Original Research Paper

Cancer Control
Volume 27: 1-27

DOI: 10.1177/1073274820934822
journals.sagepub.com/home/ccx
SAGE

Denosumab for Effective Tumor Size Reduction in Patients With Giant Cell Tumors of the Bone: A Systematic Review and Meta-Analysis

Josef Yayan, MD[1]

Abstract

Background: Denosumab is a human monoclonal antibody that has been used successfully in the treatment of giant cell tumors of bone. These tumors are rare and, in principle, benign, but they are highly aggressive, locally advanced, osteolytic bone tumors that can metastasize to the lungs. Denosumab is an effective treatment when these tumors cannot be surgically removed or when surgical resection is likely to lead to severe morbidity (eg, loss of limbs or joints). The aim of this systematic review and meta-analysis was to investigate patients with giant cell tumors of bone who experienced tumor progression during treatment with denosumab and to compare them with patients who experienced reduction of their giant cell tumors of bone during treatment with denosumab.

Methods: Embase, Cochrane Library, and MEDLINE/PubMed databases were searched for trials submitted by January 7, 2020, that reported the efficacy and safety of denosumab in patients with giant cell tumors of bone.

Results: Sixty studies were reviewed, involving a total of 1074 patients who had giant cell tumors of bone and were treated with denosumab. Of the 60 studies, 58% of the patients were from case series studies, 39% from open-label phase II studies, and 3% from case reports. The response rate for denosumab as a treatment for giant cell tumors of bone was 97.5%, with statistical significance ($P < .0001$). Pain in the limbs was statistically the most common adverse event for denosumab treatment in case series studies ($P < .0001$). No treatment-related deaths occurred in the reviewed studies.

Conclusion: Cumulative evidence supports the addition of surgery to optimal medical therapy with denosumab to reduce tumor size, clinical symptoms, and mortality among patients with giant cell tumors of bone.

Keywords

denosumab, giant cell tumor of bone, osteoclastoma, outcome, meta-analysis

Received October 25, 2019. Received revised January 16, 2020. Accepted for publication March 31, 2020.

Introduction

Denosumab was first introduced in the year 2010 for the treatment of osteoporosis and is now used at a high dosage to prevent skeletal-related complications in adults with solid bone metastasis.[1] Denosumab can also be used to treat giant cell tumors of bone (GCTB) that cannot be surgically removed.[2] Denosumab binds to and inhibits the receptor activator of nuclear factor κ-B ligand (RANKL), thereby reducing the formation and activation of osteoclasts.[3] In turn, this decreases

[1] Department of Internal Medicine, Division of Pulmonary, Allergy, and Sleep Medicine, HELIOS Clinic Wuppertal, Witten/Herdecke University, Witten, Germany

Corresponding Author:
Josef Yayan, Department of Internal Medicine, Division of Pulmonary, Allergy, and Sleep Medicine, HELIOS Clinic Wuppertal, Witten/Herdecke University, Heusnerstr. 40, 42283 Wuppertal, Germany.
Email: josef.yayan@hotmail.com

loss of bone mass, which reduces the likelihood of bone fractures and other serious bone complications.[4,5] Denosumab treatment also prevents further tumor growth.[6] However, the desired effects of denosumab that curb the spread of GCTB are accompanied by undesirable side effects.[7-10]

The approval of denosumab for use in the treatment of GCTB was based on positive results from 2 open-label phase II studies on patients whose tumors were either nonresectable or for whom surgery was associated with severe morbidity.[11,12] Despite being a local, highly aggressive tumor, GCTB is usually benign; however, it has metastatic potential for the lungs, and several chemotherapy regimens can have unfavorable outcomes.[13] The histogenesis of GCTB is still unknown, and no correlation has yet been found with either histological or clinical presentations.[13] For this reason, many investigators consider its prognosis unpredictable.

The aim of this meta-analysis was to review the benefits and risks involved in the use of denosumab for patients with GCTB tumor progression and to compare these results with those of patients who demonstrated tumor regression, according to the results of previously published studies. The analysis was designed to examine how many patients with GCTB have benefited from the introduction of denosumab and to determine whether the benefits have been greater than the potential risks, providing a critical evaluation of denosumab as a treatment for GCTB.

Materials and Methods

Patients

An intensive literature search for trials submitted by January 7, 2020, in Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and MEDLINE/PubMed was accomplished. The website tool at *www.clinicaltrials.gov* was also checked for current trials being conducted for treatment of GCTB with denosumab. A recent approval extension was based on an overall risk/benefit assessment comparing the efficacy and safety of the monoclonal antibody denosumab in patients with GCTB with tumor progression to patients with tumor regression. For this analysis, the age and gender of the patients were determined from the results of previously published studies of patients with GCTB.

End Points of this Review

This meta-analysis considered the following 9 events relevant to the end points for this systematic review: pulmonary metastasis, tumor progression, secondary tumor development, GCTB death, death from other cancers, treatment-related death, treatment rejection, noncompliance, and loss of follow-up. The following 7 end points were considered relevant to the assessment of treatment with denosumab: disease-free survival, local recurrence of GCTB, treatment failure, adverse effects, recurrence-free survival, survival without tumor progression, and overall survival.

Cohort 1: Tumor Progression During Treatment

Cohort 1 included all patients from reviewed studies with treatment failure, including tumor progression with possible lung metastasis.

Cohort 2: Tumor Regression During Treatment

Cohort 2 included all patients from reviewed studies who experienced tumor. Cohort 2 was used as the comparison group.

Data Collection

Suitable studies that included patients with GCTB who underwent drug treatment with denosumab were searched by entering the search terms "denosumab" and "giant cell tumors of bone" into the search engines of Embase, CENTRAL, and MEDLINE/PubMed, followed by the filters "humans" and "text availability in abstract." The systematic review and meta-analysis were performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[14]

Study Choice

No randomized controlled trials for denosumab treatment of GCTB were found in the literature. Therefore, this review includes nonrandomized, uncontrolled, open-label phase II studies, as well as case series studies and case reports investigating the efficacy of denosumab in patients with GCTB. The selection criteria for the literature used in the analysis required that the study reported on (a) the outcome of treatment with denosumab, (b) demographic data, (c) tumor location, (d) surgical treatment, (e) adverse reactions to denosumab, (f) duration of treatment with denosumab, and (g) follow-up time. The studies were evaluated after being classified according to study design. Within each category of the study design, the data were compared between cohorts 1 and 2. Published studies were excluded if the effectiveness of the administration of denosumab in patients with GCTB was not stated.

Definition of GCTB

Giant cell tumors of bone is a rare tumor often found in the epiphysis of long bones. It grows aggressively but is considered benign.[15] Radiographic findings of a cystic, juxta-articular, nonreactive mass typically lead to a biopsy. After tumor removal, a high risk of relapse remains.[16] In the present study, GCTB tumors were identified and referred to as a primary or recurrent, in addition to their resectable/unresectable statuses.[17]

Giant cell tumors of bone occurs mainly in the knee joint area, in the proximal humerus, and in the distal radius. For the sake of brevity, these areas were identified as the lower and upper limbs in the present study.[18] Other, less frequent localizations also considered here include the skull, the spine, the trunk, the pelvis, and the sacrum.[19-22] Metastasis to the lungs is

less common but has been included in the present study.[23] Giant cell tumors of bone usually occurs in patients between 20 and 40 years of age[24]; in the present study, age is expressed as a mean. Increased risk of broken bones, including broken bones in the spine, after stopping, skipping, or delaying of denosumab, is reported as being among the unwanted side effects of denosumab.[25,26]

Radiological Imaging

Giant cell tumors of bone is initially diagnosed upon detecting osteolytic areas on plain X-ray images. Thereafter, computerized tomography (CT) and magnetic resonance imaging (MRI) are performed on patients with GCTB.[27]

Pathohistology

The radiographic findings of cystic,[28] juxta-articular,[29] and nonreactive masses lead to biopsy.[30] The diagnosis of GCTB is made by examining biopsy tissue under a microscope after hematoxylin-eosin staining. Giant cell tumors of bone demonstrates characteristic multinuclear osteoclast-like giant cells, and the actual tumor cells are similar to mesenchymal mononuclear fibroblast-like cells.[31]

Characteristics of Denosumab

The human monoclonal antibody denosumab is used to treat GCTB when tumors cannot be surgically removed or if surgical resection is likely to lead to severe frailty (eg, loss of limbs). The aim of denosumab treatment is to reduce osteoclast activity and, thus, bone resorption.[32,33]

Dosage and Method of Denosumab Administration

Denosumab is administered as a subcutaneous injection of 120 mg in the thigh, the abdominal region, or the upper arm. The drug is injected every 4 weeks, with additional 120 mg single doses on days 8 and 15 of the first month of treatment.[34] The second cycle starts on day 29 or 4 weeks after day 15. Patients who undergo complete GCTB resection receive an additional 6 months of denosumab treatment after surgery. When additional surgical intervention is required for patients whose tumor shows incomplete regression, denosumab is used as a neoadjuvant treatment. The goal of this neoadjuvant therapy is to achieve an improved starting situation for the operation, to make the disease operable, or to forgo mutilating surgery. The timing of denosumab application before and after surgery or as a neoadjuvant treatment was addressed in all literature chosen for this study.

The participants in all studies chosen for this analysis, except those with existing hypercalcemia, had to have received at least 500 mg of calcium and 400 IU of vitamin D per day.[35] Existing hypocalcemia had to be corrected before the start of denosumab therapy. Hypocalcemia could occur at any time during therapy, requiring regular control of calcium levels.[36] Acquiring hypocalcemia during the study would require the patient to drop out of the study. Hypocalcemia was considered one of the side effects of denosumab in the studies reviewed here. The duration of denosumab treatment and follow-up was determined individually by the treating physicians, depending on the drug response and how well the participants tolerated it. When this information was indicated in the examined studies, data on the duration of denosumab therapy and follow-up were collected.

Definition of Therapy Success With Denosumab

The objective GCTB response rate is expressed based on the best response rate to denosumab, as determined by MRI or CT in the control record at the 6-month follow-up. Radiological measurement of the longest diameter of the GCTB is taken and compared to the measurement obtained at the initial MRI or CT examination. No evidence of GCTB is considered a complete response, reduction by at least 30% of diameter is considered a partial response, unchanged tumor size is considered stable disease, and tumor size increase of 20% is considered progression of disease, according to the modified response evaluation criteria in solid tumors.[37] Giant cell tumors of bone is detected using ^{18}F-fluorodeoxyglucose, a radioactively labeled tracer, by recording the metabolic processes with positron emission tomography, according to the modified European Organization for Research and Treatment of Cancer criteria.[38]

Definition of Treatment Failure With Denosumab

In this review, treatment failure was established when radiology or histology demonstrated local recurrences of GCTB, when GCTB progressed by metastasis to the lungs, or when patients had progression $\geq$20%.[37]

Side Effects of Denosumab

The evaluation of the side effects of denosumab served to establish a possible connection with GCTB progression. The comparison of the frequency of side effects reported here refers to the comparison of the 2 cohorts in this analysis and is not a frequency indication of the side effects of denosumab in general. The common side effects of denosumab considered in this study were hypocalcemia, hypophosphatemia, osteonecrosis of the jaw, pain in the limb, and skin rash.[39-41] Rare side effects, such as anemia, headache, hypercalcemia, hyperparathyroidism, parathyroid adenoma, pathological bone fracture, and peripheral neuropathy, as well as serious adverse events—which could occur at any time—were also identified in this study.[42] Severe adverse events described as life-threatening during treatment included the need for life-saving interventions, a high risk of death, and the need for hospitalization as indicated by the Common Terminology Criteria for Adverse Events developed by the US National Cancer Institute of the National Institutes of Health.[43]

Enneking and Campanacci Staging Systems

The GCTB classifications based on clinical radiological features were developed first by William Enneking, MD, and later by Mario Campanacci, MD. In many cases, these clinical radiological staging systems did not find a correlation between radiography results and local GCTB recurrence or, in other words, the aggressiveness of the tumor. In addition to histopathological classification, these staging systems are also controversial for their prognostic significance. For this reason, these staging systems are not to be seen as predictive for GCTB prognosis. Most participants in the studies chosen for this meta-analysis were mainly Campanacci stage 3, followed in frequency by stage 2. The evaluation of patients according to this staging system was disregarded in this meta-analysis. Both the Enneking and Campanacci staging systems were described here, however, in order to understand the various surgical techniques described in this meta-analysis. Efforts at staging GCTB have so far been unsuccessful, but there is an agreement in the medical community to use the Enneking staging system for planning surgery.[44] The Enneking classification is a surgical staging system developed as a guide for surgical treatment of musculoskeletal tumors. It was tested and approved in 1980 by the Musculoskeletal Tumor Society and the American Joint Committee on Cancer. The system was developed at a time when simple X-rays were the only imaging test used to examine patients. There have been no modifications to the staging system so far.[45]

Types of Surgery

En bloc resection. A high probability of GCTB recurrence inevitably leads to a radical surgical procedure in the form of *en bloc* resection, in which the tumor and any affected neighboring tissue or lymph nodes are removed in one piece.[46] *En bloc* resection is the Enneking-appropriate treatment for stage 3 GCTB. *En bloc* resection is more difficult technically. There is also the risk that, during even simple manipulation, the tumor mass will collapse, allowing tumor cells to escape and migrate. In many cases, *en bloc* resection can easily be performed in the limbs, but it becomes more difficult in anatomically unfavorable positions such as the spine. However, the best way to remove GCTB in the spine and achieve a tumor-free margin is *en bloc* resection.[44]

En bloc excision. Neighboring tissue that has been affected by GCTB can be removed via *en bloc* excision in some cases.[47] In the most favorable cases, the surgeon can perform a marginal excision to remove the tumor along with the surrounding tissue margin.[47]

Intralesional excision. Intralesional excision is the preferred treatment if it is possible to remove the entire GCTB and protect the joint. Intralesional excision is the Enneking-appropriate treatment for stage 2 GCTB. In the limbs, intralesional excision is also considered an appropriate choice for stage 3 disease, particularly if local adjuvants such as phenol, hydrogen peroxide, cryosurgery, or polymethyl acrylate are used.[44,45]

Curettage. The traditional surgical treatment for GCTB is intralesional aggressive curettage, which involves using an additional mechanical high-speed milling cutter, followed by the application of bone cement to fill the surgical defect. This cement could be replaced with bone after one or 2 years if the GCTB shows no recurrence. In addition, chemically toxic substances (eg, alcohol or phenol) are often added to kill any remaining GCTB cells.[48] Enneking stages 1 and 2 disease is usually treated with curettage.[44]

Spondylectomy. Rare localizations in the spine and sacral areas are treated with the difficult surgical procedure of spondylectomy.[49] This procedure removes one or more vertebral bodies, with subsequent replacement and stabilization of the spinal column section.

Amputation and joint or prosthesis replacement. Left untreated, GCTB can lead to the complete destruction of the affected bone, deformities, joint disorders, and even amputations. The frequency of amputation and joint or prosthesis replacement was examined among the operative measures in this analysis.[50]

No surgery. The use of denosumab can allow circumvention of an operation in the very best of cases.

Embolization. Preoperative radiologic-interventional elective embolization is sometimes useful to control a difficult GCTB and is conducted by administering liquid plastics via a catheter into the patient's artery. This procedure was also investigated in this analysis.[21]

Mortality

The number of deaths among denosumab-treated patients was surveyed after a review of the studies in this analysis.

Quality Assessment Study Tool

For open-label phase II studies. The nonrandomized, uncontrolled, open-label phase II studies were evaluated and validated using the risk assessment tool for nonrandomized studies (RoBANS).[51] The studies were evaluated based on the following 3 characteristics: (1) high risk of bias, (2) low risk of bias, and (3) unclear risk of bias. The RoBANS covers aspects such as participant selection, confounding variables, intervention measurement, outcome assessment blinding, incomplete data results, and selective outcome reporting.

For case series. The Joanna Briggs Institute is an international membership-based research and development organization within the Faculty of Health Sciences of the University of Adelaide in Australia.[52] The institute developed a critical appraisal tool for systematic reviews, and this tool was used to evaluate the case series in this work.[53] Using 10 questions, the tool rates each case series with the answers "yes," "no," or

"unclear," where "yes" corresponds to a low risk of bias, "no" to a high risk of bias, and "unclear" to an unclear risk of bias.[52] The 10 questions focus on the following: clear criteria for inclusion in the case series, measurement of the condition in a standard and reliable way for all the participants included in the case series, use of valid methods for identification of all participant conditions included in the case series, consecutive inclusion of participants in the case series, complete inclusion of participants, clear reporting of participant demographics in the study, clear reporting of clinical information for all participants, clear reporting of the outcomes or follow-up results of the cases, clear reporting of the demographic information for presenting clinics, and the use of appropriate statistical analysis.

For case reports. For evaluation of case reports, we also used the critical appraisal tool from the Joanna Briggs Institute.[52] The checklist for case reports consists of 8 questions.[54,55] The questions focus on assessment methods; patient demographic characteristics, history, current clinical condition, and postintervention clinical condition; the treatment procedure; adverse events; and the case report's takeaway lessons. These case report questions are rated either "yes" for a low risk of bias, "no" for a high risk of bias, or "unclear" for an unclear risk of bias.

Statistical Analysis

The numbers studied in proportions were expressed as percentages. Mean and standard deviation were used to calculate the mean age, the duration of treatment, and the follow-up of participants in the studies chosen for analysis.[56] For evaluation of the results in this systematic review, a P value of <0.05 was determined to be statistically significant.

A Mann-Whitney U test for unpaired data of 2 samples was used to compare age differences, duration of treatment, and follow-up time.[57]

Chi-square analysis was used in open-label studies to examine gender differences between published studies, classification of tumors, and time of denosumab administration. In case series studies, gender difference, tumor classification, administration of pre- and postoperative denosumab, neoadjuvant therapy, surgery procedures, embolization, and localization of tumors as spine, pelvic, sacrum, upper limb, or lower limb were analyzed.[58]

The calculations for sample sizes under 5 were carried out using Fisher exact test. Fisher exact test was used to analyze case reports for outcome of treatment, course of treatment, tumor localization, administration of denosumab, tumor classification, and gender differences. In case series studies, outcome of treatment, course of treatment, localization of tumors in the skull, trunk or lung, and administration of denosumab after surgery were analyzed. Open-label studies were analyzed for localization of tumors, course of treatment, outcome of treatment, side effects of denosumab, surgery procedures, and embolization.

A confidence interval (CI) for proportions with a correction for continuity was computed from the observed data for comparison of the number of participants in cohort 1 and cohort 2, as well as the total number of participants according to the study design.[59]

Results

Entry of the search criteria into the search engines of Embase, CENTRAL, and MEDLINE/PubMed retrieved a total of 382 human trials for the period up to January 7, 2020 (Figure 1). A critical review of these published studies identified 60 studies that met the inclusion criteria for the present meta-analysis (Table 1).[11,12,44,60-116] The *www.clinicaltrials.gov* website showed 7 ongoing studies of denosumab in the treatment of GCTB. The majority of the studies examined for this meta-analysis were case reports, case series studies, and nonrandomized, uncontrolled, open-label phase II studies (Figure 2). The evaluation of these eligible studies yielded a total of 1074 patients with GCTB who underwent drug treatment with denosumab. Of these, 176 (16.4%, 95% CI: 14.3%-18.8%) were in cohort 1 and 898 (83.6%, 95% CI: 81.2%-85.8%) were in cohort 2 across all study types. However, most of the patients in this meta-analysis were from case series studies (621 patients: 57.8%, 95% CI: 54.8%-60.8%), followed by the nonrandomized, uncontrolled, open-label phase II studies (422 patients: 39.3%, 95% CI: 36.4%-42.3%), and then case reports (31 patients: 2.9%, 95% CI: 2.0%-4.1%; Table 2 and Figure 2).

After evaluation of the data, sex assignment was not possible for the participants in the studies of Thomas et al[11] or Chawla et al[12] for a total of 160 patients who could not be identified by sex (11 in cohort 1, 149 in cohort 2; Table 2). Despite this fact, a narrow majority of the included study participants consisted of women: cohort 1 included 92 women (18.4% of all women included in the studies) and cohort 2 included 407 women (81.6% of all women included in the studies) for a total of 499. In contrast, cohort 1 included 73 men (17.6% of all men included in the studies) and cohort 2 included 342 men (82.4% of all men included in the studies) for a total of 415 men. However, the difference between the genders was not statistically significant at $P = .807$ (Table 2). The most common age of GCTB onset in these study participants was the third decade of life, with a median age of 30 in both cohorts, and the second decade of life was the next most common onset age (Table 2). The age and gender distributions were statistically unremarkable between cohorts 1 and 2 across all study types (Table 2). The durations of treatment and follow-up times were also not statistically different between cohorts 1 and 2 (Table 2). The classification of tumors as primary and recurrent had statistical significance only in the case reports (Table 2).

All participants in the analyzed studies received denosumab as a single subcutaneous injection in the thigh, the abdominal region, or the upper arm at the recommended dose of 120 mg and at regularly prescribed intervals of 4 weeks, with additional doses of 120 mg on days 8 and 15 of the first month of

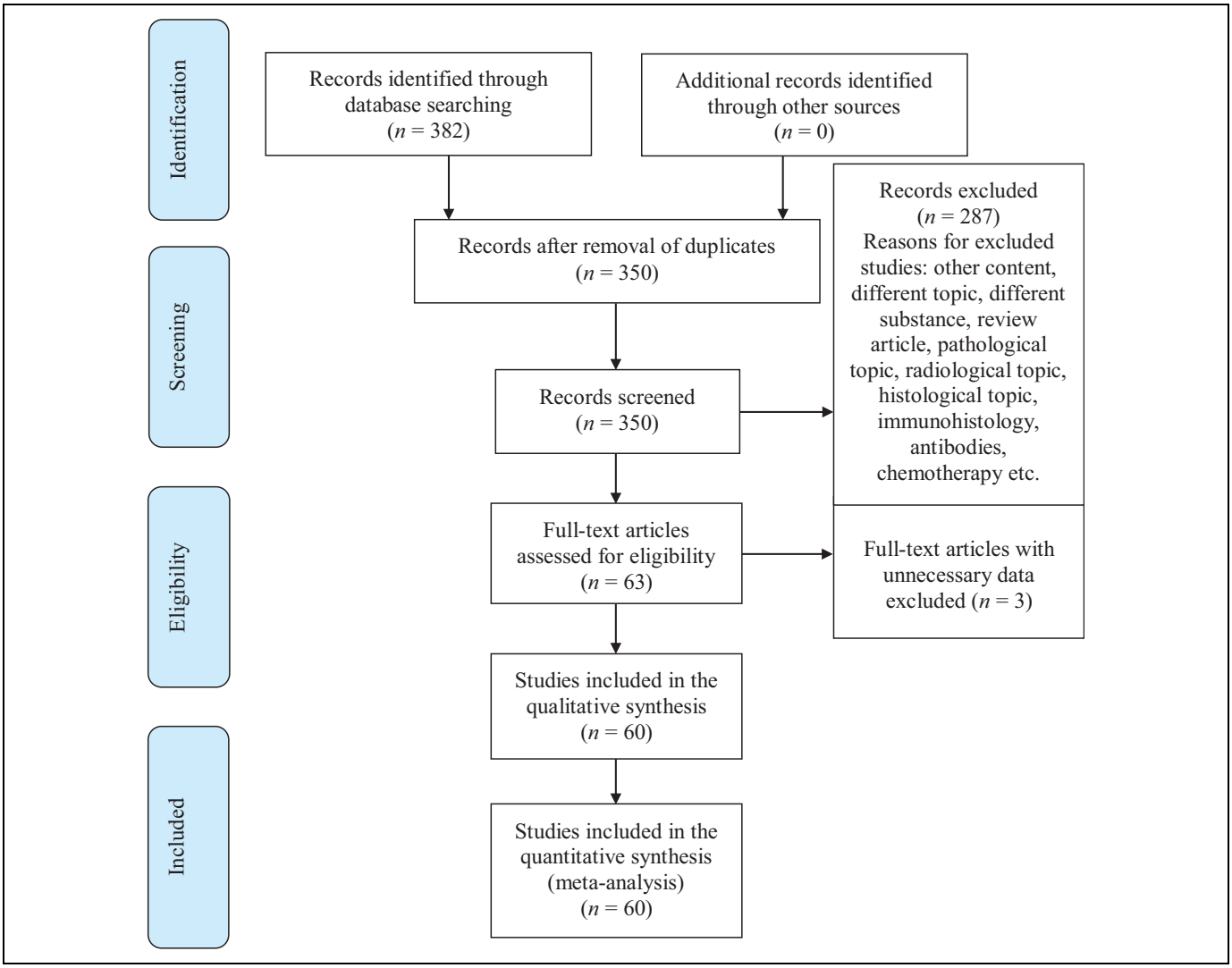

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 flow diagram for data collection after the search for suitable studies. Entry of the search criteria into the search engines of Embase, CENTRAL, and MEDLINE/PubMed retrieved a total of 382 human trials for the period up to January 7, 2020. A critical review of these published studies identified 60 studies that met the inclusion criteria for the present meta-analysis.

treatment. The second cycle started on day 29 or 4 weeks after day 15. In these published studies, denosumab was given as a neoadjuvant therapy in many cases, with statistical significance of response in open-label phase II studies, followed in frequency by the administration of denosumab pre- and postoperatively with statistical significance in case series studies (Table 2). The administration of denosumab postoperatively did not have a statistical impact in any compared studies (Table 2).

The most common body localization in both cohorts was the lower limb, with statistical significance only in case series studies, followed in frequency by the upper limb with statistical significance only in case reports, and sacral bone with no statistical significance in any of the study groups (Table 2).

Tumor progression was most frequent in the open-label phase II studies and case reports (Table 2). Nonresponse to treatment and an increased incidence of recurrence were more frequent in the case series studies (Table 2). Only in the case series studies could tumor shrinkage or even no evidence of tumor be statistically recorded in most patients in cohort 2 (Table 2). Finally, the evaluation of this analysis showed a response rate of at least 97.5% in the open-label phase II studies, and this rate was statistically significant ($P < .0001$; Table 2).

Serious adverse events were the most reported side effect of denosumab—mainly in Cohort 2—but there was no statistical relevance ($P = .230$; Table 3). Osteonecrosis of the jaw was the most common side effect in most cohort 1 participants in open-label studies ($P < .0001$; Table 3). Pain in the limbs ($P < .0001$), fatigue ($P = .004$), headache ($P = .003$), and back pain ($P = .004$) were most common for participants in cohort 2 of the case series studies (Table 3).

Table 1. Enneking Staging System: Linkage Between Stages and Surgical Margins.[45,a]

Tumor stage (benign)	Grade, location, metastases	Clinical evolution	Control margin
1	GoToMo	Latent	Intracapsular
2	GoToMo	Active	Marginal or intracapsular plus effective adjuvant
3	$GoT_{1-2}M_{0-1}$	Aggressive	Wide or marginal plus effective adjuvant

Abbreviations: Go, benign; To, intracapsular; T1, extracapsular, intracompartmental; T2, extracapsular, extracompartmental; Mo, absence metastases; M1, presence of metastases.

[a]Three tumor stages are latent, active, and aggressive. The classification is based on radiological features of surgical margins. Well-defined tumor boundaries indicate latent lesions, whereas indistinct tumor boundaries are due to permeation in the host bones and a more aggressive lesion. Higher stage numbers indicate an increase in local aggressiveness and incidence of recurrence. Metastasis is rare in locally aggressive benign giant cell tumor of bone.[45]

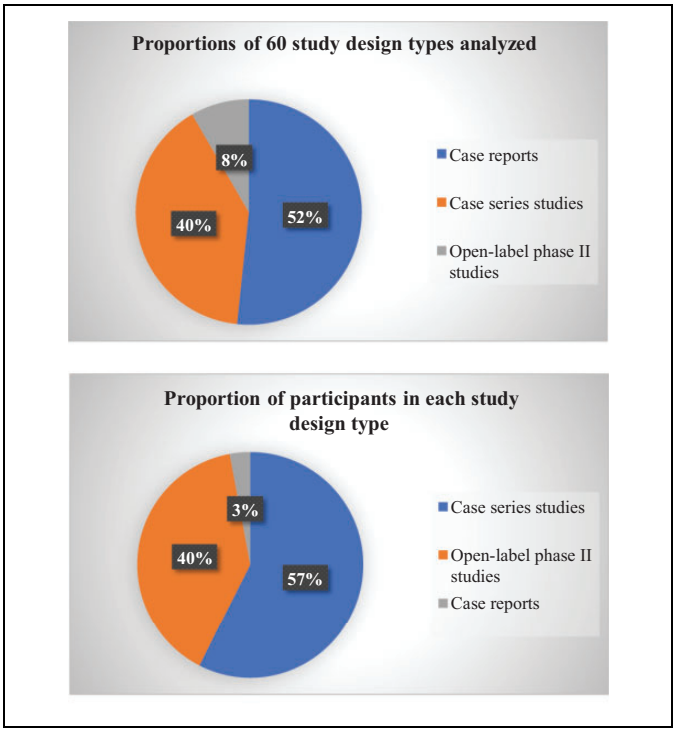

Figure 2. A, Classification of the 60 studies examined for this systematic review according to their study type. Most of the studies in this meta-analysis were from the case reports, followed by case series, and then nonrandomized, uncontrolled, open-label phase II studies. B, Proportion of participants included in analyzed studies, according to study design. Most participants in the studies analyzed were from case series studies, followed by the nonrandomized, uncontrolled, open-label phase II studies, and then case reports.

Curettage was the most common type of surgery across all participants, followed by *en bloc* resection, but curettage resulted in a statistically significant better cure rate only in the case series studies (Table 4).

Ten participants received embolization in cohort 1 and 29 participants in cohort 2. The GCTB embolization procedure was used only for a small number of the patients in this study (Table 4 and 5).

None of the studies reported any deaths from either denosumab treatment or as a result of the disease (Table 2).

Evaluation of the open-label phase II studies showed a general low risk of bias (Figure 3). However, there were 3 specific types of bias present in some open-label studies: detection bias due to insufficient blinding of the outcome assessment, attrition bias due to insufficient handling of incomplete outcome data, and reporting bias due to selective outcome reporting (Figure 3).

The quality assessment for the case series studies also showed a general low risk of bias (Figure 4). However, a high risk of bias was observed in some case series studies: statistical analysis, insufficient reporting of the following results, and incomplete inclusion of the participants (Figure 4).

The overall quality assessment of case reports showed a low risk of bias (Figure 5). Only one study had an increased risk of attrition bias due to the unclear description of the post-interventional clinical situation of a patient in the case reports (Figure 5).

Discussion

This meta-analysis showed that only 17% of participants (cohort 1) noted tumor progression after use of denosumab. In contrast, 83% of participants (cohort 2) demonstrated a good response to the drug. The 2 cohorts showed no significant difference in age, gender, and duration of treatment with denosumab. Denosumab was mainly used as a neoadjuvant therapy, and there were no significant differences between the 2 groups. In both cohorts, the most common localization was the lower limb. The most common operation performed in both cohorts was curettage. There was only one difference in the side effects between the 2 groups—cohort 2 had more serious adverse events than cohort 1. In contrast, the most common side effect for cohort 1 was osteonecrosis of the jaw.

This meta-analysis showed that denosumab can be an effective therapy for the treatment of patients with GCTB. The published studies analyzed in this review show evidence of the efficacy of denosumab in this group of patients, and the drug has made a good impression on the medical community in general. The published studies also indicate that there has been some treatment failure when denosumab was used on some participants with GCTB; however, the number of participants who failed treatment in this current assessment was small. The studies examined for this meta-analysis reported different results on the widely varying numbers of participants who experienced treatment failure with denosumab in the reviewed medical literature.[11,12,44,60-116] Despite the efficacy of denosumab, disease progression was unfortunately observed after only a short time among a small percentage of participants in some open-label phase II studies and case reports in this investigation. This result suggests a need for new treatment strategies

Table 2. List of References Used for this Systematic Review.[a]

Study number	Reference number	Citation	Study type	Country of the main author	Total number of study participants	No. of participants considered for this study	Funding
1	44	Boriani S, Cecchinato R, Cuzzocrea F, et al. Denosumab in the treatment of giant cell tumor of the spine. Preliminary report, review of the literature and protocol proposal. *Eur Spine J.* 2019;29(2):257-271. doi: 10.1007/s00586-019-05997-0.	Case series	Italy	10	10	None
2	60	Zhang RZ, Ma TX, Qi DW, et al. Short-term preoperative denosumab with surgery in unresectable or recurrent giant cell tumor of bone. *Orthop Surg.* 2019;11(6):1101-1108.	Case series	China	11	11	None
3	61	Reddy K, Ramirez L, Kukreja K, Venkatramani R. Response to denosumab in 2 children with recurrent giant cell tumor of the bone with pulmonary metastasis. *J Pediatr Hematol Oncol.* 2019.	Case series	United States	2	2	None
4	62	Bilgetekin I, Mammadkhnali O, Basal FB, et al. A case of pelvic giant cell tumor of bone, complete remission with denosumab: long duration of response. *Anticancer Drugs.* 2020;31(5):533-535.	Case report	Turkey	1	1	None
5	63	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.	Open-label	United States	532	188	Amgen
6	64	Akel U, Robinson ME, Werier J, et al. Local tumor recurrence and escape from suppression of bone resorption with denosumab treatment in two adolescents with giant cell tumors of bone. *JBMR Plus.* 2019;3(9):e10196.	Case series	Canada	2	2	Amgen
7	65	Xará-Leite F, Coutinho L, Fleming C, et al. Can denosumab cure giant cell tumors of the spine? A case report and literature review. *Eur J Orth Surg Traumatol.* 2019;16(2):1-5.	Case report	Portugal	1	1	None
8	66	Chinder PS, Hindiskere S, Doddarangappa S, Pal U. Evaluation of local recurrence in giant-cell-tumor of bone treated by neoadjuvant denosumab. *Clin Orthop Surg.* 2019;11(3):352-360.	Case series	India	123	42	None
9	67	Tsukamoto S, Mavrogenis AF, Leone G, et al. Denosumab does not decrease the risk of lung metastases from bone giant cell tumour. *Int Orthop.* 2019;43(2):483-489.	Case series	Japan	411	30	None
10	68	Marinova VV, Slavchev SA, Patrikov KD, et al. Neoadjuvant and adjuvant treatment with denosumab in aggressive giant-cell tumor of bone in the proximal fibula: a case report. *Folia Med (Plovdiv).* 2018;60(4):637-640.	Case Report	Bulgaria	1	1	None

(continued)

Table 2. (continued)

Study number	Reference number	Citation	Study type	Country of the main author	Total number of study participants	No. of participants considered for this study	Funding
11	69	Sambri A, Medellin MR, Errani C, et al. Denosumab in giant cell tumour of bone in the pelvis and sacrum: Long-term therapy or bone resection? *J Orthop Sci.* 2019;19:30136-30138.	Case series	Italy	26	26	None
12	70	Kinoshita H, Orita S, Yonemoto T, et al. Successful total en bloc spondylectomy of the L3 vertebra with a paravertebral giant cell tumor following preoperative treatment with denosumab: a case report. *J Med Case Rep.* 2019;13(1):116.	Case report	Japan	1	1	None
13	71	Osaka E, Okamura Y, Yoshida Y, Masahiko S, Yasuaki T. Intra-articular ectopic ossification associated with denosumab administration for giant cell tumor of bone with intra-articular pathological fracture. *J Orthop Sci.* 2019;24(3):558-562.	Case report	Japan	1	1	None
14	72	Jia Q, Chen G, Cao J, et al. Clinical features and prognostic factors of pediatric spine giant cell tumors: report of 31 clinical cases in a single center. *Spine J.* 2019;19(7):1232-1241.	Case series	China	31	31	None
15	73	Li S, Chen P, Yang Q. Denosumab versus zoledronic acid in cases of surgically unsalvageable giant cell tumor of bone: A randomized clinical trial. *J Bone Oncol.* 2019;15:100217.	Case series	China	250	125	None
16	74	Liu S, Zhou X, Song A, et al. Combining two-stage surgery and denosumab treatment in a patient with giant cell tumour of the lumbar spine with intraperitoneal growth. *Postgrad Me J.* 2019;95(1120):106-107.	Case report	China	1	1	None
17	75	Puri A, Gulia A, Hegde P, Verma V, Rekhi B. Neoadjuvant denosumab: Its role and results in operable cases of giant cell tumour of bone. *Bone Joint J.* 2019;101(2):170-177.	Case series	India	44	41	None
18	76	Niu X, Yang Y, Wong KC, Zhen H, Yi D, Wen Z. Giant cell tumour of the bone treated with denosumab: How has the blood supply and oncological prognosis of the tumour changed? *J Orthop Translat.* 2019;18:100-108.	Case series	China	18	18	None
19	77	Agarwal MG, Gundavda MK, Gupta R, Reddy R. Does denosumab change the giant cell tumor treatment strategy? Lessons learned from early experience. *Clin Orthop Relat Res.* 2018;476(9):1773-1782.	Case series		25	25	None
20	78	Scoccianti G, Totti F, Scorianz M, et al. Preoperative denosumab with curettage and cryotherapy in giant cell tumor of bone: is there an increased risk of local recurrence? *Clin Orthop Relat Res.* 2018;476(9):1783-1790.	Case series		12	12	Walde-mar Link (Hamburg, Germany), Adler Ortho (Milan, Italy)

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Table 2. (continued)

Study number	Reference number	Citation	Study type	Country of the main author	Total number of study participants	No. of participants considered for this study	Funding
21	79	Yang Y, Li Y, Liu W, et al. A nonrandomized controlled study of sacral giant cell tumors with preoperative treatment of denosumab. *Medicine (Baltimore)*. 2018;97(46):e13139.	Case series	China	16	6	Beijing Talents Fund
22	80	Luo Y, Tang F, Wang Y, et al. Safety and efficacy of denosumab in the treatment of pulmonary metastatic giant cell tumor of bone. *Cancer Manag Res*. 2018;10:1901-1906.	Case series	China	7	7	Yi Luo by the Support Program for Science and Technology of Sichuan Province, China
23	81	Chen Z, Yang Y, Guo W, et al. Therapeutic benefits of neoadjuvant and post-operative denosumab on sacral giant cell tumor: a retrospective cohort study of 30 cases. *J BU ON*. 2018;23(2):453-459.	Case series	China	30	21	None
24	82	Rutkowski P, Gaston L, Borkowska A, et al. Denosumab treatment of inoperable or locally advanced giant cell tumor of bone—Multicenter analysis outside clinical trial. *Eur J Surg Oncol*. 2018;44(9):1384-1390.	Case series	Poland	138	89	Amgen
25	83	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(6):496-504.	Case series	Italy	408	30	None
26	84	Wu CC, Hsieh PP. Denosumab-treated giant cell tumor of the bone mimicking low-grade central osteosarcoma. *J Pathol Transl Med*. 2018;52(2):133-135.	Case report	Taiwan	1	1	None
27	85	Law GW, Yeo NEM, Howe TS, et al. Recommencement of denosumab for unresectable giant cell tumor of the cervical spine: A case report. *Spine (Phila Pa)*. 2018;43(9): E551-E556.	Case report	Singapore	1	1	None
28	86	Ji T, Yang Y, Wang Y, Sun K, Guo W. Combining of serial embolization and denosumab for large sacropelvic giant cell tumor: case report of 3 cases. *Medicine*. 2017;96(33):e7799.	Case series	China	3	3	National Natural Science Foundation of China
29	87	Satcher RL, Ravi V, Wang WL, Oates S. Postpartum treatment of metastatic recurrent giant cell tumor of capitate bone of wrist. *Am J Orthop*. 2017;46(4): E269-E275.	Case report	United States	1	1	None
30	88	Palmerini E, Chawla NS, Ferrari S, et al. Denosumab in advanced/unresectable giant-cell tumour of bone (GCTB): for how long? *Eur J Cancer*. 2017;76:118-124.	Open-label	Italy	97	54	None
31	89	Yonezawa N, Murakami H, Kato S, Takeuchi A, Tsuchiya H. Giant cell tumor of the thoracic spine completely removed by total spondylectomy after neoadjuvant denosumab therapy. *Eur Spine J*. 2017;26(suppl. 1):236-242.	Case report	Japan	1	1	None

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Table 2. (continued)

Study number	Reference number	Citation	Study type	Country of the main author	Total number of study participants	No. of participants considered for this study	Funding
32	90	Von Borstel D, Taguibao RA, Strle NA, Burns JE. Giant cell tumor of the bone: aggressive case initially treated with denosumab and intralesional surgery. *Skelet Radiol.* 2017;46(4):571-578.	Case report	United States	1	1	None
33	91	Bardakhchyan S, Kager L, Danielyan S, et al. Denosumab treatment for progressive skull base giant cell tumor of bone in a 14 year old female—a case report and literature review. *Ital J Pediatr.* 2017;43(1):32.	Case report	Armenia	1	1	None
34	92	Tsukamoto S, Righi A, Vanel D, Honoki K, Donati DM, Errani C. Development of high-grade osteosarcoma in a patient with recurrent giant cell tumor of the ischium while receiving treatment with denosumab. *Jpn J Clin Oncol.* 2017;47(11):1090-1096.	Case report	Japan	1	1	None
35	93	Deveci MA, Paydaş S, Gönlüşen G, Ozkan C, Bicer OS, Tekin M, Ozkan C, Bicer OS, Tekin M. Clinical and pathological results of denosumab treatment for giant cell tumors of bone: prospective study of 14 cases. *Acta Orthop Traumatol Turc.* 2017;51(1):1-6.	Case series	Turkey	14	13	None
36	94	Rekhi B, Verma V, Gulia A, et al. Clinicopathological features of a series of 27 cases of post-denosumab treated giant cell tumors of bones: a single institutional experience at a tertiary cancer referral centre, India. *Pathol Oncol Res.* 2017;23(1):157-164.	Case series	India	27	27	None
37	95	Menon PD, Krishnakumar R, Jojo A. Radiological and histopathological outcome of giant cell tumor of femur with denosumab treatment: a case report. *J Clin Diagn Res.* 2016;10(12):RD01-RD03.	Case report	India	1	1	None
38	96	Müller DA, Beltrami G, Scoccianti G, Campanacci DA, Franchi A, Capanna R. 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.	Case series	Switzerland	25	25	None
39	97	Inoue A, Ohnishi T, Kohno S, Nishikawa M, Nishida N, Ohue S. Role of denosumab in endoscopic endonasal treatment for juvenile clival giant cell tumor: a case report and review of the literature. *World Neurosurg.* 2016;91:674.e1-674.e6.	Case report	Japan	1	1	None
40	98	Traub F, Singh J, Dickson BC, et al. Efficacy of denosumab in joint preservation for patients with giant cell tumour of the bone. *Eur J Cancer.* 2016;59:1-12.	Case series	Canada	20	20	None

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Table 2. (continued)

Study number	Reference number	Citation	Study type	Country of the main author	Total number of study participants	No. of participants considered for this study	Funding
41	99	De Carvalho Cavalcante RA, Marques RA, Santos VGD, Sabino E, et al. Spondylectomy for giant cell tumor after denosumab therapy. *Spine*. 2016;41:E178-E182.	Case report	Brazil	1	1	None
42	100	Yamagishi T, Kawashima H, Ogose A, et al. Disappearance of giant cells and presence of newly formed bone in the pulmonary metastasis of a sacral giant-cell tumor following denosumab treatment: a case report. *Oncol Lett*. 2016;11(1):243-246.	Case report	Japan	1	1	None
43	101	Kajiwara D, Kamoda H, Yonemoto T, et al. Denosumab for treatment of a recurrent cervical giant-cell tumor. *Asian Spine J*. 2016;10(3):553-557.	Case report	Japan	1	1	None
44	102	Nakazawa T, Inoue G, Imura T, et al. Remarkable regression of a giant cell tumor of the cervical spine treated conservatively with denosumab: a case report. *Int J Surg Case Rep*. 2016;24:22-25.	Case report	Japan	1	1	None
45	103	Setsu N, Kobayashi E, Asano N, et al. Severe hypercalcemia following denosumab treatment in a juvenile patient. *J Bone Miner Metab*. 2016;34(1):118-122.	Case report	Japan	1	1	Research Chair program at the University of Ottawa
46	104	Aponte-Tinao LA, Piuzzi NS, Roitman P, Farfalli GL. A high-grade sarcoma arising in a patient with recurrent benign giant cell tumor of the proximal tibia while receiving treatment with denosumab. *Clin Orthop Relat Res*. 2015;473(9):3050-3055.	Case report	Argentina	1	1	Stryker Corporation (Kalamazoo, Michigan, USA)
47	105	Park MJ, Ganjoo KN, Ladd AL. Denosumab, a potential alternative to the surgical treatment of distal radius giant cell tumor of bone: case report. *J Hand Surg Am*. 2015;40(8):1620-1624.	Case report	United States	1	1	None
48	106	Matcuk GR, Patel DB, Schein AJ, White EA, Menendez LR. Giant cell tumor: rapid recurrence after cessation of long-term denosumab therapy. *Skelet Radiol*. 2015;44(7):1027-1031.	Case report	United States	1	1	None
49	107	Vaishya R, Agarwal AK, Vijay V, Vaish A. Metachronous multicentric giant cell tumour in a young woman. *BMJ Case Rep*. 2015;2015:bcr2015209368.	Case report	India	1	1	None
50	108	Goldschlager T, Dea N, Boyd M, et al. Giant cell tumors of the spine: has denosumab changed the treatment paradigm? *J Neurosurg Spine*. 2015;22(5):526-533.	Case series	Canada	5	5	Stryker and Globus, Medtronic, Mesoblast Limited
51	109	Gossai N, Hilgers MV, Polgreen LE, Greengard EG. Critical hypercalcemia following discontinuation of denosumab therapy for metastatic giant cell tumor of bone. *Pediatr Blood Cancer*. 2015;62(6):1078-1080.	Case report	United States	1	1	None

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Table 2. (continued)

Study number	Reference number	Citation	Study type	Country of the main author	Total number of study participants	No. of participants considered for this study	Funding
52	110	Watanabe N, Matsumoto S, Shimoji T, et al. Early evaluation of the therapeutic effect of denosumab on tartrate-resistant acid phosphatase 5b expression in a giant cell tumor of bone: a case report. *BMC Res Notes*. 2014;7(1):608.	Case report	Japan	1	1	None
53	111	Mattei TA, Ramos E, Rehman AA, Shaw A, Patel SR, Mendel E. Sustained long-term complete regression of a giant cell tumor of the spine after treatment with denosumab. *Spine J*. 2014;14(7): e15-e21.	Case report	United States	1	1	None
54	112	Hakozaki M, Tajino T, Yamada H, et al. Radiological and pathological characteristics of giant cell tumor of bone treated with denosumab. *Diagn Pathol.* 2014;9(1):111.	Case report	Japan	1	1	None
55	113	Aghaloo TL, Dry SM, Mallya S, Tetradis S. Stage 0 osteonecrosis of the jaw in a patient on denosumab. *J Oral Maxillofac Surg*. 2014;72(4):702-716.	Case report	United States	1	1	NIH/NIDCR DE019465 and DE0214
56	114	Rossi B, Ferraresi V, Appetecchia ML, Novello M, Zoccali C. Giant cell tumor of bone in a patient with diagnosis of primary hyperpara-thyroidism: a challenge in differential diagnosis with brown tumor. *Skelet Radiol.* 2014;43(5):693-697.	Case report	Italy	1	1	None
57	115	Akaike K, Suehara Y, Takagi T, Kaneko K, Saito T. An eggshell-like mineralized recurrent lesion in the popliteal region after treatment of giant cell tumor of the bone with denosumab. *Skelet Radiol.* 2014;43(12):1767-1772.	Case report	Japan	1	1	None
58	12	Chawla S, Henshaw R, Seeger L, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. *Lancet Oncol.* 2013;14(9):901-908.	Open-label, phase II study	United States	282	125	Amgen
59	116	Branstetter DG, Nelson SD, Manivel JC, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. *Clin Cancer Res*. 2012;18(16):4415-4424.	Open-label, phase II study	United States	37	20	Amgen
60	11	Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol.* 2010;11(3):275-280. doi:10.1016/S1470-2045(10)70010-3.	Open-label, phase II study	United States	35	35	Amgen

[a]All studies found for this meta-analysis were grouped according to the study type in nonrandomized, uncontrolled, open-label phase II studies, case series studies, case reports, study number, reference number, country of the main author, total number of study patients, number of patients considered for this study, and funding.

Table 3. Comparison of basic demographic data, characteristics of giant cell tumor of bone, treatment with denosumab, and therapy outcome across case studies, case series studies, case reports, and nonrandomized, uncontrolled, open-label phase II studies.[a,b]

Open-label phase II studies	**Cohort 1 studies** **Author, n = No. of patients**	**Cohort 2 studies** **Author, n = No. of patients**	
	Chawla et al,[63] n = 10 Palmerini et al,[88] n = 8 Chawla et al,[12] n = 6 Thomas et al,[11] n = 5	Chawla et al,[63] n = 178 Palmerini et al,[88] n = 46 Chawla et al,[12] n = 119 Branstetter et al,[116] n = 20 Thomas et al,[11] n = 30	
Descriptions	**Cohort 1, N (%)**	**Cohort 2, N (%)**	***P* value**
Total number of patients	**29 (100)**	**393 (100)**	
Male/female/unknown	9 (31.0)/9 (31.0)/11 (38.0)	104 (26.5)/140 (35.6)/149 (37.9)	.831
Mean age ± SD years	36 ± 8	33 ± 2	1.0
Treatment with denosumab			
Duration of treatment mean ± SD months	26 ± 12	25 ± 17	.804
Follow-up mean ± SD months	44 ± 18	47 ± 38	.804
Classification of tumors			
Primary	10 (34.5)	114 (29.0)	.680
Recurrent	19 (65.5)	279 (71.0)	.680
Administration of denosumab			
Neoadjuvant therapy	29 (100)	393 (100)	**<.0001**
Localization of tumors			
Skull	1 (3.4)	1 (0.3)	.133
Trunk	0	3 (0.8)	1.0
Spine	1 (3.4)	44 (11.2)	.234
Pelvic	0	3 (0.8)	1.0
Sacrum	3 (10.3)	63 (16.0)	.455
Upper limb	1 (3.4)	51 (13.0)	.155
Lower limb	2 (6.9)	79 (20.1)	.090
Unknown	21 (72.4)	149 (37.9)	**.0003**
Course of treatment			
Progression of the tumor	25 (86.2)	0	**<.0001**
Tumor shrinkage	4 (13.8)	56 (14.2)	1.0
Lung metastasis	2 (6.9)	12 (3.1)	.249
Sarcoma	1 (3.4)	2 (0.5)	.193
Outcome of treatment			
Response to denosumab	0	383 (97.5)	**<.0001**
Nonresponse to denosumab	29 (100)	0	**<.0001**
Loss of evaluation	2 (10.5)	10 (2.5)	.196
Case series	**Cohort 1 studies** **Author, n = No. of patients**	**Cohort 2 studies** **Author, n = No. of patients**	
	Zhang et al,[60] n = 3 Akel et al,[64] n = 1 Chinder et al,[66] n = 18 Sambri et al,[69] n = 7 Jia et al,[72] n = 12 Li et al,[73] n = 1 Puri et al,[75] n = 12 Tsukamoto et al,[67] n = 16 Niu et al,[76] n = 5 Agarwal et al,[77] n = 11 Scoccianti et al,[78] n = *5* Yang et al,[79] n = 4 Chen et al,[81] n = 3 Rutkowski et al,[82] n = 19 Errani et al,[83] n = 15 Rekhi et al,[94] n = 5	Boriani et al,[44] n = 8 Zhang et al,[60] n = 8 Reddy et al,[61] n = 2 Akel et al,[64] n = 1 Chinder et al,[66] n = 24 Sambri et al,[69] n = 19 Jia et al,[72] n = 19 Li et al,[73] n = 124 Puri et al,[75] n = 29 Tsukamoto et al,[67] n = 14 Niu et al,[76] n = 13 Agarwal et al,[77] n = 14 Scoccianti et al,[78] n = 7 Yang et al,[79] n = 2 Luo et al,[80] n = 7 Chen et al,[81] n = 18	

(continued)

Table 3. (continued)

Case series	Cohort 1 studies Author, n = No. of patients	Cohort 2 studies Author, n = No. of patients	
	Müller et al,[96] n = 6 Goldschlager et al,[108] n = 1	Rutkowski et al,[82] n = 70 Errani et al,[83] n = 15 Ji et al,[86] n = 3 Deveci et al,[93] n = 13 Rekhi et al,[94] n = 22 Müller et al,[96] n = 19 Traub et al,[98] n = 20 Goldschlager et al,[108] n = 4	
Descriptions	**Cohort 1, N (%)**	**Cohort 2, N (%)**	***P* value**
Total number of patients	**144 (100)**	**477 (100)**	
Male/female	63 (43.8)/81 (56.2)	222 (46.9)/255 (53.1)	.624
Mean age ± SD years	29 ± 6	32 ± 8	.273
Treatment with denosumab			
Mean duration of treatment ± SD months	9 ± 5	12 ± 8	.348
Mean follow-up ± SD months	32 ± 21	36 ± 26	.516
Classification of tumors			
Primary	123 (85.4)	415 (87.0)	.729
Recurrent	21 (14.6)	62 (13.0)	.729
Administration of denosumab			
Pre- and postoperative	17 (11.8)	20 (4.2)	**.002**
Neoadjuvant therapy	125 (86.8)	439 (92.0)	.817
After surgery	2 (1.4)	18 (3.8)	.188
Localization of tumors			
Skull	0	7 (1.5)	.210
Trunk or lung	0	32 (6.7)	**.002**
Spine	13 (9.0)	45 (9.4)	1.0
Pelvic	12 (8.3)	49 (10.3)	.529
Sacrum	16 (11.1)	75 (15.7)	.182
Upper limb	36 (25.0)	102 (21.4)	.424
Lower limb	67 (46.5)	167 (35.0)	**.014**
Course of treatment			
Lack of response to denosumab	5 (3.5)	0	**.0006**
Recurrence of tumor	139 (96.5)	0	**<.0001**
Tumor shrinkage	0	92 (19.3)	**<.0001**
Tumor free	0	49 (10.3)	**.0001**
Lung metastasis	1 (0.7)	6 (1.3)	.696
Sarcoma	3 (2.1)	0	**.012**
Outcome of treatment			
Response to denosumab	0	475 (98.5)	**<.0001**
Nonresponse to denosumab	144 (100)	0	**<.0001**
Loss of evaluation	0	2 (0.4)	1.0

Case reports	Cohort 1 studies Author	Cohort 2 studies Author
	von Borstel et al[90] Tsukamoto et al[92] Matcuk et al[106]	Bilgetekin et al[62] Xará-Leite et al[65] Marinova et al[68] Kinoshita et al[70] Osaka et al[71] Liu et al[74] Wu et al[84] Law et al[85] Satcher et al[87] Yonezawa et al[89] Bardakhchyan et al[91]

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Table 3. (continued)

Case reports	**Cohort 1 studies** **Author**	**Cohort 2 studies** **Author**	
		Menon et al[95] Inoue et al[97] Cavalcante et al[99] Yamagishi et al[100] Kajiwara et al[101] Nakazawa et al[102] Setsu et al[103] Aponte-Tinao et al[104] Park et al[105] Vaishya et al[107] Gossai et al[109] Watanabe et al[110] Mattei et al[111] Hakozaki et al[112] Aghaloo et al[113] Rossi et al[114] Akaike et al[115]	
Descriptions	**Cohort 1, N (%)**	**Cohort 2, N (%)**	***P* value**
Total number of patients	**3 (100)**	**28 (100)**	
Male/female	1 (33.3)/2 (66.7)	16 (57.1)/12 (42.9)	.576
Mean age ± SD years	27 ± 2	28 ± 12	.639
Treatment with denosumab			
Mean duration of treatment ± SD months	11 ± 10	13 ± 8	.459
Mean follow-up ± SD months	75 ± 84	21 ± 12	.615
Classification of tumors			
Primary	0	23 (82.1)	**.012**
Recurrent	3 (100)	5 (17.9)	**.012**
Administration of denosumab			
Pre- and postoperative	0	2 (7.1)	1.0
Neoadjuvant therapy	2 (66.7)	22 (78.6)	1.0
After surgery	1 (33.3)	4 (14.3)	.422
Localization of tumors			
Skull	0	2 (7.1)	1.0
Spine	0	9 (32.1)	1.0
Pelvic	0	2 (7.1)	1.0
Sacrum	1 (33.3)	4 (14.3)	.422
Upper limb	2 (66.7)	2 (7.1)	**.037**
Lower limb	0	9 (32.1)	.537
Lung	0	1 (3.6)	1.0
Course of treatment			
Tumor progression	2 (66.7)	0	**.006**
Tumor recurrence	1 (33.3)	0	.097
Tumor shrinkage	0	11 (39.3)	.290
Tumor free	0	15 (53.6)	.226
Lung metastasis	1 (33.3)	0	.968
Sarcoma	1 (33.3)	1 (3.6)	.187
Death from other cancers	1 (33.3)	0	.097
Outcome of treatment			
Response to denosumab	0	28 (100)	**.0002**
Non-response to denosumab	3 (100)	0	**.0002**

Abbreviation: SD, standard deviation

[a]The majority of study participants were women, and the median age was 30. There was no significant difference in the duration of treatment and follow-up time. The classification of tumors as primary and recurrent only had statistical significance in the case reports. Denosumab was administered in most cases as neoadjuvant therapy. The most common localization of giant cell tumors of bone was the lower limb, with statistical significance only in case series studies, followed by the upper limb with statistical significance only in case reports, and sacral bone with no statistical significance in any study group. Tumor progression was statistically more frequent in the open-label phase II studies and case reports. Nonresponse to treatment with denosumab and an increased incidence of recurrence with denosumab were statistically more frequent in case series studies. Only in the case series studies could tumor shrinkage or even no evidence of tumor be documented. A statistically significant response rate was found in at least 97.5% of the tumors after treatment with denosumab in the open-label phase II studies.

[b]Significant *P* values, the total number of participants, each heading in bold.

Table 4. Adverse Events With the Use of Denosumab for Treatment of Patients With GCTB, Across Open-Label Phase II Studies, Case Series Studies, and Case Reports.[a,b]

Side effects of denosumab	Cohort 1 N (%)	Cohort 2 N (%)	*P* value
Open-label phase II studies	**29 (100)**	**393 (100)**	
Serious adverse events	1 (3.4)	46 (11.7)	.230
Hypophosphatemia	1 (3.4)	11 (2.8)	1.0
Osteonecrosis of the jaw	6 (20.7)	7 (1.8)	**<.0001**
Peripheral neuropathy	0	6 (1.5)	1.0
Skin rash	0	5 (1.3)	1.0
Pathological bone fracture	1 (3.4)	4 (1.0)	.301
Anemia	1 (3.4)	4 (1.0)	.301
Pain in the limbs	1 (3.4)	4 (1.0)	.301
Back pain	1 (3.4)	2 (0.5)	.193
Hypocalcemia	0	2 (0.5)	1.0
Case series	**144 (100)**	**477 (100)**	
Pain in the limbs	1 (0.7)	61 (12.8)	**<.0001**
Fatigue	1 (0.7)	35 (7.3)	**.004**
Headache	0	30 (6.3)	**.003**
Back pain	0	27 (5.7)	**.004**
Hypocalcemia	6 (4.2)	17 (3.6)	.801
Serious adverse events	3 (2.1)	10 (2.1)	1.0
Osteonecrosis of the jaw	3 (2.1)	6 (1.3)	.692
Pathological bone fracture	2 (1.4)	6 (1.3)	1.0
Hypophosphatemia	1 (0.7)	5 (1.0)	1.0
Abscess	2 (1.4)	0	.053
Periodontal disease	2 (1.4)	0	.053
Anemia	0	2 (0.4)	1.0
Case reports	**3 (100)**	**28 (100)**	
Back pain	1 (33.3)	0	.097
Parathyroid adenoma	1 (33.3)	0	.097
Hypocalcemia	0	2 (7.1)	1.0
Hypercalcemia	0	1 (3.6)	1.0
Osteonecrosis of the jaw	0	1 (3.6)	1.0
Hypophosphatemia	0	1 (3.6)	1.0
Pathological bone fracture	0	1 (3.6)	1.0

Abbreviation: GCTB, giant cell tumors of bone.
[a]Serious adverse events were the most reported side effect of denosumab, mainly in cohort 2, but without statistical significance. Side effects such as osteonecrosis of the jaw were most common in open-label studies for cohort 1 participants; pain in the limbs, fatigue, headache, and back pain were most common in case series studies for cohort 2 participants.
[b]Significant *P* values, the total number of participants, each heading in bold.

Table 5. Type of Surgical Treatment and Embolization of Patients With GCTB Divided Across Open-Label Phase II Studies, Case Series Studies, and Case Reports.[a,b]

Surgery procedures	Cohort 1 N (%)	Cohort 2 N (%)	*P* value
Open-label phase II studies	**29 (100)**	**393 (100)**	
Curettage	1 (3.4)	15 (3.8)	1.0
En bloc resection	2 (6.9)	36 (9.2)	1.0
En bloc excision	0	4 (1.0)	1.0
Marginal excision	0	2 (0.5)	1.0
Joint or prosthesis replacement	0	24 (6.1)	.245
Amputation	1 (3.4)	14 (3.6)	1.0
Hemipelvectomy	1 (3.4)	4 (1.0)	.301
Postcurettage	0	11 (2.8)	.623
Major surgery	0	3 (0.8)	1.0
No surgery	19 (65.5)	152 (38.7)	**.006**
Unclear resection	5 (17.2)	125 (31.8)	.143
Other	0	3 (0.8)	1.0
Case series	**144 (100)**	**477 (100)**	
Curettage	112 (77.8)	193 (40.5)	**<.0001**
En bloc resection	18 (12.5)	95 (19.9)	.058
Intralesional excision	0	2 (0.4)	1.0
Marginal excision	1 (0.7)	2 (0.4)	1.0
Joint or prosthesis replacement	0	5 (1.0)	.351
Amputation	0	1 (0.2)	1.0
Spondylectomy	12 (8.3)	20 (4.2)	.079
No surgery	0	28 (5.9)	**.006**
Unclear resection	1 (0.7)	131 (27.5)	**<.0001**
Other therapeutic methods			
Embolization	8 (5.6)	29 (6.1)	1.0
Case reports	**3 (100)**	**28 (100)**	
Curettage	0	8 (28.6)	.550
En bloc resection	0	7 (25.0)	.570
Joint or prosthesis replacement	1 (33.3)	3 (10.7)	.349
Amputation	1 (33.3)	1 (3.6)	.187
Spondylectomy	0	3 (10.7)	1.0
Postcurettage	1 (33.3)	0	.097
Post-incomplete surgical resection	0	1 (3.6)	1.0
No surgery	0	5 (17.9)	1.0
Other therapeutic methods			
Embolization	2 (66.7)	3 (10.7)	.060

Abbreviation: GCTB, giant cell tumors of bone.
[a]Curettage was the most common type of surgery, followed by en bloc resection. The difference was only statistically significant in the case series studies.
[b]Significant *P* value, the total number of participants, each heading in bold.

and substances to stop the progression of disease when conventional treatment measures are no longer effective.

Giant cell tumors of bone may well metastasize to the lungs.[117] One study examined the risk factors for lung metastasis of GCTB according to therapeutic measures and a reasonable follow-up time.[117] This early study treated participants with only surgery and radiotherapy, and lung metastasis occurred in 29.3% of the 141 participants.[117] This early study reported local recurrences and metastases of GCTB within 3 years after the first surgery; therefore, the authors of the study recommended regular imaging of the original location and the chest in patients with GCTB after the first surgical treatment and for at least 3 years after surgery.[117] In particular, the study by Errani et al noted that, after surgery, denosumab was associated with a potentially higher rate of recurrence.[118] This meta-analysis illustrated the lower frequency of a 2% rate of lung metastasis in GCTB in some open-label phase II studies, case series studies, and case reports, as well as an already existing colonization of the lungs with GCTB in 31 cases in cohort 2. Significantly fewer cases of lung metastasis were evident after treatment with denosumab compared with the finding of this early study by Errani et al.[118]

Giant cell tumors of bone occurs predominantly in young middle age and more commonly among women. The data of this assessment agree with those from large-scale published case series studies; however, it refutes the data of some other studies.[11,12,44,60-116]

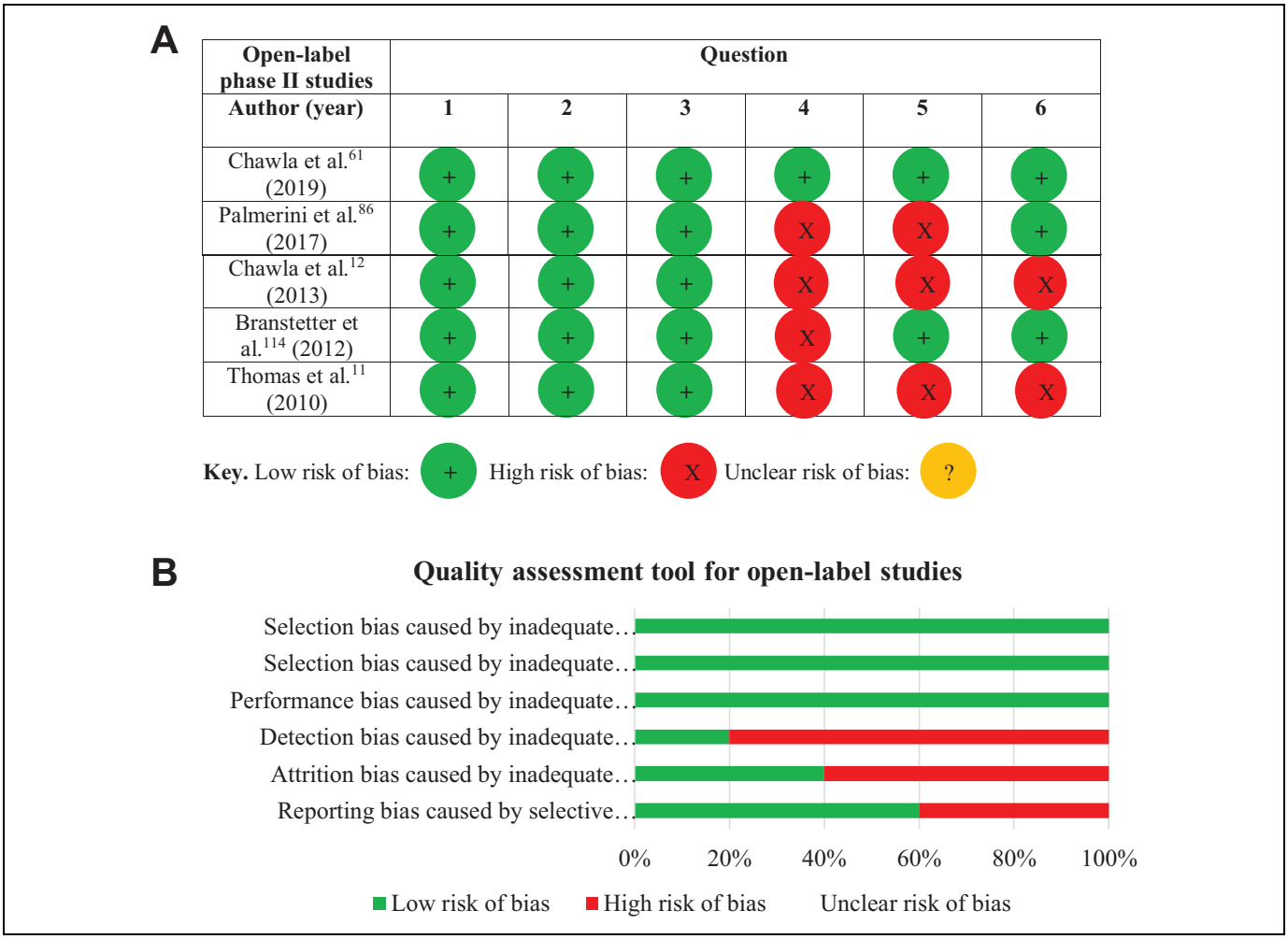

Figure 3. A, Quality assessment tool for nonrandomized, uncontrolled, open-label phase II studies. Key. Low risk of bias: + High risk of bias: X Unclear risk of bias: ?. B, Quality assessment tool for nonrandomized, uncontrolled, open-label phase II studies. Question 1: Selection bias caused by inadequate selection of participants. Question 2: Selection bias caused by inadequate confirmation and consideration of confounding variables. Question 3: Performance bias caused by inadequate measurements of intervention. Question 4: Detection bias caused by inadequate blinding of outcome assessment. Question 5: Attrition bias caused by inadequate handling of incomplete outcome data. Question 6: Reporting bias caused by selective outcome reporting.

Similar to this meta-analysis and compared with a Swedish one, the number of patients with osteosarcoma was small.[119] In the Swedish study, the number of patients with osteosarcoma was small compared to previous data from the Swedish Cancer Register.[119] This may be explained by changes in diagnostic evaluation and by the introduction of a multidisciplinary investigation of GCTB over the years.[119]

The latest clinical studies have reported that denosumab treatment has a good tumor response rate in patients with GCTB. However, these studies, which were cited in this research, reported on patients who were still undergoing denosumab treatment or on patients who had undergone denosumab treatment but had only a brief follow-up.[11,12,44,60-116] Other studies described a newly formed bone matrix and thickened cortical bone after treatment with denosumab.[116] In some cases, following denosumab treatment, the surgeon would not allow the true size of the GCTB to be determined,[118] which probably increased the risk of local recurrence.

After treatment with denosumab, the tumor partially calcifies, and the periphery of the tumor ossifies.[44] However, tumor cells can remain in this ossified tissue. If the operation performed is an intralesional resection, residual tumor may hide in the periphery, which might result in a higher recurrence rate.[44] However, if an *en bloc* resection is performed, the entire tumor is excised and no tumor cells should be left behind.[44] For this reason, denosumab is increasingly accepted as a neoadjuvant in the spine, where *en bloc* resection is the preferred treatment when acceptable morbidity is expected.[44]

An important point to note is that 9 cases of malignant transformation of GCTB during treatment with denosumab, without prior radiation treatment, have been reported in the literature.[118] Inhibition of RANKL has been reported to

Figure 4. A, Quality assessment tool for case series studies. Key. Yes; Low risk of bias: + No; High risk of bias: X Unclear risk of bias: ?. B, Quality assessment tool for case series studies. Question 1: Were clear inclusion criteria established for the case series study? Question 2: Was the condition measured in a standard, reliable way for all participants? Question 3: Were valid methods used for identification of the participants' conditions? Question 4: Did the case series study have a consecutive inclusion of participants? Question 5: Did the case series study have complete inclusion of participants? Question 6: Was there clear reporting of the participants' demographics? Question 7: Was there clear reporting of the participants' clinical information? Question 8: Were the outcomes or follow-up results of cases clearly reported? Question 9: Was there clear reporting of the demographic information of the presenting clinics? Question 10: Was the statistical analysis conducted appropriately?

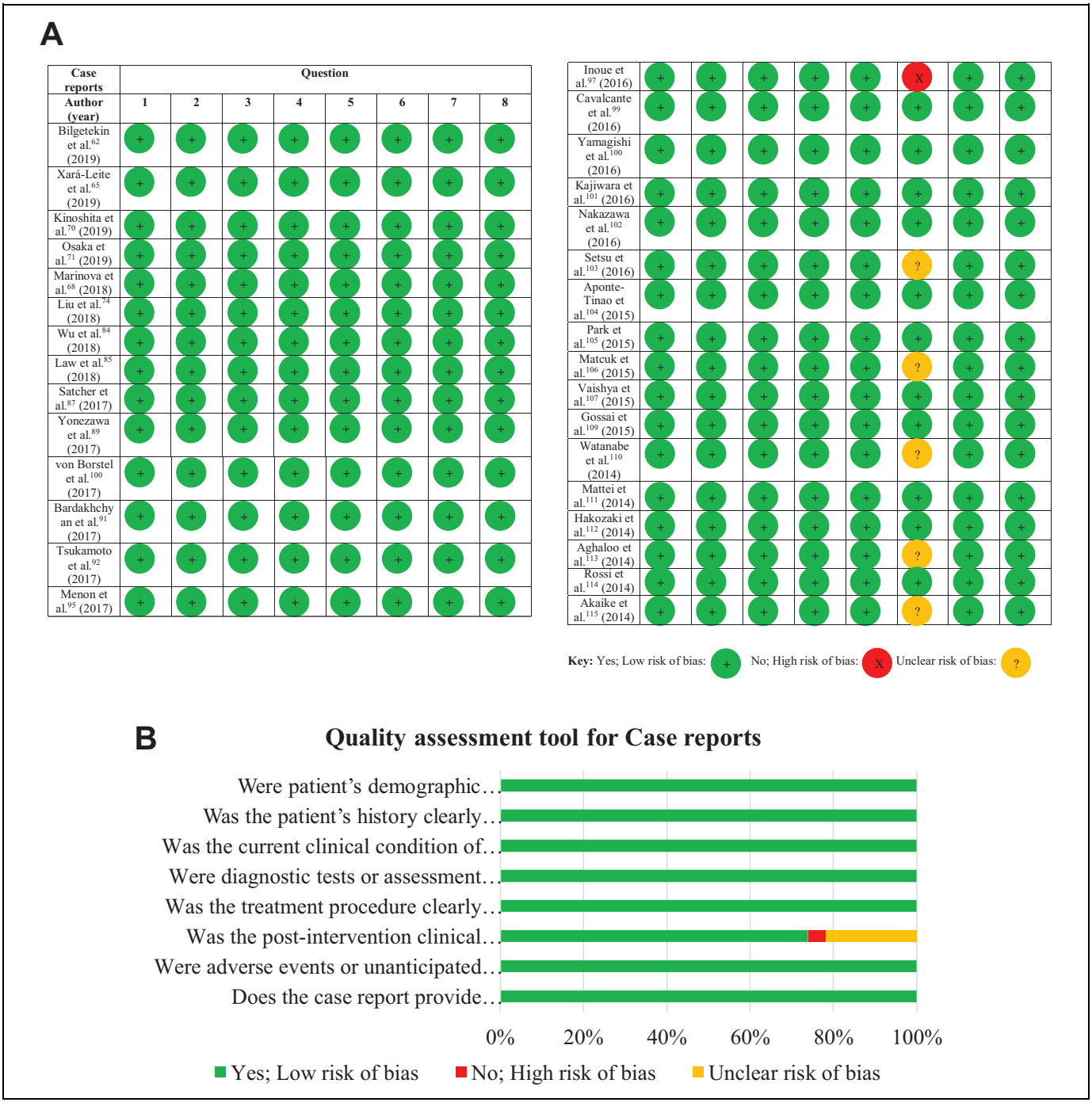

Figure 5. A, Quality assessment tool for case reports. Key: Yes; Low risk of bias: + No; High risk of bias: X Unclear risk of bias: ?. B, Quality assessment tool for case reports. Question 1: Were participant demographic characteristics clearly described? Question 2: Was each participant's history clearly described and presented as a timeline? Question 3: Was the presenting clinical condition of the participants clearly described? Question 4: Were diagnostic tests or assessment methods and the results clearly described? Question 5: Was the treatment procedure clearly described? Question 6: Was the postintervention clinical condition clearly described? Question 7: Were adverse events or unanticipated events identified and described? Question 8: Does the case report provide any takeaway lessons?

increase the risk of new malignant diseases (eg, osteosarcoma) because of immunosuppression.[91,118]

The most common location of GCTB on participants from all study types in this evaluation was the lower limbs, followed by the upper limbs and sacrum, which is in agreement with the data of another study.[120] Statistical significance for the appearance of the GCTB on different parts of the body was only observed in the lower limbs ($P = .014$), trunk and lung ($P = .002$) in case series studies, and in the upper limb ($P = .037$) in case reports in this investigation. The duration of treatment

with denosumab did not differ significantly among the reviewed studies. As was also concluded in a previously published review, optimal treatment duration remains unclear.[121]

Denosumab was mainly used as a neoadjuvant therapy in participants with GCTB in studies that were then analyzed for this evaluation. The use of denosumab as a preoperative or adjuvant treatment in patients with GCTB will still require clinical studies to gain further insights about its efficacy.[122]

The occurrence of side effects was comparatively low in this study. The most common statistically significant side effect was osteonecrosis of the jaw in the open-label phase II studies, followed by pain in the limbs, fatigue, headache, and back pain in the case series studies (Table 3). However, whether the pain in the limbs represented a drug side effect or a symptom of GCTB in individual cases can only be determined by a tentative discontinuation of denosumab. In cases of adverse effects of the drug, including any side effects not listed in the accompanying leaflet, denosumab was discontinued in participants. The most common symptom of GCTB was pain; however, distinguishing between pain in the limbs due to the tumor and pain possibly caused by denosumab was difficult. Another study indicated that the most common side effects of denosumab, when used to treat patients with other types of cancer, were infection, pain in the limbs, arthralgia, bone pain, and fatigue.[123] The malignancies assessed in that study were bone events from breast and prostate cancer[123]; one serious side effect included infections requiring hospitalization.[123] In the same study, the most common side effects of denosumab in the treatment of patients with osteoporosis were arthralgia, nasopharyngitis, back pain, and headaches.[123] In another study, the most common side effects of denosumab in the treatment of patients with osteoporosis were back pain, pain in the limbs, musculoskeletal pain, and cystitis.[123] Serious but rare side effects reported in that research included the development of severe infections, dermatological changes, and hypocalcemia.[124] The other side effects frequently reported in this meta-analysis regarding the use of denosumab in the treatment of patients with GCTB were pain in the limbs, serious adverse events, fatigue, back pain, and headache (Table 3). The side effects seen published in the medical literature did not seem to depend on the underlying disease. Denosumab should therefore be considered in patients with GCTB who cannot tolerate other therapies or have adherence problems or contraindications for other therapies. Comparison of the adverse effects of denosumab had severe limitations. Patients with metastatic GCTB are generally much more ill when compared with patients with primary GCTB. Therefore, the seriously ill patients with GCTB maybe received a much lower dose of denosumab.

The present meta-analysis was compared with a systematic review of denosumab in the treatment of GCTB published on March 15, 2019 by Luengo-Alonso et al,[125] which included a total of 19 studies involving an overall total of 1095 patients. The present work is a meta-analysis of 60 studies with 1074 patients analyzed. The proportion of women was greater than that of men in both analyses. The patient ages were not significantly different between the 2 analyses. The recurrence rate of GCTB was 9% in the study by Luengo-Alonso et al; whereas the recurrence rates in the current meta-analysis were as high as 96.5%. The metastasis rate was less than 2% in the current analysis, compared to 3% in the Luengo-Alonso et al analysis.[125] The adverse effects of denosumab also differed in the 2 reviews, as the most common adverse events were fatigue and muscle pain in the study by Luengo-Alonso et al,[125] while there were pain in the limbs, serious adverse events, fatigue, back pain, and headache in the current meta-analysis. The response rate of 97.5% to 100% determined in the current meta-analysis for therapy with denosumab indicated that the drug was very effective. By contrast, Luengo-Alonso et al[125] reported an estimated radiologic response of 66% to 100% for their patients. The slight differences between the 2 analyses may be due to the types of studies reviewed. The current meta-analysis included open-label phase II studies, case series studies, and case reports. There were also differences in the study design. Of the 19 studies reviewed by Luengo-Alonso et al, 11 were also included in the current analysis. The differences in studies chosen was probably due to different inclusion and exclusion criteria. Luengo-Alonso et al examined only studies reported from 2000 onward, and this current meta-analysis has not restricted studies done previous to 2000.

The use of denosumab as an adjuvant therapy in nonresectable GCTB in both analyses revealed positive and distinct histologic changes with consistent radiographic changes, regardless of the various types of adverse drug reactions. Positive clinical responses to denosumab were pain relief and a decrease in the morbidity of surgical procedures. Lastly, the oncological results differed when using denosumab as an adjuvant treatment for nonresectable GCTB and did not affect either lung metastasis or local recurrence rates in either analysis.

Study Limitations

The studies examined in this analysis were open-label phase II studies, case series studies, and case reports. The 2 approval trials for denosumab for patients with GCTB referred to in this review were open-label phase II studies.[11,12] Randomized placebo-controlled trials are lacking for the use of denosumab in the treatment of patients with GCTB. Therefore, a summary of up-to-date results seems useful. Nevertheless, the studies that have been conducted thus far are small and have been performed in varied clinical settings. They are also very heterogeneous, and their results have been simplified in this work. Denosumab treatment has been established as a suppressive therapy for GCTB; its effectiveness has also been confirmed here. However, denosumab drug therapy is not curative and is therefore only recommended for inoperable tumors. The duration of therapy with this drug remains unclear; however, it must be assumed to be lifelong, as local recurrences are often described after discontinuation of therapy. In any case, surgery remains the gold standard therapy for GCTB. Denosumab as a preoperative therapy is an interesting new concept that could simplify operations. However, some findings indicate that this

procedure increases the postoperative local recurrence rate, as tumor cells survive in newly formed bone and are thus more difficult to reach during curettage. For this reason, denosumab is still not accepted as a standard preoperative treatment.

Studies on pure suppression therapy and on the effectiveness of denosumab in combination with various other therapies, including surgery and embolization, are included in this meta-analysis. For this reason, the response behavior of denosumab was pooled and generalized for comparison with the results of this study design. The clinical setting and the accompanying therapies can have an equally important influence on the outcome and may not have been statistically noted.

The implementation of placebo-controlled studies for denosumab in patients with GCTB would certainly not be allowed for ethical reasons because of the severity of the disease. The open-label phase II studies examined in this study had a high risk of bias because of insufficient blinding of the outcome assessment and insufficient handling of incomplete outcome data (Figure 3). By comparison, some case series studies showed a high risk of bias for incomplete inclusion of participants and insufficient reporting of the results and statistical analysis (Figure 4). Only one study had an increased risk of bias for unclear description of the postinterventional clinical situation of a case report (Figure 5). Long-term outcomes are lacking for patients with GCTB treated with this drug. However, the heterogeneity of studies has been considered in the analyses and interpretation of the results, mainly because the evaluation of study quality as a whole illustrated a low general risk of bias across all study types.

Of a total of 60 studies considered for this meta-analysis, 14 (23.3%) were supported by funding. Of the open-label studies, 4 (80%) of 5 studies had financial support; 7 (29.2%) from a total of 24 case series studies; and 3 (9.7%) from a total of 31 case reports (Table 1).

One significant note is that 459 (42.7%) of the 1074 study participants for this meta-analysis came from the same cohort funded by Amgen, and this may have led to significant bias, so this meta-analysis may not be able to provide new information.

The response evaluation criteria in solid tumors (RECIST) used in some analyzed studies and in this meta-analysis also have potential limitations and may not be the best tool for assessing GCTB response to denosumab.[37] As former studies have already demonstrated, denosumab does not eliminate tumor cells.[44] Therefore, it is not a curative treatment but a disease-fighting treatment. It is extremely rare to receive a full RECIST response. Clinically, tumor calcification and ossification of the cortex with variable reduction in tumor size are observed.[44]

Conclusions

This meta-analysis found very little difference between participants with tumor progression, referred to as cohort 1, compared to patients with good response to denosumab, referred to as cohort 2. Approximately 17% of participants did not respond after treatment with denosumab, and the disease progressed. The evidence provided by this meta-analysis did not fully support the use of denosumab as an adjuvant therapy to reduce GCTB size, clinical symptoms, or mortality. This current study also did not really address the role of GCTB surgery and did not limit the data to cases where complete resection of GCTB with acceptable morbidity was possible. The majority of participants in cohorts 1 and 2 in the clinical trials were classified as having nonresectable GCTB. The results of this analysis showed significant limitations in view of the low number of patients with GCTB progression and the bias in reporting and publishing case reports. The evidence was insufficient to support the idea that patients with unresectable GCTB could be cured after using denosumab in addition to surgery. However, treatment with denosumab may allow long-term control of the tumor. In addition, the long-term control in the case reports and series studies was too limited to assess denosumab as a potential remedy. In this meta-analysis, denosumab was determined to be helpful in reducing tumor size and bone complications in patients with advanced GCTB. Following an approval extension of denosumab, several drug-related adverse effects were observed in patients with GCTB who received denosumab as drug therapy. The use of denosumab showed a good response rate in the treatment of GCTB. As with any new treatment, enthusiasm should go hand in hand with great vigilance.

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.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD


Josef Yayan, MD https://orcid.org/0000-0002-8363-621X

Supplemental Material

Supplemental material for this article is available online.

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