Article published online: 2024-01-30

Interferons as Neoadjuvant Chemotherapy for Giant Cell Tumor: A Hospital-Based Prospective Pilot Study

Saroj Prasad Sah[1] Anil Regmi[1] Bishwa Bandhu Niraula[1] Amit Sehrawat[2] Saroj Kumar Bhagat[1] Mohit Dhingra[1]

[1] Department of Orthopedics, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
[2] Department of Medical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

Address for correspondence Mohit Dhingra, MBBS, MS, Department of Orthopedics, All India Institute of Medical Sciences, Rishikesh 249203, Uttarakhand, India
(e-mail: mohit.orth@aiimsrishikesh.edu.in; modisbanu77@gmail.com).

Ind J Med Paediatr Oncol 2024;45:312–319.

Abstract

Introduction Neoadjuvant chemotherapy is now considered an effective way to treat Campanacci grade 2 and 3 giant cell tumors (GCTs). Assessment of these drugs is essential clinically, radiologically, and pathologically. This study analyzes the early results of angiogenesis inhibitors (interferons) in the aggressive GCT of bone.

Methodology A prospective pilot study was conducted from January 2021 to July 2022 including eight biopsy-proven GCT patients subjected to interferon therapy. Radiological assessment was done with changes on plain radiograph, computerized tomography scan, and magnetic resonance imaging. Histopathological examination was done by changes in the biopsy and resected segment.

Results Out of the eight patients included in the study, 26% ($n = 3$) were males and 62% ($n = 5$) were females, with mean age of the patients being 24.6 ± 8.48 years (range: 22–38). There was significant reduction of the size of swelling (p-value: 0.049), significant reduction in Visual Analog Scale score (p-value: 0.011), significant decrease in swelling size on radiograph (p-value: 0.012), significant marginal sclerosis (p-value: 0.001), significant neocortex formation on radiographs (p-value: 0.001), significant result in and osteoid formation (p-value: 0.001) on histology. Whereas Campanacci grade on plain radiographs, number of viable cells, and number of viable stromal cell were not statistically different in comparison with pretherapy and posttherapy status.

Conclusion Interferon therapy in a GCT has potential beneficiary effect in terms of clinical, radiological, and pathological outcomes. It might prove to be an effective alternative to standard neoadjuvant chemotherapy in the management of aggressive GCT of bones.

Level of Evidence III.

Keywords
- giant cell tumor
- neoadjuvant chemotherapy
- interferon
- Campanacci grading
- ICDS criteria
- RECIST criteria

Introduction

Giant cell tumor (GCT) is a peculiar benign neoplasm with features of local as well as distant aggressiveness. The bones around the knee are common sites, followed by the distal radius.[1] Owing to the variation in histology, clinical, and radiographic appearance, neoadjuvant chemotherapy has been used prior to different surgical options including local curettage, extended curettage to excision, and reconstructive arthroplasty.[2]

article published online
January 30, 2024

DOI https://doi.org/10.1055/s-0043-1775817.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Neoadjuvant chemotherapy, which has been used for the treatment of GCTs, are bisphosphonates (zoledronic acid), denosumab, and calcitonin.[3] Interferons were initially used for viral infection and acted by inhibiting protein synthesis. They have also been shown to act on the cells that exhibit basic fibroblast growth factor (BFGF). The cells of GCT also overexpress BFGF on them and so, in turn, will respond to interferon therapy by inhibiting angiogenesis. There have been reports of trying this drug in the GCT of the jaws and recurrent GCT with varying results, but very few studies are available for its use in musculoskeletal GCT.[4] This drug's limitation includes its increased administration frequency and prolonged use. It has also been shown to have allergic manifestation and flaring of autoimmune disorders.[5]

In view of the high recurrence rate in GCTs (0–65% depending on the type of treatment),[6] neoadjuvant chemotherapy is now considered an effective way to treat Campanacci grade 2 and 3 GCTs.[7] Quantification of response is important for the assessment of these drugs on the clinical and pathological effects of tumors.[8] These assessment tools not only help in evaluation but also guide for change in any treatment strategy. In combination with other indicators of patient condition, response evaluation helps in the therapeutic efficacy decision-making process.[9]

Clinical examination still holds good for the qualitative evaluation of the response of drugs to tumors. It not only gives the actual comparative assessment between the pre- and posttherapy but also gives an edge to the treating physician to decide the further mode in case of any untoward outcomes. Its disadvantage is that there are chances of bias and it is difficult to quantify.[9,10]

Imaging plays a pivotal role in the evaluation of the response of neoadjuvant chemotherapy in musculoskeletal disorders. The assessment of treatment response and residual tumor influence the patient's prognosis and surgical strategy.[11] The radiographic response has been correlated with improved local control and overall survival.[12]

Quantification of this radiological information in advanced imaging modalities like computed tomography (CT) scan and magnetic resonance imaging (MRI) identifies the early benefits of neoadjuvant chemotherapy and helps in limb salvage resections.[13] Since both clinical and radiological assessment is done before the biopsy and after the completion of neoadjuvant chemotherapy, comparative analysis can be easily done to establish the response to the drug treatment.[14]

In the available literatures, interferon has been used as an effective method for the treatment in recurrent GCT of the mandible and recurrent and metastatic GCT of the spine.[15,16] Its use in GCT has proven to play an effective role in various nonappendicular skeleton. However, there are lacunae in knowledge regarding the use of interferon as a neoadjuvant chemotherapy. This research aims to analyze the changes in the tumor in terms of clinical, radiological, and histological parameters to establish the drug treatment response after the use of interferons in musculoskeletal GCTs.

Methodology

A single center-based prospective cohort pilot study was conducted from January 2021 to July 2022 after obtaining clearance from the institutional ethical committee. Verbal and written consent was taken from all patients included in the study.

The histologically proven case of GCT of any bone between the ages of 20 and 40 years with Campanacci grade 2 and 3 GCT, including locally aggressive and recurrent GCT, subjected to interferon therapy, were included in the study. All patients with Campanacci grade 1 GCT, not ready to undergo systemic therapy or not fit for systemic therapy due to any systemic and autoimmune cause, and patients subjected to other systemic therapy like denosumab were excluded from the study.

After a biopsy-proven histopathological diagnosis of GCT, patients were subjected to routine biochemical investigations in the form of renal function test, liver function test, and thyroid function test, in addition to hemogram and dental examination. After ruling out possible autoimmune disorders, these patients were given interferons on alternate days. A total of 45 doses of interferons alfa-2b in a dose of 3 miu/m^2 of body surface area via a subcutaneous route on alternate days were given for a total 3 months' course, all patients received a full course of therapy of 45 cycles over 90 days on an alternate day basis.

The patient demographic data, site and side of the lesion and the duration of symptoms was assessed at the time of biopsy. Clinical, radiological, and histological assessment was done at the time of biopsy, followed by evaluation by the same parameters after the completion of interferons alfa-2b. Clinical assessment was done by the size of swelling, consistency of swelling as soft, firm, and hard, and pain score in the form of a Visual Analog Scale (VAS) from 0 to 10.[17] Radiological assessment was done with a plain radiograph, CT scan, and MRI. In the plain anteroposterior radiograph, the size of the lesion, the border of the lesion (Campanacci grading),[10] marginal sclerosis as an increase in opacity on a margin of radiolucent lesion, and neocortex formation were assessed (►**Supplementary Fig. S1**, available in the online version only). CT scan and MRI were performed where the longest diameter in the axial view in the CT scan and MRI was used in the pretherapy and posttherapy period, and the reduction in % of the size and increase in % of density was assessed (►**Figs. 1** ►**Fig. 2**).

% reduction in size (%S): The % reduction in size (%S) was calculated as:

$$\%S = \text{longest diameter pretherapy} - \text{longest diameter posttherapy} \times 100.$$[18]

Longest diameter pretherapy: The % increase in the density (%D) was assessed as:

$$\%D = (\text{pretherapy density}) - (\text{posttherapy density}) \times 100.$$[19]

Pretherapy Density

Size and density were calculated with the help of Radiant DICOM software. On the Radiant DICOM in the axial view of

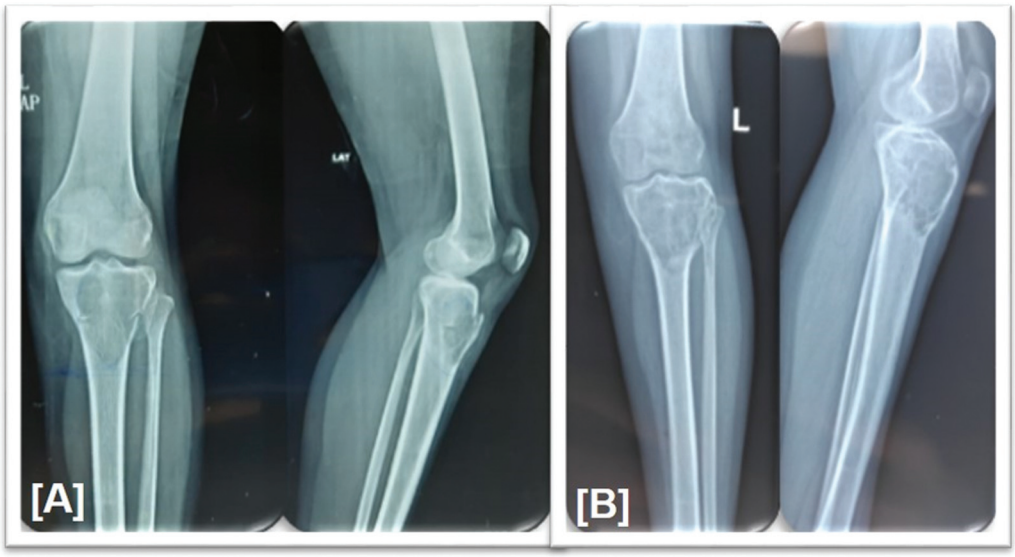

Fig. 1 Representative image of plain radiograph of patient with giant cell tumor (GCT) in the proximal tibia. (**A**) Pretherapy and (**B**) posttherapy, for the assessment of the size of the lesion, the border of the lesion (Campanacci grading), marginal sclerosis, and neocortex formation.

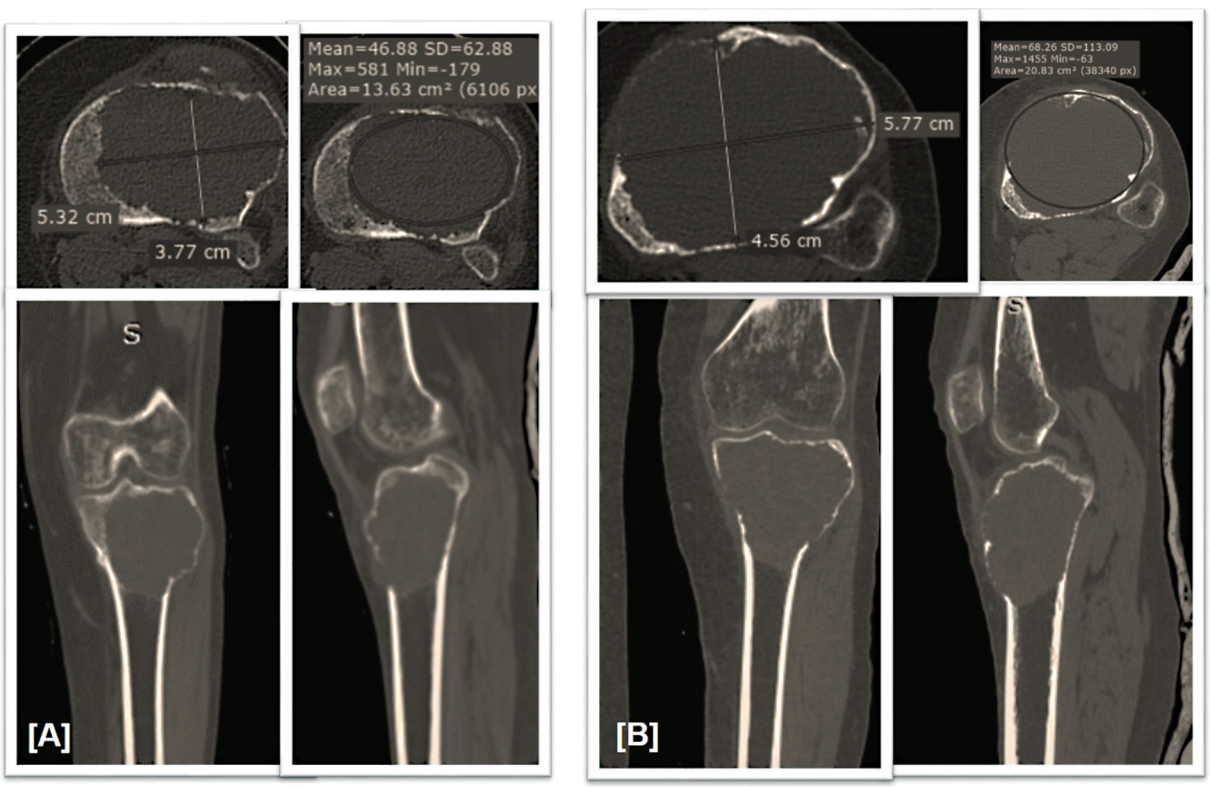

Fig. 2 Representative image of computed tomography (CT) scan of patient with giant cell tumor (GCT) in the proximal tibia. (**A**) Pretherapy and (**B**) posttherapy, where the longest diameter in the axial view used to compare the reduction in % of the size and increase in % of density.

the involved segment, an ellipse was measured, and the mean density of the tumor was measured and calculated. The assessment criterion used was: inverse Choi density/size criteria (ICDS)[20] and Response Evaluation Criteria in Solid Tumor (RECIST).[21]

Histopathological assessment was done in the specimen of biopsy (pretherapy) and in the final histopathology obtained after curettage/resection in terms of the number of viable tumor cells, number of viable stromal cells, and osteoid formation (►**Fig. 3**).[22]

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, New York, United States). Results on continuous measurement is presented as mean ± standard deviation; median (interquartile range) and categorical as frequency and percentage. Paired *t*-test used to compare between the mean of the paired

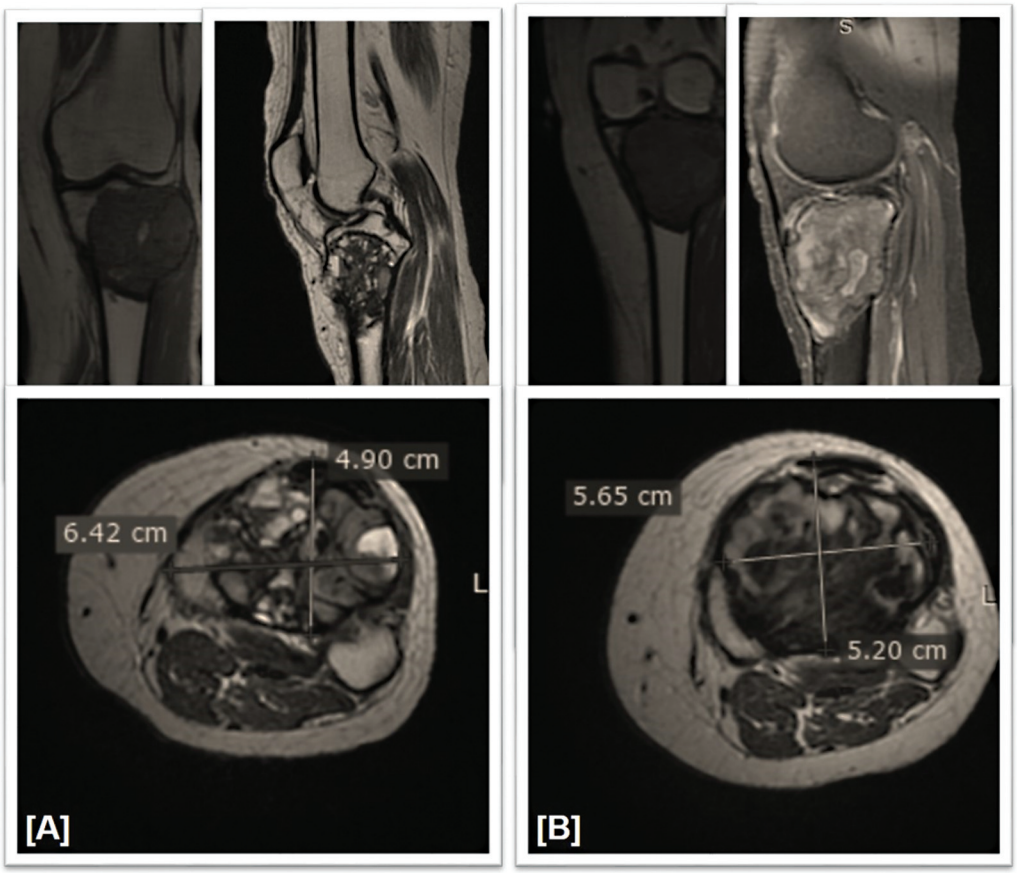

Fig. 3 Representative image magnetic resonance imaging (MRI) of patient with giant cell tumor (GCT) in the proximal tibia. (**A**) Pretherapy and (**B**) posttherapy, where the longest diameter in the axial view used to compare the reduction in % of the size and increase in % of density.

samples.Inferential statistics like the Wilcoxon signed rank test (to compare median values pre- and posttherapy) and the McNemar test (compare count pre- and posttherapy) were used. A p-value of < 0.05 was considered statistically significant.

Result

Out of a total of 37 patients with proven histological GCT who attended to the tumor clinic of the department during the study period, five were between the ages of < 20 and > 40 years. Four patients were of Campanacci grade 1, two patients were not willing to systemic therapy, and one patient was fit for systemic therapy due to antinuclear antibody positive autoimmune disease, systemic lupus erythematosus. Out of 25 patients of Campanacci grade 2 and 3 fit for systemic therapy, patients were offered either denosumab or interferon according to the duration of systemic therapy required, compliance to more prolonged doses of therapy, and its cost-effectiveness. Among those included, 17 patients were willing to go for denosumab, and were excluded, and the final eight patients willing to go for interferon therapy were included in the study (►**Supplementary Fig. S2**, available in the online version only).

Patient's Demography

Out of the eight patients included in the study, 26% ($n = 3$) were males and 62% ($n = 5$) were females. The mean age of the patients was 24.6 ± 8.48 years (range: 22–38), with a median age of 21 years. Among the included cases, 37.5% ($n = 3$) were GCT of proximal tibia, 25% ($n = 2$) were GCT of distal end femur, 25% ($n = 2$) were GCT of distal end radius, and 12.5% ($n = 1$) were GCT of proximal humerus. The mean duration of symptoms of swelling was 6.12 ± 4.24 months (range: 2–12), with median duration of symptoms being 6 months (►**Supplementary Table S1**, available in the online version only). All the patients completed the treatment course and follow-up evaluation after completion of the course. Initial therapy manifested flu-like symptoms, myalgia, and fever after the first dose within 12 to 48 hours in three cases, which were managed by symptomatic nonsteroidal anti-inflammatory drugs, but on subsequent doses, there were no such side effects.

Clinical Assessment

The mean size of swelling prior to therapy was $27.20 \pm 10.57\,cm^2$ (18.0–42.0), and it was decreased to $22.62 \pm 8.66\,cm^2$ (15.0–36.0 after therapy) with a p-value of 0.049, which suggests there is a statistically significant reduction of the size of swelling observed pre- and posttherapy (►**Table 1**). The mean pretherapy VAS score for pain was 7.50 ± 0.54 (7.0–8.0) with median value of 7.50 (7.0–8.0), which decreased to mean VAS score of 2.88 ± 0.84 (2.0–4.0) with median value of 3.0 (2.0–3.5) after therapy with a p-value of 0.011, which suggests there is a statistically significant decrease in VAS score observed

Table 1 Comparison of clinical and radiological assessment pre- and posttherapy

Assessment	Status	*N*	Range	Median (IQR)	Mean ± SD	*p*-Value
Swelling	Pretherapy	8	18.0–42.0	20.5 (19.80–38.5)	27.20 ± 10.57	0.049[a]
	Posttherapy	8	15.0–36.0	20 (15–30)	22.62 ± 8.66	
VAS	Pretherapy	8	7.0–8.0	7.50 (7.0–8.0)	7.50 ± 0.54	0.011[a]
	Posttherapy	8	2.0–4.0	3.0 (2.0–3.5)	2.88 ± 0.84	
X-ray size	Pretherapy	8	10.50–48.0	22.14 (17.22–25)	24.17 ± 12.84	0.012[a]
	Posttherapy	8	9.81–48.28	11.95 (11.90–19.76)	18.94 ± 14.77	

Abbreviations: IQR, interquartile range; SD, standard deviation; VAS, Visual Analog Scale.
[a]Significant ($p < 0.05$).

pre- and posttherapy (►**Table 1**). All patients had firm consistency prior to therapy, which later changed to the firm to hard consistency after the completion of therapy.

Radiological Assessment

The mean size of tumor pretherapy was $24.17 \pm 12.84\,cm^2$ (10.50–48.0), which was decreased to $18.94 \pm 14.77\,cm^2$ (9.81–48.28) after therapy, with a *p*-value of 0.012, signifying a statistically significant decrease in swelling size pre- and posttherapy (►**Table 1**). Campanacci grading border of the lesion was grade 3 pretherapy in all cases, which remains constant in grade 3 after therapy in all cases with a *p*-value of 1.00, signifying improvement in Campanacci grade by the therapy. There was no marginal sclerosis and neocortex formation in all (100%, $n = 8$) cases prior to the therapy, but after the completion of therapy, there was marginal sclerosis and neocortex formation in all (100%, $n = 8$) cases, with a *p*-value of 0.001 in each, signifying there was a statistically significant marginal sclerosis and neocortex formation after the completion of therapy (►**Table 2**). The ICDS and RECIST score were taken posttherapy on CT scan and MRI. ICDS scoring according to the CT scan was partial response in 25% ($n = 2$), progressive in 25% ($n = 2$), and stable disease in 50% ($n = 4$). Whereas in MRI, the ICDS score was partial response in 37.5% ($n = 3$), progressive in 25% ($n = 2$), and stable disease in 37.5% ($n = 3$) (►**Table 3**). The RECIST score on CT scan was partial response in 12.5% ($n = 1$), progressive in 25% ($n = 2$), and stable disease in 67.5% ($n = 5$). Whereas in MRI, the RECIST score was partial response in 37.5% ($n = 3$), progressive in 25% ($n = 2$), and stable disease in 37.5% ($n = 3$) (►**Table 3**).

Pathological Assessment

The number of viable cells in pretherapy was 100%, which remained the same at 100% in posttherapy, with a *p*-value of 1.00, signifying no statistically significant result in the number of viable cells on histology by the therapy. The density of stromal cells before therapy was 3+ in 100% ($n = 8$) of cases, which changed to 2+ in 50% ($n = 4$) of cases and remained constant at 3+ in 50% ($n = 4$) of cases, with a *p*-value of 0.368, signifying no statistically significant result in the number of viable stromal cell on histology by the therapy. There was no osteoid formation in any of the cases pretherapy, whereas there was 5% osteoid formation in 37.5% ($n = 3$) cases and 10% osteoid formation in 67.5% ($n = 5$) cases, with a *p*-value of 0.001, showing statistically significant result in osteoid formation on histology after therapy.

Discussion

One of the most common primary musculoskeletal tumors is GCT of the bone.[1] In South India, the incidence was 30.3%, while in western India, the incidence was 6.3%.[23,24] The incidence of GCTs among patients between 20 and 40 years of age is higher.[25] A majority of these tumors occur in the epiphysis of bones around the knee, with a 66% incidence rate, followed by distal radius and proximal humerus.[25] In our study, we took cases between 20 and 40 years as GCT is most prevalent in this age. Our studies show almost similar results to the previous studies as the most common site affected by GCT in our study is around the knee, with 67.5% incidence, followed by the distal end radius (25%) and proximal humerus (12.5%).

Table 2 Comparison of radiological assessment pre- and postchemotherapy

		Yes *N* (%)	No *N* (%)	*p*-Value
X-ray Marginal sclerosis	Pretherapy	0	8 (100)	0.001[a]
	Posttherapy	8 (100)	0	
X-ray Neocortex formation	Pretherapy	0	8 (100)	0.001[a]
	Posttherapy	8 (100)	0	

[a]Significant ($p < 0.05$).

Table 3 Comparison of radiological assessment on CT scan and MRI in terms of ICDS and RECIST

CT ICDS versus MRI ICDS						
	Responses	MRI ICDS				Total
		Partial response	Progressive	Stable disease	Unable to evaluate	
CT ICDS	Partial response	1	0	1	0	2
	Progressive	0	2	0	0	2
	Stable disease	2	0	2	0	4
	Unable to evaluate	0	0	0	0	0
	Total	3	2	3	0	8
CT RECIST versus MRI RECIST						
	Responses	MRI RECIST				Total
		Partial response	Progressive	Stable disease	Unable to evaluate	
CT RECIST	Partial response	0	0	1	0	1
	Progressive	0	2	0	0	2
	Stable disease	0	0	5	0	5
	Unable to evaluate	0	0	0	0	0
	Total	0	2	6	0	8

Abbreviations: CT, computed tomography; ICDS, inverse Choi density/size criteria; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumor.

In most cases, surgery is the most effective treatment, especially for indolent, bone-confined tumors. A curettage procedure has been combined with adjuvant chemotherapy or radiation for biologically aggressive tumors or recurrent tumors.[26] Moderate-dose radiation therapy has been the typical treatment for patients with nonresectable GCT.[27] It has been reported that chemotherapy may provide palliative treatment for primary or secondary malignancies in GCT despite having marginal benefits in advanced stages.[28] In previous literature, it was found that denosumab reduced pain and improved functional status in nearly 90% of patients with recurrent or unresectable GCTs of the bone (either by eliminating giant cells or not progressing on radiographs).[29] For patients with metastatic GCT or advanced GCT who cannot undergo surgery, denosumab may be a viable treatment option.[29] In our study, we subjected the patients to neoadjuvant chemotherapy interferon just after the diagnosis of GCT on the patient's preference; it was found to decrease the size of the swelling and the tumor significantly. The patient's pain status in terms of VAS score was also significantly improved after the completion of interferon therapy. There is a significant improvement in radiographs on the development of marginal sclerosis and neocortex formation, which helps in the regression of the tumor and improvement in tumor progression. On interferon therapy, most of the tumor lesions stay at the stable lesion on radiographic ICDS and RECIST criteria.

Natural interferon alfa produced by leukocytes is both an antitumor and antiangiogenic protein.[30] By enhancing antigen expression, antiproliferative activity, and cytostatic activity, antitumor effects can be directly observed on cells, while indirect mechanisms include the cytocidal activity of macrophages, lymphocytes, and natural killer cells, cytokine production, and antibody modulation.[31] In addition to downregulating BFGF gene expression, interferon alfa and beta also inhibit tumor cell protein production.[5]

Kaban et al reported in 1999 using it to treat recurrent GCTs of the mandible.[15] Interferon therapy combined with curettage was a promising treatment strategy for aggressive GCTs. The combined treatment resulted in a higher tumor control rate with lower operative morbidity than conventional approaches.[26] Wei et al concluded that interferon alfa-2b might be an effective and safe treatment for spine GCT recurrence and metastasis in soft tissue after studying interferon alfa-2b for recurrent and metastatic GCT of the spine.[16] In a similar fashion, Goldman et al, Schütz et al, O'Connell and Kearns, and Tarsitano et al studied interferon alfa-2A after mandible surgery and found complete tumor remission.[32–35]

In the available literature, fever and flu-like symptoms were documented during the first 24 to 48 hours of the treatment, which disappeared spontaneously without treatment. Also, there is evidence of the development of leukocytopenia and thrombocytopenia, which might need to stop the therapy temporarily.[16] Similarly, in our study, 37.5% ($n = 3$) manifested flu-like symptoms, myalgia, and fever after the first dose within 12 to 48 hours, which were managed by symptomatic nonsteroidal anti-inflammatory drugs, but on subsequent doses, there were no such side effects. Compliance is another problem that needs to be dealt with for the longer duration of injectable dose, which may result in poor compliance. In our case, drugs were administered either under direct supervision or with proper instruction at a nearby primary health center with proper documentation of the drug chart to maintain good compliance, hence all patients completed the full course of therapy.

A thorough search of the literature revealed that the experience has been limited to patients with metastatic disease or locally aggressive, unresectable GCTs or those refractory to radiation therapy. To our knowledge, no previous studies were conducted to see early results of interferon in GCTs after the histological diagnosis. In our study, interferon demonstrated early clinical and radiological improvements after the completion of therapy by reducing tumor size and increase in stromal density. Histologically, it maintained a constant number of viable cells, stromal cells, and osteoid formation following therapy.

Conclusion

To conclude,

- Clinical, radiological, and histological evaluation of interferons has its potential role in the treatment of aggressive GCTs of the bone as neoadjuvant chemotherapy, which helps in tumor regression and progression with a reduction in tumor grading, which smoothens the surgical procedure and overall improvement in a functional outcome.
- With the use of interferon alfa-2b, there was a significant reduction of the size of swelling, a reduction in a VAS score, decrease in swelling size on radiograph, significant marginal sclerosis, significant neocortex formation on radiographs, and significant result in osteoid formation on histology. Whereas no significant improvement in Campanacci grade on plain radiographs, number of viable cells, and number of viable stromal cells were seen in comparison with pretherapy and posttherapy status.
- Taking the drug for a long duration on alternate days by parenteral route is the only disadvantage seen, which needs proper documentation and instruction for compliance.
- The limitation of this study includes small sample size due to less preference of patients in terms of prolonged doses and its compliance. Long-term effect of this drug on the recurrence of the tumor still needs to be evaluated. In addition, large studies are still required to know the potentiality of interferons in comparison to the standard neoadjuvant therapy.

Patient Consent

Consent was taken with each individual for the enrollment of study and publication of data on research paper. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical Review Committee Statement

Clearance obtained from institutional ethical clearance committee. A copy of the Certificate of Ethical Clearance is available for review by the Editor-in-Chief of this journal on request.

Authors' Contributions

S.P.S.: Planning of study, data management, writing, and revising the manuscript.
A.R.: Data management and manuscript preparation.
B.B.N.: Data management and manuscript preparation.
A.S.: Data management.
M.D.: Planning of study, revising the manuscript, and as corresponding author.

Financial Support and Sponsorship

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

None declared.

References

1 Sobti A, Agrawal P, Agarwala S, Agarwal M. Giant cell tumor of bone - an overview. Arch Bone Jt Surg 2016;4(01):2–9
2 Baptista AM, Camargo Ade F, Caiero MT, Rebolledo DCS, Correia LFM, de Camargo OP. GCT: what happened after 10 years of curettage and cement? Retrospective study of 46 cases. Acta Ortop Bras 2014;22(06):308–311
3 Singh AS, Chawla NS, Chawla SP. Giant-cell tumor of bone: treatment options and role of denosumab. Biologics 2015; 9:69–74
4 Houglum JE. Interferon: mechanisms of action and clinical value. Clin Pharm 1983;2(01):20–28
5 Yasko AW. Interferon therapy for giant cell tumor of bone. Curr Opin Orthop 2006;17(06):568–572
6 Klenke FM, Wenger DE, Inwards CY, Rose PS, Sim FH. Giant cell tumor of bone: risk factors for recurrence. Clin Orthop Relat Res 2011;469(02):591–599
7 van der Heijden L, Dijkstra S, van de Sande M, Gelderblom H. Current concepts in the treatment of giant cell tumour of bone. Curr Opin Oncol 2020;32(04):332–338
8 Righi A, Pacheco M, Palmerini E, et al. Histological response to neoadjuvant chemotherapy in localized Ewing sarcoma of the bone: a retrospective analysis of available scoring tools. Eur J Surg Oncol 2021;47(07):1778–1783
9 Therasse P. Measuring the clinical response. What does it mean? Eur J Cancer 2002;38(14):1817–1823
10 Campanacci M, Baldini N, Boriani S, Sudanese A. Giant-cell tumor of bone. J Bone Joint Surg Am 1987;69(01):106–114
11 Priolo F, Cerase A. The current role of radiography in the assessment of skeletal tumors and tumor-like lesions. Eur J Radiol 1998; 27(Suppl 1):S77–S85
12 Meric F, Hess KR, Varma DGK, et al. Radiographic response to neoadjuvant chemotherapy is a predictor of local control and survival in soft tissue sarcomas. Cancer 2002;95(05):1120–1126
13 Engellau J, Seeger L, Grimer R, et al. Assessment of denosumab treatment effects and imaging response in patients with giant cell tumor of bone. World J Surg Oncol 2018;16(01):191
14 Pramesh CS, Deshpande MS, Pardiwala DN, Agarwal MG, Puri A. Core needle biopsy for bone tumours. Eur J Surg Oncol 2001;27 (07):668–671
15 Kaban LB, Mulliken JB, Ezekowitz RA, Ebb D, Smith PS, Folkman J. Antiangiogenic therapy of a recurrent giant cell tumor of the mandible with interferon alfa-2a. Pediatrics 1999;103(6 Pt 1):1145–1149
16 Wei F, Liu X, Liu Z, et al. Interferon alfa-2b for recurrent and metastatic giant cell tumor of the spine: report of two cases. Spine 2010;35(24):E1418–E1422
17 Langley GB, Sheppeard H. The visual analogue scale: its use in pain measurement. Rheumatol Int 1985;5(04):145–148
18 Frenette A, Morrell J, Bjella K, Fogarty E, Beal J, Chaudhary V. Do diametric measurements provide sufficient and reliable tumor assessment? An evaluation of diametric, areametric, and

volumetric variability of lung lesion measurements on computerized tomography scans. J Oncol 2015;2015:632943
19 Wang Y, Huang K, Chen J, et al. Combined volumetric and density analyses of contrast-enhanced CT imaging to assess drug therapy response in gastroenteropancreatic neuroendocrine diffuse liver metastasis. Contrast Media Mol Imaging 2018;2018:6037273
20 Alothman M, Althobaity W, Asiri Y, Alreshoodi S, Alismail K, Alshaalan M. Giant cell tumor of bone following denosumab treatment: assessment of tumor response using various imaging modalities. Insights Imaging 2020;11(01):41
21 Park JO, Lee SI, Song SY, et al. Measuring response in solid tumors: comparison of RECIST and WHO response criteria. Jpn J Clin Oncol 2003;33(10):533–537
22 Teo KY, Daescu O, Cederberg K, Sengupta A, Leavey PJ. Correlation of histopathology and multi-modal magnetic resonance imaging in childhood osteosarcoma: predicting tumor response to chemotherapy. PLoS One 2022;17(02):e0259564
23 Reddy CR, Rao PS, Rajakumari K. Giant-cell tumors of bone in South India. J Bone Joint Surg Am 1974;56(03):617–619
24 Gupta R, Seethalakshmi V, Jambhekar NA, et al. Clinicopathologic profile of 470 giant cell tumors of bone from a cancer hospital in western India. Ann Diagn Pathol 2008;12(04):239–248
25 Errani C, Ruggieri P, Asenzio MAN, et al. Giant cell tumor of the extremity: a review of 349 cases from a single institution. Cancer Treat Rev 2010;36(01):1–7
26 López-Pousa A, Martín Broto J, Garrido T, Vázquez J. Giant cell tumour of bone: new treatments in development. Clin Transl Oncol 2015;17(06):419–430
27 Feigenberg SJ, Marcus RB Jr, Zlotecki RA, Scarborough MT, Berrey BH, Enneking WF. Radiation therapy for giant cell tumors of bone. Clin Orthop Relat Res 2003;(411):207–216
28 Puri A, Agarwal M. Treatment of giant cell tumor of bone: current concepts. Indian J Orthop 2007;41(02):101–108
29 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(12):1719–1729
30 Antonelli G. Biological basis for a proper clinical application of alpha interferons. New Microbiol 2008;31(03):305–318
31 Baron S, Tyring SK, Fleischmann WR Jr, et al. The interferons. Mechanisms of action and clinical applications. JAMA 1991;266 (10):1375–1383
32 Goldman KE, Marshall MK, Alessandrini E, Bernstein ML. Complications of alpha-interferon therapy for aggressive central giant cell lesion of the maxilla. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100(03):285–291
33 Schütz P, El-Bassuoni KH, Munish J, Hamed HH, Padwa BL. Aggressive central giant cell granuloma of the mandible. J Oral Maxillofac Surg 2010;68(10):2537–2544
34 O'Connell JE, Kearns GJ. Aggressive giant cell granuloma of the jaws treated with interferon alpha: a report of two cases. Ir J Med Sci 2013;182(02):163–170
35 Tarsitano A, Del Corso G, Pizzigallo A, Marchetti C. Aggressive central giant cell granuloma of the mandible treated with conservative surgical enucleation and interferon-α-2a: complete remission with long-term follow-up. J Oral Maxillofac Surg 2015;73 (11):2149–2154