



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

Astrid Lipplaa^a, Sander Dijkstra^b, and Hans Gelderblom^a

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

^aDepartment of Medical Oncology and ^bDepartment of Orthopedic Surgery, Leiden University Medical Center (LUMC), Leiden, the Netherlands

Correspondence to Hans Gelderblom, MD, PhD, Department of Medical Oncology, Leiden University Medical Center (LUMC), Postal Zone C7-P, PO Box 9600, 2300 RC Leiden, the Netherlands. Tel: +31 71 5263486; e-mail: a.j.gelderblom@lumc.nl

Curr Opin Oncol 2019, 31:329–335

DOI:10.1097/CCO.0000000000000529

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

KEY POINTS

- There is evidence for short-term neoadjuvant use of denosumab for downstaging high-risk GCTB 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.

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].

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 non-denosumab-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.

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 curettage 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 response 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, curettage, 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. Curettage 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/m² 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 higher 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 antitumor 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

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 120mg 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.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

The author's institution LUMC has received research grants from Amgen.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Athanasou N, Bansal M, Forsyth R, *et al.* Giant cell tumour of bone. In: Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F, editors. WHO classification of tumours in soft tissue and bone, 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2013.
2. Liede A, Bach BA, Stryker S, *et al.* Regional variation and challenges in estimating the incidence of giant cell tumor of bone. *J Bone Joint Surg Am* 2014; 96:1999–2007.
3. Forsyth RG, De Boeck G, Baelde JJ, *et al.* CD33+ CD14- phenotype is characteristic of multinuclear osteoclast-like cells in giant cell tumor of bone. *J Bone Miner Res* 2009; 24:70–77.
4. Branstetter DG, Nelson SD, Manivel JC, *et al.* Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. *Clin Cancer Res* 2012; 18:4415–4424.
5. Atkins GJ, Kostakis P, Vincent C, *et al.* RANK Expression as a cell surface marker of human osteoclast precursors in peripheral blood, bone marrow, and giant cell tumors of bone. *J Bone Miner Res* 2006; 21:1339–1349.
6. Lindeman JH, Hanemaaijer R, Mulder A, *et al.* Cathepsin K is the principal protease in giant cell tumor of bone. *Am J Pathol* 2004; 165:593–600.
7. Maggiani F, Forsyth R, Hogendoorn PC, *et al.* The immunophenotype of osteoclasts and macrophage polykaryons. *J Clin Pathol* 2011; 64:701–705.
8. Arbeitsgemeinschaft K, Becker WT, Dohle J, *et al.* Local recurrence of giant cell tumor of bone after intralesional treatment with and without adjuvant therapy. *J Bone Joint Surg Am* 2008; 90:1060–1067.
9. Algawahmed H, Turcotte R, Farrokhya F, Ghera M. High-speed burring with and without the use of surgical adjuvants in the intralesional management of giant cell tumor of bone: a systematic review and meta-analysis. *Sarcoma* 2010; 2010; pii: 586090.
10. Balke M, Schremper L, Gebert C, *et al.* Giant cell tumor of bone: treatment and outcome of 214 cases. *J Cancer Res Clin Oncol* 2008; 134:969–978.
11. Kivioja AH, Blomqvist C, Hietaniemi K, *et al.* Cement is recommended in intralesional surgery of giant cell tumors: a Scandinavian Sarcoma Group study of 294 patients followed for a median time of 5 years. *Acta Orthop* 2008; 79:86–93.
12. van der Heijden L, Dijkstra PD, van de Sande MA, *et al.* The clinical approach toward giant cell tumor of bone. *Oncologist* 2014; 19:550–561.
13. Gao ZH, Yin JQ, Xie XB, *et al.* Local control of giant cell tumors of the long bone after aggressive curettage with and without bone cement. *BMC Musculoskelet Disord* 2014; 15:330.
14. Klenke FM, Wenger DE, Inwards CY, *et al.* Giant cell tumor of bone: risk factors for recurrence. *Clin Orthop Relat Res* 2011; 469:591–599.
15. van der Heijden L, van de Sande MA, Dijkstra PD. Soft tissue extension increases the risk of local recurrence after curettage with adjuvants for giant-cell tumor of the long bones. *Acta Orthop* 2012; 83:401–405.
16. Gouin F, Rochwerger AR, Di Marco A, *et al.* Adjuvant treatment with zoledronic acid after extensive curettage for giant cell tumours of bone. *Eur J Cancer* 2014; 50:2425–2431.
17. Yu X, Xu M, Xu S, Su Q. Clinical outcomes of giant cell tumor of bone treated with bone cement filling and internal fixation, and oral bisphosphonates. *Oncol Lett* 2013; 5:447–451.

18. Heijden Lvd, Dijkstra, PDS, Jutte F PC. Adjuvant zoledronic acid in high-risk giant cell tumor of bone – preliminary results of a randomized phase II study. *CTOS*; 2016.
19. Kostenuik PJ, Nguyen HQ, McCabe J, *et al*. Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. *J Bone Miner Res* 2009; 24:182–195.
20. Chawla S, Henshaw R, Seeger L, *et al*. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. *Lancet Oncol* 2013; 14:901–908.
21. Thomas D, Henshaw R, Skubitz K, *et al*. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol* 2010; 11:275–280.
22. Ueda T, Morioka H, Nishida Y, *et al*. Objective tumor response to denosumab in patients with giant cell tumor of bone: a multicenter phase II trial. *Ann Oncol* 2015; 26:2149–2154.
23. Traub F, Singh J, Dickson BC, *et al*. Efficacy of denosumab in joint preservation for patients with giant cell tumour of the bone. *Eur J Cancer* 2016; 59:1–12.
24. Deveci MA, Paydas S, Gonlusen G, *et al*. Clinical and pathological results of denosumab treatment for giant cell tumors of bone: prospective study of 14 cases. *Acta Orthop Traumatol Turc* 2017; 51:1–6.
25. Rutkowski P, Ferrari S, Grimer RJ, *et al*. Surgical downstaging in an open-label phase II trial of denosumab in patients with giant cell tumor of bone. *Ann Surg Oncol* 2015; 22:2860–2868.
26. Errani C, Tsukamoto S, Leone G, *et al*. Denosumab may increase the risk of local recurrence in patients with giant-cell tumor of bone treated with curettage. *J Bone Joint Surg Am* 2018; 100:496–504.
- Large European retrospective study on the efficacy of denosumab in advanced and unresectable GCTB from the six largest European referral centers.
27. Urakawa H, Yonemoto T, Matsumoto S, *et al*. Clinical outcome of primary giant cell tumor of bone after curettage with or without perioperative denosumab in Japan: from a questionnaire for JCOG 1610 study. *World J Surg Oncol* 2018; 16:160.
- Extensive Japanese retrospective study on the effects of peri-operative denosumab in advanced and unresectable GCTB.
28. Medellin MR, Fujiwara T, Tillman RM, *et al*. Prognostic factors for local recurrence in extremity-located giant cell tumours of bone with pathological fracture. *Bone Joint J* 2018; 100-B:1626–1632.
- Important article on the prognostic factors for recurrence in patients with pathological fractures in GCTB.
29. Girolami I, Mancini I, Simoni A, *et al*. Denosumab treated giant cell tumour of bone: a morphological, immunohistochemical and molecular analysis of a series. *J Clin Pathol* 2016; 69:240–247.
30. Gaston CL, Grimer RJ, Parry M, *et al*. Current status and unanswered questions on the use of Denosumab in giant cell tumor of bone. *Clin Sarcoma Res* 2016; 6:15.
31. Muller DA, Beltrami G, Scoccianti G, *et al*. Risks and benefits of combining denosumab and surgery in giant cell tumor of bone—a case series. *World J Surg Oncol* 2016; 14:281.
32. van der Heijden L, Dijkstra PDS, Blay JY, Gelderblom H. Giant cell tumour of bone in the denosumab era. *Eur J Cancer* 2017; 77:75–83.
33. Yang Y, Li Y, Liu W, *et al*. A nonrandomized controlled study of sacral giant cell tumors with preoperative treatment of denosumab. *Medicine (Baltimore)* 2018; 97:e13139.
34. Hakozaki M, Tajino T, Yamada H, *et al*. Radiological and pathological characteristics of giant cell tumor of bone treated with denosumab. *Diagn Pathol* 2014; 9:111.
35. Borkowska A, Goryn T, Pienkowski A, *et al*. Denosumab treatment of inoperable or locally advanced giant cell tumor of bone. *Oncol Lett* 2016; 12:4312–4318.
36. Rutkowski P, Gaston L, Borkowska A, *et al*. Denosumab treatment of inoperable or locally advanced giant cell tumor of bone - multicenter analysis outside clinical trial. *Eur J Surg Oncol* 2018; 44:1384–1390.
- Important retrospective study on the efficacy of denosumab in advanced and unresectable GCTB from six largest European referral centers.
37. Boye K, Jepsen NL, Zaikova O, *et al*. Denosumab in patients with giant-cell tumor of bone in Norway: results from a nationwide cohort. *Acta Oncol* 2017; 56:479–483.
38. Fedenko AA, Tararykova A. Neoadjuvant denosumab for the treatment of resectable giant cell tumor of bone: first results of Russian multicenter study. *J Clin Oncol* 2018; 36:15.
39. Palmerini E, Chawla NS, Ferrari S, *et al*. Denosumab in advanced/unresectable giant-cell tumour of bone (GCTB): for how long? *Eur J Cancer* 2017; 76:118–124.
40. Stopeck AT, Fizazi K, Body JJ, *et al*. Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. *Support Care Cancer* 2016; 24:447–455.
41. Uday S, Gaston CL, Rogers L, *et al*. Osteonecrosis of the jaw and rebound hypercalcemia in young people treated with denosumab for giant cell tumor of bone. *J Clin Endocrinol Metab* 2018; 103:596–603.
42. Chawla NS, Sudan M, Syed I, *et al*. Long-term treatment of giant cell tumors of bone (GCTB) with denosumab: a two institutions 8-year experience. *J Clin Oncol* 2016. [Conference]
43. Lau CP, Huang L, Wong KC, Kumta SM. Comparison of the antitumor effects of denosumab and zoledronic acid on the neoplastic stromal cells of giant cell tumor of bone. *Connect Tissue Res* 2013; 54:439–449.
44. Mak IW, Evaniew N, Popovic S, *et al*. A translational study of the neoplastic cells of giant cell tumor of bone following neoadjuvant denosumab. *J Bone Joint Surg Am* 2014; 96:e127.
45. Shibuya I, Takami M, Miyamoto A, *et al*. In vitro study of the effects of denosumab on giant cell tumor of bone: comparison with zoledronic acid. *Pathol Oncol Res* 2017; 25:409–419.
- Seminal preclinical study on the in-vitro effects of denosumab versus zoledronic acid on osteoclast differentiation, survival and bone resorption in a GCTB cell-line.
46. van der Heijden L, van de Sande MA, Hogendoorn PC, *et al*. Neoadjuvant denosumab for extensive giant cell tumor in os ischium: a case report. *Acta Orthop* 2015; 86:393–395.
47. Tsourdi E, Langdahl B, Cohen-Solal M, *et al*. Discontinuation of denosumab therapy for osteoporosis: a systematic review and position statement by ECTS. *Bone* 2017; 105:11–17.
48. Agarwal A, Larsen BT, Buadu LD, *et al*. Denosumab chemotherapy for recurrent giant-cell tumor of bone: a case report of neoadjuvant use enabling complete surgical resection. *Case Rep Oncol Med* 2013; 2013:496351.
49. Lopez-Pousa A, Martin Broto J, Garrido T, Vazquez J. Giant cell tumour of bone: new treatments in development. *Clin Transl Oncol* 2015; 17:419–430.
50. Tsukamoto S, Righi A, Vanel D, *et al*. Development of high-grade osteosarcoma in a patient with recurrent giant cell tumor of the ischium while receiving treatment with denosumab. *Jpn J Clin Oncol* 2017; 47:1090–1096.
51. Broehm CJ, Garbrecht EL, Wood J, Bocklage T. Two cases of sarcoma arising in giant cell tumor of bone treated with denosumab. *Case Rep Med* 2015; 2015:767198.
52. Aponte-Tinco LA, Piuze NS, Roitman P, Farfalli GL. A high-grade sarcoma arising in a patient with recurrent benign giant cell tumor of the proximal tibia while receiving treatment with denosumab. *Clin Orthop Relat Res* 2015; 473:3050–3055.
53. Flanagan AM, Tirabosco R, Gikas PD. Osteoclast-rich lesions of bone: a clinical and molecular overview. In: D H, editor. *Bone cancer*, 2nd ed. MA, USA: Academic Press; 2015. pp. 257–272.
54. Park HY, Yang SK, Sheppard WL, *et al*. Current management of aneurysmal bone cysts. *Curr Rev Musculoskelet Med* 2016; 9:435–444.
55. de Lange J, van den Akker HP, van den Berg H. Central giant cell granuloma of the jaw: a review of the literature with emphasis on therapy options. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104:603–615.
56. Won KY, Kalil RK, Kim YW, Park YK. RANK signalling in bone lesions with osteoclast-like giant cells. *Pathology* 2011; 43:318–321.
57. Hakim DN, Pelly T, Kulendran M, Caris JA. Benign tumours of the bone: a review. *J Bone Oncol* 2015; 4:37–41.
58. Kurucu N, Akyuz C, Ergen FB, *et al*. Denosumab treatment in aneurysmal bone cyst: evaluation of nine cases. *Pediatr Blood Cancer* 2018; 65:4.
- Large retrospective series on the use of denosumab in advanced or recurrent ABC.
59. Cottalorda J, Bourelle S. Current treatments of primary aneurysmal bone cysts. *J Pediatr Orthop B* 2006; 15:155–167.
60. Rosenberg AE, Nielsen GP. Giant cell containing lesions of bone and their differential diagnosis. *Curr Diagn Pathol* 2001; 7:235.
61. Palmerini E, Ruggieri P, Angelini A, *et al*. Denosumab in patients with aneurysmal bone cysts: a case series with preliminary results. *Tumori* 2018; 300891618784808.
- Retrospective series on the use of denosumab in advanced or recurrent ABC from a large orthopedic center.
62. Lange T, Stehling C, Frohlich B, *et al*. Denosumab: a potential new and innovative treatment option for aneurysmal bone cysts. *Eur Spine J* 2013; 22:1417–1422.
63. Skubitz KM, Peltola JC, Santos ER, Cheng EY. Response of aneurysmal bone cyst to denosumab. *Spine (Phila Pa 1976)* 2015; 40:E1201–E1204.
64. Pelle DW, Ringle JW, Peacock JD, *et al*. Targeting receptor-activator of nuclear kappaB ligand in aneurysmal bone cysts: verification of target and therapeutic response. *Transl Res* 2014; 164:139–148.
65. Dubory A, Missenard G, Domont J, Court C. Interest of denosumab for the treatment of giant-cells tumors and aneurysmal bone cysts of the spine. About nine cases. *Spine (Phila Pa 1976)* 2016; 41:E654–E660.
66. Ghermandi R, Terzi S, Gasbarrini A, Boriani S. Denosumab: nonsurgical treatment option for selective arterial embolization resistant aneurysmal bone cyst of the spine and sacrum. *Case report. Eur Rev Med Pharmacol Sci* 2016; 20:3692–3695.
67. Ntalos D, Priemel M, Schlickevei C, *et al*. Therapeutic management of a substantial pelvic aneurysmal bone cyst including the off-label use of denosumab in a 35-year-old female patient. *Case Rep Orthop* 2017; 2017:9125493.
68. Patel RS, Dhamne CA, Gopinathan A, *et al*. Denosumab: a potential treatment option for aneurysmal bone cyst of the atlas. *Eur Spine J* 2018; 27(Suppl 3):494–500.
69. Pauli C, Fuchs B, Pfirrmann C, *et al*. Response of an aggressive periosteal aneurysmal bone cyst (ABC) of the radius to denosumab therapy. *World J Surg Oncol* 2014; 12:17.

70. Jaffe HL. Giant-cell reparative granuloma, traumatic bone cyst, and fibrous (fibro-osteous) dysplasia of the jawbones. *Oral Surg Oral Med Oral Pathol* 1953; 6:159–175.
71. Whitaker SB, Waldron CA. Central giant cell lesions of the jaws. A clinical, radiologic, and histopathologic study. *Oral Surg Oral Med Oral Pathol* 1993; 75:199–208.
72. Cohen MM Jr, Gorlin RJ. Noonan-like/multiple giant cell lesion syndrome. *Am J Med Genet* 1991; 40:159–166.
73. Ficarra G, Sapp JP, Eversole LR. Multiple peripheral odontogenic fibroma, World Health Organization type, and central giant cell granuloma: a case report of an unusual association. *J Oral Maxillofac Surg* 1993; 51:325–328.
74. Chuong R, Kaban LB, Kozakewich H, Perez-Atayde A. Central giant cell lesions of the jaws: a clinicopathologic study. *J Oral Maxillofac Surg* 1986; 44:708–713.
75. Ficarra G, Kaban LB, Hansen LS. Central giant cell lesions of the mandible and maxilla: a clinicopathologic and cytometric study. *Oral Surg Oral Med Oral Pathol* 1987; 64:44–49.
76. Bredell M, Rordorf T, Kroiss S, *et al.* Denosumab as a treatment alternative for central giant cell granuloma: a long-term retrospective cohort study. *J Oral Maxillofac Surg* 2018; 76:775–784.
Relevant review and largest case series up to date on the use of denosumab in GCG.
77. Schreuder WH, Coumou AW, Kessler PA, de Lange J. Alternative pharmacologic therapy for aggressive central giant cell granuloma: denosumab. *J Oral Maxillofac Surg* 2014; 72:1301–1309.
78. Naidu A, Malmquist MP, Denham CA, Schow SR. Management of central giant cell granuloma with subcutaneous denosumab therapy. *J Oral Maxillofac Surg* 2014; 72:2469–2484.
79. Gupta B, Stanton N, Coleman H, *et al.* A novel approach to the management of a central giant cell granuloma with denosumab: a case report and review of current treatments. *J Craniomaxillofac Surg* 2015; 43:1127–1132.
80. Akeda K, Kasai Y, Sakakibara T, *et al.* Effect of denosumab on recurrent giant cell reparative granuloma of the lumbar spine. *Spine (Phila Pa 1976)* 2015; 40:E601–E608.
81. O'Connell JE, Bowe C, Murphy C, *et al.* Aggressive giant cell lesion of the jaws: a review of management options and report of a mandibular lesion treated with denosumab. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015; 120:e191–e198.
82. Kim TS, Usera GL, Ruggiero SL, Weinerman SA. Improvement of giant cell lesions of the jaw treated with high and low doses of denosumab: a case series. *JBMR Plus* 2017; 1:101–106.
Relevant case series on the use of denosumab in giant cell lesions of the jaw.