper cares are provided. The diagnosis remains clinical and is sustained by a clinical observation only. A histological exclusion of bone metastases from a primary malignant disease and confirmation of osteonecrosis have to sustain the clinical diagnosis. Pamidronate and zoledronate are the most frequently BPs involved, taking into account that we lack of setback for ibandronate [15,16,19]. Nevertheless, some cases have been reported in benign diseases (*i.e.* osteoporosis, Paget's disease) with the use of oral nitrogen-containing BP, such as alendronate, and risedronate [14]. Rare cases of ONJ or non-traumatic osteonecrosis, regardless of its location, have been reported in few patients receiving chemotherapy and/or corticosteroids without BP therapy [20,21].

Clinically, the occurrence of bone necrosis is, most of the time, consecutive with dental procedures affecting bone tissue (mainly tooth extraction or dental implant placement), but it can be spontaneous. In terms of relationship, circumstances of detection may be unclear. Indeed, following the onset of BP, some patients present with conditions requiring a dental extraction, when an underlying ONJ induces atypical symptoms. In almost 70% of cases, the ONJ appears in a context of unstable painful tooth, but this is also described among patients with healthy teeth, and even in the event of toothless jaw (Fig. 1) [22]. The disorder is often painful, although some patients remain asymptomatic. The ONJ sits in the mandible in 62–82% of cases, less frequently in the maxilla (8–18%), whereas a mixed involvement of mandible and maxilla have