Use of Denosumab in Aneurysmatic Bone Cyst: Literature Review

Uso de denosumab en quiste óseo aneurismático: Revisión de la literatura

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Abstract

Introduction Aneurysmal Bone Cysts (ABCs) are locally-aggressive benign tumors with relevant potential for recurrence, representing approximately 1% of all bone tumors. Multiple treatments are described for them, such as: intralesional excision, selective arterial embolization, injection of sclerosing agents, and radiation. These treatments have a variable efficacy rate, can reach 20% and may be associated with serious comorbidities such as functional loss of the limb.

Objective To perform an integrative review of the literature on the use of denosumab in the treatment of ABCs, describing the epidemiological profile, the dosage used, and the complications.

Methodology Articles published in the past five years were retrieved from the PubMed database. The information collected from the cases reported was age, gender, tumor location, the performance of surgery before and/or after the denosumab treatment, the dose used, the complications, and recurrence.

Results We analyzed 7 articles, 4 case reports and 3 case series, written in English, and published from 2014 to 2019. Most patients were female, with an average age of 14 years, with the tumor located in the spine.

Conclusion The use of denosumab in the treatment of ABCs yielded good results, with low rates of recurrence and complications. However, further studies are needed to define a treatment protocol.

Keywords

- aneurysmatic bone cyst (MeSH ID: D017824)
- denosumab (MeSH ID: 000069448)
- literature review (MeSH ID: D003211).

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Resumen

Introducción Los quistes óseos aneurismáticos (QOAs) son tumores benignos, localmente agresivos, y con importante potencial de recidiva, que representan aproximadamente el 1% de todos los tumores óseos. Se describen múltiples tratamientos, como: escisión intralesional, embolización arterial selectiva, inyección de agentes esclerosantes, y radiación. Estos tratamientos tienen una tasa variable de eficacia, ya que la recurrencia puede llegar al 20% y puede estar asociada a comorbidades graves como la pérda funcional de la extremidad.

Objetivo Realizar una revisión integradora de la literatura sobre el uso de denosumab para el tratamiento de QOAs, describiendo el perfil epidemiológico, la dosis utilizada, y las complicaciones.

Método Se recopilaron artículos publicados en los últimos cinco años en la base de datos PubMed. La información recogida de los casos reportados fue la edad, el sexo, la ubicación del tumor, la realización de cirugía antes y/o después del tratamiento con denosumab, la dosis utilizada, las complicaciones, y la recurrencia.

Resultados Se analizaron 7 artículos, 4 reportes de casos y 3 series de casos, escritos en inglés, y publicados de 2014 a 2019. La mayoría de los pacientes eran del sexo femenino, con una edad promedio de 14 años, y el tumor localizado en la columna.

Palabras clave

- quiste óseo aneurismático (MeSH ID: D017824)
- denosumab (ID MeSH: 000069448)
- revisión de la literatura (MeSH ID: D003211)

Introduction

Aneurysmatic bone cysts (ABCs) are considered locally-aggressive benign tumors with a significant potential for recurrence.[1,2]

They represent approximately 1% of all bone tumors, with an incidence of 0.14 per 100 thousand inhabitants. Approximately 75% to 90% of the cases occur before the age of 20. The most common sites are the long bones (67%), the spine (15%), and the pelvis (9%).[3,4]

Regarding pathophysiology, evidence shows genetic alteration, specifically a positive regulation induced by translocation of the ubiquitin-specific peptidase 6 (*USP6*) gene located at chromosome *17p13*, which favors a primary neoplastic process. This particular translocation increases *TRE17* production, a protease that leads to an increase in metalloproteinase in the matrix and in the activity of matrix metalloproteinase-10 (MMP-10). This is associated with a block in osteoblast maturation through an autocrine mechanism and increased release of vascular endothelial growth factor (VEGF), thus increasing vascularization.[1,4]

Clinically, it usually presents as a simple lesion associated with a mass that increases in volume over time, edema, and pain. Histopathologically, the tumor is characterized by the formation of a cavity that contains uncoagulated blood and is divided by septations of fibrous connective tissue comprising a mixture of components, including multinucleated giant cells, osteoclasts, and fibroblast-like stromal cells.[3]

Multiple treatments are described, such as: intralesional excision, selective arterial embolization, injection of sclerosing agents, and radiation. These treatments have a variable rate of efficacy, since recurrence can reach 20% and can be associated with serious comorbidities such as functional loss of the limb.[3,5]

A recent study[6] suggests that the pathophysiology of ABC is similar to that of giant-cell tumors (GCTs) of the bone. In the TCG, malignant cells secrete the receptor activator of nuclear factor kappa-B ligand (RANKL).

Denosumab is a human monoclonal antibody that binds specifically to RANKL. This prevents activation of osteoclast receptor activator of nuclear factor kappa-B (RANK) by inhibiting its function. This drug is highly effective in GCT of the bone and, in principle, similar effects can be expected in ABC. It is important to know that today there is no treatment protocol or recommendation for the use of denosumab in ABC.[1]

The present article aims to review the literature on the use of denosumab for the treatment of ABC, describing the epidemiological profile, the dosage, and the complications.

Methodology

On the PubMed database, we retrieved articles published in the last five years with the following keywords: *ANEURYSMAL BONE CYST AND DENOSUMAB*.

Case reports, case series, and clinical trials regarding any bone segments and patients of any age were used as inclusion fcriteria.

Articles regarding other tumors were excluded.

The information collected from the cases was age, gender, tumor location, the performance of surgery before and/or after the treatment with denosumab, the dose used, the complications, and recurrence.

Results

Using the keywords and the 5-year period, 31 articles were found. When using the inclusion and exclusion criteria, eight articles remained. As one article presented preliminary results, it was excluded from the research. In the end, 7 articles remained: 4 case reports and 3 case series, all written in English and published from 2014 to 2019.

There was a total of 24 (11 male and 13 female) patients with an average age of 14 (range: 5–35) years.

The most frequent location was the spine (45.8%), followed by the long bones (20.8%), and the pelvis (20.8%). In one case, the article did not report the location.

In total, 54% of the patients did not undergo surgery before the denosumab treatment. As for those submitted to surgery, the majority (36%) underwent curettage plus bone grafting.

In total, 5 articles used the same treatment protocol as that used for GCT of the bone, that is, subcutaneous (SC) administration of denosumab at a dose of 120mg on days 1, 8, 15 and 28 in the first month, followed by a monthly application of 120 mg until clinical and radiological resolution. In the article by Kurucu et al.[3] (2018), the protocol used was the weekly SC administration of denosumab at a dose of 70 mg/m^2 during the first month, and then monthly, until clinical and radiological resolution.[3] In the article by Ntalos et al.[7] (2017), the protocol used was the monthly SC administration of denosumab at a dose of 60 mg until clinical and radiological resolution, as it would decrease the risk of side effects such as hypocalcemia. In all studies except the one by Ntalos et al.,[7] supplementation with calcium and vitamin D to avoid hypocalcemia was performed.

Most patients (66.7%) did not require surgical treatment after using denosumab. In the cases submitted to surgery, the majority (62.5%) underwent curettage.

Regarding recurrence, most patients (66.7%) did not present this complication. In cases that presented the complication, 50% were treated with another period of denosumab. It is noteworthy that in two patients the monthly administration of 120 mg of the medication was maintained until the end of the study.

Another reported complication was hypercalcemia as a rebound effect after the discontinuation of denosumab, which occurred in 3 (12.5%) patients.

Discussion

Though benign, ABCs are locally-aggressive tumors. Wide resections with an oncological margin can lead to major defects, serious complications, and, in some patients, they are contraindicated due to the location of the tumor. Intralesional curettage with or without bone grafting is the therapy predominantly used, but it carries a 20% risk of local recurrence.[1] Some authors[4] advise using phenol as an adjuvant, as the recurrence rate drops to 7%.

To reduce these complications with extensive resections, less invasive methods have been developed, such as: cryotherapy, sclerotherapy, doxycycline injections, radionucleotide ablation, arterial embolization, and radiotherapy. Good results have been reported, but the recurrence rate remains a problem.[7]

In GCT of the bone, the interaction between RANK and RANKL is an important factor that regulates the formation of giant cells and tumor progression. Denosumab effectively blocks the RANK–RANKL interaction, and has been approved for the treatment of osteoporosis, bone metastases, multiple myeloma, and GCT of the bone. The pathophysiology of ABC is similar to that of GCT of the bone, and the use of denosumab in ABC was first reported in 2013 in a study by Lange et al.[8]

The present research showed a slight predominance of females with an average age in their teens. The most common location was the spine, which is different from what is reported in the literature, probably because the articles used in the present review did not show an indication of resection with an oncological margin, and ABC located in the spine constitutes a challenge in terms of treatment, since it requires treatment with low rates of sequelae and recurrences.

The present research showed that just over half of the patients underwent surgical treatment before the administration of denosumab; therefore, one of the indications for the use of the drug is tumor recurrence.

As reported by Dürr et al.[1] (2019), so far there is no protocol or treatment recommendation for the use of denosumab in ABC, so the strategy employed is the same as the one for GCT of the bone, that is, SC administration of 120mg (or 70mg/m^2) of denosumab on days 1, 8, 15 and 28 in the first month, and after that, the monthly SC administration of 120mg (or 70mg/m^2). Calcium at a dose of 500mg and vitamin D at a dose of 1000IU were prescribed for daily use. This strategy was used in 6 articles, except in the study by Ntalos et al.[7] (2017), who administered 60 mg SC monthly and did not mention supplementation with calcium and vitamin D. The authors reported that they decided to evaluate the therapeutic effect and reduce the potential side effect. In this report, the patient received denosumab and then underwent the curettage surgery plus bone graft; the patient evolved with recurrence, and the medication was restarted following the same schedule for a 17-month period before surgery. Then, the patient evolved with no signs of tumor recurrence, but showed signs of osteoporosis and low levels of calcium, phosphate, and 25-hydroxyvitamin D3 combined with high levels of parathyroid hormone (PTH).[7]

The main complication found was recurrence in 80% of the cases. Half of the cases were submitted to a new denosumab regimen. Only two patients continued using denosumab until the end of the study due to a history of several recurrences.[1] The conclusion of all articles in the present research is that none of the patients showed signs of ABC recurrence.

Another reported complication was hypercalcemia as a rebound effect after the discontinuation of Denosumab, which occurred in 3 (12.5%) patients. Unlike adults and apparently quite common in patients under 10 years of age, rebound hypercalcemia has been reported 3 to 4 months after the last dose of Denosumab.[4] The 3 cases in the study were younger than 10 years of age.

The other complications described in the literature are hypocalcemia, jaw necrosis, fatigue, muscle pain and atypical femoral fracture.[1]

With the present research, we have noticed that the negative points are the low number of patients and the

lack of protocols regarding dosage, treatment time, and when to use a neoadjuvant, an adjuvant, or both.

Conclusion

The present research has shown that the use of denosumab for ABC treatment yielded good results because it has low rates of recurrence and complications. However, further studies are needed to define the treatment protocol.

Conflict of Interests

The author has no conflict of interests to declare.

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