

Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study



David Thomas, Robert Henshaw, Keith Skubitz, Sant Chawla, Arthur Staddon, Jean-Yves Blay, Martine Roudier, Judy Smith, Zhishen Ye, Winnie Sohn, Roger Dansey, Susie Jun

Summary

Background Giant-cell tumour (GCT) of bone is a primary osteolytic bone tumour with low metastatic potential and is associated with substantial skeletal morbidity. GCT is rich in osteoclast-like giant cells and contains mononuclear (stromal) cells that express RANK ligand (RANKL), a key mediator of osteoclast activation. We investigated the potential therapeutic effect of denosumab, a fully human monoclonal antibody against RANKL, on tumour-cell survival and growth in patients with GCT.

Methods In this open-label, single-group study, 37 patients with recurrent or unresectable GCT were enrolled and received subcutaneous denosumab 120 mg monthly (every 28 days), with loading doses on days 8 and 15 of month 1. The primary endpoint was tumour response, defined as elimination of at least 90% of giant cells or no radiological progression of the target lesion up to week 25. Study recruitment is closed; patient treatment and follow-up are ongoing. The study is registered with Clinical Trials.gov, NCT00396279.

Findings Two patients had insufficient histology or radiology data for efficacy assessment. 30 of 35 (86%; 95% CI 70–95) of evaluable patients had a tumour response: 20 of 20 assessed by histology and 10 of 15 assessed by radiology. Adverse events were reported in 33 of 37 patients; the most common being pain in an extremity (n=7), back pain (n=4), and headache (n=4). Five patients had grade 3–5 adverse events, only one of which (grade 3 increase in human chorionic gonadotropin concentration not related to pregnancy) was deemed to be possibly treatment related. Five serious adverse events were reported although none were deemed treatment related.

Interpretation Further investigation of denosumab as a therapy for GCT is warranted.

Funding Amgen, Inc.

Introduction

Giant-cell tumour (GCT) of bone is a primary osteolytic bone tumour of low metastatic potential with a propensity for metastasis to the lung.¹ GCT is a rare tumour that is slightly more prevalent in women than in men (1.5 to one ratio),² and typically occurs in skeletally mature individuals, with 50% of cases in the region of the knee and other long bones.^{3,4} Radiographically, GCT appears as an osteolytic lesion and often results in pathological fracture. Manifestations of GCT include localised pain, tenderness, swelling, and decreased joint motion. GCT lesions in the spine and sacrum may result in neurological deficits. Malignant GCT is rare at diagnosis;⁵ however, GCT may undergo malignant transformation after radiation therapy or several recurrences.

Surgery is the definitive therapy; about 80% of patients with primary GCT have tumours amenable to surgical resection. However, surgical intervention may cause substantial morbidity, and recurrence varies from 10% to 75% depending on the size and location of the lesion and the surgical intervention.^{6,7} Patients with surgically unsalvageable GCT because of multiple lesions, including distant metastases, or because of anatomical location (eg, spine) have limited treatment options. Arterial embolisation or radiation therapy are options,^{8–10} but radiation can lead to transformation of GCT of bone to

high-grade sarcoma, or to development of secondary malignancies.⁸ Although some patients live for a long time with pulmonary metastases, distant metastases of GCT typically do not respond well to chemotherapy and may lead to death.¹¹ Limited case reports and one retrospective case-control study have suggested that bisphosphonates reduce local recurrences after surgical treatment in the lower extremities and might induce apoptosis of giant cells and stromal cells within the tumour.^{12–14}

Histologically, GCT of bone consists of sheets of neoplastic ovoid mononuclear cells evenly interspersed with osteoclast-like giant cells.⁵ The osteoclast-like giant cells and their precursors express RANK, and some of the mononuclear cells (stromal cells) express RANK ligand (RANKL).¹⁵ RANKL is an essential mediator of osteoclast formation, function, and survival.^{16–19} It is possible that the recruitment of osteoclast-like giant cells is related to stromal-cell expression of RANKL,^{15,20} and that the giant cells are responsible for the aggressive osteolytic activity of the tumour.

Denosumab is a fully human monoclonal antibody that specifically inhibits RANKL,²¹ thereby inhibiting osteoclast-mediated bone destruction. Subcutaneous administration of denosumab provides rapid and sustained suppression of bone turnover in patients with multiple myeloma and osteolytic bone disease, and in patients with breast and

Lancet Oncol 2010; 11: 275–80

Published Online

February 10, 2010

DOI:10.1016/S1470-

2045(10)70010-3

See [Reflection and Reaction](#)

page 218

Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia (D Thomas FRACP); Washington Cancer Institute, Georgetown University School of Medicine, Washington, DC, USA (R Henshaw MD); Division of Hematology, Oncology, and Transplantation and Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA (Prof K Skubitz MD); Sarcoma Oncology Center, Santa Monica, CA, USA (S Chawla MD); University of Pennsylvania School of Medicine, Philadelphia, PA, USA (Prof A Staddon MD); Pennsylvania Hematology and Oncology Associates, Philadelphia, PA, USA (Prof A Staddon); University Claude Bernard Lyon I, Lyon, France (Prof J-Y Blay MD); Hôpital Edouard Herriot, Lyon, France (Prof J-Y Blay); Amgen Inc, Seattle, WA, USA (M Roudier MD); and Amgen Inc, Thousand Oaks, CA, USA (J Smith BA, Z Ye PhD, W Sohn PhD, R Dansey MD, S Jun MD)

Correspondence to:

Dr David Thomas, Peter MacCallum Cancer Centre, St. Andrews Place, East Melbourne 3002, VIC, Australia
david.thomas@petermac.org

	Number
Sex (male)	17
Ethnic origin (white)	27
GCT disease status	
Primary unresectable	13
Recurrent unresectable	18
Recurrent resectable	6
ECOG performance status of 0 or 1	34
Percent giant cells in tumour on baseline biopsy*	30.0 (20.0–40.0)
Locations of largest lesion*	
Pelvis	10
Spine or sacrum	4
Lung	9
Lower extremity	8
Upper extremity	5
Prior GCT therapies	
Surgery	28
Radiation	8
Chemotherapy	6
Intravenous bisphosphonates	5
Oral bisphosphonates	1
Interferon	2
Calcitonin	0

Data are n or median (IQR). GCT=giant-cell tumour. ECOG=Eastern Cooperative Oncology Group. *One patient did not have baseline radiological or biopsy assessments.

Table 1: Baseline demographics and disease characteristics (N=37)

prostate cancer with bone metastases.^{22–25} Inhibition of RANKL by denosumab in patients with GCT might inhibit bone destruction and eliminate giant cells. Here, we describe the safety and efficacy of denosumab in patients with recurrent or unresectable GCT.

Methods

Patients

Adult patients (18 years or older) were enrolled at eight centres in the USA, Australia, and Europe. Eligible patients had histologically confirmed GCT of bone with measurable GCT confirmed by radiology (≥ 10 mm in greatest dimension), that was recurrent or considered unresectable (eg, resection could not be done without nerve damage or substantial impairment of joint function). Patients had an Eastern Cooperative Oncology Group (ECOG) status of 0, 1, or 2. Key exclusion criteria included surgery to the affected limb or area planned within 28 days after the first dose of denosumab; radiation to the affected region within 28 days before enrolment; known diagnosis of osteosarcoma or brown tumour of bone; known history of second malignancy within the past 5 years (except for basal-cell carcinoma or cervical carcinoma in situ); previous treatment with denosumab; concurrent treatment with intravenous or oral bisphosphonates, calcitonin, or interferon alpha-2a; and pregnancy.

The study was approved by the institutional review board or ethics committee for each site, and all patients provided written informed consent.

Procedures

In this single-group, multicentre study, patients received subcutaneous injections of denosumab 120 mg monthly (every 28 days), with additional loading doses on days 8 and 15 of month 1. All patients were instructed to take daily supplements of calcium 500 mg and vitamin D 400 IU. No concomitant treatment for GCT of bone was allowed during the study. Patients were to continue to receive denosumab until one of the following occurred: complete tumour resection, disease progression without clinical benefit, or decision by the patient to discontinue for any reason.

Histopathological analyses of biopsy samples were done before and after treatment. Pretreatment biopsy was obtained, unless deemed clinically unacceptable, in which case the most recent biopsy was used. Post-treatment biopsies or resections were obtained for all patients between the fifth and ninth dose of denosumab (ie, months 3 and 7), unless the procedures were deemed clinically unsafe. Patients who had complete resections were discontinued from study treatment at the time of resection and followed up for long-term safety and overall survival.

Histological response to treatment was assessed by a central pathologist who had no contact with pathologists at the investigation sites and who was masked to patient number and time point on study. Between one and ten unstained slides of each paraffin-embedded biopsy were prepared at each investigation site and sent to Amgen (Thousand Oaks, CA, USA), where they were made anonymous, numbered, then shipped to another Amgen site (Seattle, WA, USA). Haematoxylin and eosin staining was used to determine the percentage of giant cells in the whole tumour area of the biopsy. Giant cells were defined as cells containing three or more separated nuclei. RANKL expression was detected by immunohistochemistry using an anti-human RANKL monoclonal antibody (M366, an IgG1 antibody developed at Amgen) at a concentration of 0.75 $\mu\text{g/mL}$, that has been characterised with western blot, flow cytometry, and immunohistochemistry specific for human RANKL.¹⁵ Staining was done by use of an automated machine (Universal Staining System Model LV-1, Dako North America Inc, Carpinteria, CA, USA).

For those who did not have evaluable tissue samples, disease status was assessed radiologically at each site, with progression defined as a 20% or more increase from baseline (change in single longest dimension) of the target lesion, as measured by CT or MRI. If this criterion for disease progression was met, the patient was discontinued from denosumab unless, in the opinion of the investigator, a clinical benefit was seen.

Physical examination, ECOG performance status, blood samples, and urinary N-telopeptide corrected by creatinine

(uNTx/Cr), were assessed on days 1 and 29 and every month thereafter. Anti-denosumab antibodies were measured by electrochemiluminescent bridging assay every 6 months. Spiral CT scan and MRI imaging were done every 3 months until the end of the study. PET imaging was done for additional assessment of tumour response. Adverse events were recorded at every visit (days 1, 8, 15, and 29; monthly until the end of treatment, and every 6 months for up to 2 years). Serum samples for assessment of denosumab trough concentrations were collected on days 8, 15, and 29, and at months 3, 4, 7, and 13.

The primary efficacy endpoint was the proportion of patients with a tumour response, defined as the following: 90% or greater elimination of giant cells relative to baseline after the fourth dose and before the ninth dose (between weeks 5 and 25); complete elimination of giant cells, in cases where giant cells represented less than 5% of tumour cells at baseline; or lack of radiological progression of the target lesion by week 25, as assessed by CT or MRI, in cases where histopathology was not available. Secondary endpoints included suppression of bone-turnover markers—including the percentage change from baseline in uNTx/Cr and serum C-telopeptide I (sCTX), adverse events, and incidence of serum anti-denosumab antibody formation. Investigator assessments of clinical benefit and bone repair were also reported. Observed mean and individual denosumab concentrations were summarised.

Statistical analysis

We assumed that a sample size of about 25 patients was needed to detect a response rate of 30%, assuming a null hypothesis rate of 11%, with 80% power and 5% significance level. In response to investigators' reports of clinical improvement during the course of the study, we did an interim analysis of the first 15 evaluable patients. Based on the results of the interim analysis, and increasing requests for access to denosumab for GCT, we planned to open a follow-on study to allow patients with GCT expanded access to denosumab. We increased the sample size of the current study to about 35 patients, to provide access to denosumab for patients with GCT until we were able to open the follow-on study.

A successful result was defined as an observed tumour response in 23% (eight of 35 patients) or more. If the true response rate was 30% or higher, the probability of concluding that denosumab was efficacious was greater than 85%. If the true response rate was 11% or lower, the probability of concluding that denosumab was efficacious was less than 5%. Efficacy analyses included all patients who had histological or radiological assessments at baseline and at least one post-treatment visit between months 2 and 7. Safety analyses included all patients who received at least one dose of denosumab.

Percent changes from baseline in uNTx and sCTX were reported as median (IQR); statistical significance of the change at 2 months was calculated using the Sign test. Summary statistics for trough serum-denosumab

concentrations were calculated with WinNonlin version 5.1.1. Denosumab serum concentrations below the lower limit of quantification or below quantifiable limits were converted to zero for the calculation of summary statistics. This study is registered with ClinicalTrials.gov, number NCT00396279.

Role of the funding source

The sponsor designed this study in collaboration with the investigators. The sponsor developed the protocol and statistical analysis plan, provided the study drug, coordinated the activities of study sites, did the statistical analysis, participated in the interpretation of data, and provided writing assistance. Data were collected by the investigators. All authors contributed intellectually to the content of the manuscript, had full access to the data, and vouch for the completeness and accuracy of the data and analyses. The corresponding author had the final responsibility to submit for publication.

Results

37 patients, median age 30 years (range 19–63), were enrolled between July 10, 2006, and Jan 25, 2008. 13 patients had primary unresectable GCT, 18 had recurrent unresectable GCT, and six had recurrent resectable GCT (table 1). The most common sites for GCT lesions included the pelvis, lungs, and lower extremities. Nine patients had recurrent lesions in the

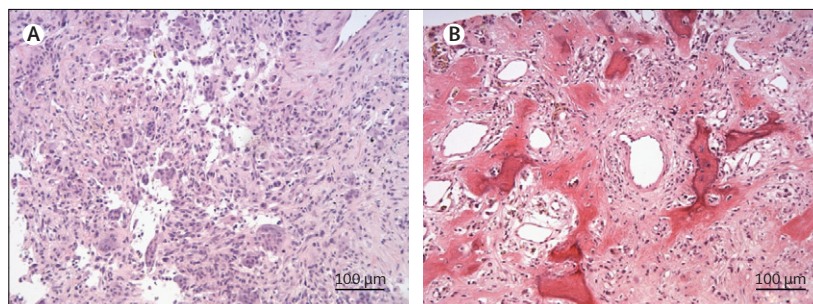


Figure 1: Pretreatment (A) and week 13 post-treatment biopsy (B)
Cells stained with haematoxylin and eosin.

	Number of events	Grade
Events reported		
Acute respiratory distress syndrome	1	4
Ankle fracture	1	4
Back pain	1	3
Increased human chorionic gonadotropin in blood	1	3
Bone sarcoma	1	3
Dyspnoea	1	3
Lower respiratory tract infection	1	3
Metastases to lung	1	5
Nausea	1	3

Table 2: Grade 3, 4, and 5 adverse events reported during the study (N=37)

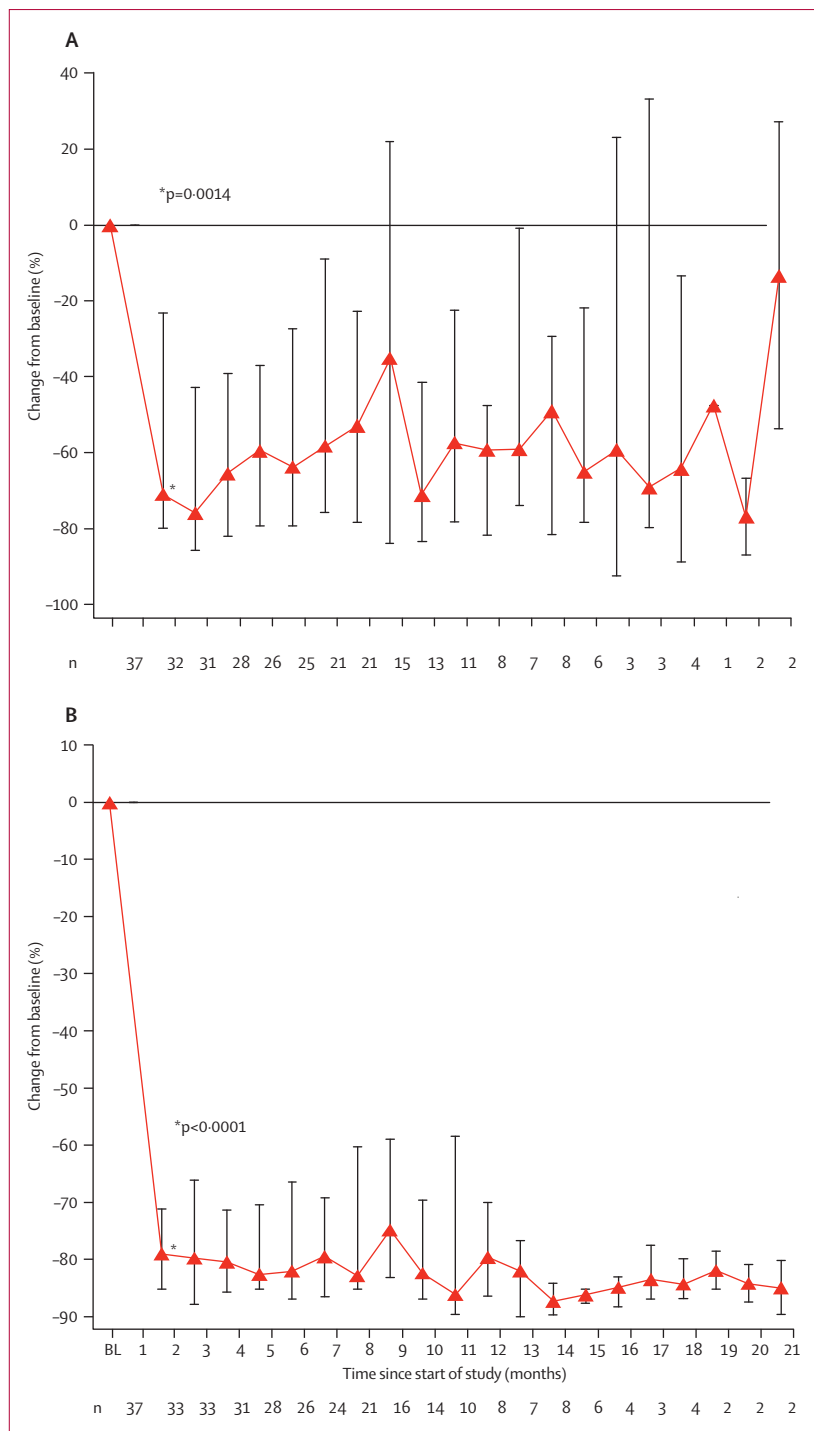


Figure 2: Effect of denosumab on the concentration of urinary N-telopeptide (A) and serum C-telopeptide I (B) over time

Points are median value, error bars are IQR. BL= Baseline.

lung. The most commonly used concomitant medications were calcium and vitamin D supplements.

Although enrolment has finished, the study is ongoing, with patients being treated and followed up for survival.

All 37 patients were included in safety analyses; 35 were assessed for efficacy (20 by histopathology, 15 by radiology; two patients had insufficient histology or radiology data; one of these patients showed no giant cells on review of the baseline biopsy and a subsequent biopsy after denosumab treatment also showed no giant cells). Seven patients had tumour resection and completed the study. Four patients discontinued before completion of planned treatment: two because of disease progression of a malignant GCT, one for an administrative decision, and one withdrew consent.

30 of 35 patients (86%; 95% CI 70–95) met the tumour response criteria at 25 weeks. Figure 1 shows a typical example of elimination of giant cells after denosumab treatment. All 20 patients assessed by histology had a tumour response (ie, 90% or greater elimination of giant cells, relative to baseline). Additionally, post-treatment tissue samples from 16 patients, some of whom had more than one specimen, showed the spindle-shaped cell-dense stroma replaced with a less cellular stroma, with embedded new osteoid formation lined by RANKL-expressing cells, particularly in the central area of the resected tumours. Peripheral to the areas of osteoid formation, there was a progressive transition to areas of irregular small woven bone trabeculae. These trabeculae were lined with a smaller number of osteoblast-like RANKL-expressing cells. At the peripheral margin of the resected tumour, woven bone transitioning to normal lamellar bone was observed.

Ten of the 15 patients assessed by radiology had a tumour response (lack of progression). Similar to other connective tissue tumours, fluorodeoxyglucose (FDG)-PET showed considerable baseline activity in GCTs, presumably related to the high metabolic activity of the giant cells. The reduction in the number of giant cells after denosumab treatment was associated with a reduction in FDG uptake, suggesting that PET may be a sensitive and early biomarker for clinical response in GCT of bone. The reduction in PET activity was also associated with histological evidence of new bone formation, and measured by both CT and technetium-99m-MDP bone scan.

Among the 31 patients with baseline and post-dose investigator assessments of clinical response (made at various stages of treatment), investigators reported that 26 patients (84%; 66–95) experienced clinical benefit (ie, reduced pain or improvement in functional status) and nine patients (29%; 14–48) had bone repair.

33 of 37 patients reported an adverse event of any grade between study initiation and the data cutoff date of April 7, 2008. The most frequently reported events were pain in an extremity (n=7), back pain (n=4), and headache (n=4). Five patients had grade 3–5 adverse events (table 2), of which only one was deemed to be possibly treatment-related: a grade 3 increase in human chorionic gonadotropin concentration that was not related to pregnancy. Denosumab treatment was discontinued, and subsequent resection of the upper extremity lesion showed high-grade sarcoma.

Five patients had serious adverse events, none of which were deemed to be treatment-related. One patient developed nausea and pain, which resolved after a short hospitalisation. A second patient, with a history of asthma and GCT that had metastasised to lung, had a lower respiratory tract infection that resolved with intravenous antibiotics. A third patient developed dyspnoea and tightness in the chest that was attributed to the injection of an isotope dye before a PET scan of the head; the event resolved. The fourth patient, who had metastatic GCT, had a sudden onset of dyspnoea after a thoracotomy with resection of lung nodules; a chest radiograph suggested left-sided pneumonia that resolved with intravenous antibiotics. The last serious adverse event (grade 5) involved a patient with recurrent, unresectable GCT with metastases to lung, who experienced depression while on treatment. After denosumab treatment, she underwent complete resection of the recurrent lung lesion, and 8 months after discontinuing denosumab, developed new lesions in the lung. The pathological diagnosis was consistent with malignant GCT of bone; dyspnoea and acute respiratory distress syndrome occurred in the post-treatment follow-up phase and eventually resulted in death.

Serum calcium concentrations corrected for albumin were normal except for a transient decrease below 2.0 mmol/L (1.9 mmol/L) at week 41 for one patient. No neutralising anti-denosumab antibodies were observed. uNTx and sCTx are well-characterised markers for bone resorption in patients with bone metastases.^{26,27} In this study, rapid and substantial suppression of uNTx and sCTx concentrations were seen as early as 28 days after the first dose. Median reductions from baseline to month 2 in bone-resorption markers were 71% (IQR 15–80) for uNTx ($p=0.0014$) and 79% (71–85) for sCTx ($p<0.0001$). These reductions were sustained over time (figure 2).

The mean serum denosumab trough concentration at month 2 was 36 400 ng/mL (SD 20 600; figure 3). Mean serum trough values from months 3 to 13 were similar (range 19 900–27 500 ng/mL), suggesting that denosumab pharmacokinetics did not change with time or upon multiple dosing in this population. Systemic exposures based on serum trough concentrations increased as expected for the loading dose regimen, indicating that the dose regimen was successful at attaining target concentrations by day 29.

Discussion

The results of this study suggest that denosumab, which acts specifically to target RANKL, thereby interfering in the interactions between RANK-positive osteoclast-like giant cells and RANKL-positive stromal cells, has activity as a therapeutic agent for GCT of bone. GCT of bone causes pain, impaired function and mobility, loss of productivity, and may be limb-threatening or life-threatening because of affected anatomical sites (eg, base of the skull or vertebrae). Distant metastases to lung and malignant transformation to high-grade sarcoma have been associated with GCT.^{11,28}

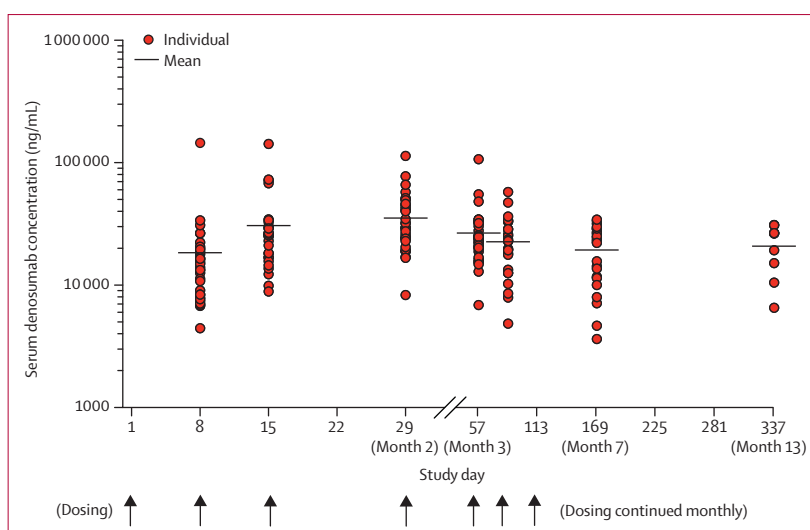


Figure 3: Individual and mean serum denosumab concentrations after subcutaneous administration of denosumab 120 mg monthly with two loading doses

Histological results showed near complete or complete elimination of giant cells in all patients for whom histology was available. Most radiological assessments showed stable disease, and in some cases objective partial responses were observed. These observations were associated with reports of clinical benefit by several investigators, including reduction in pain requiring less analgesia, and improvements in function, mobility, and bone repair. Denosumab also led to rapid and sustained suppression of bone turnover.

Limitations of the current study include the small sample size of a select population with recurrent or unresectable GCT of bone, the short study duration, and the single-group study design. Additional studies are needed to assess the potential benefit of denosumab in a broader population of patients with GCT, its benefit for individual cohorts of patients, and its potential therapeutic effects in reducing tumour size before surgery. Although it is possible that the effect of denosumab could be confounded by previous treatments with chemotherapy, radiation therapy, bisphosphonate therapy, or surgery, none of these treatments has been prospectively and rigorously assessed independently. Core biopsies used for assessment of treatment response may not always provide representative specimens. Finally, radiological changes indicative of the true response may not be apparent within the 6 months specified for this study—osteolysis may occur slowly, untreated tumours may not have increased in size, and reproducible measurements between scans may be difficult to obtain for some lesions. Nevertheless, this study establishes the therapeutic potential of denosumab to inhibit progressive bone destruction and metastatic progression in patients with unsalvageable GCT, and also provides key insights into the biology of GCT.

Whereas the giant cells are clearly dependent on RANKL signalling by stromal cells,^{15,20} it seems that the immature state of the neoplastic stromal cells is reciprocally

dependent on giant cells. Stromal expression of RANKL is decreased after elimination of the giant cells, and expression is evident in cells forming new osteoid and bone. The genetic basis for stromal overexpression of RANKL is unknown, and it is possible that GCT represents a pathological variation of the normal physiological interdependence of osteoblast and osteoclast populations in bone. Support for this possibility is the existence of currently unknown reciprocal signals that maintain the stromal population in an immature and presumably RANKL-expressing state. These findings suggest that continued denosumab may have a therapeutic role in cases of unsalvageable GCT, particularly with pulmonary metastases, but also in the neoadjuvant setting where the drug might improve surgical outcomes. Further investigation of the use of denosumab as a new therapy for GCT is warranted.

Contributors

DT led the development and writing of the manuscript, provided critical analysis and interpretation of the data, and critically reviewed and revised the manuscript. RH, KS, SC, AS, and J-YB provided critical analysis and interpretation of the data, and critical review of the manuscript. MR, JS, ZY, WS, RD, and SJ assisted in development of the first draft and provided critical review and revisions. ZY also performed statistical analysis.

Conflicts of interest

DT has received consulting fees from Amgen Inc, research grants from Pfizer and Novartis, and is supported by a Victorian Cancer Agency Clinician Researcher fellowship. KS has received research funding, consulting fees, and/or honorarium from Novartis, Pfizer, Amgen Inc, Johnson and Johnson, SMI, Keryx, Ariad/Merck, GlaxoSmithKline, Daiichi, Cell Therapeutics, Infinity, Schering Plough, and Cellgene, and has served as an expert witness involving bisphosphonates. J-YB has received consulting fees and honoraria from Novartis, Pfizer, GlaxoSmithKline, and PharmaMar, and research funding from Novartis. MR, JS, ZY, WS, RD, and SJ are employees of Amgen and have received Amgen stocks and stock options. The remaining authors declared no conflicts of interest.

Acknowledgments

This study was sponsored by Amgen, Inc. Medical writers Ting Chang and Linda Melvin were involved in all stages of the writing of this manuscript. Ting Chang is an employee of Amgen Inc; the freelance services of Linda Melvin were funded by Amgen Inc.

References

- Mendenhall WM, Zlotnick RA, Scarborough MT, Gibbs CP, Mendenhall NP. Giant cell tumour of bone. *Am J Clin Oncol* 2006; **29**: 96–99.
- Zheng MH, Robbins P, Xu J, Huang L, Wood DJ, Papadimitriou JM. The histogenesis of giant cell tumour of bone: a model of interaction between neoplastic cells and osteoclasts. *Histol Histopathol* 2001; **16**: 297–307.
- Szendroi M. Giant-cell tumour of bone. *J Bone Joint Surg Br* 2004; **86**: 5–12.
- Szendroi M, Kiss J, Antal I. Surgical treatment and prognostic factors in giant-cell tumour of bone. *Acta Chir Orthop Traumatol Cech* 2003; **70**: 142–50.
- Bullough PG, Bansal M. Malignancy in giant cell tumour. In: Fletcher CDM, Unni K, Mertens F, eds. *World Health Organization classification of tumours: pathology and genetics of tumours of soft tissue and bone*. Lyon: International Agency for Research on Cancer (IARC), 2002.
- Malawer M, Helman L, O'Sullivan B. Giant cell tumour of the bone. In: DeVita V, Lawrence T, Rosenberg S, eds. *Principles and Practice of Oncology*, 8th edn. Philadelphia: Lippincott, Williams, and Wilkins, 2008.
- Balke M, Ahrens H, Streibuerger A, et al. Treatment options for recurrent giant cell tumours of bone. *J Cancer Res Clin Oncol* 2009; **135**: 149–58.
- Brien EW, Mirra JM, Kessler S, Suen M, Ho JK, Yang WT. Benign giant cell tumour of bone with osteosarcomatous transformation ("dedifferentiated" primary malignant GCT): report of two cases. *Skeletal Radiol* 1997; **26**: 246–55.
- Lin PP, Guzel VB, Moura MF, et al. Long-term follow-up of patients with giant cell tumour of the sacrum treated with selective arterial embolization. *Cancer* 2002; **95**: 1317–25.
- Hosalkar HS, Jones KJ, King JJ, Lackman RD. Serial arterial embolization for large sacral giant-cell tumours: mid- to long-term results. *Spine* 2007; **32**: 1107–15.
- Siebenrock KA, Unni KK, Rock MG. Giant-cell tumour of bone metastasising to the lungs. A long-term follow-up. *J Bone Joint Surg Br* 1998; **80**: 43–47.
- Chang SS, Suratwala SJ, Jung KM, et al. Bisphosphonates may reduce recurrence in giant cell tumour by inducing apoptosis. *Clin Orthop Relat Res* 2004; **426**: 103–09.
- Cheng YY, Huang L, Lee KM, Xu JK, Zheng MH, Kumta SM. Bisphosphonates induce apoptosis of stromal tumour cells in giant cell tumour of bone. *Calcif Tissue Int* 2004; **75**: 71–77.
- Tse LF, Wong KC, Kumta SM, Huang L, Chow TC, Griffith JF. Bisphosphonates reduce local recurrence in extremity giant cell tumour of bone: a case-control study. *Bone* 2008; **42**: 68–73.
- Roudier MP, Kellar-Graney KL, Huang LY, et al. RANK and RANKL expression in giant cell tumours of the bone: an immunohistochemical study. 12th Annual Connective Tissue Oncology Society Meeting; Nov 2–4, 2006; Venice, Italy.
- Fuller K, Wong B, Fox S, Choi Y, Chambers TJ. TRANCE is necessary and sufficient for osteoblast-mediated activation of bone resorption in osteoclasts. *J Exp Med* 1998; **188**: 997–1001.
- Huang L, Xu J, Wood DJ, Zheng MH. Gene expression of osteoprotegerin ligand, osteoprotegerin, and receptor activator of NF-kappaB in giant cell tumour of bone: possible involvement in tumour cell-induced osteoclast-like cell formation. *Am J Pathol* 2000; **156**: 761–67.
- Lacey DL, Tan HL, Lu J, et al. Osteoprotegerin ligand modulates murine osteoclast survival in vitro and in vivo. *Am J Pathol* 2000; **157**: 435–48.
- Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* 1998; **93**: 165–76.
- Roudier MP, Kellar-Graney KL, Huang LY, et al. Increased expression of RANKL in giant cell tumours of the bone correlates with recurrence. 13th Annual Connective Tissue Oncology Society Meeting; Nov 1–3, 2007; Seattle, WA, USA.
- Bekker PJ, Holloway DL, Rasmussen AS, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. *J Bone Miner Res* 2004; **19**: 1059–66.
- Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res* 2006; **12**: 1221–28.
- Fizazi K, Lipton A, Mariette X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *J Clin Oncol* 2009; **27**: 1564–71.
- Lipton A, Steger GG, Figueroa J, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J Clin Oncol* 2007; **25**: 4431–37.
- Lipton A, Steger GG, Figueroa J, et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. *Clin Cancer Res* 2008; **14**: 6690–96.
- Brown JE, Cook RJ, Major P, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumours. *J Natl Cancer Inst* 2005; **97**: 59–69.
- Coleman RE, Major P, Lipton A, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *J Clin Oncol* 2005; **23**: 4925–35.
- Bertoni F, Bacchini P, Staals EL. Malignancy in giant cell tumour of bone. *Cancer* 2003; **97**: 2520–29.