Comparison of Denosumab and Zoledronic acid as neoadjuvant therapy in patients with giant cell tumor of bone

Himanshu Kanwat¹, Roshan Banjara¹, Venkatesan Sampath Kumar¹, Abdul Majeed¹, Shivanand Gamnagatti² and Shah Alam Khan¹

Abstract
Objectives: Both Zoledronic acid and denosumab have been utilized in neo-adjuvant setting for facilitating surgery and downsizing the lesion in Giant cell tumor (GCT). This study is aimed at comparing Zoledronic acid and Denosumab, when used in neo-adjuvant setting, in terms of radiological and clinical outcomes in GCT undergoing surgical intervention.

Patients and Methods: Patients undergoing surgical intervention for GCT who received either denosumab or Zoledronic acid as neoadjuvant agents were retrospectively analyzed for reduction in tumor load radiologically, change in surgical plan after therapy, facilitation of surgery, therapy related complications, cost of treatment, rate of local recurrence and clinical outcomes. Results: Twenty patients received denosumab and 19 patients received Zoledronic acid as neoadjuvant agent. There was no significant difference in radiological outcomes, facilitation of surgery and clinical outcomes at end of follow-up. Zoledronic acid group had lower number of recurrences, however, not statistically significant. Therapy with Zoledronic acid was significantly cheaper (p = 0.001).

Conclusion: Zoledronic acid is a cheaper alternative to denosumab in terms of solidification of lesion, reducing recurrence rates and improving clinical outcomes. Larger prospective studies required to further delineate this outcome with Zoledronic acid.

Keywords
curettage, denosumab, giant cell tumor, neo-adjuvant, zoledronic acid

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Introduction
Giant cell tumor (GCT) of bone, traditionally labeled as a benign lesion, classified by world health organization as a locally aggressive, potentially malignant lesion with pulmonary metastases occurring in 1–4% cases.¹ Intralesional curettage carries a recurrence risk of 12–65% as compared to 7% with resection.² However, resection is fraught with surgical morbidity accompanied with significant functional impairment.³

Histologically, GCTs are composed of osteoclast like giant cells, monocyes and fibroblast like stromal cells with over-expression of receptor activator of nuclear factor kappa B (RANK) ligand.⁴ RANK-RANKL interaction is responsible for osteoclast differentiation and bone resorption. Over-expression of RANKL in GCT is responsible for local osteolysis.⁴

Denosumab is a humanized monoclonal IgG2 antibody to RANKL which prevents it from activating RANK receptor on osteoclasts thus inhibiting bone resorption.⁵ It is

¹ Department of Orthopaedics, All India Institute of medical sciences, New Delhi, India
² Department of Radiodiagnosis, All India Institute of Medical Sciences, New Delhi, India

Corresponding author:
Shah Alam Khan, Department of Orthopaedics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, Indi.
Email: shahalamkhan70@gmail.com
approved by the FDA for use in GCT. However, as shown by Lau et al. and Shibuya et al. in their in vitro studies, Denosumab is primarily tumoristatic and not tumorici
dal. There are several recent reports of high recurrence rates associated with denosumab use before surgical inter-
vention. Dubey et al. showed that Zoledronic acid (ZA) acts by inducing apoptosis of bone resorbing cells, namely, osteoclasts and has also been shown to effect apoptosis of neoplastic GCT stromal cells, thus, acting as tumoricidal agent. Clinically, ZA has been shown to reduce pain, prevent disease progression and reduce recurrence rates when used in neoadjuvant settings.

Both Denosumab and ZA have been used as neoadjuvant agents in GCT of bone undergoing surgical interven-
tion with a purpose of reduction in tumor load and of recurrence rates. However, to the best of our knowledge, there is no in-vivo study directly comparing the outcomes of Denosumab and ZA as neo-adjuvant agents. This study was aimed at comparing tumor load reduction, facilitation of surgery and clinical outcomes including recurrences for the two neoadjuvant agents.

Materials and methods

Ethical approval from institute ethics committee was obtained. It was a retrospective analysis wherein medical records of all the patients who underwent treatment for GCT of bone at our institute were studied. Inclusion criteria included cases which were histologically proven GCT, received either ZA or denosumab as a neo-adjuvant agent, underwent surgical intervention from January 2013 to January 2018, had a minimum follow-up of 2 years, no adju-
vant used during follow-up, had complete records and gave consent for being included at the time of last follow-up. As per such criteria, 39 patients were included, 20 of whom had received denosumab and 19 received ZA as neo-adjuvant therapy.

Demographic data and tumor characteristics were noted i.e. site (location), type (primary/recurrent), Campanacci grade, initial surgical plan (wide resection/ intra-lesional curettage) and presence of metastasis at presentation.

Patients received either ZA or denosumab as neo-adjuvant therapy. No. of doses, total duration of ther-
apy, time delay between surgery and last dose, cost of ther-
apy and any therapy related adverse events were noted. The patients received either Denosumab or ZA based on surgeon preference, affordability and ease of administration after discussion with the patient at the start of the therapy. ZA was administered 4 mg intravenously once 4 weekly for minimum of three doses (upto six doses). Denosumab was administered 120 µg subcutaneously in abdominal area 4 weekly for minimum of four doses (upto eight doses). Administration of either agent required short hospital admission to observe for any immediate adverse events.

Radiographs and MRI before and after completion of neoadjuvant therapy were analyzed by a single musculoskeletal radiologist. Pre and post therapy radiographs were compared for central sclerosis and peripheral new bone rimming. Pre and post MRI were analyzed using RECIST criteria for solid tumors to quantify changes in tumor size as no response, partial response, complete resolution and disease progression. RECIST criteria are four part quantification of disease progression and response to therapy and has been validated for solid tumors. It utilizes a surrogate measure of disease load by measuring sum of greatest diameters and comparing temporally.

Change in plan regarding the type of intervention was noted. The surgeries were performed by a single team of surgeons. The type of procedure, duration and blood loss was noted from records. All intra-lesional curettage were extended by use of high speed burr, carbolic acid and hydrogen peroxide.

The included patients had minimum 24 months follow-
up. Wound complications, MSTS score at 2 year follow-up and recurrences were noted. All the recurrences were con-
firmed by histopathology and treated as per standard pro-
tocol of the institute. The cost analysis for either therapy included cost of drug, disposables used during drug administration, hospital stay, cost of surgery and cost of follow-up and management of complications.

Statistical analysis was done using “R” software version 3.6.3. Categorical variables were analyzed using chi square test. Fisher’s exact test was used if expected frequency in any cell was less than 5. Continuous variable were analyzed using student t-test if the variable followed a normal distribution. P-value of < 0.05 was considered statistically significant.

Results

Demographic data

There was no statistically significant difference between the two groups in terms of age, gender, weight, height and BMI (Table 1). None of our patients had any co-morbidities.

Tumor characteristics

There was no statistically significant difference between the groups in terms of site and type of GCT (primary or recurrent). There was no difference in the two groups in terms of tumor grade. None of the patients presented with any metastasis (Table 1). The patients in our study pre-
sented with tumors localized to Distal femur (n = 8), Distal
humerus (n = 1), proximal tibia (n = 15), Distal radius (n = 8), Distal tibia (n = 2), Metacarpal bones (n = 2), femoral head (n = 1), scapula (n = 1) and talus (n = 1). There was no difference between the two therapy groups in terms of location of tumors.

Neoadjuvant therapy specifications
Patients receiving ZA received lower number of doses for lesser duration as compared with denosumab group (no. of doses: p-value = 0.03, duration: p-value = 0.08). However, patients receiving ZA had greater time delay from last dose to surgery (p-value = 0.05). There was significant difference in cost of therapy (p-value = 0.001) (Table 1).

Follow-up
The mean follow-up for deosumab group was 24.5 months and for ZA group was 19.2 months. No significant difference in follow-up time between the two groups.

### Table 1. Comparison of demographic, tumor related and therapy related variables between the two therapy groups.

|                          | Denosumab group (n = 20) | Zoledronic acid group (n = 19) | p-value |
|--------------------------|--------------------------|-------------------------------|---------|
| Age (years)              | 30.80 ± 9.92             | 26.36 ± 6.45                 | 0.106   |
| BMI (kg/m²)              | 27.20 ± 4.34             | 26.20 ± 5.66                 | 0.245   |
| Gender:                  |                          |                               | 0.527   |
| Males                    | 11 (55%)                 | 8 (42.10%)                   |         |
| Females                  | 9 (45%)                  | 11 (57.89%)                  |         |
| Type of tumor:           |                          |                               | 0.56    |
| Primary                  | 19 (95%)                 | 16 (84.21%)                  |         |
| Recurrent                | 1 (5%)                   | 3 (15.78%)                   |         |
| Campanacci grade:        |                          |                               | 0.329   |
| Grade 1                  | 0 (0%)                   | 2 (10.52%)                   |         |
| Grade 2                  | 6 (30%)                  | 5 (26.31%)                   |         |
| Grade 3                  | 14 (70%)                 | 12 (63.15%)                  |         |
| No. of doses             | 5.60 ± 0.94              | 4.89 ± 0.99                  | 0.03    |
| Therapy duration (Months)| 5.54 ± 1.09              | 4.84 ± 1.01                  | 0.08    |
| Time delay from last dose(Months)| 3.40 ± 2.64 | 5.86 ± 4.66                  | 0.053   |
| Cost of therapy (INR)    | 60,112.34 ± 3,002.54     | 12,564.45 ± 2,556.82         | 0.001   |
| Adverse effects          | None                     | None                          | -       |

### Table 2. Comparison of outcomes between the two therapy groups.

|                          | Denosumab group (n = 20) | Zoledronic acid group (n = 19) | p-value |
|--------------------------|--------------------------|-------------------------------|---------|
| Peripheral bone rimming on Radiographs | 19 (95%)                 | 14 (73.68%)                  | 0.161   |
| Radiological response on MRI as per RECIST criteria: |                          |                               | 0.559   |
| Complete resolution      | 0 (0%)                   | 0 (0%)                        |         |
| Partial response         | 11 (55%)                 | 9 (47.36%)                    |         |
| Stable disease           | 5 (25%)                  | 4 (21.05%)                    |         |
| Disease progression      | 4 (20%)                  | 6 (31.57%)                    |         |
| Downgrading of surgical plan | 5 (25%)                 | 5 (26.31%)                    | 0.614   |
| Duration of surgery (mins)| 108.5 ± 39.10            | 118.42 ± 36.85               | 0.419   |
| Blood loss (ml)          | 322.50 ± 130.25          | 257.89 ± 56.89               | 0.314   |
| Post op wound complications | 2 (10%)                  | 2 (10.52%)                   | 0.636   |
| Recurrence               | 5 (25%)                  | 2 (10.52%)                    | 0.447   |
| MSTS score at 2 year follow-up | 26.40 ± 3.84            | 26.21 ± 3.88                 | 0.87    |

Radiological response and plan change
There was no statistically significant difference in the two groups in terms of MRI evaluation (p-value = 0.559). Peripheral bone rimming and sclerosis was seen more in patients receiving denosumab as compared to those receiving ZA (p-value = 0.161). A total of 10 patients (25.64%) had a change of surgical plan from wide resection to intralesional curettage with no difference between the groups (Table 2, Figures 1–3).

Intraoperative and postoperative parameters
Extended curettage was performed in 89.74% cases and wide resection in rest of them. No statistical differences seen in terms of blood loss, surgery duration and wound complications (Table 2).

Clinical outcome
Mean MSTS score comparison showed no statistically significant difference (Table 2).
Recurrence

The recurrence rates were higher in denosumab group (25%) as compared to that in ZA group (10.52%) (p-value = 0.447). Recurrence was correlated with various factors like patient demographics, tumor characteristics, therapy specifications, radiological response, operative intervention and wound complications. Recurrences were statistically more common in patients with stable disease rather than in those with progressive/partial response as per RECIST criteria (p-value = 0.038). Rest of the parameters including Campanacci grade were not significant.

Discussion

Experimental studies have shown that ZA causes dose-dependent inhibition as well as apoptosis in stromal cell lines while denosumab showed no such response. However, direct comparison in clinical settings is scarce in literature. Li et al. in a recent RCT involving in-operable GCTs demonstrated that ZA and denosumab had similar clinical effects, however, denosumab therapy was more costly. Our study aims at directly comparing denosumab and ZA in a neo-adjuvant setting in operable patients of GCT which, to the best of our knowledge, has not been reported in literature yet.

Both denosumab and ZA have been known to downsize the tumor by causing central and peripheral new bone formation. Our study also shows a similar finding with both groups showing peripheral bone rimming and about 50% patients in each group showing partial response on MRI. This finding suggests that ZA and denosumab have comparable tumor reduction potential.

Müller et al. showed 64% of their patients had a down staging of surgical plan from wide resection to intralesional curettage and reported surgery to be easier to perform following denosumab therapy. Traub et al. also demonstrated similar findings. Our study showed down staging in 25.6% cases overall but no statistical difference between the two groups. All down staged patients demonstrated partial response on MRI. Similarly, no statistical difference was found between the two therapies in terms of blood loss, duration of surgery and incidence of wound complications suggesting equal efficacy in facilitating surgery.

Li et al. elucidated various side effects of denosumab and ZA treatment like arthralgia, alopecia, hypocalcemia, jaw osteonecrosis and back pain. However, direct comparison is scarce in literature. Surprisingly, we did not encounter a single complication in either therapy group. All patients had a dental screening to rule out carries. The smaller size of the cohort may explain this finding to some extent. They also demonstrated ZA to be significantly cheaper than denosumab, which is also shown by our study using same methods of cost calculation.

Neo-adjuvant therapy with both denosumab and ZA has shown to reduce recurrences. Kundu et al. showed reduced recurrence rates in patients receiving ZA before surgery as compared to controls who underwent surgery alone (1/19 vs 4/19, respectively). Lipplaa et al. showed no effect of ZA on local recurrences, however, in this study ZA was given as an adjuvant. Recurrence rates with denosumab have been variable in literature. Jamshidi et al. reported a recurrence rate of 2% with denosumab, whereas, Errani et al in their study with controls demonstrated 60% recurrence. Puri et al. reported a recurrence rate of 29% and also concluded that local control rates are unlikely to improve.
with neoadjuvant denosumab.\textsuperscript{9} Our study demonstrated recurrence rates of 25\% with denosumab and 10.52\% with ZA which, although, is not statistically significant, but trends in favor of ZA. Limited number of participants in our study may be the reason for this difference being not statistically significant.

The trend toward lower recurrence rates in ZA group can be explained in light of experimental studies.\textsuperscript{5,7,10} Since denosumab doesn’t have an inhibitory effect on stromal tumor cells and also doesn’t induce apoptosis, the pockets created by new bone formation might tend to house live tumor cells which may not be effectively removed during curettage. On the other hand, ZA tends to be inhibitory to tumor population and also leads to apoptosis. Therefore, such new bony niches formed should house lesser live tumor load that may result in recurrences later on.

Denosumab being tumoristatic might lead to late reactivation of stromal cells in the sclerotic rim leading to higher rate of recurrence. In our opinion, patients receiving Denosumab therapy should be adequately counseled for possibility of recurrence and regular follow-up if they are undergoing curettage of the lesion.

Significant number of recurrences were found in patients classified as having “no response” on post-therapy MRI as per RECIST criteria i.e. no increase or decrease in tumor load by the neo-adjuvant therapy (p-value $= 0.03$). There are certain subsets of patients who may not show any clinico-radiological response to either denosumab or ZA. Further studies must be undertaken to identify them pre-therapy as most recurrences are found in such patients according to our study.

There were no statistically significant differences in functional outcome (i.e. MSTS score at 2 years follow-up) between the two treatment groups. There is no existing literature regarding comparison of outcome scores between the two therapy groups. Although, Li et al. evaluated and compared pain relief and improved mobility between denosumab and ZA in in-operable cases and found no significant difference.\textsuperscript{15} There are several limitations in this study. As this was a retrospective study, we could not randomize the subjects into the two arms. However, the two groups were comparable in terms of baseline demographic and clinical parameters, making our results meaningful. We also had limited number of patients in our study because of the stringent inclusion and exclusion criteria. Based on the observed recurrence rates in the two groups, for an alpha error of 0.05 and power of 80\%, one would need a total of 216 patients (108 in each group) to get a statistically significant difference in recurrence rate. Such a large prospective study will require collaboration of multiple centers around the world in view of the rarity of the disease. As our primary aim was to prove the equivalence of ZA to denosumab in the neo-adjuvant setting, our sample size is justifiable in view of the pilot nature of the study. Moreover, to the best of our knowledge, this is the first study to directly compare the effects of ZA and denosumab in operable GCTs in the same set of population.

In conclusion, while this study opens up a research avenue requiring greater sample sizes and prospective study designs, it also hints toward ZA being a cheaper and equally effective alternative to denosumab for treatment of GCT of bone.

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**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.

**Ethics**

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.
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ORCID iDs
Roshan Banjara https://orcid.org/0000-0003-1106-2904
Shah Alam Khan https://orcid.org/0000-0001-9205-9082

References
1. 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.
2. Klenke FM, Wenger DE, Inwards CY, et al. Giant cell tumor of bone: risk factors for recurrence. *Clin Orthop Relat Res* 2011; 469(2): 591–599.
3. Gitelis S, Mallin BA, Piasecki P, et al. Intralesional excision compared with en bloc resection for giant cell tumors of bone. *J Bone Joint Surg Am* 1993; 75(11): 1648–1655.
4. Wu PF, Tang JY and Li KH. RANK pathway in giant cell tumor of bone: pathogenesis and therapeutic aspects. *Tumor Biol* 2015; 36(2): 495–501.
5. Lau CP, Huang L, Wong KC, et al. Comparison of antitumor effects of denosumab and zoledronic acid on neoplastic stromal cells of giant cell tumor of bone. *Connect Tissue Res* 2013; 54(6): 439–449.
6. Luengo-Alonso G, Mellado-Romero M, Shemesh S, et al. Denosumab treatment for giant-cell tumor of bone: a systematic review of the literature. *Arch Orthop Trauma Surg* 2019; 139(10): 1339–1349.
7. Shibuya I, Takami M, Miyamoto A, et al. In vitro study of the effects of denosumab on giant cell tumor of bone: comparison with ZA. *Pathol Oncol Res* 2019; 25: 409–419.
8. 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.
9. Puri A, Gulia A, Hegde P, et al. Neoadjuvant denosumab: Its role and results in operable cases of giant cell tumor of bone. *Bone Joint J* 2019; 101-B: 170–177.
10. Dubey S, Rastogi S, Sampath V, et al. Role of intravenous ZA in management of giant cell tumor of bone- a prospective, randomized, clinical, radiological and electron microscopic analysis. *J Clin Orthopaedics Trauma* 2019; 10: 1021–1026.
11. Tse LF, Wong KC, Kumta SM, et al. Bisphosphonate reduce local recurrence in extremity giant cell tumor of bone: a case control study. *Bone* 2008; 42(1): 68–73.
12. Balke M, Campanacci L, Gebert C, et al. Bisphosphonate treatment of aggressive primary, recurrent and metastatic giant cell tumor of bone. *BMC Cancer* 2010; 10: 462.
13. Kundu ZS, Sen R, Dhimn A, et al. Effect of intravenous ZA on histopathology and recurrence after extended curettage in giant cell tumors of bone: a comparative prospective study. *Indian J Orthop* 2018; 52: 45–50.
14. Li S, Chen P and Yang Q. Denosumab versus ZA in cases of surgically unsalvageable giant cell tumor of bone: a randomized clinical trial. *J Bone Oncol* 2019; 15: 100217.
15. Fournier L, Ammari S, Thiam R, et al. Imaging criteria for assessing tumor response: RECIST, mRECIST, Cheson. *Diagn Interv Imaging* 2014; 95: 689–703.
16. Palmerini E, Chawla NS, Ferrari S, et al. Denosumab in advanced/unresectable giant-cell tumor of bone (GCTB): for how long? *Eur J Cancer* 2017; 76:118–124.
17. Roitman PD, Jauch F, Farfalli GL, et al. Denosumab-treated giant cell tumor of bone. Its histologic spectrum and potential diagnostic pitfalls. *Hum Pathol* 2017; 63: 89–97.
18. Traub F, Singh J, Dickson BC, et al. Efficacy of denosumab in joint preservation for patients with giant cell tumor of the bone. *Eur J Cancer* 2016; 59: 1–12.
19. Müller 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(1): 281.
20. Lipplaa A, Kroep J, Heijden L, et al. Adjuvant ZA in high-risk giant cell tumor of bone: a multicenter randomized phase II trial. *Oncologist* 2019; 24: 889–e421.
21. Jamshidi K, Gharehdagh M, Hajialiloo SS, et al. Denosumab in patients with giant cell tumor and its recurrence: a systematic review. *Arch Bone Jt Surg* 2018; 6: 260–268.