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REVIEW ARTICLE

Denosumab and giant cell tumour of bone—a review and future management considerations

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ABSTRACT

Giant cell tumour of bone (GCTB) is one type of giant-cell-rich bone lesion characterized by the presence of numerous multinucleated osteoclast-type giant cells. Giant cells are known to express RANKL (receptor activator of nuclear factor κB ligand) and are responsible for the aggressive osteolytic nature of the tumour. No available treatment option is definitively effective in curing this disease, especially in surgically unsalvageable cases. In recent years, several studies of denosumab in patients with advanced or unresectable GCTB have shown objective changes in tumour composition, reduced bony destruction, and clinical benefit.

Denosumab is a fully human monoclonal antibody that targets and binds with high affinity and specificity to RANKL. Several large phase III studies have shown that denosumab is more effective than bisphosphonates in reducing skeletal morbidity arising from a wide range of tumours and that it can delay bone metastasis. The relevant articles are reviewed here. The controversies related to the future use of denosumab in the treatment of GCTB are discussed.

KEY WORDS

Denosumab, giant cell tumour of bone, receptor activator of nuclear factor κB ligand, RANKL, bone turnover

1. INTRODUCTION

Recently, successful cure in a case of unusual giant cell tumour in the thyroid was reported[1]. A 38-year-old man with a giant cell tumour of bone (GCTB) in the thyroid cartilage—initially treated as a thyroid cancer—was proposed for treatment with denosumab, a RANKL (receptor activator of nuclear factor κB ligand) inhibitor. After 3 months, computed tomography imaging showed significant modification of the lesion, with several calcifications involving more than 50% of the initial tumour volume. The surgical specimen revealed a tumour mass with histologic features of pronounced osteogenesis and no more evidence of GCTB. This case demonstrated a major tumour response to denosumab in the neoadjuvant setting, with a complete pathologic response.

Is denosumab a breakthrough in the treatment of GCTB? We reviewed the literature focusing on denosumab and GCTB, and here we discuss the biggest questions related to the future management of GCTB.

2. GIANT CELL TUMOUR OF BONE

As one type of giant-cell-rich lesion of bone, GCTB is characterized by the presence of numerous multinucleated osteoclast-type giant cells, and in this mesenchymal tumour, the mononuclear stromal cells are the neoplastic cell type[2]. The giant cells have been confirmed to express RANKL and are responsible for the aggressive osteolytic nature of the tumour[3]. Although generally benign, atypical GCTB may be associated with multiple local recurrences, multicentricity, pulmonary metastases, or lesions that cannot be removed surgically without causing substantial morbidity[4]. The World Health Organization therefore classifies GCTB as "an aggressive, potentially malignant lesion"[5].

In the United States, GCTB accounts for approximately 5% of all primary bone tumours and 20% of all benign bone tumours in adults[6]. About 50–60 new cases of GCTB are managed by specialist health care services each year in the United Kingdom[7]. The disease is more common in China and India, where it constitutes approximately 20% of all primary bone tumours[5]. Giant cell tumour of bone occurs most commonly during the second to fourth decades of life (60%–75%) and has a male-to-female ratio in the range 1:1.2 to 1:1.5[2,5]. Most lesions develop in the long bones (75%–90%), with most cases (50%–65%) occurring near the knee[1,2,8]. Other frequent sites are the distal radius, proximal humerus, fibula, sacrum, and vertebral body (fewer than 3% of cases)[2,8]. In no reported case has GCTB

extended from the metaphysis into the epiphysis across an unfused physis[8].

In 80% of cases, the course of GCTB is benign, but the local recurrence rate is 20%–50%. About 10% of tumours undergo malignant transformation at recurrence, and 1%–4% give rise to pulmonary metastases even in cases of benign histology[5,9]. Most pulmonary lesions are histologically benign, with an appearance similar to that of the primary bone tumour. Although some patients live a long time with pulmonary metastases, distant metastasis of GCTB typically does not respond well to chemotherapy[2]. Recurrent GCTB may undergo malignant transformation to malignant osteoclastoma, fibrosarcoma, or osteosarcoma. Radiation therapy can lead to a transformation to high-grade sarcoma (fewer than 1% of treated patients) or development of secondary malignancies (up to 15% of treated patients)[2,5,8].

Surgery is the typical treatment for GCTBs, with recurrence rates of 15%–45%[8,10]. The recurrence rate after intralesional surgery dropped to 12%–14% with the use of a high-speed burr and allograft or bone cement[11,12]. In cases of local recurrence, therapy consists of repeated intralesional curettage or wide surgical resection, avoiding mutilating procedures. Compared with intralesional surgery, wide resection is associated with a lower recurrence rate (5% vs. 25%), which raises the complicated problem of reconstruction[9].

When pulmonary involvement is diagnosed, surgical resection of the metastasis, if feasible, may be proposed, because prognosis remains favorable in 80% of cases[13]. About 20% of the patients with metastases of the continuously slow-growing and rapidly growing types would die of their disease if untreated. Radiation therapy can be considered. Recently, seemingly improved local control in 65 of 77 patients (84%) was reported[14]. However, the main limitation of irradiation is the potentially high risk of sarcomatous transformation (5%–29%), especially for doses above 45 Gy[15].

Medical therapy for GCTB is experimental and based largely on theories about the causes of the disease. Bisphosphonate therapy is currently used in GCTB because of its anti-osteoclastic effects. The local recurrence rate was 4.2% in patients treated with bisphosphonate and 30% in a control group[16]. Combined treatment followed by administration of interferon alfa resulted in a high rate of GCTB control and reduced surgical morbidity[17]. Based on the therapeutic effect up to 6 years, it has also been supposed that there is a role for interferon in chemotherapy-refractory GCTB[18].

3. RANKL SIGNALLING

Since the early 1990s, bisphosphonates have been the standard treatment for benign and malignant bone diseases alike, with zoledronic acid being the most commonly used drug in oncologic settings[19]. However, elucidation of the signalling pathways that regulate bone cell function and, in particular, recognition of the role of RANKL in bone resorption has provided potential therapeutic targets for inhibiting osteoclast activity.

Expression of RANKL on stromal cells is regulated by a wide range of endogenous hormones and factors that either upregulate RANKL itself or inhibit the expression of osteoprotegerin (OPG). RANKL is essential to the formation, function, and survival of osteoclasts. In bone metastasis, stimulation of osteoblasts by tumour-secreted factors increases the expression of RANKL, which binds osteoprotegerin and leads to increased bone resorption. Denosumab interrupts that cycle by binding to RANKL and preventing the formation and function of osteoclasts[20,21].

The first study to test the therapeutic potential of RANKL inhibition with respect to osteoclast function used a recombinant OPG molecule (AMGN0007)[22]. An antiapoptotic role of OPG has also been proposed in various preclinical tumour models[23], and although its relevance in human malignancy is unknown, this potential adverse effect of OPG in the cancer setting led to the selection of alternative (antibody-based) approaches to RANKL inhibition for further development.

Inhibition of RANKL not only reduces the rate of bone resorption, but might also inhibit the development of bone metastases. In animal models, inhibition of RANKL activity by binding to recombinant antibody constructs of either OPG–Fc or RANK–Fc have unequivocally demonstrated a functional inhibition of RANKL-induced osteoclastogenesis[24]. Furthermore, inhibition of RANKL prevents invasion and metastasis by human osteosarcoma cells[25] and reduces the development of lung metastases in a murine model of osteosarcoma[26].

Denosumab is a fully human monoclonal RANKL antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing its binding to RANK on the surface of osteoclast precursors and osteoclasts, thereby inhibiting osteoclast differentiation, activation, and survival. Denosumab inhibits osteoclast-mediated bone destruction and provides rapid and sustained suppression of bone turnover in patients with multiple myeloma, osteolytic bone disease, and bone metastases from breast and prostate cancers[27–29]. Inhibiting RANK and RANKL may eliminate osteoclast-like giant cells and their associated mononuclear cells in GCTB[7].

Studies in cynomolgus monkeys show a dose-dependent inhibition of bone resorption and an increase in bone mineral density (BMD) with denosumab[30]. The first clinical study of denosumab in postmenopausal women showed that a single dose of denosumab (3 mg/kg) resulted in a rapid, dose-dependent, and sustained decrease in urinary N-terminal telopeptide, which remained suppressed for 6 months after

treatment[31]. Studies in patients with breast cancer and bone metastases indicated that treatment with 120–180 mg of denosumab every 4 weeks provided the most reliable and consistent suppression of urinary N-terminal telopeptide[29]. As a result, treatment with denosumab 120 mg every 4 weeks was chosen in subsequent studies to provide the optimal balance of efficacy and tolerability.

A study of 252 postmenopausal women with early-stage breast cancer found a significant difference of 7.6% in lumbar spine BMD between the denosumab and placebo groups[32]. In a placebo-controlled trial of denosumab in 1468 men receiving androgen-deprivation therapy for nonmetastatic prostate cancer, 36 months of denosumab treatment was associated with a significantly reduced incidence of new vertebral fractures[33].

A study published in *The Lancet* reached the conclusion that denosumab treatment significantly increased bone metastasis–free survival and significantly delayed both the time to first bone metastasis and the time to first symptomatic bone metastasis[34]. The first evidence suggesting that denosumab might be superior to bisphosphonates in terms of preventing skeletal morbidity was reported in a randomized phase II study conducted in patients with bone metastases caused by various tumour types[28]. Subsequently, three identical double-blind phase III registration studies of denosumab were completed[35–37]. Denosumab treatment delayed the occurrence of all types of skeletal-related events (SREs), including pathologic fractures, the need for either radiotherapy or surgery to bone, and the occurrence of spinal cord compression. The suppression of markers of bone resorption was significantly higher with denosumab than with zoledronic acid in all three studies. Overall, efficacy with denosumab was significantly superior to that with zoledronic acid[35–37]. Because of those findings, denosumab was granted marketing authorization in the United States in 2010 and in Europe in 2011 for the prevention of SREs in adult patients with solid tumours. On October 24, 2012, the U.K. National Institute for Health and Clinical Excellence published guidelines for the use of denosumab to prevent SREs in adults with bone metastases from solid tumours[38].

4. ACTIVITY OF DENOSUMAB IN GCTB

In 2000, it was reported that, in patients with GCTB, inhibition of RANKL by denosumab could potentially inhibit the destructive process and eliminate the population of giant cells[3]. The osteoclast-like giant cells and their precursors express RANK, and some mononuclear cells (stromal cells) express RANKL. It is possible that the recruitment of osteoclast-like giant cells is related to stromal cell expression of RANKL and that the giant cells are responsible for the aggressive osteolytic activity of the tumour[39]. Because denosumab has been shown to inhibit osteoclast function via the RANK/RANKL pathway, it has been thought to inhibit the activity of osteoclast-like giant cells in GCTB.

Given the clear role of RANKL in GCTB, denosumab was studied in a proof-of-principle phase II study in 35 patients with recurrent or unresectable GCTB[39]. Denosumab was administered by subcutaneous injection at 120 mg every 4 weeks, with an additional loading dose of 120 mg on days 8 and 15 of the first cycle. Of 35 evaluable patients, 30 (86%) experienced a tumour response, defined as near-complete elimination of giant cells upon repeat biopsy after treatment (all evaluable patients) or radiographic stabilization of disease at 6 months (10 of 15 evaluable patients). Although formal assessment of pain and quality of life was not mandated in this proof-of-principle study, data collected from 31 patients showed that 26 reported reduced pain or functional improvement. Radiologic evidence of bone repair was reported in 9 patients. Response was usually associated with rapid changes in metabolic uptake as measured by fluorodeoxyglucose positron-emission tomography imaging, usually within 4 weeks of treatment start. As noted earlier, marked suppression of bone turnover was observed, with reductions in urinary N-terminal telopeptide and serum C-telopeptide as early as 28 days after the first dose that were sustained for the duration of the study. The treatment was generally well tolerated, without serious treatment-related adverse events. Blockade of RANKL signalling in patients with recurrent or unresectable GCTB resulted in objective changes in tumour composition, reduced bony destruction, and clinical benefit—at least to the extent measured in this particular study.

In a recent phase II study, denosumab given to patients with surgically salvageable and unsalvageable GCTB was well tolerated and associated with inhibited disease progression (99%) and a reduced requirement for surgery[40]. At least 90% tumour necrosis was also reported to have been found among GCTB cases after the administration of denosumab[8]. Preoperative denosumab treatment was also suggested to potentially make subsequent surgical resection easier in patients with aggressive GCTB who are poor surgical candidates or in whom the tumour is in a location difficult to treat surgically.

Given all of the foregoing findings, denosumab can be used for the treatment of recurrent GCTB and surgically unsalvageable GCTB (for example, sacral or spinal GCTB, or multiple lesions including pulmonary metastases), and in patients whose planned surgery includes joint resection, limb amputation, hemipelvectomy, or another procedure resulting in severe morbidity.

The most common adverse events associated with denosumab during use for its licensed indications include urinary tract infection, upper respiratory tract infection, dyspnea, sciatica, cataracts, constipation,

diarrhea, rash, hyperhidrosis, pain in extremities, hypocalcemia, hypophosphatemia, tooth extraction, and osteonecrosis of the jaw[41]. Daily supplements of calcium 500 mg and vitamin D 400 IU are recommended to prevent these adverse events[39].

In all three of the phase III registration studies discussed earlier, osteonecrosis of the jaw was associated with both denosumab (1.8%) and zoledronic acid (1.3%)[35–37]. Acute-phase reactions characterized by fever, myalgia, and bone pain were observed within the first 3 days of treatment in about 20% of patients treated with zoledronic acid; only 8.7% of patients treated with denosumab experienced such reactions[42]. Hypocalcemia was more frequent with denosumab than with zoledronic acid (9.6% vs. 5.0%), although all patients were encouraged to take calcium and vitamin D supplements[42]. Reassuringly, the incidence of infectious episodes was similar in the groups of patients treated with denosumab and zoledronic acid in all three studies[35–37]. No statistically significant differences were reported in the incidence of cardiovascular adverse events, new malignancies, or injection site reactions, and no patient developed neutralizing anti-denosumab antibodies.

A systematic review of 25 studies for denosumab in osteoporosis concluded that, compared with placebo and alendronate, denosumab was associated with greater and sustained increases in BMD and a reduction in bone turnover markers. Denosumab was also associated with a risk of urinary infections and eczema[43].

In a network meta-analysis, denosumab was found to be more effective than zoledronic acid, placebo, and pamidronate in delaying the time to a first SRE and in reducing the risk of first and subsequent SREs during treatment of bone metastases secondary to solid tumours[44]. Recently, a systematic review of the literature that included 6142 patients set out to determine the efficacy and safety of denosumab in reducing SREs in patients with bone metastases[45]. Denosumab was more effective than zoledronic acid in reducing the incidence of SREs; it also delayed the time to SREs. No differences were found between denosumab and zoledronic acid in overall mortality reduction or in the overall frequency of adverse events.

5. CONTROVERSIES

Clearly, for some patients with advanced, progressive, or symptomatic heavily pretreated GCTB, denosumab provides a therapeutic option not previously available. However, the risk–benefit balance of therapeutic alternatives (including denosumab) remains a complex problem requiring more data. A common scenario is a large sacral GCTB for which surgical or radiotherapeutic approaches carry significant long-term consequences. In particular, reproductive decision-making appears to be an important factor in a younger population. Pregnancy is absolutely contraindicated in patients on denosumab, but radiotherapy to the pelvis is likely to affect gonads and uterus. A decision either way depends on how long denosumab is required, because GCTB is rarely life-threatening and can be considered a chronic disease. The initial phase II study of denosumab in GCTB did not address outcomes in participants who stop treatment[39]. Oral side effects (suspected by investigators to be osteonecrosis of the jaw, or meeting predefined criteria for osteonecrosis of the jaw) should be assessed[46]. The relapse rate, the biomarkers that predict relapse, and the options for therapy after relapse also need to be defined. Follow-up to the study might not have been adequate to document the safety and efficacy of denosumab in the treatment of GCTB[47].

A separate issue is whether denosumab can facilitate definitive therapy. Whether denosumab can reduce the extent of surgery required for patients with Campanacci III[48] GCTB and can reduce recurrence rates after definitive surgery is unknown. If lifelong denosumab is required for GCTB, what is the optimal schedule of therapy? If patients have to receive long-term therapy, is a monthly dosing schedule optimal? The effect of denosumab on the developing skeleton has not been established. More generally, a long-term safety program in younger patients who receive prolonged therapy with denosumab ought to include formal measures of BMD as well as SREs. The question of whether the effect of denosumab for GCTB is only temporary or whether long-term or definitive control can be achieved remains open. The genetic basis for stromal overexpression of RANKL is unknown, and it is possible that GCTB represents a pathologic variation of the normal physiologic interdependence of osteoblast and osteoclast populations in bone. Support for the latter possibility is found in the existence of currently unknown reciprocal signals that maintain the stromal population in an immature and presumably RANKL-expressing state. Hopefully, a current clinical study (search for NCT00680992 at http://www.clinicaltrials.gov) with 511 enrollments, whose eligibility criteria now extend to skeletally mature patients 12 years of age and older will address those questions; however, randomized studies will ultimately be required.

Finally, denosumab may offer clinical utility in other giant-cell-rich neoplastic disorders, including giant cell reparative granuloma of the mandible, tenosynovial giant cell tumour, chondroblastoma, giant-cell-rich pilar tumours, and perhaps malignant conditions associated with giant cell infiltration.

6. CONCLUSIONS

Denosumab is a highly effective and specific antagonist of RANKL, which represents an exciting paradigm for targeted translational research in diseases such

as GCTB. Denosumab clearly interdicts bone destruction and may offer symptom and disease control for patients with few other options. The optimal use and long-term effects of denosumab in the young population primarily affected by GCTB remain to be defined. Further investigation of the use of denosumab as a new therapy for GCTB is warranted. In the near future, denosumab may offer a treatment option for unresectable GCTB or an alternative to surgical procedures that would result in severe morbidity.

7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare. Among the authors of this report, none has any relationships such as employment contracts, consultancy, advisory boards, speaker bureaus, membership of Board of Directors, and stock ownership with pharmaceutical companies or other entities.

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