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CURRENT OPINION

Challenges of denosumab in giant cell tumor of bone, and other giant cell-rich tumors of bone

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Purpose of review
Giant cell tumor of bone (GCTB) is an uncommon benign primary bone tumor, consisting of receptor activator of nuclear factor kappa-B (RANK) expressing reactive osteoclast-like giant cells and neoplastic spindle-shaped cells. Denosumab was approved by FDA in 2013 and by EMA in 2014 to treat adults and skeletally mature adolescents with unresectable GCTB or when resection is likely to result in severe morbidity. However, there is much discussion regarding the optimal applied treatment strategy.

Recent findings
Neoadjuvant treatment of GCTB with denosumab can effectively downstage tumors to facilitate less morbid surgery or completely avoid the need for resection, but there is concern about local recurrence postsurgery. Definitive treatment of unresectable GTCB improves symptoms and halts tumor progression. The optimal treatment duration is unclear and long-term treatment is associated with adverse events like osteonecrosis of the jaw (ONJ) and atypical femoral fractures. Denosumab maintenance dose interval is currently being investigated.

Summary
For the related but heterogenous group of giant cell rich tumors of bone, like aneurysmal bone cysts (ABC) and central giant cell granuloma (CGCG), denosumab is a new treatment modality under investigation. Given the effectiveness in GCTB, this could be a promising treatment option for selected patients with advanced disease.

Keywords
aneurysmal bone cysts, central giant cell granuloma of the jaw, denosumab, giant cell tumor of bone, neoadjuvant, palliative

INTRODUCTION

Giant cell tumor of bone (GCTB) is an uncommon benign primary bone tumor that mainly affects the long bones [1]. Their occurrence is most frequent in patients between 30 and 40 years old [2]. Although a large part of its morbidity is derived from local complications, like pain, joint involvement and pathological fractures, the tumors do have rare metastatic potential [1]. GCTB consists of reactive osteoclast-like giant cells expressing receptor activator of nuclear factor kappa-B (RANK) [3], mononuclear osteoclast precursor cells and spindle-shaped cells expressing RANK-ligand, which constitute the neoplastic cell population [4]. RANK signaling promotes the generation of multinuclear osteoclast, resulting in bone resorption [5–7].

Treatment of GCTB mainly consists of surgery, either en-bloc resection or curettage with or without local adjuvants like phenol, liquid nitrogen or polymethylmethacrylate (PMMA) [8–12]. Currently, the biggest challenge in GCTB management is the recurrence rate after surgery, which has been described as high as 19–50% after curettage alone [8–11,13,14]. The majority of recurrences after primary intralesional surgery are seen in so-called high-risk GCTB. This group includes tumors with extension into surrounding soft tissue, pathologic fracture, absence of local adjuvant therapy after primary

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KEY POINTS

- There is evidence for short-term neoadjuvant use of denosumab for downstaging high-risk GTCB to facilitate less morbid surgical procedures or avoid surgery altogether.
- En-bloc resection of GCTB, especially in the case of soft-tissue involvement, can be facilitated by a neoadjuvant denosumab regime.
- Neoadjuvant denosumab treatment has not shown to improve recurrence rates postsurgery.
- There is strong evidence for the effect of denosumab for nonresectable GCTB.
- The optimal treatment duration and maintenance dose and interval of denosumab in unresectable disease is still unknown.
- For the related group of giant cell-rich tumors of bone like ABC and CGCG, the place of denosumab is still up for further investigation.

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curettage, recurrent tumors and localization in the spine or sacrum [14,15].

Alternatively, systemic treatment with bisphosphonates was explored on a limited scale before the introduction of denosumab. Two small prospective trials investigated the effects of adjuvant treatment with bisphosphonates (alendronate and zoledronic acid) after intralesional curettage. Recurrence rates were 0 and 15%, respectively, after an average follow-up of 28 and 63.6 months [16,17]. The results of a small phase II, randomized study with adjuvant zoledronic acid vs. placebo in high-risk GCTB patients (NCT00889590) was thus far only presented in abstract form [18].

DENOSUMAB

Denosumab is a human monoclonal IgG2 antibody derived from mammalian cell lines that inhibits activation and differentiation of osteoclast-like giant cells and consequent osteolytic damage by binding RANK-ligand [4,19]. Denosumab was approved by the U.S. Food and Drug Administration (FDA) in 2013 and European Medicines Agency (EMA) in 2014 to treat adults and skeletally mature adolescents with unresectable GCTB or when resection is likely to result in severe morbidity. This approval was granted after publication of the results of two phase II trials showing an objective and lasting response in this patient group [20,21]. The first trial resulted in an 86% (30/35) objective response rate, defined as elimination of osteoclast-like giant cells on histology or no radiological progression [21]. The second larger study showed no disease progression in 69% of surgically unsalvageable patients after median 13 months of treatment, and of 100 patients with salvageable GCTB 74 needed no surgery and 16/26 less morbid surgery than previously scheduled [20].

The introduction of denosumab has changed the treatment landscape of GCTB drastically. However, the best use of this new systemic treatment modality is currently subject of discussion. The scope of this article is to discuss the current challenges of GCTB treatment with denosumab and review recent publications and new insights on this subject. Denosumab treatment of giant cell-rich tumors of bone will be highlighted as well.

CURRENT CHALLENGES OF DENOSUMAB IN GIANT-CELL TUMOUR OF BONE

Neoadjuvant treatment with denosumab

Prospective trials have investigated the use of denosumab in the neoadjuvant setting or as definitive treatment for tumors that are considered unresectable [20–24]. The majority of unresectable GCTB are recurrent lesions or lesions located in the axial skeleton, such as the sacrum or posterior part of the spine, where resection often causes unacceptable nerve damage. Rutkowski *et al.* [25] reported on successful downstaging of unresectable tumors in 222 patients from the largest phase II trial, either resulting in less morbid procedures than planned, like native joint preservation (24/25 patients, 96%) and conversion of en-bloc resection to curettage (39/85, 46%), or avoidance of high-morbid procedures like hemipelvectomy (8/10, 80%) or amputation (32/40, 80%) [25]. During a median follow-up of 13 months, 15% recurrences were seen after (mostly intralesional) surgery [25], which is comparable to recurrence rates in literature [8,10,11,14,15]. Many of these patients received additional adjuvant denosumab therapy for 6 months; however, this was not randomized, so this does not answer the question whether adjuvant denosumab is useful [25].

Some recent literature suggests that neoadjuvant treatment followed by curettage might lead to higher recurrence rates [26▪,27▪▪,28▪]. This could be explained by the transformation of the original soft tissue tumor matrix to a more osseous and fibrotic mass [29–31], which could make it more difficult to distinguish and mechanically remove the tumor from adjacent bone and to perform an optimal intralesional curettage. Neoplastic cells can easily be left behind in the curettage space, increasing the risk of recurrence [32].

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On the other hand, it is reported that denosumab facilitates en-bloc resection of GCTB, because of decreased vascularity, leading to less perioperative blood loss [29,33]. The formation of a sclerotic rim of bone around the lesion facilitates resection, especially in case of soft tissue involvement [30,31,34,35].

Additional data on recurrences after neoadjuvant treatment is available from retrospective series. In a series from Rutkowski, 89 patients with advanced GCTB were treated with neoadjuvant denosumab. Local recurrence rate was 21% (7.7% after wide excision and 32% after curettage) [36▪▪]. Urakawa *et al.* reported recurrence rates of 28.6% (6/21 patients), 22.2% (2/9 patients) and 0% (0/10 patients) after neoadjuvant, adjuvant and neoadjuvant plus adjuvant denosumab, versus 21.5% (34/158 patients) in a nondenosumab-treated group [27▪▪]. In this report, a higher cumulative dose of preoperative denosumab was associated with lower relapse rates [27▪▪]. Smaller series have shown a wide range of recurrence rates ranging from 8% to as high as 67% [31,35,37,38].

In a series by Errani, neoadjuvant denosumab treatment was a risk factor for local recurrence ($P < 0.0001$), based on 25 patient treated with denosumab and curettage. Median follow-up was 42.1 months, and recurrence rate was 60% (15/25 patients), versus 16% (36/222 patients) in the nondenosumab-treated group [26▪]. Patients in the denosumab group did have more disease recurrences ($P < 0.0001$), less adjuvant treatment with phenol (<0.0001) and higher Campanacci stage ($P = 0.053$), which might have led to selection bias in favor of the group that underwent curettage alone.

Definitive treatment with denosumab

In the setting of definitive or palliative treatment, the benefits of denosumab are clear: halt of tumor progression and symptom improvement [20,21]. The main unanswered questions involve optimal treatment duration versus cumulative toxicity. In the largest phase II trial published by Chawla *et al.* [20], patients were treated for up to 13 months with acceptable toxicity and sustained response to denosumab. Palmerini evaluated the long-term toxicity in a retrospective series in which 97 patients were treated for a median of 12 months (range 6–45 months). Overall, six patients (6%) developed ONJ, and patients on prolonged treatment developed mild peripheral neuropathy (6/54, 54%), skin rash (5/54, 9%), hypophosphatemia (2/54, 4%) and atypical femoral fracture (2/54, 4%) [39]. More data on toxicity can be derived from the osteoporotic patient population in which patients are treated with denosumab for up to 2 years [40]. Information on longer term toxicity is not yet available at this moment. Main safety issues of concern with longer term treatment are cumulative dose-dependent osteonecrosis of the jaw (ONJ) and atypical femoral fractures [41,42].

Relapse after cessation of denosumab is a major concern. Especially as histological evaluation of surgical specimens after denosumab treatment only show disappearance of osteoclast-like giant cells, and no apoptosis of the stromal cell population [43,44,45▪,46]. Girolami *et al.* published on the persistent presence of the H3F3A mutation in surgical specimens, further supporting the persistence of the neoplastic cell population [29]. From the osteoporotic patient population, we have learned that the positive effects of denosumab on bone mineral density disappear within several months after discontinuation of treatment, as denosumab is not incorporated into the bone matrix, in contrast to bisphosphonates for example [47].

Reintroduction of denosumab after recurrence is a strategy that has been applied, nonetheless this does not solve above-mentioned toxicity issues. Reducing dose density in maintenance treatment could be a good alternative to complete withdrawal of denosumab. This strategy has been described in case reports [48], and will be further investigated in a prospective trial. The EORTC-REDUCE trial, which is now in set-up, is a multicenter phase II trial investigating reduced dose density of denosumab as maintenance therapy for unresectable GCTB (http://clinicaltrials.gov, NCT03620149). Denosumab will be administered at intervals of 12 weeks until progression or unacceptable toxicity occurs, starting after 1 year of initial standard treatment at 4-week intervals. The aim is to reduce the cumulative dose-dependent toxicity while maintaining efficacy. A similar trial in the United States is being discussed.

In rare cases, transformation of benign GCTB to a malignant bone tumor like osteosarcoma has been described [49]. This can be a consequence of dedifferentiation of the tumor because of prior radiation therapy, misdiagnosis or malignant transformation. A handful of case reports on malignant transformation after denosumab therapy have been published [50–52]. However, the phase II trials by Chawla *et al.* [20] and Thomas *et al.* [21] reported secondary malignant transformation in only 1 of 282 versus 1 out of 37 patients in total. Different theories on the mechanism by which denosumab could increase the risk of malignant transformation have been postulated. Inhibition of RANK ligand could increase susceptibility to oncogenes, and affect T-cell and

B-cell differentiation and dendritic cell survival and cause immunosuppression leading to new malignancies [50]. We would suggest caution is warranted for the development of malignancy in GCTB in general, this is not specific for denosumab-treated cases. A denosumab nonresponding GCTB should, therefore, always be re-biopsied.

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DENOSUMAB IN OTHER GIANT CELL-RICH LESIONS

Giant cell-rich tumors of bone are a group of rare bone tumors that harbour different clinical and histological features, but are all characterized by the presence of osteoclast-like giant cells [53]. This group includes aneurysmal bone cysts (ABC) and central giant cell granuloma (CGCG) amongst others. Resection or curretage is usually the approach in this group of tumors if and when they cause unacceptable morbidity [54,55].

As the histological presence of osteoclastic giant cells and expression of RANK/RANKL is a feature that GCTB and other giant cell-rich tumors have in common [56], it is hypothesized that giant cell-rich tumors show the same reponse to denosumab as previously seen in classical GCTB (see below).

Aneurysmal bone cysts

ABC are rare cystic lesions of bone typically found in the long bones or vertebral bodies, accounting for approximately 9.1% of benign bone tumors with an incidence of 0.14 per 100 000 [57,58▪]. The cysts contain fibroblasts, osteoclast-type giant cells and reactive woven bone, and are most frequently seen in the first two decades of life [57,59]. ABC can present as a primary bone lesion (in about 70% of cases) or as a secondary lesion as a consequence of a reactive process to a preexisting osseous lesion (30%).

Surgery is the current mainstay of treatment for ABC, for example, curretage, resection, embolization. En-bloc resection is the treatment modality with the lowest recurrence rate, though is associated with the high morbidity because of the loss of bone and need for reconstructive surgery. Curretage usually involves local adjuvant therapies, such as sclerotherapy or cryotherapy to lower the risk of recurrence, which has been described as high as 31% [57,60]. The current role of other, nonsurgical treatments of ABC-like radiotherapy [59] or bisphosphonates [55] is limited.

Increasing experience with the use of denosumab in patients with ABC is derived from a number of published case series and case reports. Kurucu *et al.* described nine pediatric patients with ABC treated with denosumab 70 mg/m^2 monthly for a median of 12 (range 6–14) months. Within 3 months, all patients experienced reduction in pain and volume reduction of tumors radiologically ranging from 18 to 82% [58▪]. Two cases of rebound hypercalcemia because of increased osteoclast activity were seen after cessation of treatment.

Another case series by Palmerini *et al.* [61▪] of nine patients treated with 120 mg denosumab monthly with a median of eight (range 3–61) injections, showed replacement of the cystic formations with solid, bone-like tissue by computed tomography as well as pain relief in all treated patients. No significant side effects of denosumab were seen in these cases, apart from asymptomatic hypocalcemia [62]. Several other case reports on patients with sacral ABC presented comparable results [62–69].

Central giant cell granuloma

CGCG is another giant cell-rich benign bone tumor, and is believed not to be a true neoplasm, but the result of a local reparative reaction [55,70]. CGCG are rare with an estimated incidence of 1.1 per million with most patients aged 10–25 years old [55,71]. When multiple lesions are present, the condition is often associated with an underlying syndrome, such as Noonan syndrome or neurofibromatosis type 1, or cherubism [72,73].

A differentiation can be made between aggressive and indolent lesions based on clinical and radiological findings. CGCG usually present as a slow-growing, painless swelling, mostly affecting the jaw bones [55]. In aggressive lesions, pain, paresthesia, rapid growth and cortical perforation can be seen, and these lesions are generally bigger and associated with higher postsurgical recurrence rates [74]. Histologically these aggressive forms of CGCG show a higer percentage of giant cells within the cellular fibroblastic stroma than is typically seen in CGCG [75].

Surgical procedures including enucleation and curettage are still the most frequently used therapy for GCT. En-bloc resection often leads to unacceptable loss of function and poorer esthetic results. Recurrence rates after curettage are high, ranging from 11 to 49% and up to 72% in aggressive lesions [55]. Several alternative treatments have been suggested in the literature, such as intralesional corticosteroid injection, systemic calcitonin, interferon alpha and antibone resorption agents like bisphosphonates and also denosumab [55,76▪].

Several case series and reports describing cases of patients with CGCG treated with denosumab have been published to date [76▪,77–81,82▪]. Most of these cases were CGCG of the jaw, one adult female

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presented with a CGCG of the lumbar spine [80]. All patients were treated with denosumab injections 120 mg subcutaneously monthly, either as an alternative to surgery or if disease had recurred after initial surgery. In all cases, ossification of CGCG lesions was described, and in some regression. Several responses were confirmed histologically with a repeat biopsy that did not show any residual osteoclast-like giant cells or granular tissue [77,78,81,82▪]. All symptomatic patients reported improvement of pain [76▪,78,79,81,82▪]. Follow-up was limited in most reports, the recurrence rate after discontinuation of denosumab is, therefore, still unclear.

A European phase II trial is currently opened for recruitment to assess the use of denosumab in giant cell-rich tumors of bone. Patients with ABC, CGCG and other nonmalignant giant cell-rich lesions like will be treated with denosumab 120 mg once monthly, either as definitive treatment for unresectable disease or as neoadjuvant treatment until surgery. Primary endpoint for salvageable lesions is surgical outcome, and for unresectable disease a combined endpoint including radiological response, clinical disease assessment and patient-reported outcomes. Translational research will be performed on tumor material including evaluation of USP6 rearrangement and proportion of patients with pathological response for patients undergoing surgery (http://clinicaltrials.gov, NCT03605199).

CONCLUSION

In conclusion, the available evidence supports the use of neoadjuvant denosumab for downstaging high-risk GTCB to facilitate less-morbid surgical procedures or avoid surgery altogether. En-bloc resection of GCTB, especially in the case of soft-tissue involvement, can be facilitated by a neoadjuvant denosumab regime. There is no confirmation of improved local control postsurgery, but more importantly no increase of recurrence rates has been confirmed either. Different publications suggest to limit the neoadjuvant treatment time to 3–4 months in order to avoid excessive new bone formation and fibrosis and allowing surgeons to perform an optimal curettage [32,35,36▪▪]. Longer follow-up information from prospective trials regarding recurrence rates is pending, and could provide more insight. Further trials on the addition of adjuvant treatment in this setting are awaited as well.

In the palliative setting, an optimal balance between treatment duration and control of cumulative toxicity is currently being studied. Further studies on maintenance strategies with reduced dose levels and intervals are awaited.

For the related group of giant cell-rich tumors of bone, the place of denosumab is still up for further investigation, but given reported case series and the successes in GCTB, this could be still a promising treatment option for selected patients with advanced disease.

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Conflicts of interest

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