Role of Denosumab in the Management of Giant Cell Tumor, a Cross Sectional Study

CROSS SECTIONAL STUDY

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ABSTRACT

Background: Giant cell tumor (GCT) of bone is a benign lesion which is characterized by presence of multinucleated osteoclasts type giant cells. Nuclear factor kappa B (RANKL) serves as the trigger factor for osteoclasts cells formation. Although surgery is the primary treatment for GCT of bone but recurrence remains the concern. Therefore, the development of denosumab, a monoclonal antibody for treating GCT for both primary and recurrent disease cases. The present study aims to show the role of denosumab along with surgery when given as neo-adjuvant drug to patients of GCT for their treatment.

Methodology: A total of 23 patients diagnosed with GCT were included in this study from January 2016–December 2019 and all of these patients had received neo adjuvant denosumab dose of 120 mg SC on day 0, 15, 30 & 45. All patients were treated at the section of Orthopedics, department of surgery, Aga Khan University hospital, Karachi. Other benign lesions were excluded from the study.

Results: Out of 23 patients we had 12 (52.2%) males and 11 (47.8%) females. The mean age of our patients was 34±13.8 years and mean follow up duration of all patients was 20.5 ± 10.7 months. There were 15 (65.2%) primary cases of GCT while 8 (34.8%) were recurrent cases. In 8 (34.8%) of the cases primary site of lesion was distal femur followed by 7(30.4%) proximal tibia cases and 3(13%) distal radius cases. In surgical procedure 20 (87%) patients underwent wide margin excision and only 3 (13%) had intralesional curettage. Reconstruction was performed in 21 patients which consist of bone grafting in 9 patients and mega prosthesis insertion in 12 patients. Only two patients had no reconstruction. On final histopathology, there was no residual GCT and we observed no denosumab induced adverse effects. Post-operative complications included wound infection and peri prosthetic infection in 3 patients. On follow-up we had 4(17.4%) cases of recurrence that were offered revision surgery while 19 (82.6%) were disease free.

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Conclusion: Denosumab has shown successful results in treating patients with GCT along with surgical intervention and it can be a best option for treating recurrent disease as well.

HIGHLIGHTS

- Giant cell tumor of bones is aggressive non-cancerous tumor.
- Denosumab, a human monoclonal antibody that inhibits RANK-L, has shown good results in its management along with surgery in neo adjuvant setting.
- In our study, most of the patients underwent wide margin excision followed by few treated intralesional curettage ins surgical management.
- Our study reported few cases of recurrence after neoadjuvant Denosumab treatment showing its efficacy inthe disease management.

Research registration no: researchregistry4695

BACKGROUND

Giant cell tumour of bone (GCT) is a bone neoplasm which is locally aggressive and can rarely metastasize [1]. It is more prevalent in women than in men, that is 1.5:1 ratio [2] and typically affects skeletally mature adults up to 40 years of age [3]. Clinically, patients present with localised pain, tenderness, swelling, decreased joint motion, and in some cases with pathological fractures. 50% of cases involve the region of the knee and other long bones while some may involve the spine [4].

Malignancy is rare at time of diagnosis but GCT may undergo malignant transformation after radiation therapy or several recurrences [5]. This is often suspected if atypical mitotic figures are present. Surgery is the definitive therapy with 80% of patients presenting with primary GCT responding to surgical intervention [6]. This includes curettage, en bloc resection, and amputation. However, surgical intervention may cause substantial morbidity. Morbidity is often balanced against risk of recurrence which under the influence of size, location and surgical intervention ranges from approximately 50% with curettage to less than 10% with other aggressive procedures [6].

In light of this variability and high recurrence rate due to surgical intervention, the role of Denosumab, a human monoclonal antibody that inhibits RANK-L, continues to be explored [7], allowing inhibition of osteoclast mediated bone destruction. Subcutaneous administration provides rapid and sustained suppression of bone turnover in patients with multiple myeloma and osteolytic bone disease, and in patients with breast and prostate cancer with bone metastases Inhibition of RANKL by denosumab in patients with Giant cell tumor of bone (GCTB) might inhibit bone destruction and eliminate giant cells [8, 9]. In addition, it provides for a calcified rim surrounding the soft tissue component often seen in advanced GCTB, facilitating curettage with local adjuvants, or en-bloc resection, at a later stage, in previously uncurettable GCTB [10, 11]. Recent literature indicates that continued denosumab may have a therapeutic role in cases of unsalvageable GCT, particularly with pulmonary metastases, but also in the neoadjuvant setting where the drug might improve surgical outcomes in both primary and recurrent disease cases [11]. This claim requires further investigation; hence our present study aims to show the role of denosumab along with surgery when given as neo-adjuvant drug to South-Asian patients of GCT for their treatment.

METHODOLOGY

A retrospective study was planned, and all patients (adult and paeds) diagnosed with GCT were included in this study from January 2016 – December 2019 and all of these patients had received neo -adjuvant Denosumab dose of 120 mg SC on day 0, 15, 30 & 45 [20]. Only those patients who were treated at the section of Orthopedics, department of surgery, Aga Khan University hospital (AKUH), Karachi were included. All patients had minimum 6 months follow up. Patients presented with ambiguous biopsy results/ other benign lesions were excluded. No sampling technique was required, as all the patients meeting the inclusion criteria were enrolled for study. Patients were identified from orthopedic tumor registry data \ health information management system and data collection forms were filled through review of medical records. Study was reviewed by ethics review committee of AKUH, and exemption from ERC was granted. The following data was reviewed: demographic data (patient age at operation, gender, tumor type, and histologic diagnosis), surgical details (reconstructive procedures, lesion resected, and surgical margins), neo-adjuvant therapy and post-operative status of patients (alive, expire, tumor recurrence). Data was entered on

statistical software SPSS 21 for analysis. All quantitative variables were reported as means and standard deviation while frequencies were reported for qualitative variables. For measuring histological outcomes, standard criteria for reviewing pathological slides were followed and all biopsies prior to neo-adjuvant Denosumab dose and post-surgery were evaluated for outcomes. This study has been registered in the research registry, the number is researchregistry4695 and it is being reported in line with STROCSS research reporting guidelines [19].

RESULT

There were 23 patients that matched the inclusion criteria of our study. Out of these 23 patients, there were 12 males (52.2%) and 11 females (47.8%). The mean age of our patients was 34±13.8 years and mean follow up duration of all patients was 20.5 ± 10.7 months (Table 1). There were 15 (65.2%) primary cases of GCT while 8 (34.8%) were recurrent cases. In 8 (34.8%) of the cases primary site of lesion was distal femur followed by 7(30.4%) proximal tibia cases and 3 distal radius cases (Figure 1: **Primary site of lesions**). There were no side effects of denosumab in our patients. The side effects can be observed immediately after administration of denosumab injection which includes redness, swelling or bone pain and none of our patient showed such signs and symptoms. In surgical procedure 20 (87%) patients underwent wide margin excision and only 3 (13%) had intralesional curettage. Reconstruction was performed in 21(91.3) patients which consist of bone grafting in 9 patients and mega prosthesis insertion in 12 patients (Figure 2: **Giant Cell tumor of proximal tibia after wide margin excision and mega-prosthesis insertion).**

Only two patients had no reconstruction. In bone grafting, 4(17.4%) patients had non-vascular fibula grafting,3(13%) had vascular fibula, 1 (4.3%) had iliac crest bone graft, 1 had iliac crest bone graft with strut fibula. On final histopathology, there was no residual GCT and we observed no denosumab induced adverse effects. Post-operative complications included wound infection and peri prosthetic infection in 3 patients. On follow-up we had 4(17.4%) cases of recurrence that were offered revision surgery while 19 (82.6%) were disease free.

	N	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION
Age	23	18	65	34	13.84
Follow-up (Months)	23	2	40	20.57	10.7

Table 1 Descriptive Analysis Of Age And Follow Up Of Patients.

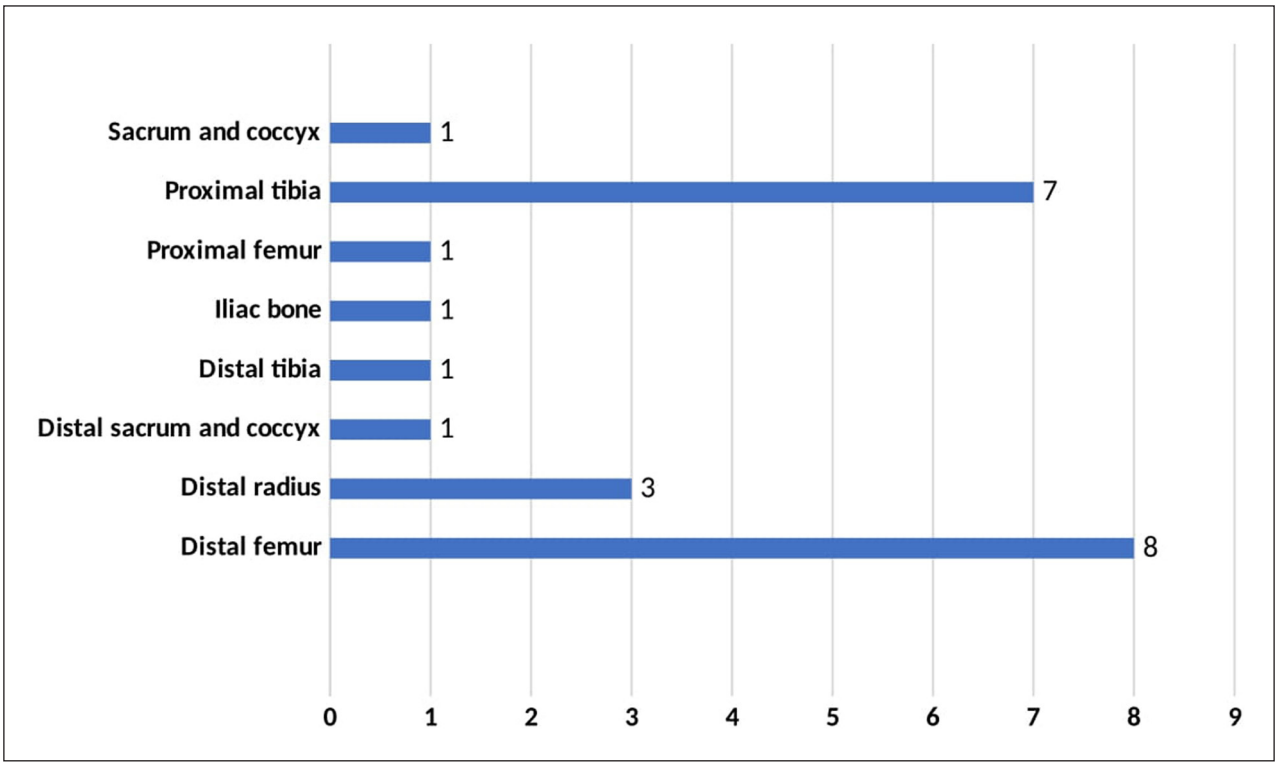

Figure 1 Primary Sites of Lesion.

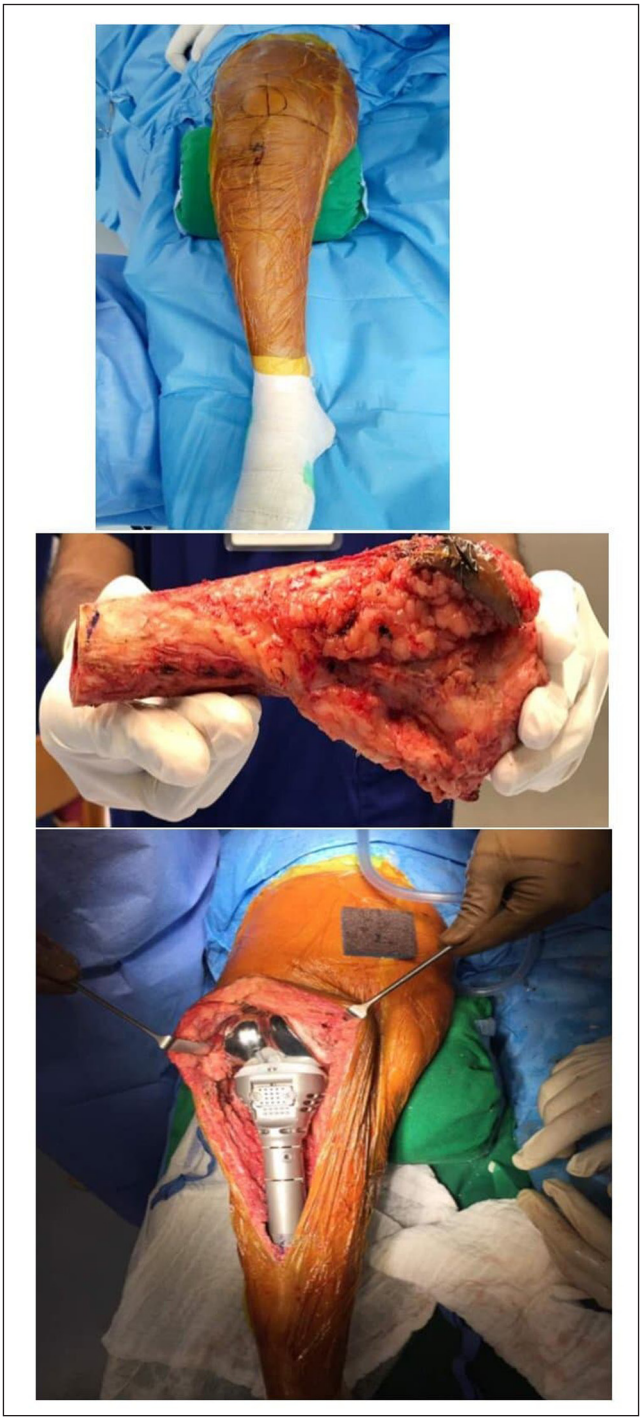

Figure 2 Giant Cell tumor of proximal tibia after wide margin excision and mega-prosthesis insertion.

DISCUSSION

The results of this study propose that denosumab, which particularly targets RANKL, hence hindering the interplay between RANK-positive osteoclast-like giant cells and RANKL-positive stromal cells, has activity as a therapeutic agent for GCT of bone. The unearthing of giant cells in GCTB expressing RANKL [12, 13] has brought about the clinical utilization of denosumab in the management of tumor which were previously deemed unresectable or led to bigger disability after resection. Inevitably Thomas el al conducted the first open-label phase II proof of concept study [11]. He reported 90% histological elimination of giant cells in 30 of 35 (86%) patients. However, in our study all patients underwent wide margin excision with or without reconstruction after receiving denosumab and the final histopathology reported complete response to tumor, defined as no residual tumor cells in final histological evaluation, in all 23 (100%) patients. A second phase II study containing 282 patients claims that denosumab is safe and efficient for GCTB [10]. 163 of 169 (96%) patients with unresectable disease (cohort 1) had no progress in disease following denosumab treatment.in second cohort of 100 patients planned for surgery, majority (16 of 26) encountered less morbid procedure than initially planned and no surgery