https://doi.org/10.29309/TPMJ/2022.29.05.6890

The Professional Medical Journal
www.theprofesional.com
2022, Volume, 29 Issue, 05

ORIGINAL ARTICLE

Analgesic effect of neoadjuvant denosumab in Grade III giant cell tumor of bone.

Badaruddin Sahito[1], Sana Shahid[2], Arsia Hanif[3], Nasim Munshi[4], Muhammad Soughat Katto[5], Azam Kamboh[6], Sheikh Muhammad Ebad Ali[7]

Article Citation: Sahito B, Shahid S, Hanif A, Munshi N, Katto MS, Kamboh A, Ali SME. Analgesic effect of neoadjuvant denosumab in Grade III giant cell tumor of bone. Professional Med J 2022; 29(5):613-617. https://doi.org/10.29309/TPMJ/2022.29.05.6890

ABSTRACT… Objective: To assess the pain relief after denosumab use in grade III giant cell tumor of bone (GCT-B). **Study Design:** Retrospective Cohort study. **Setting:** Department of Orthopedic Surgery Dow University of Health Sciences / Dr Ruth KM Pfau Civil Hospital Karachi. **Period:** 2018 May to 2020 June. **Material & Methods:** Total 27 patients were included in the study with diagnosis of grade III GCT-B. Patients with Stage I & II excluded from study. **Results:** After the first dose of Denosumab, 24 (88.9%) patients reported no pain relief while the other 3 (11.1%) patients had mild pain. A second dose of Denosumab was given to these patients. After the second dose, 3 (11.1%) patients scored mild pain and 24 patients had a score of ≥4 on VAS. The pain severity reduced significantly after administration of 2nd dose of Denosumab (p=0.019). Pain severity was remeasured after the third dose of Denosumab where they had VAS of 0 to 6, with inconsistent use of simple analgesics. The pain severity reduced significantly after administration of 3rd dose of Denosumab (p=0.001). **Conclusion:** We conclude that denosumab have excellent analgesic effect in grade III giant cell tumor of bone. We recommend the use denosumab in perioperative therapy for grade III GCT-B bone and we found analgesic effect as additional one. It may gain some time for patient specially in developing nations where oncology surgery centers are limited. It also reduces the use of NSAIDS during window period of definitive surgery.

Key words: Analgesic Effect, Denosumab, Giant Cell Tumor.

INTRODUCTION

Giant cell tumor of bone (GCT-B) is benign and aggressive bone tumor with stromal cells and giant cells on microscope.[1] Radiologically it appears as lytic lesion at metaphysis in eccentric fashion. It is common in female > male with age between 20-40 years.[2,3] 1-4% patients develop metastasis.[3] Pain and swelling remains the most common complain among patients that causes significant hindrance in routine activities. The recent use of denosumab in treatment revolutionize the treatment of GCT-B.[4] GCT-B expresses interplay between receptor activator of nuclear factor -kappa B (RANK) and RANK-ligand (RANK-L).[5]

Denosumab is monoclonal antibody that blocks the RANK-RANK-L pathway and prevent tumor cell proliferation.[6,7,8] FDA and EMA approved its use as neoadjuvant in 2013 and 2014 to downstage the tumor.[9,10] It was initiated to produce osteosclerotic rim around the tumor that makes the margin well-defined and easier for resection. There were two regimens where once monthly regimen is used for long-term disease control while once weekly regimen for four weeks is employed as neoadjuvant adjunct before surgery.

The objective of our study was to appraise the pain relief in neoadjuvant treatment with denosumab in grade III GCT-B.

MATERIAL & METHODS

This Retrospective cohort study was conducted at Department of Orthopedic Surgery Dow University of Health Sciences / Dr Ruth KM Pfau Civil Hospital Karachi. 2018 May to 2020 June.

1. MBBS, FCPS, Associate Professor Orthopaedic Surgery, Dow University of Health Sciences/Civil Hospital Karachi.
2. MBBS, Resident General Surgery, Dow University of Health Sciences/Civil Hospital Karachi.
3. MBBS, Resident General Surgery, Dow University of Health Sciences/Civil Hospital Karachi.
4. MBBS, FCPS, Assistant Professor Orthopaedic Surgery, Ziauddin Hospital, Karachi.
5. MBBS, FCPS, Assistant Professor Orthopaedic Surgery, Dow University of Health Sciences/Civil Hospital Karachi.
6. MBBS, Resident Orthopaedic Surgery, Dow University of Health Sciences/Civil Hospital Karachi.
7. MBBS, Research Associate Emergency Medicine, Aga Khan University Hospital, Karachi.

Correspondence Address:
Dr. Badaruddin Sahito
Department of Orthopaedic Surgery
Dow University of Health Sciences/
Dr Ruth K M Pfau Civil Hospital Karachi.
sahito.badar@hotmail.com

Article received on: 08/11/2021
Accepted for publication: 12/01/2022

All patients with grade III giant cell tumor of bone. Giant cell tumor I and II, Non-complaint patients and Patients on NSAIDS after first dose were excluded from the study. After consent and counselling to the patients with grade III giant cell tumor of bone registered for the study. Total 27 patients were included in the study. All patients were given neoadjuvant Denosumab subcutaneously 120 mg on day 0,8,15 and 28 days or three doses only. The pain scoring was performed before first dose than at weekly before another dose of denosumab consequently. The pain records were further analyzed for the use of analgesics such as NSAIDs and opioids.

At baseline before the administration of the first dose of Denosumab, 4 patients had pain score of 8 (14.8%), 10 had pain score of 9 (37%) and 13 had pain score of 10 (48.1%) as shown in Figure-1. Most of the patients had 4 doses of Denosumab (n=18, 66.7%) and 9 patients had 3 doses of Denosumab (33.3%).

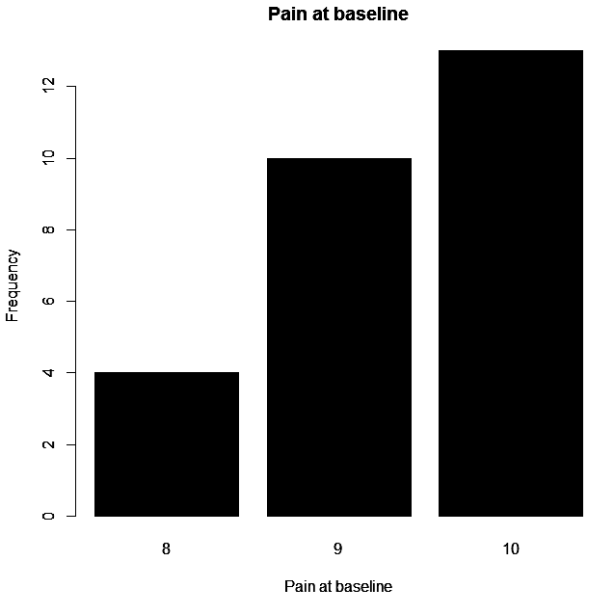

Figure-1. Frequency distribution of pain score at baseline.

IBM SPSS version 20.0 was used to analyze data. Mean and SD was reported for quantitative variables and frequency and percentage was reported was qualitative variables. The data were compared using independent t-test where baseline pain score was compared to the pain score after each injection. Visual Analogue Scale (VAS) was used for pain calculation.

RESULTS

The mean age of the study sample was estimated as 30.19±7.3 years. Out of the 27 patients who consented to participate, 16 (59.3%) were males, and the other 11(40.7%) were female patients. About 13 patients had tumor of the right side of the body and 14 had left laterality. Distal femur was the most frequent site (22.2%) followed by distal radius (18.5%) and proximal tibia (18.5%) respectively as shown in (Table-I).

After the first dose of Denosumab, 24 (88.9%) patients reported no pain relief (severe pain), while the other 3 (11.1%) patients had a score of 4-6 on VAS (Mild pain). A second dose of Denosumab was given to these patients. After the second dose, 3 (11.1%) patients scored <4 on VAS (Mild pain) and 24 patients had a score of ≥4 on VAS who also required non-steroidal inflammatory drugs (NSAIDs) for pain relief. The pain severity reduced significantly after administration of 2nd dose of Denosumab (p=0.019). Pain severity was again measured after the third dose of Denosumab was administered. All patients, after the third dose of Denosumab, had a score of 0 to 6 on the VAS, with inconsistent use of simple analgesics. The pain severity reduced significantly after administration of 3rd dose of Denosumab (p=0.001). After that, 7 patients did not receive the fourth dose due to unaffordability, while the rest of the 11 patients had no pain and 8 patients had a substantial resolution of pain after the fourth dose, without needing any analgesics. (Table-II).

DISCUSSION

Denosumab a new era in the treatment of giant cell tumor have variable effects on tumor as it localizes and calcify the tumor. It has analgesic effect as well but very sparse data published related to pain relief in GCT-B.[12]

Characteristics	Value
Age (years)*	30.19 (7.3)
Gender	
Male	16 (59.3%)
Female	11 (40.7%)
Laterality	
Right	13 (48.1%)
Left	14 (51.9%)
Site	
Distal radius	5 (18.5%)
Distal femur	6 (22.2%)
Distal tibia	1 (3.7%)
Distal ulna	2 (7.4%)
Proximal femur	2 (7.4%)
Proximal tibia	5 (18.5%)
Proximal humerus	3 (11.1%)
Proximal fibula	1 (3.7%)
Patella	1 (3.7%)
Multifocal	1 (3.7%)
* Mean (SD)	

Table-I. Baseline characteristics.

Denosumab inhibits RANK-RANK-L interaction that is key to giant cell proliferation which are responsible for bone resorption.[13] Furthermore, the drug has gained FDA approval in 2013 for treatment of unresectable GCT-B and has proven to be effective. We have also used Denosumab in lower doses and less frequently as previous studies employed higher dosing regimens including monthly, fortnightly, and weekly doses for three or more months. The response achieved in terms of pain reduction was adequate while cost was also conserved. Patients also regained some routine activities that were ceased previously due to pain.

A cohort study results revealed that 42% of the patients with unresectable GCBT had a clinical reduction in pain after 1 month of treatment with Denosumab and 50% of patients had clinically significant pain reduction after 2 months of treatment with denosumab.[5] Another study conducted on 222 patients revealed that treatment with Denosumab for a median of 19.5 (12.4–28.6) months improved the pain in 61% of the patients, along with improved functionality.[11] Our study found a complete resolution of pain in 100% of the patients who received the fourth dose of Denosumab. A cohort study showed analgesic use after denosumab significantly drops to no need after four doses. It declines to minimum to none in 39% of 56 patients who were taking strong opioids before denosumab initiation.[5] We also find significant reduction of analgesic use to no use. According to the pain ladder of World Health Organization (WHO), none of the candidates required strong or weak opioids of level 2 and 3, respectively. Few candidates took NSAIDs that were stopped after the last dosage of Denosumab.

Denosumab showed significant role when used before surgery in untreatable and aggressive GCT-B.[14] Study on histological specimen showed loss of RANKL expression on tumor cells.[15] We limited our study only to analgesic effect of denosumab in GCT-B. Limited published studies available on this aspect of denosumab. We found significant pain relief after denosumab use in subsequent doses in grade III GCT-B with less need of NSAIDS and analgesic. Such an effect of Denosumab has never been studied in Asia, making our study the first of its kind, particularly in Southeast Asian population. Therefore, through this study, our aim to document the effects of Denosumab on pain in patients with GCT-Bs. A similar study from China showed that 86% of patients had pain relief treated with denosumab conducted by Niu X et al.[16]

Severity of Pain	Baseline	1st Dose	2nd Dose	3rd Dose	4th Dose
No pain (VAS=0)	-	-	-	7(25.9%)	11(40.7%)
Mild pain (VAS=1-3)	-	-	3(11.1%)	16(59.3%)	8(29.6%)
Moderate pain (VAS=4-6)	-	3 (11.1%)	19(70.4%)	4(14.8%)	-
Severe pain (VAS=7-10)	27 (100%)	24(88.9%)	5(18.5%)	-	-
p-value	-	0.222	0.019*	0.001*	0.999

Table-II. Frequency distribution of severity of pain after administration of denosumab.

Phase II clinical trials conducted by Martin et al. showed significant pain relief in GCT-B over two-month periods and most of the patients used no or low doses of analgesics.[17]

Sant Chawla and colleagues present the long-term follow-up results of their phase 2 trial of denosumab to treat giant cell tumour of bone on 532 patients the drug can be used safely and with reasonable activity in both unresectable and resectable giant-cell tumours.[18]

Puri et al; recommend 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.[19]

Denosumab demonstrated improved pain prevention and comparable pain palliation compared with zoledronic acid in bone metastasis and breast cancer.[20]

CONCLUSION

We conclude that denosumab have excellent analgesic effect in grade III giant cell tumor of bone. We recommend the use denosumab in perioperative therapy for grade III GCT-B bone and we found analgesic effect as additional one. It may gain some time for patient specially in developing nations where oncology surgery centers are limited. It also reduces the use of NSAIDS during window period of definitive surgery.

REFERENCES

1. M, Forsyth R, Reid RP, Sapi Z. **Giant cell tumor of bone. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. WHO classification of tumors of soft tissue and bone.** 4 ed. Lyon: International Agency for Research on Cancer (IARC); 2013. p. 32e4.
2. Turcotte RE. **Giant cell tumor of bone.** Orthop Clin North Am. 2006; 37(1):35-51.
3. Van der Heijden L, Dijkstra PS, van de Sande MA, Kroep JR, Nout RA, van Rijswijk CS, Bovée JV, Hogendoorn PC, Gelderblom H. **The clinical approach toward giant cell tumor of bone.** The oncologist. 2014 May; 19(5):550.
4. Raskin KA, Schwab JH, M ankin HJ, S pringfi eld DS, Hornicek FJ. **Giant cell tumor of bone.** J Am Acad Orthop Surg 2013; 21:118–26.
5. Martin-Broto J, Cleeland CS, Glare PA, Engellau J, Skubitz KM, Blum RH, Ganjoo KN, Staddon A, Dominkus M, Feng A, Qian Y. **Effects of Denosumab on pain and analgesic use in giant cell tumor of bone: Interim results from a phase II study.** Acta Oncologica. 2014 Sep 1; 53(9):1173-9.
6. Van der Heijden L, Dijkstra PS, Blay JY, Gelderblom H. **Giant cell tumor of bone in the denosumab era.** European Journal of Cancer. 2017 May 1; 77:75-83.
7. Abu-Zaid A, Alaqaili SI, Ahmad SO, Hazzaa IB, Alharbi H. **Preoperative denosumab plus surgery in the management of giant cell tumor of bone: A comprehensive narrative literature review.** Gulf J Oncolog. 2019 May; 1(30):67-75.
8. Palmerini E, Picci P, Reichardt P, Downey G. **Malignancy in giant cell tumor of bone: A review of the literature. Technology in cancer research & treatment.** 2019 Jul 19; 18:1533033819840000.
9. Lipplaa A, Dijkstra S, Gelderblom H. **Challenges of Denosumab in giant cell tumor of bone, and other giant cell-rich tumors of bone.** Current opinion in oncology. 2019 Jul; 31(4):329.
10. Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, Blay JY, et al. **Denosumab in patients with giant-cell tumor of bone: An open-label, phase 2 study.** Lancet Oncol 2010; 11:275–80
11. Chawla S, Henshaw R, Seeger L, et al. **Safety and efficacy of Denosumab for adults and skeletally mature adolescents with giant cell tumor of bone: Interim analysis of an open-label, parallel-group, phase 2 study.** Lancet Oncol 2013; 14:901–908.
12. Martin-Broto J, Cleeland CS, Glare PA, Engellau J, Skubitz KM, Blum RH, Ganjoo KN, Staddon A, Dominkus M, Feng A, Qian Y. **Effects of Denosumab on pain and analgesic use in giant cell tumor of bone: Interim results from a phase II study.** Acta Oncologica. 2014 Sep 1; 53(9):1173-9.

13. Jamshidi K, Gharehdaghi M, Hajialiloo SS, Mirkazemi M, Ghaffarzadehgan K, Izanloo A. **Denosumab in Patients with Giant Cell Tumor and Its Recurrence: A Systematic Review.** Arch Bone Jt Surg. 2018 Jul; 6(4):260-268. PMID: 30175172; PMCID: PMC6110426.

14. Thomas DM. RANKL. **Denosumab, and giant cell tumor of bone.** Curr Opin Oncol. 2012 Jul; 24(4):397-403.

15. Mak I.Y.M, Evaniew N, Popovic S, Tozer R, Ghert M; **A Translational Study of the Neoplastic Cells of Giant Cell Tumor of Bone Following Neoadjuvant Denosumab,** The Journal of Bone and Joint Surgery: 2014 Aug 6, 96; 15: 127.

16. Niu X, Yang Y, Wong KC, Huang Z, Ding Y, Zhang W. **Giant cell tumor of the bone treated with Denosumab: How has the blood supply and oncological prognosis of the tumor changed?** J Orthop Translat. 2019 Jul; 18: 100–108.

17. Martin-Broto J, Cleeland CS, Glare PA, Engellau J, Skubitz KM, Blum RH, Ganjoo KN, Staddon A, Dominkus M, Feng A, Qian Y. **Effects of Denosumab on pain and analgesic use in giant cell tumor of bone: Interim results from a phase II study.** Acta Oncologica. 2014 Sep 1; 53(9):1173-9.

18. Chawla S, Blay JY, Rutkowski P, Le Cesne A, Reichardt P, Gelderblom H, Grimer RJ, Choy E, Skubitz K, Seeger L, Schuetze SM. **Denosumab in patients with giant-cell tumour of bone: A multicentre, open-label, phase 2 study.** The Lancet Oncology. 2019 Dec 1; 20(12):1719-29.

19. Singh VA, Puri A. **The current standing on the use of denosumab in giant cell tumour of the bone.** Journal of Orthopaedic Surgery. 2020 Dec 16; 28(3):2309499020979750.

20. Cleeland CS, Body JJ, Stopeck A, Von Moos R, Fallowfield L, Mathias SD, Patrick DL, Clemons M, Tonkin K, Masuda N, Lipton A. **Pain outcomes in patients with advanced breast cancer and bone metastases: Results from a randomized, double□blind study of denosumab and zoledronic acid.** Cancer. 2013 Feb 15; 119(4):832-8.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Badaruddin Sahito	Conception & Design.	
2	Sana Shahid	Data collection & Critics.	
3	Arsia Hanif	Data interpretation.	
4	Nasim Munshi	Drafting.	
5	M. Soughat Katto	Data collection.	
6	Azam Kamboh	Drafting.	
7	Sheikh M. Ebad Ali	Data analysis.	