CASE REPORT

Neoadjuvant and Adjuvant Treatment with Denosumab in Aggressive Giant-cell Tumor of Bone in the Proximal Fibula: a Case Report

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INTRODUCTION

Giant cell tumor of bone (GCTB) is a histologically benign but locally aggressive osteolytic lesion composed of rounded mononuclear histiocytic cells and spindle-shaped stromal cells of mesenchymal origin which are the true neoplastic component of the lesion and which promote the formation of the eponymous giant cells that are responsible for the extensive bone resorption characteristic of GCTB.1,2 GCTB typically affects the metaphyses of the long bones of young adults and skeletally mature adolescents, females slightly more often than males, and accounts for 5% of all bone tumors and 20% of benign bone tumors. It has an unpredictable natural course with metastases in 2%-3%, mainly to the lungs.3 Surgery is the mainstay of treatment, usually intralesional curettage being the method of choice, supplemented with local adjuvants, aiming to minimize the risk of recurrence. Advanced understanding of the biology of GCTB proved that signaling through the receptor activator of nuclear factor kappa B (RANK) expressed by the giant cells and its ligand (RANKL) expressed by the stromal cells is critical to tumor growth and osteolysis.4-7 In 2013, the Food and Drug Administration (FDA) extended the approval of denosumab for use in...
patients with GCTB that is unresectable or where surgical resection is likely to result in severe morbidity, followed by the European Medicines Agency (EMA).6

CASE REPORT

A 45-year-old, otherwise healthy, Caucasian male presented to our institution with painful swelling of the left calf of several-months duration and necessitating the use of walking aids. The patient had received non-steroid anti-inflammatory drugs without therapeutic effect.

On clinical examination the proximal lateral portion of the calf was occupied by a firm unmovable mass with distended overlying skin. Pain was exacerbated on weight-bearing. There was no neurological or vascular impairment. Range of motion in the neighboring joints was unaffected.

Plain radiographs revealed subtotal osteolysis of the proximal fibula with no reactive osteosclerotic rim or periosteal reaction with the fibular meta-epiphysis having significantly increased volume (Fig. 1A). Computed tomography showed an isodense lesion with scalloping of the inner cortex that was very thin and expanded (Fig. 1B). On MRT, the signal was heterogeneous, low in T1 and high in T2 with limited cystic areas (Fig. 1C). The results of the imaging studies allowed for the diagnosis of GCTB that was confirmed histologically. Preoperative target therapy was initiated by four subcutaneous applications of 120 mg of denosumab at days 1, 8, 15, and 21, followed by four applications of 120 mg of denosumab every 28 days and checking serum calcium and phosphate levels each time. The patient received daily supplements of calcium (500 mg) and vitamin D (400 IU) to prevent hypocalcemia, tooth loss or osteonecrosis of the jaw. Along with gradual diminution of pain, at 4 months radiographs revealed ossification of the tumor and radiographic demarcation of the fibula relative to the surrounding soft tissues which was an effective reversion from an aggressive stage 3 lesion with breaching of the cortex to an active stage 2 lesion confined within the bone (Fig. 2A). Pain was greatly reduced but still present and target therapy was continued for two more months. At six months of denosumab treatment the patient was pain-free. Supraperiosteal resection of the proximal fibula was performed. The bone was hard, dense, with normal gross appearance apart from the altered shape, and had a distinct margin from the fibular muscles and the common peroneal nerve. When sectioned, it was very hard and had cancellous-like structure (Fig. 2B). The postoperative course was uneventful with weight-bearing as tolerated. Histological re-examination showed absence of osteoclast-like giant cells, virtually no stromal cells, and abundance of newly formed bone (Fig. 2C).

Following surgery, the patient continued to receive 120 mg of denosumab every 28 days for four months. During the ten months of target treatment, the patient did not experience any adverse reactions and calcium and phosphate levels were within normal range. At 12 months of follow-up the patient was pain-free with full restoration of limb function. No evidence of local recurrence or metastatic spread was detected through clinical examination and CT.

DISCUSSION

In the present case, the patient had an excellent response to denosumab treatment prior to surgery with a clear downstaging effect. Following denosumab therapy, the resected specimen contained no osteoclast-type giant cells and new bone formation was observed when compared with the incisional biopsy. Neoadjuvant denosumab therapy created a situation where safe marginal resection could be performed instead of more extensive surgery which would probably impair limb function, given the anatomical location of the tumor. There were no complications or evidence of metastatic, residual, or local recurrent disease one year after initiation of treatment with denosumab. However, different adverse events have been reported in the literature after denosumab treatment: hypercalcemia, infection, possible malignant transformation, osteonecrosis of the jaw, and increased human chorionic gonadotropin concentration.8-10 In spite of this, Dubory et al.8 stated that the use of denosumab could be accepted as safe. Usually, after denosumab treatment, RANKL expression and osteoclast-type giant cells fully disappear and new bone is formed but a few neoplastic stroma cells persist thus increasing the risk of local recurrence. Therefore, additional surgical treatment is mandatory.8,10 Dubory et al.8 pointed out that the effect of denosumab reaches a peak in the first six months and plateaus later on.

In conclusion, denosumab is effective as neoadjuvant treatment in cases of aggressive GCTB because it reduces the volume of tumor tissue and allows for safe marginal surgery and lower recurrence rates.
Figure 1. Imaging studies at presentation. A. AP radiograph – expanded proximal fibula with subtotal osteolysis; B. CT slice – inner cortex scalloped by isodense tumor tissue; C. T1-weighted axial MRT slice – heterogeneous tissue with cystic areas.

Figure 2. Effects of neoadjuvant target therapy. A. AP radiograph showing downstaging with advanced ossification and clear demarcation of the tumor from the soft tissues; B. Gross appearance of the sectioned specimen with hard bone-like tissue; C. HE staining (×40) of the tumor after four months of target therapy. There is abundance of newly formed bone and virtually no observable neoplastic cells.

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Неoadъювантное и адъювантное лечение деносумабом при агрессивной гигантской клеточной опухоли костей в проксимальной малоберцовой кости: клинический случай

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Ключевые слова: деносумаб, гигантская клеточная опухоль костей, RANKL (лиганд-рецепторная система RANK), остеокласты, неoadъювантная терапия

Гигантская клеточная опухоль костей является гистологически доброкачественным, но локально агрессивным остеолитическим поражением, которое может распространять «доброкачественные» метастазы в основном в лёгкие. С тех пор как оно описано как отдельная единица, хирургическое вмешательство является основным методом лечения. Недавно была введена целевая терапия, включающая деносумаб - ингибитирующее антитело для лиганда рецептора активатора ядерного фактора каппа В, имеющего существенное влияние на естественное развитие опухоли. Здесь мы представляем редкий случай агрессивной опухоли проксимальной малоберцовой кости третьей стадии, чей объём успешно уменьшены при помощи неoadъювантной терапии с деносумабом, а затем удалили хирургическим путем и применили адъювантную целевую терапию. Также кратко обсуждаются клинические особенности и формы лечения гигантской клеточной опухоли костей, индикаторы целевой терапии, терапевтический ответ и гистологические изменения.

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