Current concepts in the treatment of giant cell tumour of bone

Lizz van der Heijden[a], *Sander Dijkstra*[a], *Michiel van de Sande*[a], *and Hans Gelderblom*[b]

Purpose of review
Giant cell tumour of bone (GCTB) is an intermediate, locally aggressive primary bone tumour. In addition to local therapy, new drugs became available for this disease. Denosumab, a receptor activator of nuclear factor κ-B-ligand inhibitor, was introduced as systemic targeted therapy for advanced or inoperable and metastatic GCTB. Also, the bisphosphonate zoledronic acid has activity in GCTB by directly targeting the neoplastic stromal cells.

Recent findings
In a small RCT, bisphosphonates were successful in controlling tumour growth and a higher apoptotic index of tumour cells was seen after zoledronic acid versus controls. Although bisphosphonate-loaded bone cement has not been studied to a large extent, it does not seem harmful and may constitute a logical local adjuvant. From the largest clinical trial to date, the risk-to-benefit ratio for denosumab in patients with advanced GCTB remains favourable, also in facilitating less morbid surgery. Concerns have arisen that recurrence rates would be higher than after conventional treatment, ranging from 20 to 100% in a systematic review, although this may be because of bias. H3F3A (G34W) driver mutations are helpful in the differentiation between GCTB and other giant cell-containing malignancies. H3.3-G34W proved sufficient to drive tumourigenesis. The cumulative incidence of malignancy in GCTB is estimated at 4%, of which primary malignancy 1.6% and secondary malignancy 2.4%, the latter mainly after radiation. To date, a potential causal relationship between denosumab and pulmonary metastases has not been confirmed; if they do not behave indolently, it would be advised to reassess diagnosis and consider malignancy.

Summary
Denosumab remains a highly effective treatment option for patients with advanced GCTB. A short duration of 2–4 months neoadjuvant denosumab is advised to facilitate less morbid surgery and prevent incomplete curettage by macroscopic tumour alterations. Reduced dose intensity is being studied to reduce long term side-effects. Further research on bisphosphonates and other targets including H3.3-G34W remains warranted.

Keywords
bisphosphonates, curettage, denosumab, giant cell tumour of bone, local recurrence, neoadjuvant

INTRODUCTION

Giant cell tumour of bone (GCTB) is a primary intermediate but locally aggressive bone tumour, most commonly occurring in long bones of patients aged 30–50 and has a rare tendency to metastasize [1–3]. GCTB is composed of reactive multinuclear osteoclast-like giant cells expressing receptor activator of nuclear factor κ-B (RANK) and neoplastic mononuclear stromal cells expressing RANK-ligand (RANKL); the latter promotes osteoclast formation, migration, and survival, resulting in bone resorption [4,5].

Preferential treatment is curettage and high-speed drilling with local adjuvants including

[a]Department of Orthopaedic Surgery and [b]Department of Medical Oncology, Leiden University Medical Centre, Leiden, the Netherlands

Correspondence to Hans Gelderblom, MD, PhD, Department of Medical Oncology, Leiden University Medical Centre, Postal Zone C7-P, P.O. Box 9600, 2300 RC Leiden, the Netherlands. Tel: +31 71 526 3486; e-mail: a.j.gelderblom@lumc.nl

Curr Opin Oncol 2020, 32:332–338

DOI:10.1097/CCO.0000000000000645

KEY POINTS

- Bisphosphonates are the only systemic adjuvant directly affecting neoplastic stromal cells in GCTB. Randomized trials on its efficacy and the comparison of denosumab versus zoledronic acid are warranted.
- Denosumab remains a highly effective treatment option for patients with advanced GCTB. Data on optimal duration of denosumab are not (yet) conclusive.
- A short duration of maximum 2–4 months of neoadjuvant denosumab is advised to facilitate intralesional surgery.
- Screening for GCTB specific H3F3A (G34W) driver mutations is helpful in the differentiation from giant cell-containing malignancies. H3.3-G34W proved sufficient to drive tumourigenesis and should be further studied as a possible new target.

phenol, alcohol or liquid nitrogen, and cavity filling with bone graft and/or polymethylmethacrylate (PMMA), resulting in recurrence rates of 27–31% [6–10]. In more advanced cases, when joint salvage is regarded impossible, en-bloc resection and endoprosthetic joint replacement is often considered, resulting in lower recurrence risks, but higher complication rates and lesser functional outcome. Also, GCTB in the axial skeleton and pelvis or other non-long bone localizations are less amenable to non-mutilating surgery and often intralesional surgery is the only achievable option surgically.

The high recurrence risk after intralesional surgery in advanced GCTB, and subsequent need for (multiple) reoperations and sometimes extensive surgery can result in functional loss in this intermediate but locally aggressive disease. This major clinical problem resulted in the quest for systemic targeted therapy aiming at the facilitation of less-invasive surgery or even replacing surgery in metastatic patients or cases that are not amenable to surgery. Currently, two different drugs are used. The bisphosphonate zoledronic acid may stabilize local and metastatic disease by its apoptotic effect on neoplastic mononuclear cell population in GCTB [11]. The recently approved RANKL inhibitor denosumab inhibits recruitment of osteoclast-like giant cells by neoplastic stromal cells and thereby prevents osteolysis; a calcified rim is formed around tumourous soft tissue, facilitating intralesional surgery in previously 'uncurettable' GCTB [4,12].

There are still some unanswered questions in the multidisciplinary treatment of GCTB [13], especially now concerns have arisen on increased recurrence rate, side-effects after prolonged systemic therapy and case reports on secondary malignancy after denosumab. In this regard, optimal treatment dose and duration have not yet been affirmed. Linguistically, these concerns are reflected in titles of scientific articles, shifting from 'Denosumab: A breakthrough in treatment of GCTB?' [14] towards 'Challenges' [15▪], 'Lessons learned from early experience' [16▪] and 'Present day controversies' [17▪]. In addition, due to denosumab's high efficacy, alternative targeted therapies including directly working zoledronic acid, are studied to a lesser extent. This review article outlines latest evidence and discusses current concepts and difficulties in GCTB treatment, including indications and duration of systemic therapies, recurrences, secondary malignancy, and metastases.

BISPHOSPHONATES

The first systemic drugs studied in multidisciplinary GCTB treatment were bisphosphonates. In different in-vitro and animal studies, it was shown that zoledronic acid induced neoplastic stromal cell inhibition and apoptosis and osteogenic differentiation [11,18–22]. Two small prospective nonrandomized trials with different adjuvant bisphosphonates after curettage demonstrated recurrence rates of 0 and 15% after a median follow-up of 28 and 64 months, respectively [23,24].

Owing to the later introduction of denosumab in the treatment arena of advanced GCTB and promising results on its efficacy, bisphosphonates have not been studied as extensively in a clinical setting. As denosumab only indirectly targets the neoplastic stromal cell population, it is assumed that after withdrawal, regrowth of GCTB will occur. To date, bisphosphonates are the only systemic adjuvant directly affecting the neoplastic stromal cell population. They might be a more suitable systemic targeted treatment option in the adjuvant setting, although clinical studies to prove this are lacking. Larger randomized trials on the efficacy of zoledronic acid and on the comparison of adjuvant denosumab versus zoledronic acid for advanced GCTB are still warranted. Yet, some promising new evidence has been published.

Recurrence rate after zoledronic acid

Lipplaa *et al.* [25▪] published a small multicentre randomized phase II trial with adjuvant zoledronic acid ($n = 8$; 4 mg IV at 1, 2, 3, 6, 9, 12 months after surgery) versus placebo ($n = 6$) in advanced GCTB. Primary study aim was the two-year recurrence rate. At a median follow-up of 94 months (range 48–111), recurrence rate was 3/8 (38%) in the intervention

group versus 1/6 (17%) in the control group ($P = 0.58$); all occurred within 15 months postoperatively. The authors concluded that adjuvant zoledronic acid did not decrease local recurrence rate. Unfortunately, its efficacy could not be determined because of small sample size and early trial closure, as a result of the introduction of denosumab in the clinic.

In-vivo effects of zoledronic acid

Dubey *et al.* [26▪▪] published another small randomized trial with neoadjuvant zoledronic acid and surgery ($n = 15$) versus surgery alone ($n = 15$) in extremity GCTB. Their study aims were to evaluate radiological changes after bisphosphonates in correlation with transmission electron microscopy findings on ultrastructural changes and tumour cell apoptosis, hereby evaluating in-vivo effects of zoledronic acid. In the intervention group, neoadjuvant zoledronic acid (three doses of 5 mg IV each four weeks) was followed by curettage with adjuvants (phenol 10%, H_2O_2, high-speed burr) and bone grafting in 12 patients, resection and endoprosthetic replacement in one, and postponement of surgery because of improvements of complaints and stabilization of disease in two patients. In the control group, 13 patients underwent curettage with similar adjuvants and bone grafting and two patients underwent resection. Pain diminished (visual analogue scale (VAS) score from 5.3 to 1.8) and increased bone density was seen at the periphery of lesions on follow-up radiographs. The authors state that bisphosphonates were successful in controlling tumour growth, as no growth was observed after three months of neoadjuvant zoledronic acid. Furthermore, they observed a significant higher apoptotic index of tumour cells after zoledronic acid (mean 41% after bisphosphonates versus mean 6% in control group).

Bisphosphonate-loaded bone cement

Zwolak *et al.* [27] studied elution dynamics of zoledronic acid release from bone cement and in-vitro antitumour efficacy. The cytotoxic effect was measured on cultures of GCTB, multiple myeloma, and renal cell carcinoma (RCC) cell lines. The authors found that zoledronic acid remains biologically active despite cement polymerization. Its release was highest in the first 24 h for various concentrations and reached a plateau phase after four days. Zoledronic acid demonstrated higher cytotoxic effect on GCTB stromal cells and RCC than on multiple myeloma, and decrease in number of viable cells was seen in a dose-dependent manner. Afterwards, zoledronic acid may become incorporated in adjacent healthy bone and rereleased at a later stage, thereby possibly targeting eventual residual tumour cells – in contrast to denosumab [15▪].

Chen *et al.* [28] treated four patients with sacral GCTB with curettage without chemical adjuvants because of vicinity of neurovascular structures, but they filled the cavity with vancomycin and bisphosphonate-loaded bone cement balls. At a median follow-up of 28 months, increased sclerosis was seen on plain radiographs surrounding the bone cement balls. There were no recurrences, no complications, and all patients regained motor and sensory functions. Removal or late complications of the in-situ cement balls were not mentioned.

Greenberg *et al.* [29▪] treated 17 patients with extended curettage, local adjuvants and filling of the cavity with bisphosphonate-loaded bone cement. At a follow-up ranging from 1 to 12 years, one local recurrence was observed (6%). No localized (e.g. osteonecrosis) or systemic adverse events were reported.

Although bisphosphonate-loaded bone cement has not been studied to a large extent, it does not seem harmful and may constitute a logical local adjuvant, directly targeting residual neoplastic tumour cells (by incorporation in healthy host bone and later rerelease). As filling the cavity after curettage with PMMA cement is common practice, one could consider a multicentre RCT evaluating the effect of bisphosphonate-loaded cement on recurrence-free survival after intralesional treatment of GCTB.

DENOSUMAB

Neoadjuvant treatment

Safety and efficacy of either neoadjuvant or definitive denosumab in advanced or unsalvageable GCTB, respectively, have been studied in prospective phase II trials by Thomas *et al.* [12] and Chawla *et al.* [4]. An unplanned interim analysis of the latter confirmed surgical downstaging of initially planned surgery that would result in severe morbidity or in unresectable GCTB [30]. Definitive and long-term follow-up trial results of this largest clinical trial to date have recently been published [31▪▪]. In this multicentre, open-label, phase II trial conducted at 30 participating centres over 12 countries, patients were included in three cohorts: surgically unsalvageable GCTB ($n = 267$), surgically salvageable GCTB with planned surgery that would result in high morbidity ($n = 253$) and after previous denosumab in another trial ($n = 12$). Median follow-up was 58 months (interquartile range (IQR) 34–74). Adverse events included hypophosphatemia (5%),

osteonecrosis of the jaw (ONJ) (3%) and anaemia (2%). Late complications included atypical femoral fracture (1%) and hypercalcemia after discontinuation (1%). Four patients had malignant transformation (1%). In cohort 1, only 11% (28/262) had progression after 60 months follow-up. Twenty-three previously deemed inoperable patients underwent surgery; 19 discontinued because of side-effects and 68 remain on long-term denosumab. In cohort 2, 92% (227/248) had no surgery during the first six months. For the 157 patients that underwent surgery during the study period, progression and recurrence-free survival reached a plateau of 60% after three years. Seventeen discontinued because of side-effects and 30 remain on long-term denosumab. The authors conclude that the risk-to-benefit ratio for denosumab in patients with advanced GCTB remains favourable. Patients in cohort 2 also received six months adjuvant denosumab after surgery, but no conclusions can be drawn on the efficacy of adjuvant denosumab.

Rutkowski *et al.* [32▪▪] reported on a large multicentre retrospective study of advanced, unresectable or metastatic GCTB, treated with denosumab outside of trials in six tertiary centres ($n = 138$). Median follow-up was 23 months (6–48). Median denosumab treatment duration was eight months. Recurrence rate was 32% after curettage with adjuvants and 7% after resection; 13/16 patients with recurrence after curettage received denosumab again, they all responded.

Recurrence rates

Because of macroscopic changes in tumour tissue after denosumab, resulting in several osseous rims and crypts, it becomes difficult to distinguish tumour borders from healthy bone and completely curette the lesion, hereby potentially leaving residual neoplastic stromal cells behind. Concerns have arisen that denosumab might actually increase local recurrence risk – contrary to previous expectations when introducing this systemic therapy.

Tsukamoto *et al.* [33▪] published a systematic review on local recurrence rates after neoadjuvant denosumab, ranging from 20 to 100% after neoadjuvant denosumab and curettage, and 0 to 50% for curettage alone. They found no evidence on altered recurrence rates for different treatment duration cut-off points, such as shorter or longer than six months. The authors state that it is difficult to interpret and compare study results, because of indication bias in most studies in which denosumab was given for more advanced cases with in itself a higher recurrence risk. This was also the case for several recently published retrospective comparative studies [34▪,35▪]. Agarwal *et al.* [16▪] published a case-matched comparison study with 34 control patients from a previous retrospective study matched to 25 denosumab patients, in terms of patient and tumour characteristics. The difference observed in recurrence rates (44% after denosumab and 21% in controls) did not reach significance. The authors advise to adhere to pretreatment radiological tumour borders when performing curettage, to ascertain extensive tumour removal and minimize recurrence risk.

Urakawa *et al.* [36▪] previously performed an extensive questionnaire study on the effects of denosumab in advanced and unresectable GCTB, after which they started a multicentre randomized phase III trial on sufficient dose and duration of neoadjuvant therapy (UMIN 000029451) [37▪].

Definitive treatment

The EORTC (European Organisation for Research and Treatment of Cancer)-REDUCE trial is a multicentre phase II trial that started recruiting in September 2019, investigating, after a run-in of one year of standard dose, reduced dose density of denosumab as a maintenance therapy for unsalvageable GCTB, with therapy intervals of 12 weeks until disease progression or unacceptable toxicity, aiming at reducing the cumulative dose-dependent toxicity while maintaining efficacy (NCT03620149). Similar trials are being planned in the United States and Japan.

NEW POTENTIAL TARGETS

Cleven *et al.* [38] first demonstrated H3F3A (G34W) driver mutations in 69% of 60 GCTB samples and defined this as highly specific for the differentiation of GCTB from other giant cell containing tumours. H3.3-G34W is a highly sensitive and specific surrogate marker for this mutation in GCTB and is useful for differential diagnoses of histological mimics [39]. H3F3A may be preserved or lost with malignant transformation. In a recent study, 24/25 GCTBs had the H3F3A mutation compared with 5/35 giant cell-rich sarcomas; all sarcomas with the mutation were secondary malignant GCTB [40▪,41]. Fellenberg *et al.* [42▪▪] demonstrated the mutation in 94% of 84 samples. After selective knockdown of H3.3-G34W in primary neoplastic stromal cells isolated from GCTB tumour tissue, a significant inhibition of cell proliferation, migration and colony formation capacity was seen *in vitro*, and after transplantation onto chorioallantoic membrane of fertilized chicken eggs also *in vivo*. The authors conclude that H3.3-G34W is sufficient to drive tumourigenesis in

GCTB and that H3.3-G34W screening may be used as diagnostic tool and possible new target.

Lau *et al.* [43▪] recently reported on a new potential therapy directly targeting neoplastic stromal cells: simvastatin lets stromal cells (i.e. incompletely differentiated preosteoblasts) differentiate into mature osteoblasts, hereby potentially counteracting bone resorption. In GCTB, simvastatin inhibited cell viability by suppressing proliferation and inducing apoptosis in neoplastic stromal cells. Upregulated expression of genes related to osteogenic maturation was seen. This could be an easily available and inexpensive potential adjuvant therapy, but further investigation is warranted.

MALIGNANT TRANSFORMATION

Malignancy in GCTB can be a consequence of dedifferentiation after previous radiation therapy, malignant transformation or misdiagnosis (e.g. primary pathological diagnosis giant cell-rich osteosarcoma). Over the years, several case reports were published on malignant transformation after denosumab; but only recently data of larger trials became available [4,12].

Palmerini *et al.* estimated the incidence of malignancy in GCTB in a sound review article including four large series with a total of 2315 patients [40▪]. The cumulative incidence of malignancy was 4%, of which primary malignancy 1.6% and secondary malignancy 2.4%, the latter mainly after radiation. Eight smaller series revealed an estimated incidence of 4.8% of secondary malignancy after radiation.

Overall, primary malignancy was associated with a better prognosis (low to intermediate-grade sarcoma) and secondary malignancy with a poor prognosis (high-grade sarcoma). The review article does not mention malignant transformation of GCTB after denosumab.

Lin *et al.* [44▪] published a population based study from 1984 to 2013 including 250 malignant GCTB. Data was derived from the Surveillance, Epidemiology and End Results Program (SEER) database, a population-based cancer registry from the National Cancer Institute in the United States. They concluded that older age (>60), larger tumour size (>7 cm) and metastases were associated with poorer overall survival of malignant GCTB. The SEER database does not contain information on systemic therapy such as denosumab or bisphosphonates; however, during the study-period systemic therapy was not used to a wide extent.

In the largest published long-term follow-up phase II trial on denosumab in GCTB, 20/526 patients with a potential malignancy were identified (4%) [31▪▪]. All were reviewed in more detail by an independent expert panel because of the importance of this matter. Fifteen of 526 patients were suspected to be misdiagnoses of benign GCTB at baseline, before the start of denosumab (3%). Of the remaining patients, after denosumab, four were malignant transformation of previous histologically proven benign GCTB (1%) and one was secondary malignant GCTB after radiation therapy (<1%). Even though this is a very low percentage, Healey [13] commented that it should be interpreted with caution, as the majority of malignancies in this trial were eliminated from the analysis because of later pathological confirmation of misdiagnosis at baseline. It remains therefore uncertain whether denosumab was of influence on the malignant development, or – if indeed primary malignant – denosumab should never have been used.

METASTATIC DISEASE

Approximately 1–6% of benign GCTB develop pulmonary metastases with generally an indolent behaviour. Overall survival is good after metastasectomy for latent pulmonary metastases. However, metastases from secondary malignant GCTB or giant cell-rich sarcomas are often fatal [40▪].

Conflicting reports are published on the causal relationship between denosumab and pulmonary metastases. Tsukamoto *et al.* [45▪] questioned whether denosumab would prevent pulmonary metastases and evaluated univariate and multivariate predictors for pulmonary metastases. Retrospectively, 381 GCTB patients with surgery alone and 30 GCTB patients with surgery and denosumab were studied. After a median follow-up of 85 months (IQR 54–124), metastases were diagnosed in 4.7% of patients with surgery alone and 3.3% after surgery and denosumab. The use of (neoadjuvant) denosumab was not a predictor for the development of lung metastases, although number of cases was too small to perform multivariate analyses. Campanacci grade and type of surgery were the only predictors associated with pulmonary metastases in this study; both were probably cross-correlated, as a higher grade is often a reason for more extensive surgery.

To date, a potential causal relationship between denosumab and pulmonary metastases has not been confirmed. If pulmonary metastases do not behave in an indolent fashion, it would be advised to reassess primary diagnosis, and consider malignancy.

CONCLUSION

This review outlined the latest evidence and discussed current concepts and difficulties in advanced GCTB treatment.

To date, bisphosphonates are the only systemic adjuvant directly affecting neoplastic stromal cells, and might be a more suitable systemic targeted treatment option than denosumab. However, mature clinical studies to support their adjuvant use are lacking. Larger randomized trials on its efficacy and on the comparison of denosumab versus zoledronic acid are still warranted. In addition, although bisphosphonate-loaded bone cement has not been studied to a large extent, it does not seem harmful. Its use may constitute an easy to use, widely available and inexpensive local adjuvant that should be assessed in a multicentre RCT.

Concerns have arisen on elevated recurrence rates after neoadjuvant denosumab and curettage, because of macroscopic alterations and subsequent risk of leaving residual neoplastic stromal cells behind. Data on potentially elevated recurrence rates after denosumab should be interpreted with the risk of indication bias in mind, as in most studies denosumab was given for more advanced cases within itself a higher recurrence risk.

For neoadjuvant therapy, data on optimal duration of denosumab are not (yet) conclusive, a short duration of maximum 2–4 months of neoadjuvant denosumab is advised to facilitate intralesional surgery and prevent for incomplete curettage due to macroscopic tumour alterations.

Denosumab remains a highly effective treatment option for selected patients with advanced GCTB, although lifelong treatment is not desirable. As long-term side-effects such as ONJ are of concern, several dosing interval reduction studies have been initiated. From a systemic review, the cumulative incidence of malignancy was estimated at 4%; of which primary malignancy 1.6% and secondary malignancy 2.4%, the latter mainly after radiation. The role of denosumab in malignant transformation has not yet fully been clarified. To date, a potential causal relationship between denosumab and pulmonary metastases has not been confirmed. If pulmonary metastases do not behave in an indolent fashion, it would be advised to reassess primary diagnosis and consider malignancy.

Screening for GCTB specific H3F3A (G34W) driver mutations is helpful in the differentiation from giant cell-containing malignancies. Also, H3.3-G34W proved sufficient to drive tumourigenesis should be further studied as a possible new target for therapy.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

Amgen and Daiichi provided an institutional research support but not related to this work. The authors have no conflicts of interest in terms of honoraria or personal grants.

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 NA, Bansal M, Forsyth R, *et al.* Giant cell tumour of bone. In: Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F, editors. WHO classification of tumours of soft tissue and bone, 4th ed International Agency for Research on Cancer (IARC); 2013pp. 321–324. ; IARC WHO Classification of Tumours Series, vol 5.
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. Rockberg J, Bach BA, Amelio J, *et al.* Incidence trends in the diagnosis of giant cell tumor of bone in Sweden since 1958. J Bone Joint Surg Am 2015; 97:1756–1766.
4. 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.
5. 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.
6. 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.
7. Becker WT, Dohle J, Bernd L, *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.
8. 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.
9. Algawahmed H, Turcotte R, Farrokhyar F, Ghert 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; 2010:586090. doi: 10.1155/2010/586090. PMID 20706639. PMC 2913811.
10. Errani C, Ruggieri P, Asenzio MA, *et al.* Giant cell tumor of the extremity: a review of 349 cases from a single institution. Cancer Treat Rev 2010; 36:1–7.
11. 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.
12. 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.
13. Healey JH. Denosumab for giant cell tumour of bone: success and limitations. Lancet Oncol 2019; 20:1627–1628.
14. Balke M, Hardes J. Denosumab: a breakthrough in treatment of giant-cell tumour of bone? Lancet Oncol 2010; 11:218–219.
15. ■ Lipplaa A, Dijkstra S, Gelderblom H. Challenges of denosumab in giant cell tumor of bone, and other giant cell-rich tumors of bone. Curr Opin Oncol 2019; 31:329–335.

Previous review article of recent literature on all giant cell-rich tumors.

16. ■ Agarwal MG, Gundavda MK, Gupta R, Reddy R. Does denosumab change the giant cell tumor treatment strategy? Lessons learned from early experience. Clin Orthop Relat Res 2018; 476:1773–1782.

Case-matched analysis recurrence risk in patients treated with or without denosumab and complications of denosumab

17. ■ Errani C, Tsukamoto S, Ciani G, Donati DM. Present day controversies and consensus in curettage for giant cell tumor of bone. J Clin Orthop Trauma 2019; 10:1015–1020.

Systematic review on ideal treatment for GCTB, being joint salvage procedures for primary and recurrent GCTB

18. Lau CP, Wong KC, Huang L, *et al.* A mouse model of luciferase-transfected stromal cells of giant cell tumor of bone. Connect Tissue Res 2015; 56:493–503.
19. Chang SS, Suratwala SJ, Jung KM, *et al.* Bisphosphonates may reduce recurrence in giant cell tumor by inducing apoptosis. Clin Orthop Relat Res 2004; 103–109; PMID 15346059.

20. Balke M, Neumann A, Szuhai K, *et al.* A short-term in vivo model for giant cell tumor of bone. BMC Cancer 2011; 11:241.
21. Cheng YY, Huang L, Lee KM, *et al.* Bisphosphonates induce apoptosis of stromal tumor cells in giant cell tumor of bone. Calcif Tissue Int 2004; 75:71–77.
22. Yang T, Zheng XF, Li M, *et al.* Stimulation of osteogenic differentiation in stromal cells of giant cell tumour of bone by zoledronic acid. Asian Pac J Cancer Prev 2013; 14:5379–5383.
23. 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.
24. Gouin F, Rochwerger AR, Di MA, *et al.* Adjuvant treatment with zoledronic acid after extensive curettage for giant cell tumours of bone. Eur J Cancer 2014; 50:2425–2431.
25. ■ Lipplaa A, Kroep JR, van der Heijden L, *et al.* Adjuvant zoledronic acid in high-risk giant cell tumor of bone: a multicenter randomized phase II trial. Oncologist 2019; 24:889–e421.
Small randomized trial on the efficacy of zoledronic acid, stopped early because of introduction of denosumab in clinic.
26. ■■ Dubey S, Rastogi S, Sampath V, *et al.* Role of intravenous zoledronic acid in management of giant cell tumor of bone: a prospective, randomized, clinical, radiological and electron microscopic analysis. J Clin Orthop Trauma 2019; 10:1021–1026.
Results on pain reduction, increased bone mineral density, and also a higher apoptotic index of neoplastic stromal cells after zoledronic acid.
27. Zwolak P, Manivel JC, Jasinski P, *et al.* Cytotoxic effect of zoledronic acid-loaded bone cement on giant cell tumor, multiple myeloma, and renal cell carcinoma cell lines. J Bone Joint Surg Am 2010; 92: 162–168.
28. Chen KH, Wu PK, Chen CF, Chen WM. Zoledronic acid-loaded bone cement as a local adjuvant therapy for giant cell tumor of the sacrum after intralesional curettage. Eur Spine J 2015; 24:2182–2188.
29. ■ Greenberg DD, Lee FY. Bisphosphonate-loaded bone cement as a local adjuvant therapy for giant cell tumor of bone: a 1 to 12-year follow-up study. Am J Clin Oncol 2019; 42:231–237.
Clinical study on bisphosphonate-loaded bone cement.
30. 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.
31. ■■ Chawla S, Blay JY, Rutkowski P, *et al.* Denosumab in patients with giant-cell tumour of bone: a multicentre, open-label, phase 2 study. Lancet Oncol 2019; 20:1719–1729.
Largest clinical trial on the efficacy of denosumab in the literature so far.
32. ■■ 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.
Unplanned interim analysis of surgical downstaging of GCTB after denosumab.
33. ■ Tsukamoto S, Tanaka Y, Mavrogenis AF, *et al.* Is treatment with denosumab associated with local recurrence in patients with giant cell tumor of bone treated with curettage? A systematic review. Clin Orthop Relat Res 2020; 478:1076–1085.
Systematic review on recurrence rate after denosumab and curettage.
34. ■ Scoccianti G, Totti F, Scorianz M, *et al.* Preoperative denosumab with curettage and cryotherapy in giant cell tumor of bone: is there an increased risk of local recurrence? Clin Orthop Relat Res 2018; 476:1783–1790.
Clinical article suggesting higher recurrence risk after denosumab.
35. ■ Chinder PS, Hindiskere S, Doddarangappa S, Pal U. Evaluation of local recurrence in giant-cell tumor of bone treated by neoadjuvant denosumab. Clin Orthop Surg 2019; 11:352–360.
Clinical article on recurrence risk after denosumab.
36. ■ 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.
Questionnaire study before planning a large phase III RCT.
37. ■ Urakawa H, Mizusawa J, Tanaka K, *et al.* A randomized phase III trial of denosumab before curettage for giant cell tumor of bone: Japan Clinical Oncology Group Study JCOG1610. Jpn J Clin Oncol 2019; 49:379–382.
Announcement of a large phase III RCT on neoadjuvant denosumab.
38. Cleven AH, Hocker S, Briaire-de Bruijn I, *et al.* Mutation analysis of H3F3A and H3F3B as a diagnostic tool for giant cell tumor of bone and chondroblastoma. Am J Surg Pathol 2015; 39:1576–1583.
39. Yamamoto H, Ishihara S, Toda Y, Oda Y. Histone H3.3 mutation in giant cell tumor of bone: an update in pathology. Med Mol Morphol 2020; 53:1–6.
40. ■ Palmerini E, Picci P, Reichardt P, Downey G. Malignancy in giant cell tumor of bone: a review of the literature. Technol Cancer Res Treat 2019; 18:1533033819840000.
A profound systematic review of the literature on malignancy in GCTB.
41. Righi A, Mancini I, Gambarotti M, *et al.* Histone 3.3 mutations in giant cell tumor and giant cell-rich sarcomas of bone. Hum Pathol 2017; 68:128–135.
42. ■■ Fellenberg J, Sahr H, Mancarella D, *et al.* Knock-down of oncohistone H3F3A-G34W counteracts the neoplastic phenotype of giant cell tumor of bone derived stromal cells. Cancer Lett 2019; 448:61–69.
First article proving that H3F3A-G34W is involved in tumorigenesis in stromal cells.
43. ■ Lau CP, Fung CS, Wong KC, *et al.* Simvastatin possesses antitumor and differentiation-promoting properties that affect stromal cells in giant cell tumor of bone. J Orthop Res 2020; 38:297–310.
First article mentioning simvastatin as a potential target for stromal cells in GCTB.
44. ■ Lin JL, Wu YH, Shi YF, *et al.* Survival and prognosis in malignant giant cell tumor of bone: a population-based analysis from 1984 to 2013. J Bone Oncol 2019; 19:100260.
Large population-based study from the SEER database on malignant GCTB.
45. ■ Tsukamoto S, Mavrogenis AF, Leone G, *et al.* Denosumab does not decrease the risk of lung metastases from bone giant cell tumour. Int Orthop 2019; 43:483–489.
Pulmonary metastases and denosumab.