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Giant Cell Tumor of Bone: Effect of Longer Dosing Intervals of Denosumab on Tumor Control and Bone-related Complications

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Abstract

Background: Denosumab is an effective treatment for giant cell tumor of the bone (GCTB) but can cause clinically significant adverse effects. Current approved dosing is every 4 weeks after 3 weekly loading doses. We assessed whether alternative, longer dosing intervals are associated with differences in efficacy or bone toxicity.

Methods: Single institution retrospective chart review was conducted on patients with GCTB over 18 years old who received at least 1 year of standard denosumab dosing. Patients identified using a free-text search engine with keywords "giant cell tumor" and "denosumab" from January 1998 to August 2020.

Results: Approximately 37 patients with GCTB (19F, 18M) were identified with median age of 37 years (range 22-73). Dosing interval was increased in 38% ($n = 14$), with the most common final dosing interval 12 weeks ($n = 8$). Six patients (16%) had bone complications: osteonecrosis of the jaw ($n = 5$), atypical fracture ($n = 1$), and nonhealing dental wounds ($n = 2$). All patients with bone complications were on the monthly dosing schedule, but there was no statistically significant difference compared to longer dosing intervals ($P = .22$). No statistically significant difference in median PFS was noted ($P = .97$). However, 5-year PFS was superior in patients treated with less frequent versus standard dosing of denosumab ($P = .036$).

Conclusions: Increasing the interval of denosumab dosing for GCTB provided similar tumor control compared to standard dosing and lower absolute number of bone toxicity events. Larger studies are needed to better define the optimal interval of denosumab administration and the effect on efficacy, toxicity, and associated healthcare expense.

Key words: giant cell tumor of bone; denosumab; administration and dosing; adverse effects

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Implications for Practice

Denosumab is the only FDA approved medication to treat giant cell tumor of bone in cases that are unresectable or when resection will likely cause severe morbidity. However, the current dosing schedule is monthly, which can become burdensome and potentially lead to adverse events. Currently, there is no optimal duration of therapy or dosing schedule. This study demonstrated that longer dosing intervals provided similar tumor control and potentially clinically less bone complications. With additional retrospective studies in the future, this could potentially change the current guidelines for treatment.

Introduction

Giant cell tumor of bone (GCTB) is a rare benign, but locally aggressive neoplasm that is most commonly found in long bones (distal femur, proximal tibia), although it can occur at any bony site.[1] Estimated incidence of GCTB is 1.7 cases per million persons and peak incidence occurs in the third and fourth decades of life with slight female predominance.[2,3] The standard of care for localized disease is surgical removal, most commonly with intralesional curettage +/– additional adjunct therapies such as high-speed burring, alcohol/phenol, and argon beams.[4] Unfortunately, even with surgical intervention,

there are high rates of disease recurrence, reported up to 19%-50%.[5] For patients with tumors located in the axial skeleton, recurrent disease, and locally advanced disease—surgical management may not be recommended and could have significant adverse effects on morbidity.[6]

Denosumab, a human monoclonal antibody against RANKL, has emerged as an effective treatment for GCTB in unresectable cases or instances where surgical resection would likely result in severe morbidity. It has led to reduction in pain, halted bone destruction, and induced tumor regression.[7-10] Currently, the FDA approved dosing schedule

of denosumab is 120 mg administered subcutaneously every 4 weeks after initial loading doses on days 1, 8, and 15. This schedule was determined based on prior denosumab studies inferring RANKL occupancy exceeds 97% at steady state with monthly dosing.[11] Additionally, denosumab's half-life is approximately 4 weeks and the inhibitory effects on osteolysis lasts at least 3 months.[12] Notably, the optimal duration of therapy and dosing schedule for maintenance therapy has not yet been determined.[13] In our single institution study, we aimed to assess if alternative, longer denosumab dosing intervals affected efficacy or development of bone toxicities.

Methods

This retrospective, single center study was approved by the University of Michigan Institutional Review Board. Patients were identified using the free text search engine EMERSE (Electronic Medical Record Search Engine)[14] using the keywords "giant cell tumor" and "denosumab" which generated a list of 204 patients with GCTB seen at the University of Michigan from January 1998 to August 2020. Patients over 18 years old who had received at least 1 year of standard denosumab dosing (monthly administration) were included in the study. Data were collected from review of the electronic health record (EHR) and all patient information was de-identified and maintained on secure, password protected electronic files.

We collected data on patient demographics (gender, age, race), primary tumor location, metastases, prior interventions (radiation or surgical), denosumab therapy timeline, resection after therapy, radiologic response (based on clinical documentation and review of imaging reports noting calcification or shrinkage), radiologic progression (noted in clinical documentation or on review of imaging reports), symptomatic progression (based on clinical documentation), bone toxicity, and malignant transformation of GCTB. Cumulative dose was calculated based on the date denosumab therapy was started and the date of the most recent dose administered, while adjusting for changes in dosing interval. The decision to increase interval between doses was based on provider and patient discussion and preference as part of routine medical care.

Continuous variables were summarized using mean and range, categorical variables were summarized using frequencies and percentages, and PFS outcomes were summarized using medians. Simple comparison of survival between patients with standard and interval increased dosing schedule is subject to bias. We used a Cox proportional hazards regression with time-varying covariate for the comparison, and this covariate had a value of 0 before the increased dosing schedule and 1 after the increased dosing schedule; for patients who did not have increased dosing schedule, this covariate had a value of 0 during the entire follow-up period. We also used landmark analysis to compare the PFS rate at 5 years between patients with standard vs. interval increased dosing schedule, using a Fisher's exact test. This analysis included patients with at least 5 years of follow-up or had progression before 5 years. Similar approaches were used to compare toxicity between patients with standard and interval increased dosing schedule. Wilcoxon rank-sum tests were used to compare cumulative dose and dose density between dosing schedules. SAS (version 9.4) was used for the analyses and significance was defined by a 2-tailed *P* value <.05. Of note,

given the small sample size of this study, covariate analysis was not performed.

Results

Patient Demographics and Clinical Data

A total of 37 patients were identified with a median age of 37 years (range 22-73 years), and there were similar number of females (*n* = 19, 51%) and males (*n* = 18, 49%). The most common primary location was the lower extremity (*n* = 14, 38%) followed by pelvis (*n* = 13, 35%). Metastasis were present in 14% (*n* = 5) of the patients to the lung (*n* = 4, 80%) and spine (*n* = 1, 20%). All patients received 120 mg weekly for 3 weeks as the loading dose. The median cumulative dose of denosumab patients received was 43 (range 15-139 doses). The majority of patients had radiologic response to denosumab with reduction in tumor size and increased calcification in the tumor noted on imaging (*n* = 36, 97%). Eight patients (22%) underwent resection after denosumab therapy with 3 (38%) of these patients' experiencing recurrence of disease afterward. Median time to recurrence after surgical intervention was 19.5 months (range 16.8-23.1). Five patients (14%) received adjuvant denosumab after resection with 2 receiving a year of adjuvant treatment, one received 6 months, and another continues to remain on denosumab. All (*n* = 5) of the patients who received adjuvant denosumab underwent curettage and 3 of them experienced disease recurrence at 11.2 months, 11.6 months, and 10 months after discontinuation of denosumab therapy. Ten patients (27%) experienced radiologic progression of disease; however, 90% of these patients were off therapy at the time of progression. Only one patient experienced symptomatic and radiologic progression while on therapy (monthly dosing interval). There was one patient who experienced transformation of GCTB to high grade osteosarcoma after 26 doses of denosumab with no prior history of malignancy (biopsy proven). Refer to Table 1 for summary of data and additional clinical information.

Dosing Interval

The dosing interval was changed to be less frequent than every 4 weeks in 38% of the patients (*n* = 14). Fifty percent of these patients (*n* = 7) only had one interval change, 29% had 2 changes (*n* = 2), 7% had 3 changes (*n* = 1), and 21% had 4 changes (*n* = 3) (Fig. 1). With the first interval change, 43% were changed to every 6 weeks (*n* = 6), 29% to every 8 weeks (*n* = 4), and 29% to every 12 weeks (*n* = 4). The most common final dosing interval was every 12 weeks (*n* = 8). The median progression-free survival (PFS) was not yet reached for the entire cohort. There was no statistically significant difference in PFS with standard versus interval increased dosing schedule (*P* = .97). However, 5-year PFS was superior with interval increased versus standard dosing (91% vs. 47%, *P* = .036). Notably, 30% of the cohort (*n* = 11) did not reach 5 years of denosumab therapy and did not have progression of disease. For patients with dosing interval increased, 21% (*n* = 3) did not reach 5 years of denosumab therapy and did not have progression of disease (median follow up time 85 months). This occurred in 35% (*n* = 8) of patients on standard dosing schedule (median follow up time 47 months). In the evaluable patients for this endpoint, we assessed for presence of high-risk factors for recurrence (ie, soft-tissue involvement, Campanacci grade 3, axial involvement, pathologic fractures). There was overall

similar presence of the risk factors for recurrence in patients with interval increased versus standard dosing (soft tissue involvement = 55% vs. 40%, axial involvement = 45% vs. 33%) with the exception of presence of pathological fracture (0% vs. 13%).

Table 1. GCTB patient demographics and clinical data.

| Age, years—Median	37 (range 22-73)
Gender—No. (%)	
Female	19 (51)
Male	18 (49)
Primary Location—No. (%)	
Head and neck	2 (5)
Lower extremity	14 (38)
Pelvis	13 (35)
Spine	3 (8)
Upper extremity	5 (14)
Metastasis—Total No. (%)	5 (14)
Lung	4 (80)
Spine	1 (20)
Prior therapy	
Surgical resection—No. (%)	22 (59)
Radiation therapy—No. (%)	3 (8)
Campanacci Grade Prior to Denosumab—Median	3 (range 1-3)
Total doses of denosumab per patient—Median	43 (range 15-139)
Initial Radiologic Response to Denosumab—No. (%)	36 (97)
Radiologic Progression of Disease—Total No. (%)	10 (27)
On Denosumab	1 (10)
Off Denosumab	9 (90)
Symptomatic Progression of Disease—No. (%)	1 (3)
Malignant Transformation—No. (%)	1 (3)
Ongoing Denosumab Therapy—No. (%)	
Yes	15 (41)
No	16 (46)
Unknown	6 (14)

Bone Adverse Events

Sixteen percent of patients experienced bone adverse events ($n = 6$). Half of these patients experienced osteonecrosis of the jaw (ONJ) only ($n = 3$), 7% patient had atypical fracture plus ONJ ($n = 1$), 7% had nonhealing dental wound only ($n = 1$), and 7% had ONJ plus non-healing dental wound ($n = 1$) (refer to Fig. 2). All these patients were on the monthly dosing schedule. See Fig. 3 for imaging example of bone complication experienced by a patient. Median cumulative number of denosumab doses for each event was: atypical fracture, 34 doses; ONJ, 43 doses (range 18-87); nonhealing dental wounds, 82 doses (range 77-86). When comparing the development of bone events in those who had an interval change versus those who remained on the standard dosing schedule there was no statistically significant difference ($P = .22$). Additionally, there was no statistically significant difference with cumulative doses ($P = .13$) or dose density ($P = .15$) on development of nonhealing dental wounds. Also, no significant difference in development of ONJ with cumulative doses ($P = .74$) or dose density ($P = 1.0$) of denosumab.

Discussion

This single-center retrospective study supports the safety and efficacy of longer intervals between denosumab doses for patients with GCTB after at least 1 year of standard therapy. Our results revealed similar efficacy on tumor control between extended interval dosing and monthly dosing, with no difference identified in PFS and even slightly improved 5-year PFS (91% vs. 47%, $P = .036$) in the extended interval dosing cohort. We did not identify an etiology for this improved 5-year PFS as the presence of high risk factors for recurrence were similar in both of the dosing groups. Interestingly, all 6 patients who developed bone toxicities were on the standard monthly dosing schedule, however no statistical significance was detected. The clinical significance of bone toxicities and improved 5-year PFS remains unclear in the setting of this relatively small study.

Commonly reported adverse effects of denosumab include arthralgias, muscle pain, and fatigue.[15] Other complications include electrolyte disturbances, such as hypophosphatemia and hypercalcemia. More serious, but less common adverse events include bony events like osteonecrosis of the jaw (ONJ) and atypical fracture. To the best of our knowledge,
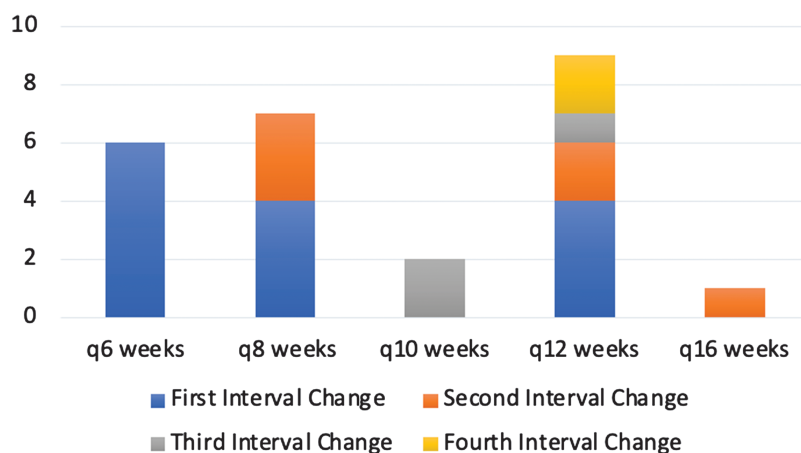
Figure 1. Number of patients with change in denosumab dosing interval.
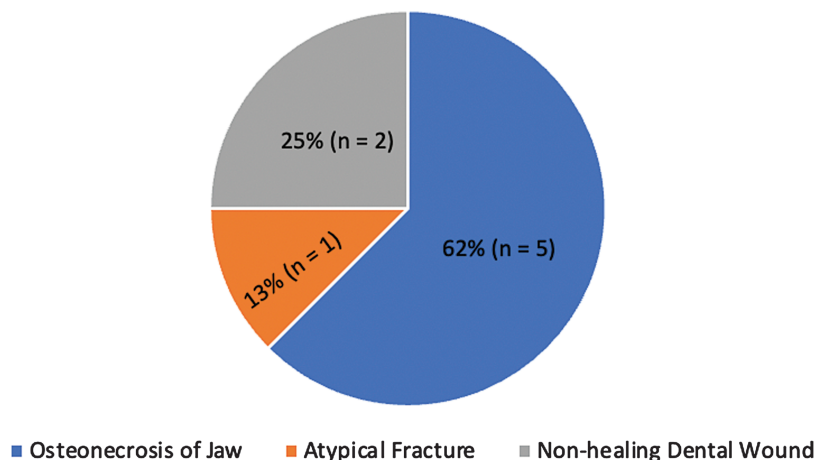
Figure 2. Bone complications of patients with GCTB on denosumab.

Figure 3. GCTB patient with osteonecrosis of the Jaw due to denosumab. (A) Sagittal View; (B) Axial view.*Red arrows noting areas concerning for discontinuity of the lingual cortex and bony destruction.

one prior GCTB study evaluated long-term denosumab use and toxicity. In this retrospective study, 6% of patients developed ONJ and 4% atypical bone fracture in the 97 patients included.[16] Findings were dose-dependent and only patients on long-term treatment were also noted to experience skin rash, peripheral neuropathy, and hypophosphatemia. In non-GCTB related studies on denosumab, such as metastatic breast/prostate cancer, the data showed higher risk of ONJ after receiving denosumab every 4 weeks for 12-18 months.[17] For osteoporosis, patients who received denosumab for 3 years had no reports of ONJ (of note, denosumab dose and frequency is much less in osteoporosis compared to GCTB); however, when therapy was continued for 10 years, there were subsequently reports of ONJ.[18] The above studies suggest that long-term denosumab administration or increased dose accumulation may be related to development of bone complications; however, our study did not detect any significance. The major limitation of our study was the small sample size, potential bias in provider/patient decision to change denosumab dosing interval, and the retrospective design. Due to the small sample size, our study may not have had the power to reveal the impact that increased cumulative dose and dose density have on the development of bone complications.

The majority of patients with GCTB in our study who experienced progression of disease were off denosumab treatment.

Due to no established duration of treatment needed, it is difficult to foresee how long patients will require denosumab therapy. Increased interval between doses of denosumab may improve financial burden experienced by patients compared to the standard interval. Out of pocket costs patients may cover include medical co-payments, transportation, parking fees, and potential wages lost while attending appointments.[19] Additionally, patients may experience less mental and social burden associated with fewer clinic and drug administration visits. The average cost of denosumab is $2512.80 per each 120 mg dose[20] and given the long term use of denosumab for unresectable GCTB, over time this can pose a significant economic healthcare impact. Receiving less frequent treatment could lead to significant healthcare savings in administration and drug costs and potentially also in management of adverse effects. However, due to the rarity of GCTB requiring denosumab treatment and the overall nonmalignant nature of the disease coupled with limited governmental, foundational, and pharmaceutical support to study alternative dosing schedules for approved drugs, a definitive prospective study is unlikely to be completed. Instead, retrospective experiences could significantly aid in the revision of guidelines set forth by national organizations (ie, American Society of Clinical Oncology, National Comprehensive Cancer Network). The REDUCE trial activated in Europe in 2019 aimed to reduce dose density and compare standard every 4-week denosumab dosing to alternative every 12-week dosing,

but was ultimately terminated due to low accrual (http://clinicaltrials.gov, NCT03620149). Therefore, multicenter retrospective studies across national and international institutions may provide large enough sample sizes to further assess increased interval dosing on tumor control and adverse effects of therapy.

In conclusion, denosumab is the only FDA-approved drug for treatment of patients with GCTB that is unresectable or in situations where resection is likely to cause severe morbidity; however, the approved monthly dosing schedule for denosumab may be burdensome for some patients and associated with an increased risk of bone related complications. Our study demonstrates that extending the interval of denosumab dosing for GCTB provided similar tumor control as compared to standard monthly dosing and is potentially associated with fewer adverse bone events. Larger scale studies are needed to better define the optimal interval of denosumab administration in GCTB and the effect on efficacy, adverse events, and associated healthcare expense, and will require multi-institutional collaboration.

Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/Design: C.J., R.C., S.S. Provision of study material/patients: R.C., S.S. Collection and/or assembly of data: C.J. Data analysis and interpretation: C.J., L.Z., R.C., S.S. Manuscript writing: C.J., L.Z., R.C., S.S. Final approval of manuscript: C.J., L.Z., R.C., S.S.

Data Availability

The data underlying this article will be shared at reasonable request to the corresponding author.

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