LETTER TO THE EDITOR

OSTEONECROSIS OF THE JAWS AND BEVACIZUMAB THERAPY: A CASE REPORT

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Received June 28, 2011 – Accepted May 14, 2012

Bevacizumab is a humanized recombinant monoclonal antibody that blocks Vascular Endothelial Growth Factor (VEGF). Recently, its use has been related with osteneocrosis of the jaws (ONJ), a disease showing a histological pattern similar to bisphosphonate-related ONJ. The aim of this study is to describe an ONJ case-report following bevacizumab chemotherapy without bisphosphonate therapy. We monitored ONJ development associated with the use of bevacizumab in a 47-year-old male with primitive adenocarcinoma of the parotid gland. Our results could suggest a possible correlation between the eruption of the lower third molar tooth and ONJ development following bevacizumab therapy. Clinicians should be aware of the potential risk of bevacizumab-related ONJ complication; moreover, since there are no effective therapeutic protocols for ONJ treatment, it is very important that patients develop good oral hygiene habits and undergo regular dental status evaluation by dentists.

Bevacizumab is a recombinant, humanized monoclonal antibody that binds to VEGF, thus inhibiting VEGF biological activity and thus angiogenic processes (1). It was approved by the US Food and Drug Administration for metastatic colorectal cancer; nevertheless, its clinical efficacy in combination with other agents has been demonstrated in many other cancers, including breast, lung and renal cancer (2-4). The use of bevacizumab has been recently correlated with the development of osteonecrosis of the jaws (ONJ) (5-8), which showed a similar histological alteration of bisphosphonate-related ONJ, a rare and late iatrogenic effect with significantly higher incidence in cancer patients that could occur after minimal invasive dentoalveolar surgery, e.g. tooth eruptions, teeth extractions and implantology (9, 10).

In this study we report a case of ONJ following bevacizumab chemotherapy without bisphosphonate therapy.

A 47-year-old male patient with a primitive adenocarcinoma of the left parotid gland was treated by surgical approach and after six weeks received an anthracycline-based chemotherapy (epirubicin 70mg/m2 plus cisplatin 100mg/m2) every three weeks for six months. Eighteen months after the surgical procedure, skeletal metastases involving the ribs, the cervical spine and the pelvis were observed by bone scintigraphy.

Key words: osteonecrosis, bevacizumab, jaws

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0394-6320 (2012)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

Bevacizumab was started at the dose of 15mg/Kg for six months for a total of eight doses, according to the experimental protocol. Some months following the last dose of Bevacizumab, skeletal metastases persisted and reactive hypertrophy of lymph nodes in the left temporal region was observed. Positron emission tomography confirmed the progression of the primary neoplastic pathology and the patient was treated with additional cycles of bevacizumab treatment. No bisphosphonate and/or radiotherapy treatments were used. Ten months after the end of bevacizumab chemoterapy, the patient related pain sensation due to a recent symptomatic eruption of the lower third molar tooth (number 38) associated with a compromised status of periodontal structures. Our anamnesis suggested that eruption was dated six months previously, corresponding to approximately four months after the last dose of bevacizumab. Clinical examination showed exposed lingual alveolar cortical bone in the lower jaw and the presence of edema with moderate exudates in the associated mucosa; moreover, a severe pain sensation and trismus of masseter muscle were reported. The lingual cortical bone exposed appeared greyish and necrotic. The patient reported paresthesia of the left lower lip, due probably to an involvement of homolateral inferior alveolar nerve. No significant correlation was observed by orthopantomographic analysis, whereas dental scan computer tomography showed the presence of bone loss in this area and the mandibular scintigraphy showed hypercaptation in the same area that was consistent with the inflammatory status.

Serological analysis during subacute phase resulted: VES:32; PCR:1,56 mg/dl; Fibrinogen: 670 mg/dl; the oral swab performed for pathogen detection was negative.

According to the guidelines of the American Association of Oral and MaxilloFacial Surgeons and literature data (11), ONJ is defined by the presence of exposed bone for more than 8 weeks in the absence of cervical-facial radiotherapy before ONJ onset, we diagnosed a case of ONJ.

Since the patient was in compromised systemic conditions and was subjected to additional cycles of chemotherapy with bevacizumab, we started an antibiotic therapy and local treatment, without surgical removal of the necrotic area. Following the resolution of the acute phase, (about eight days from the start of antibiotic therapy), we administered antibiotic therapy (amoxicillin and clavulanic acid 3g/day and metronidazole 1.5g/day) and we removed part of the exposed necrotic bone in order to avoid traumatic ulceration of the tongue due to the direct contact with the bone lesion. Fifteen days following surgery, we observed a stabilization of the clinical status of the patient; nevertheless, we did not obtain the regeneration of the mucosal layer and three months after surgery, a portion of the exposed alveolar bone was observed. Serological parameters had also improved: VES:14; PCR:0,7 mg/dl; fibrinogen:380 mg/dl.

Clinical conditions were unvaried for the following seven months, when the patient died due to the sudden systemic complications of the primary disease.

Our results agree with previous studies, showing a case of bevacizumab-related ONJ (5-8). The anti-angiogenic property of bevacizumab might compromise microvessel integrity of the jaws and lead to alteration of bone metabolism (5). VEGF inhibition, in fact, blocks the growth of the blood vessels, leading a reduction in the nutrients and oxygen tissue support, inducing deleterious effects on bone cell function and differentiation and thereby causing a failure to repair physiological trauma (e.g. tooth brushing or chewing): these effects could be summarized as bevacizumab-related ONJ (5, 6).

Moreover, our results could suggest a possible correlation among the eruption of the lower third molar tooth and ONJ development following bevacizumab therapy; nevertheless, the exact role of tooth eruption is not well defined and other important aspects, such as the advanced primary tumor and/or bevacizumab treatment could contribute to ONJ. Since, to date, there are few literature data, other studies could be important to confirm our hypotheses.

Considering the potential risk of bevacizumab-related ONJ complication, clinicians should take this into consideration, and since there are no effective therapeutic protocols for ONJ treatment, it is very important that patients should develop good oral hygiene habits and undergo regular dental status evaluation by dentists.

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