The current standing on the use of denosumab in giant cell tumour of the bone

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Abstract
Giant cell tumour of the bone (GCTB) has been classically treated surgically. With the advent of denosumab, there is potential to use it as a targeted therapy to downstage the tumour and control its progression. Like all new therapies, the dosage, duration, and long-term effects of treatment can only be determined over the time through numerous trials and errors. The current recommendation of use of the monoclonal antibody is 3–4 months of neoadjuvant denosumab in patients with advanced GCTB for cases who were not candidates for primary curettage initially, and prolonged use for surgically unsalvageable GCTB. The use of Denosumab in the adjuvant setting to prevent recurrence is not established.

Keywords
bone, denosumab, giant cell tumour, neoadjuvant

Date received: 18 April 2020; Received revised 19 November 2020; accepted: 19 November 2020

Introduction
Denosumab, a fully humanised monoclonal antibody to RANK ligand (RANKL) is a new tool in the armamentarium against giant cell tumour of the bone (GCTB) in orthopaedic oncology. It is approved by the Food and Drug Administration (FDA) and European Medical Agency (EMA) for use in conditions such as osteoporosis, bone metastases, and GCTB. In this article we review the current status and questions regarding the use of denosumab in the treatment of GCTB.

What is giant cell tumour of the bone (GCTB)
GCTB is a relatively rare, locally aggressive but benign osteolytic tumour of the bone that commonly affects young adults (patients aged between 30 and 50 years). It accounts for 4–10% of all primary bone tumours.¹⁻³ These are usually solitary tumours but can be multifocal in less than 1% of the cases. It has an estimated incidence of 1.3 per million per year.⁴⁻⁵ Although it is classically a locally aggressive lesion, it can metastasize to the lungs (1–4%) especially in recurrent cases.⁶⁻⁹ In the lungs, these tumours are slow-growing and are considered to be ‘benign pulmonary deposits’. These should be assessed cautiously to differentiate them from malignant deposits from giant cell rich sarcomas or giant cell sarcomas. Figure 1 shows a case of a 19 years old lady with GCT distal tibia. The chest radiograph at presentation showed no evidence of metastatic disease at presentation but subsequently on follow up, she develop progressive lung metastasis. Despite this, clinically she remain asymptomatic and currently is being followed up.

Radiographically GCTB appears as an eccentric, expansile, lytic lesion with well-defined borders (narrow zone of transition), arising from the metaphysis of long bones and

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extending into the epiphysis up to the subarticular region on a plain radiograph (Figure 2). On MRI, it typically appears as intermediate to high signal intensity on T2 and low to intermediate intensity on T1-weighted images (Figure 3). Hemosiderin depositions within the tumour gives rise to areas of low signal intensity on gradient-echo sequences. Fluid–fluid levels can be found in 10–14% of the cases due to secondary aneurysmal bone cyst-like changes.

GCTB is usually classified radiologically with the Campanacci system, where Grade I tumours are well contained within the bone with an intact cortex, Grade II tumours are more extensive with cortical erosion and expansion but no break in the cortex, and Grade III tumours have a cortical break and soft tissue extension (Figure 4).

Histologically, the cells are composed of osteoclast-like multinucleated giant cells, rounded mononuclear histiocytic cells, and round or ovoid mononuclear stromal cells, which are considered the neoplastic component of the tumour. The reactive multinuclear osteoclast-like giant cells express receptor activator of nuclear factor kappa-B (RANK) and the neoplastic mononuclear stromal cells express RANK ligand (RANKL). RANK-RANKL interactions are important in the recruitment of osteoclastic cells from blood-borne mononuclear osteoclast precursor cells that differentiate into multinucleated osteoclast-like giant cells.

Recently, some researchers have identified some immunostaining factors (MIB-1, GPX-1, cyclin D1 and β-catenin) that are associated with predilection for GCTB recurrence. This is still experimental and has the potential for clinical use to determine cases that are more likely to recur. GCTB is different from Giant Cell Rich Malignancies where there is presence of giant cells in the malignant tumours. These tumours are rare and aggressive with 13.4% having nodal metastasis and 32.9% having distant metastasis. The commonest variety of these tumours being the Giant cell rich Osteosarcoma. The 5-year survival is less than 50%.

GCTB are commonly treated by extended curettage, which comprises thorough bone curettage followed by use of a high-speed burr and may be augmented with use of local adjuvants such as phenol, liquid nitrogen, and polymethylmethacrylate cement (PMMA). It is debatable if adjuvants help decrease the recurrence rates though some studies have documented PMMA helping to lower the risk of local recurrence. Wide resection poses the lowest risk of local recurrence as the whole tumour is removed but does increase the morbidity of the surgery and may result in reduced functional outcomes.

In the treatment of complex cases of GCTB and in anatomically challenging sites may also include the additional use of embolization, bisphosphonates, or denosumab. Chemotherapy is not used as it is not effective in the management of GCTB. Moderate dose radiotherapy (40–55 Gy) has also been used in the treatment of unresectable GCTB, and in cases of residual or recurrent
disease where surgery is not feasible. However, radiotherapy does carry a risk of malignant transformation. Figure 5 demonstrates a case of GCT of the sacrum diagnosed at the age of 17 and treated with embolization and radiotherapy. Seven years later, there is no evidence of recurrence of disease.

**Denosumab and GCTB**

Denosumab is a fully humanised monoclonal antibody to RANK ligand (RANKL). It inhibits osteoclastic activity by inhibiting RANK-RANKL interaction, which in turn results in reduction in osteoclast-induced bone destruction.

For GCTB treatment, denosumab is dosed at 120 mg, administered subcutaneously every 28 days with loading doses on days 8 and 15 (in the first month of therapy). This treatment regimen was established in a proof of principle Phase II study. Tumour response was confirmed in 86% of the patients tested, where more than 90% of the giant cells were eliminated on histopathological examination and there was no radiographical progression of the lesion. Denosumab showed an
improvement in Quality of Life (QOL), good response in patients with inoperable GCTB, and reduced the need for otherwise morbid surgery in a second, larger Phase 2 clinical trial. Clinically, the patients start experiencing improvement is symptoms such as reduction pain, improvement in neurology (return of bladder and bowel control for GCT sacrum) and then if patient has swelling, the swelling becomes firmer. Radiologically on plain radiographs, the lesion becomes better demarcated by developing a sclerotic neo-cortex and matrix osteosclerosis. F-FDG-PET shows lower activity.

How does denosumab help in the treatment of GCTB?

Denosumab causes new bone to form, downgrading a Campanacci Grade III lesion to a lesser grade. With an increasing rim of ossified bone on the periphery, intraleisional curettage is facilitated in extensive lesions. Even in cases that need resection especially in those cases with a large soft tissue component in close proximity to neurovascular structures where there is a potential risk of intraoperative injury, the osseous rim which forms after denosumab helps decrease the possibility of injury to these adjacent neurovascular structures. It also facilitates intraoperative manipulation and prevents inadvertent contamination with tumour.

In addition to the benefit of reducing tumour volume, the potential of denosumab in reducing blood loss from intraleional curettage of pelvic GCT is alluded to by Watanabe et al. Girolami et al. reported a conversion of the neoplastic stromal cells to a fibrous matrix with decreased angiogenesis, which could explain the decreased vascularity of the treated tumours.

However, some authors noted higher local recurrence rates after curettage in patients treated with neoadjuvant denosumab. There is a concern that the rim of new bone that forms with denosumab treatment may contain neoplastic cells that may reactivate once it is stopped. In the Phase 2 clinical trial, denosumab treatment was given around 2 years prior to surgery, and it resulted in a thick layer of new bone formation on the periphery of the tumour, entrapping the neoplastic tissue. Performing definitive surgery much earlier (3–4 months after starting denosumab) to prevent too thick a rim of bone from forming may make complete removal much more feasible. The use of cryotherapy after curettage may penetrate this layer of new bone and help reduce the incidence of local recurrence.

Although early reports recommended the use of Denosumab as an adjuvant treatment to minimise the rate of local recurrence, current available evidence suggests that it does not reduce the incidence of local recurrence. However, there are reports of successful use of denosumab in inoperable cases, where its continuous usage causes regression of the lesion and prevents disease progression in cases of lung metastasis. Figure 6 are plain radiographs of the chest of a 16 years old girl who presented with GCT of the left distal femur and presentation she had a metastatic deposit over the right lung attach to the pericardium. She was started on denosumab and this mass eventually regress. She is currently in maintenance therapy. Sometimes Denosumab can be given in cases of pathological fractures or Campanacci grade 3 lesions with soft tissue extension to solidify the tumour prior to wide resection. Figure 7 is a case of a 73 year old man who presented with a pathological fracture of the left proximal humerus secondary to GCT and was given four doses of denosumab prior to wide resection and endoprosthesis replacement. Figure 8 is a case of GCT of the sacrum. She was given six doses of denosumab to solidify the tumour prior to wide resection.

The current consensus appears to favour the use of denosumab for a shorter duration in a neoadjuvant setting for a maximum of 3–4 months prior to an intraleional...
procedure. Longer duration of treatment results in a gum-like layered substance within the tumour cavity, making complete tumour removal by intralesional curettage more difficult, thus leading to a higher local recurrence rate.

How long should we continue denosumab?
A major concern is the high rate of local recurrence after stopping denosumab in the absence of adequate surgery. This suggests that denosumab alone does not give rise to complete eradication of the disease. Mak et al. found that neoplastic stromal cells persisted and continued to proliferate at a slower rate compared to untreated GCTB and Lau et al. found that denosumab does not cause apoptosis of the stromal cell but merely has an inhibitory effect. Girolami et al. also found $H3F3A$ mutation in both pre-treatment and post-treatment surgical specimen of GCTB, supporting the hypothesis that denosumab does not totally eliminate tumour cells. There is currently insufficient data to quantify this risk, but many recurrences may arise within 7–9 months of treatment stoppage.

In cases such as inoperable GCTB or GCTB with lung metastasis which require long-term treatments, ‘drug holidays’ can be used to minimise side effects. This can be monitored with certain biomarkers for bone turnover to determine the duration of the ‘drug holiday’. Denosumab can be restarted once these markers show an increase in bone turnover. Examples of such markers are Urinary N-telopeptide and serum C-telopeptide. Another marker such as Tartrate-resistant acid phosphatase 5b, a bone resorption marker secreted by osteoclasts can also be used as it is shown to correlate with osteoclast activity systemically.

Is there a role for post-operative denosumab after curettage?
Whether continuing denosumab post operatively helps to reduce the rate of recurrence in cases undergoing curettage is debatable. In Errani et al.’s series, patients received post-operative denosumab, yet they reported a 60% rate of local recurrence. In a Phase 2 Open-Label Trial by Rutkowski et al. many of the 157 patients that underwent surgery received adjuvant denosumab for 6 months after surgery. Local recurrence still occurred in 34% of patients after curettage.

Agarwal et al. suggested the use of denosumab 3 monthly as a ‘maintenance’ dose after treatment of extensive spinal disease. Up to now, it is still not yet clear whether alterations in dosing schedule or ‘drug holidays’ may affect the longevity of tumour response.

Denosumab or zoledronic acid — which acts better in GCTB?
Prior to the introduction of denosumab, zoledronic acid was widely used in the management of GCTB. Denosumab and zoledronic acid both inhibit osteoclast differentiation from mononuclear cells containing osteoclast precursors. In addition, zoledronic acid also inhibits osteoclast survival, which is not seen in denosumab treatment.

However, a non-randomised prospective Phase II trial using adjuvant zoledronic acid post-curettage with adjuvants did not show a lower recurrence rate. The efficacy of zoledronic acid in a neoadjuvant setting has also not been validated. There may be an advantage in local control by using zoledronic acid admixed with artificial bone or PMMA, but it requires further evaluation and standardisation as the reported series are small.

Are there complications with denosumab?
Reported complications and side effects from denosumab include bone pain, fatigue, headache, nausea (18–25%), hypocalcaemia (3.2%), hypophosphatemia (2.7%),
osteonecrosis of the jaw (1–2%), and atypical femoral fractures.\textsuperscript{39,40,63}

Gossai et al. reported critical hypercalcaemia in one patient 5 months after discontinuation of denosumab and it was attributed to rebound osteoclast activity and osteoporotic bone. They advised careful monitoring of electrolyte status after discontinuation of denosumab.\textsuperscript{51} Chawla et al.\textsuperscript{40} recently presented data showing the increasing risk of toxicity after 2 years of treatment.

Till date no definitive causal-relationship between malignancy and denosumab has been established. However, concerns have arisen on progression of GCTB to high-grade sarcoma during denosumab therapy.\textsuperscript{64} Mattei et al. reported malignant transformation in 1.8% of their patients. Two of these had previous radiotherapy and in another two patients, it was attributed to sampling error at initial biopsy.\textsuperscript{35} Gaston et al. reported a case of high-grade sarcoma development during denosumab therapy for recurrent GCTB.\textsuperscript{43}

\textbf{Figure 7.} 73 years old man who presented with pathological fracture of the humerus. Biopsy confirmed the diagnosis of GCT. He was given four doses of Denosumab to solidify the tumour and subsequently an extra articular resection was done with endoprosthesis reconstruction.
Whether these occurrences represent a true malignant transformation or a missed diagnosis of primary malignant GCTB due to sampling error at the time of the initial biopsy remains debatable. As the response rate of denosumab in GCTB is very high, it may be prudent to repeat a biopsy in patients who do not show a positive response to denosumab.

**Future considerations**

The use of denosumab only indirectly affects GCTB, as the neoplastic stromal cells are not directly targeted, thus making it a temporary therapy. Targeted therapy directed towards the neoplastic stromal cells should be identified so
as to enable systemic therapy to be utilised as definite therapy for GCTB.

**Authors opinion**
Cases with GCTB ideally should be referred at a tertiary referral centre, so that an accurate diagnosis can be made and medical or surgical intervention can be used appropriately. This too allows the centres to gain as much experience as possible in the medical management of giant cell tumour cell tumour of bone.

**Conclusion**
- Denosumab is not recommended in cases that can easily be primarily treated by curettage or resection. (Figure 9)
- Three to four doses of neoadjuvant denosumab (at a dose of 120 mg subcutaneously at day 1, 8, 15 and 29) can be given in patients with advanced GCTB where denosumab can help facilitate the surgical curettage (convert a lesion needing resection to one that could possibly be treated with curettage).
- Three or more doses can be given in cases of advance GCT or pathological fractures to solidify the tumours prior to wide resection to decrease the morbidity of surgery.
- Long-term denosumab can be used for surgically unsalvageable GCTB. The ideal dose, duration and frequency that balances disease control against the side effects of long-term treatment have yet to be determined.

**Declaration of conflicting interests**
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**
The author(s) received no financial support for the research, authorship, and/or publication of this article.

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**Figure 9.** Shows the flow chart of the use of denosumab in GCT of the bone.
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