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REVIEW

Denosumab efficacy in giant cell tumors of the bone - short review

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Abstract

Giant cell tumors of the bone are tumors whose malignant character has long been debated. Lung metastases have been reported in some cases. They usually represent osteolytic, locally aggressive bone tumors for which surgery is the standard of care. Denosumab is the most effective systemic treatment in these cases, but both the timing and the duration are a matter of debate.

The aim of this short review was to describe the most important trials that treated patients with this drug and to discuss both advantages and long-term toxicity. It can be concluded from the presented data that the choice of adding denosumab in the treatment sequence of giant cell tumor of the bone has to be taken in a personalized manner for each patient.

Keywords: denosumab, giant cell tumor of the bone

Introduction

Giant cell tumors of the bone (GCTB), also referred to as osteoclastoma, represent a rare entity comprising 3-5% of bone malignancy and 20% of the benign tumors. Most of these tumors are a result of aberrant RANKL secretion of the malignant bone stoma, after which an important number of osteoclast precursors are recruited [1].

Most tumors are osteolytic and occur in the distal parts of the long bones. The stoma cells usually carry a mutation in H3F3A, which results in protein methylation and gene expression altering. However, their malignant status is debatable, most of them having a tendency to recur just locally after incomplete resection. Lung metastases that usually have an indolent behavior have been described in 1-4% of the patients. Women between 30-50 years old are most often affected [2].

Local recurrence remains the most critical issue in the evolution of these tumors. The radical resection, considered curable, can sometimes be impossible due to anatomical reasons. Soft tissue invasion is more frequently associated with local recurrence. However, if en-bloc resection is possible, the local recurrence rate is between 0-12%. If the patient presents with malignant bone fracture at presentation, curative surgery is often an issue [3].

Denosumab

Denosumab, a fully human monoclonal anti-RANK-L antibody is present in most studies and up until now the most effective treatment for GCTB. It prevents the osteoclast precursors to generate differently into active osteoclasts, therefore reducing bone resorption and bettering bone density. The usual dose of denosumab in this disease is 120 mg intravenously, administered every four weeks [4].

The most frequent adverse reactions include lumbar pain, pain in the extremities, asthenia, hypophosphatemia, and hypocalcemia. Less frequent but more dangerous reactions include infection that mandates hospitalization (most frequently intraabdominal and urinary tract), severe musculoskeletal pain, and last but not least, osteonecrosis of the jaw [5].

Jaw osteonecrosis is a dose-dependent, disability adverse event. At the beginning of denosumab treatment, dental evaluation is mandatory and if local infection exists, it should be treated before the treatment initiation. When under treatment, dental extraction should be avoided, this being the proven procedure that initiates osteonecrosis of the jaw. However, if a patient needs any invasive dental treatment when under denosumab, risks and benefits have to be weighed. Postmarketing reposts on denosumab include some other adverse reactions that were not described in the prospective trials. They include hypersensitivity reactions, including anaphylaxis, bone marrow suppression, and atypical femoral fracture. This last impairment should be considered whenever a patient under denosumab presents with inguinal and thigh pain [6,7].

Denosumab efficacy was proven in several clinical trials that included patients with unresectable, relapsed, or metastatic GCTB. A phase II trial that included 37 patients found a response in 86% of the assessable patients (30 of the 35 assessable patients). The response criteria were somewhat particular, defined as the disappearance of more than 90% of giant cells in the specimen or the absence of radiological progression at 25 weeks from initiation of the treatment. It should be taken into account that RECIST criteria cannot be used for bone lesions [8].

Another phase II trial included patients with unsolvable GCTB who were separated into three subgroups: the first one - only unresectable patients, the second one - resectable, but with high morbidity and the third one included patients from another denosumab trial. After 13 months of therapy n=163 of the 169 patients in cohort, one had no progression of the disease. All the patients in this trial reported pain relief with the treatment. In group II (n=222) 48% of the patients postponed or did not need surgery at all and 38% were operated upon by less aggressive procedures than initially planned, proving that neoadjuvant treatment is a very promising option in this disease. Even if this high evidence trial supports the efficacy of denosumab in advanced GCTB patients, adverse events were reported. 98% of the patients had severe adverse events and 5% of the patients had to stop denosumab due to toxicity. The most frequent events that mandated treatment cessation were osteonecrosis of the jaw, hypocalcemia, hypophosphatemia, and severe infection. Probably one of the most interesting events to take into consideration was the reported 1% of new primary malignancy [9,10].

Denosumab is a controversial choice for patients with unresectable or metastatic disease. Data on lifelong denosumab use is still unclear. It is certain that denosumab not only inhibits dedifferentiation of osteoclasts but also limits the osteoclast osteoblast signaling. If this signaling pathway is inhibited for a long time, a drop in bone density can appear. Moreover, given the fact that GCTB are tumors that appear in the young, one has to take into consideration pregnancy in the young female patients. The contraindication of pregnancy during denosumab treatment has to be explained to

the patient. The use of bisphosphonates can be an option to avoid these two situations [11-13].

Conclusion

To sum up, even after the introduction of denosumab as primary systemic treatment, GCTB remains a therapeutic challenge. Radical surgery is the ideal treatment, but sometimes, clear margins are hard to achieve. Denosumab is very useful, but the duration of the benefit and the long-term side effects are still under research. The sequence of therapies has to be adapted to every patient.

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