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Research Paper

Denosumab versus zoledronic acid in cases of surgically unsalvageable giant cell tumor of bone: A randomized clinical trial

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ABSTRACT

Background: Giant-cell tumor of bone (GCTB) is a relatively benign, but locally aggressive osteoclastogenic stromal tumour of the bone. Although denosumab has been approved as an monoclonal antibody against RANK ligand for the treatment of GCTB, few clinical trials of the benefit in tumor response have been conducted to prove the efficiency in Chinese population.

Objectives: In this multicentric, random controlled, clinical trial, 160 patients were enrolled to compare the therapeutic efficacy and safety of denosumab and zoledronic acid treatment in patients with surgically unsalvageable GCTB.

Methods: Between 2nd Jan 2015 and 1st Jan 2018, 160 adults (aged $\geq$ 18 years) with ①surgically unsalvageable GCTB, ②surgically salvageable GCTB with planned surgery expected to result in severe morbidity were included in this randomized clinical trial. Patients received either subcutaneous denosumab (DB group; 120 mg once every 4 weeks with loading doses of 120 mg subcutaneously admininstered on days 8 and 15; n = 80) or intravenous zoledronic acid (ZA group; 4 mg once every 4 weeks; n = 80) for six cycles. Disease status, clinical benefits, treatment-emergent adverse effects, overall survival, and cost of treatment were evaluated during the follow-up period. Statistical significance was determined using 95% confidence intervals.

Results: Denosumab and zoledronic acid had similar tumor responses ($p = 0.118$) and clinical benefits ($p = 0.574$). Disease progression was observed in fewer patients in the DB group (12.5%) than ZA group (15.0%). Denosumab caused fatigue ($p = 0.001$) and back pain ($p < 0.0001$), while zoledronic acid caused hypocalcemia ($p < 0.0001$), flu-like symptoms ($p = 0.059$) and hypotension ($p = 0.059$). Denosumab treatment was markedly more expensive than zoledronic acid treatment ($p < 0.0001$). The cost to manage treatment-emergent adverse effects was the same for the ZA group and the DB group ($p = 0.425$). The accumulate recurrence-free survival rate at 4-year follow-up is higher in DB group ($p = 0.035$).

Conclusions: Denosumab is a safe but costly alternative to zoledronic acid for treatment of surgically unsalvageable GCTB.

1. Background

Giant cell tumor of bone (GCTB) is a rare, locally aggressive osteolytic lesion, accounting for 4 ~ 5% of all primary bone tumors with the peak incidence from age 20 to 40 [1]. GCTB is considered histologically benign with behavior in a malignant fashion [2], which cause significant bone destruction and severe soft tissue invasiveness. Pain, joint dysfunction and substantial morbidity are the primary symptoms of GCTB, while the risk of pulmonary metastasis are relatively elevated in those advanced or recurrent patients [1–3]. In most cases, GCTB occurs

Abbreviations: GCTB, Giant cell tumor of bone; US FDA, The United States Food and Drug Administration; EMA, The European Medicines Agency; RANKL, Receptor activator of nuclear factor kappa-B ligand; CONSORT, Consolidated standards of reporting trials; MRI, magnetic resonance imaging; CT, The computed tomography; RECIST, Response evaluation criteria in solid tumors; AST test, Aspartate aminotransferase test; ALT test, Alanine aminotransferase test; CTCAE, Common Terminology Criteria for Adverse Events; ANOVA, Analysis of variance; EORTC, European organization for research and treatment of cancer.

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in the extremity of long bones in skeletally mature adolescents and young adults, the sacrum and the vertebral body are affected in lower incidence with severe local symptoms. The occurrence rate is slightly higher in females than in males [1]. The parthenogenesis of GCTB is not fully understood, and the biological behavior is unpredictable [4].

The standard curative treatment for GCTB involve surgical removal (intralesional curettage or en-bloc resection) followed by bone cement packing and/or bone grafting to compensate for resection and restore limb function [3]. Although surgery is the standard treatment [1,5], local tumor recurrence rates are high due to the absence of effective adjuvant therapies [2]. The local recurrence rate of GCTB ranges 27 ~ 65% for curettage alone, 12 ~ 27% for curettage combined with adjuvants and 0 ~ 12% for en-bloc resection. However, en-bloc resection minimize the risk of local recurrence, the broader-range of bone destruction and soft tissue extension result in a higher rate of surgical complications and functional impairment [6]. For patients with unsalvageable GCTB, radiotherapy with serial embolization is also a treatment option, but significant responses have not been reported and malignant transformation may occur after radiation [7]. Chemotherapeutic agents and bisphosphonates have also been used in GCTB patients, but show inconsistent results [8].

Histological analysis reveals that osteoclast-like giant cells and stromal cells are the dominant in GCTB, where osteoclast-like giant cells localized at the perimeter of bone erosion. The stromal cells function as the neoplastic component of GCTB with proliferate readily and expression of receptor activator of nuclear factor-kappa β ligand (RANKL). The giant cells express RANK and are activated by excessive RANKL expression, resulting in bone lysis and destruction. The interaction of the osteoclasts with RANKL potentially functions as the therapeutic target to inhibit the osteoclast-induced bone destruction [7].

As a human monoclonal antibody that inhibits RANKL, denosumab has been approved for the treatment of unresectable GCTB and those when surgical resection is likely to result in severe morbidity [1,9] by the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) in 2013. XGEVA®(denosumab) injection for GCTB was approved by the National Medical Products Administration (NMPA) in 2019. Even though results from clinical trials have shown tumor responses to denosumab as assessed by radiology and histology [10], relevant controlled studies targeting Chinese population are still rarely reported. The safety profile [9], curative efficiency, economic burden [11,12], treatment-emergent toxic effects [5,7], and long-term effects of denosumab treatment are also not well-established [13], and the cost of treatment is high. The objectives of this study were to compare the efficacy, safety, and cost between denosumab and zoledronic acid treatment, in adult patients with surgically unsalvageable GCTB.

2. Methods

2.1. Ethics approval and consent to participate

This study was registered at the Research Registry**https://www.researchregistry.com**. The protocol (CMU/CL/12/15) was approved by our institutional review board, and adhered to the 2013 Declaration of Helsinki and Consolidated Standards of Reporting Trials (CONSORT) guidelines. Informed consent was obtained from all patients or their legally authorized agents regarding the interventions, radiology and pathology tests, and publication of personal data and images (if any) in all formats (hard and/or electronic), irrespective of time and language.

2.2. Study design and participants

Between 2nd Jan 2015 and 1st Jan 2018, adults patients (aged ≥ 18 years) with pathologically confirmed GCTB were selected for the enrollment of this study. All subjects suffered from the measurable active disease within 1 year of enrollment, symptoms include increased pain at the nearest joint, swelling, limited motion of joint and pathological fracture. Radiographic imaging confirms the osteolysis within the tumor in conjunction with histopathological evidence of giant cells.

2.3. Inclusion criteria

Adults patients (aged ≥ 18 years) weighting at least 50 kg admitted in our cohort from 2nd Jan 2015 to 1st Jan 2018 were included in the trial. Patients with surgically unsalvageable GCTB were defined as ①sacral or spinal GCTB, or multiple lesions including pulmonary metastases and ②surgically salvageable GCTB with attainable complete resection, however, severe morbidities were inevitable, including joint resection, limb amputation, hemipelvectomy, or increased risk of nerve or vascular injury. All subjects have Karnofsky Performance Status scores ≥ 50% (11-point scale; 0%=death and 100%=no evidence of disease or symptoms [14]). All patients provided written, informed consent.

2.4. Exclusion criteria

Patients with renal impairment (creatinine clearance rate < 30 mL/min), asthma, scheduled surgery, a history of hypersensitivity to denosumab or zoledronic acid, pregnancy, active lactation, or who had been receiving radiotherapy/serial embolization were excluded from the trial. Patients with non-GCTB giant-cell-rich tumors, suspected bone sarcoma, brown cell bone tumor, Paget's disease, secondary malignancy, osteonecrosis, osteomyelitis, or jaw and/or dental problems were excluded from the trial.

2.5. Randomization and blinding

This study enrolled a total of 160 patients with histologically diagnosed of GCTB by CT guided or open biopsy. All subjects were conducted to the simple randomization procedure (1:1 ratio). The required sample size was determined, using the online tool OpenEpi 3.01-English ((https://www.openepi.com)), as 80 in each group. The other parameters were set as follows: finite population correction factor (fpc, N), 160; hypothesized percentage frequency of outcome factor, 80 ± 5%; power of randomization, 80%; confidence limits, 5% ($\alpha = 0.05$); and design effect, 1. The randomization procedure was carried out using opaque envelopes. The physicians participating in the randomization were not involved in any treatment decisions. A CONSORT flow diagram of the study is presented in Fig. 1.

2.6. Drugs and reagents

Denosumab (XGEVA®) was purchased from Amgen Technology (Dublin, Ireland). Zoledronic acid (Zometa®) was purchased from Novartis Pharma Co., Ltd. (Beijing, China). Normal saline was purchased from Baxter Healthcare Co., Ltd. (Shanghai, China). Calcium (500 mg) and 25-hydroxyvitamin D (400 IU) tablets were purchased from Glenmark Pharmaceuticals Ltd. (Mumbai, India).

2.7. Interventions

Patients in the DB group received six cycles of denosumab administered subcutaneously in the abdomen, upper thigh, or upper arm. A cycle was defined as 120 mg denosumab once every 4 weeks, with loading doses of 120 mg on days 8 and 15. Patients in the ZA group received six cycles of zoledronic acid, a cycle was defined as 4 mg zoledronic acid via 16-min intravenous infusion in normal saline once every 4 weeks [15]. Both groups also received daily oral administration of 500 mg calcium [7] with 400 IU 25-hydroxy vitamin D [16]. The interventions comprised six cycles with 4 weeks in each, where 6 months of denosumab [17] and zoledronic acid [15] have been reported to be sufficient to induce anti-tumor responses. Intralesional extensive

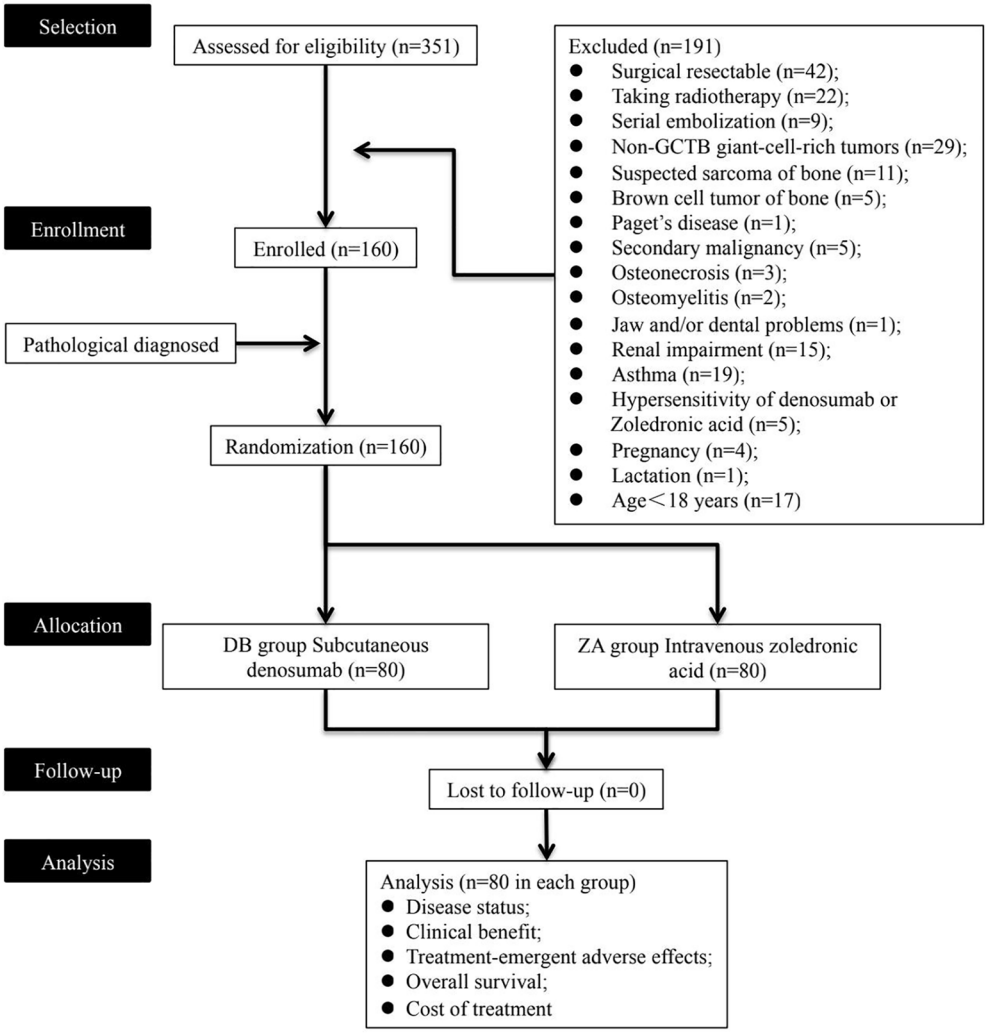

Fig. 1. CONSORT flow diagram of the study. Finite population correction factor (fpc, N), 160; hypothesized percentage frequency of outcome factor, 80 ± 5%; power of randomization, 80%; confidence limits, 5% (α = 0.05); and design effect, 1. GCTB, giant cell tumor of bone. An intention-to-treat analysis method was adopted.

curettage and allogeneic bone grafting or cement packing was performed for Campanacci Grade I and II GCTB after the downgrading of preoperative drug therapy.

2.8. Disease status

Study visit for all assessment, including radiological imaging (X-ray, MRI and CT scan) occurred once every 4 weeks until the end of the interventions [18]; the follow-up of disease status continued to be evaluated every 6 month and stopped at the 36 months. All radiological imaging parameters were evaluated by the same experienced radiologist. Disease status was categorized at the time of enrollment and at the last follow-up, following the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) guidelines [19], as either progressive (new malignancy appearing), stable (presence of targeted lesions), fractional response (decrease of $\geq$ 30% in tumor size), or complete response (disappearance of all targeted lesions).

2.9. Clinical benefits

All patients were subjected to a physical examination once every 4 weeks; any improvements in pain, mobility or functional activity [7] were noted to determine the clinical benefits of the treatment [17]. All physical examination parameters were evaluated by the same experienced physiotherapist, the visual analog scale (VAS) was used to assess the pain relief and the Musculoskeletal Tumor Society (MSTS) scoring system was used to assess the mobility or functional improvement.

2.10. Treatment-emergent adverse events

Adverse events related to medication use were monitored. All patients underwent liver function (ALT, AST, albumin, and bilirubin) and renal function (blood serum creatinine) tests [7,15] once every month in the intervention period. Other treatment-emergent adverse effects were evaluated over the 36 months. All clinical parameters were evaluated by one pathologist, one nephrologist, one hepatologist, one physician, and one hematologist, each of whom had at least 3 years of experience in their specialty. The treatment-emergent adverse events were considered in accordance with Common Terminology Criteria for Adverse Events (CTCAE, v5.0) [20]. Hospitalization was considered to indicate serious treatment-emergent adverse effects. Overall survival was defined as the period of survival after disease detection [21]. Follow-up to monitor patient survival continued for 3 years after the interventions.

2.11. Cost analysis

Cost analysis included the costs of pathology, intervention(s), hospital stay, radiology examination, experts consultation, and follow-up costs [12].

2.12. Statistical analysis

InStat (Windows version; GraphPad Inc., La Jolla, CA, USA) was used for statistical analysis. Chi-square tests for independence and one-way repeated measures analysis of variance (ANOVA) were used for statistical analysis of categorical and continuous data, respectively. Results were considered significant at a 95% confidence level. An intention-to-treat analysis method was adopted.

3. Results

3.1. Demographic and clinical characteristics

Based on the radiographic appearance, patients with GCTB were categorized into one of three Campanacci grades (I, II, or III): a grade I lesion (latent) has a well-defined margin with an intact cortex; a grade II lesion (active) has a relatively well-defined margin with no radiopaque rim, the cortex moderately expanded with attenuation; a grade 3 lesion (aggressive) has indistinct borders with severe cortical destruction. The other demographic and clinical parameters of the enrolled patients are presented in Table 1, none of which showed a group difference at the time of enrollment ($p \geq 0.01$ for all).

3.2. Evaluation parameters

Disease status, as per radiological imaging findings, indicated that denosumab and zoledronic acid did not differ in tumor response ($p = 0.118$) or clinical benefits ($p = 0.574$) in GCTB patients, although the complete response rate was higher in the DB group than in the ZA group (10 *vs.* 2, $p = 0.032$) and disease progression was observed in fewer patients in the DB group (12.5%) than ZA group (15.0%, Table 2).

3.3. Treatment-emergent adverse effects

Denosumab and zoledronic acid both induced arthralgia and alopecia. Denosumab caused fatigue ($p = 0.001$) and back pain ($p < 0.0001$). Zoledronic acid caused hypocalcemia ($p = 0.059$), flu-like symptoms ($p = 0.059$), hypotension ($p = 0.059$) and hypophosphatemia ($p = 0.369$), one case suffered from hypophosphatemia with muscle weakness and respiratory failure in ZA, which led to hospitalization. Overall, zoledronic acid was associated with a higher number of serious treatment-emergent adverse events during the follow-up period than denosumab (Table 3).

3.4. Cost

Denosumab treatment was markedly more expensive than zoledronic acid treatment for each patient ($9693.6 ± 170.9 *vs.* $3679.2 ± 127.0, $p < 0.0001$, Fig. 2A). However, the cost of managing treatment-emergent adverse effects for each patient was same for zoledronic versus denosumab treatment with no statistical significance ($1335.1 ± 54.5 *vs.* $1320.1 ± 66.4, $p = 0.425$, Fig. 2B).

3.5. Survival

Overall survival rate of disease at the last follow-up was not statistically significant between these two treatments (97.5% *vs.* 95.0%, $p = 0.681$), 1 patient in DB group and 2 in ZA group die of the GCTB malignancy. 12 patients in DB group and 23 in ZA group relapsed with either local or distant metastasis. The accumulate 4-year recurrence-free rate in DB group is higher compared with the ZA group ($p = 0.035$, Fig. 3).

3.6. Case presentation

A 51-year-old female patient presented at our institution after experiencing progressive swelling and pain in the left knee over the previous 7 months. The patient reported no history of trauma and underwent observation for 1 months with painkiller prescribed. The initial examination revealed the limited range of motion in the left knee with 10-90° flexion with severe pressing pain at the lateral tibial plateau. Radiography and CT scan (Fig. 4A) revealed an expansive Campanacci grade II osteolytic lesion. The proximal lateral cortex of the tibia is damaged, and there is a significant risk of collapse of the tibial plateau. Incisional biopsy was performed using local anaesthesia, and a pathological diagnosis of GCTB was confirmed.

The patient received 120 mg of denosumab to reduce the tumor volume. Denosumab was administrated subcutaneously once every 4 weeks, with loading doses of 120 mg on days 8 and 15 for six cycles. The

Table 1
Demographic characteristics and clinical status of the enrolled patients.

Characteristics		Groups		Comparison between groups
		DB	ZA	
Intervention		Denosumab	Zoledronic acid	–
Sample size (Patients enrolled in the study)		80	80	*p*-value
Gender	Male	31(38.8%)	34(42.5%)	0.748
	Female	49(61.2%)	46(57.5%)	
Age (years)	Min	28	25	0.416
	Max	52	57	
	Mean ± SD	34.3 ± 3.9	33.8 ± 4.7	
Weight (kg)	Min	50	50	0.924
	Max	72	72	
	Mean ± SD	54.8 ± 5.3	54.7 ± 4.6	
Karnofsky Performance Status	Min	5	6	0.215
	Max	10	10	
	Mean ± SD	7.7 ± 1.0	7.5 ± 0.9	
Location of GCTB lesion	Femur	7(8.8%)	9(11.3%)	0.999
	Tibia	4(5.0%)	6(7.5%)	
	Fibula	10(12.5%)	8(10.0%)	
	Sacrum	9(11.3%)	11(13.8%)	
	Lung	5(6.3%)	4(5.0%)	
	Pelvic bone	12(15.0%)	11(13.8%)	
	Humerus	5(6.3%)	6(7.5%)	
	Radius	6(7.5%)	5(6.3%)	
	Ulna	6(7.5%)	5(6.3%)	
	Metacarpus	2(2.5%)	2(2.5%)	
	Cervical Vertebrae	2(2.5%)	3(3.8%)	
	Thoracic Vertebrae	6(7.5%)	6(7.5%)	
	Lumbar Vertebrae	2(2.5%)	1(1.3%)	
	Skull	4(5.0%)	3(3.8%)	
Status of GCTB	Primary surgically unsalvageable	43(53.8%)	40(50.0%)	0.752
	Secondary surgically unsalvageable	37(46.3%)	40(50.0%)	
Ethnicity	Non-Chinese	1(1.3%)	0(0)	1.000
	Chinese	79(98.8%)	80(100%)	
[**]Campanacci grade of GCTB	I	4(5.0%)	7(8.8%)	0.614
	II	30(37.5%)	27(33.8%)	
	III	46(57.5%)	46(57.5%)	

Continuous values are represented as mean ± SD and categorical data as a number (percentage).
GCTB, giant cell tumor of bone.
Chi-square independence tests and repeated measures ANOVA were used to analyze categorical and continuous variables, respectively. $p < 0.01$ was considered significant.
Pathological, nursing, radiological, and other medical staff (blinded to the groups assignments) with at least 3 years of experience were involved in the evaluation of outcomes.
11-point scale: 0 = death, 10 = no evidence of symptoms or disease.
[**] Based on cytology.

Table 2
Evaluation parameters at the end of drug intervention.

Parameters	Disease status	Groups		Comparison between groups
		DB	ZA	
	Intervention	Denosumab	Zoledronic acid	
	Sample size	80	80	*p*-value
Clinical benefits	*Pain reduction	24(30.0%)	22(27.5%)	0.574
	Improved mobility	18(22.5%)	14(17.5%)	
	Improved functional activity	17(21.3%)	15(18.8%)	
	Slight or no significant clinical improvement	21(26.3%)	29(36.3%)	
Disease Status	¥Disease progression	10(12.5%)	12(15.0%)	0.118
	$Stable disease	35(43.8%)	37(46.3%)	
	¶Fractional response	25(31.3%)	29(36.3%)	
	#Complete response	10 (12.5%)√	2(2.5%)	
Second-stage treatment	Surgical Intervention	57(71.3%)	60(75.0%)	0.722
	&Conservative Treatment	23(28.7%)	20(25.0%)	

Data are numbers (percentage). Radiological imaging was used for assessing disease status. All radiological imaging parameters were evaluated by the same experienced radiologist.
All physical examination parameters were evaluated by the same experienced physiotherapist.
Chi-square independence tests were used for the statistical analysis. $p < 0.05$ was considered significant.
Evaluation as per RECIST v1.1 guideline.
* Visual analogue scale (VAS) score: 0 = no pain, 10 = worst pain imaginable.
¥ New malignancy appeared.
$ Persistence of targeted lesions.
¶ Decrease of ≥ 30% in tumor size.
# Disappearance of all targeted lesions.
& Regular physical check and radiological examination.
√ Significant compared with ZA group at $p = 0.014$.

patient reported alleviation in pain and improvement in ROM. Radiography and MRI revealed tumor shrinkage and osteosclerosis of the margins (Fig. 4B). The intralesional curettage was performed under general anaesthesia 5 months after the first denosumab administration. The lesion was filled with bone cement to restore the support of the lateral tibial plateau (Fig. 4C). Pain and dysfunction of the knee were not reported at the last follow-up 6 month postoperative.

4. Discussion

Tumor progression during the follow-up period was consistent compare to previous reports in patients with surgically unsalvageable GCTB treated with either denosumab or zoledronic acid (12.5% for DB group and 15.0% for ZA group). Denosumab and zoledronic acid both have a bone resorption-inhibiting effect [12], and the results of this clinical trial were in line with previous studies [7,15,17,21–24]. However, those investigations presented technical issues and limitations to some extent. For example, the phase II study carried out by Branstetter et al. did not perform statistical analyses or power calculations to show the significance of its results [23], while the case-control study carried out by Tse et al. had small-sized groups (n = 20 and 24) with relative insignificance in statistics [15]. The phase II study done by Thomas et al. also included a small population (N = 37) without any control group [17]. Therefore, these studies were insufficiently reliable to present novelty and significance to the existing literature. The phase II denosumab study performed by Chawla et al. [7] enrolled patients younger

Table 3
Treatment-emergent adverse effects during the follow-up period.

Adverse event	Groups		Comparison between groups
	DB	ZA	
Intervention	Denosumab	Zoledronic acid	
Sample size	80	80	*p*-value
Arthralgia (joint pain)	16(20.0%)	18(22.5%)	0.847
Fatigue	15(18.8%)	3(3.8%)	0.005
Headache	15(18.8%)	16(20.0%)	1.000
Pain in extremity	14(17.5%)	13(16.3%)	1.000
Nausea	19(23.8%)	21(26.3%)	0.855
Back pain	18(22.5%)	1(1.3%)	<0.001
Depression	1(1.3%)	2(2.5%)	1.000
Musculoskeletal pain	1(1.3%)	1(1.3%)	1.000
¶Hypocalcemia	6(7.5%)	29(36.3%)	<0.001
Vomiting	1(1.3%)	3(3.8%)	0.620
Constipation	1(1.3%)	1(1.3%)	1.000
Flu-like symptoms	0(0)	5(6.3%)	0.059
Shortness of breath	0(0)	2(2.5%)	0.497
Diarrhea	1(1.3%)	1(1.3%)	1.000
Loss of appetite	2(2.5%)	3(3.8%)	1.000
Cough	0(0)	1(1.3%)	1.000
Dizziness	0(0)	1(1.3%)	1.000
Insomnia	0(0)	1(1.3%)	1.000
Abdominal pain	0(0)	2(2.5%)	0.497
Paresthesia	0(0)	2(2.5%)	0.497
Urinary tract infection	0(0)	2(2.5%)	0.497
Alopecia	3(3.8%)	3(3.8%)	1.000
Osteonecrosis of the jaw	2(2.5%)	1(1.3%)	1.000
¥ Hypophosphatemia	4(5.0%)	8(10.0%)	0.369
Weight gain	1(1.3%)	0(0)	1.000
βAnemia	2(2.5%)	2(2.5%)	1.000
Infections (non-specific)	3(3.8%)	4(5.0%)	1.000
Osteomyelitis	2(2.5%)	0(0)	0.497
Ostealgia	0(0)	2(2.5%)	0.497
Decreased kidney function	0(0)	2(2.5%)	0.497
Weight loss	0(0)	3(3.8%)	0.245
αHypokalemia	0(0)	5(6.3%)	0.059
Candidiasis	0(0)	1(1.3%)	1.000
#Hypotension	0(0)	5(6.3%)	0.059
$Hypomagnesemia	0(0)	1(1.3%)	1.000
Dysphasia	0(0)	1(1.3%)	1.000
θ Fever	0(0)	3(3.8%)	0.245

All clinical parameters were evaluated by one pathologist, one nephrologist, one hepatologist, one physician, and one hematologist (all with ≥ 3 years of experience).
N/A, not applicable.
Evaluation as per CTCAEv5.0 guidelines.
Data are represented as numbers (percentage).
Chi-square independence tests were used for the statistical analysis. $p < 0.05$ was considered significant.
Our study reports the primary analysis results of a randomized clinical trial of denosumab and zoledronic in 160 patients with GCTB with a 3-year follow-up. To our knowledge, this is the first clinical trial so far targeting the Chinese population with unsalvageable GCTB. This study shows the mid-term safety and activity of denosumab. Most patients had a radiological response and clinically meaningful decreases in pain scores and function improvement of the extremities. Denosumab and zoledronic can effectively control the disease progression. About 40% of patients improved from the unresectable state to the surgically operable state. Moreover, the overall recurrence rate at 4-year follow-up of patients with denosumab is lower than that of zoledronic.
¶ Blood serum calcium concentration < 2.1 mM/L.
¥ Serum phosphate concentration < 2.5 mg/dL(0.81 mM/L).
β Hemoglobin level < 13.5 g/100 mL for men and < 12.0 g/100 mL for women.
α Blood serum potassium level < 3.5 mM/L.
Blood pressure < 90/60 mmHg.
$ Serum magnesium concentration < 1.8 mg/dL (0.70 mM/L).
θ Body temperature ≥ 100.4^{0}F (38 °C) with chills.

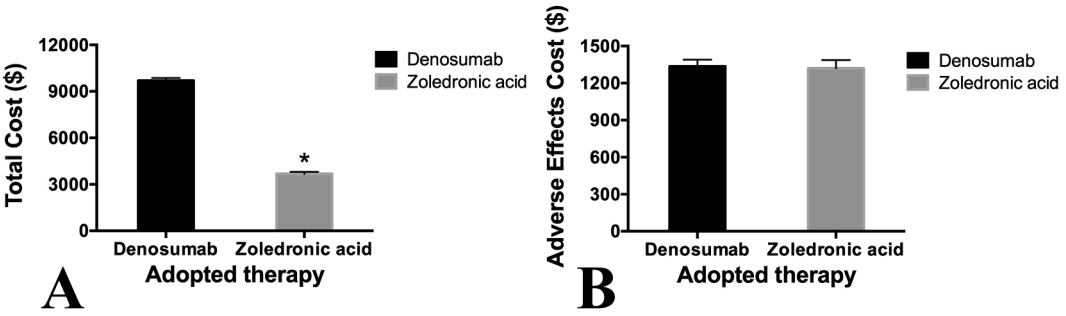

Fig. 2. Cost analysis of the therapies. **A.** Comparison of the total cost between denosumab and zoledronic acid treatment ($p < 0.0001$). **B.** Comparison of cost to manage treatment-emergent adverse effects between denosumab and zoledronic acid ($p = 0.425$ by one-way repeated measures ANOVA). Costs are in $.

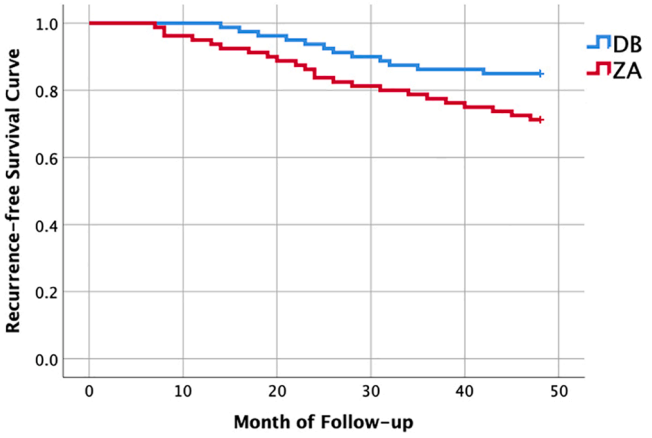

Fig. 3. Comparison of the accumulate 4-year recurrence-free survival rate between denosumab and zoledronic acid treatment, the patients in DB group had a lower accumulate recurrence-free survival rate at 48-month follow-up ($p = 0.035$ by Kaplan-Meier analysis).

than 18 years, even though the safety of denosumab has not been well-established in pediatric patients and the manufacturers do not recommend the use of those in patients aged below 18 years. Therefore, the results of Chawla et al. require further validation. Although the phase III studies carried out by Henry et al. [21,24] (treatment groups of n = 797 and 800 and n = 890 and 886) had large sample sizes, no measures were adopted to control for β-errors (false-negative results). Shibuya et al. examined the bone resorption-inhibiting effect of denosumab on GCTB [22], but an *in vitro* experimental design was used. The present study investigated the use of denosumab and zoledronic acid as antiresorptive agents in patients with surgically unsalvageable GCTB, in an authentic clinical context.

The number of patients in whom all targeted lesions disappeared after six treatment cycles were higher in the DB group than in the ZA group in this study (10 *vs.* 2, $p = 0.032$). Denosumab significantly reduce tumor size and progression [18], as it binds to RANKL [9,17,25], inhibit osteoclast-like giant cells activity, and suppresses osteolysis and proliferative tumor stroma. The osteolysis lesion is replaced with densely woven, differentiated, non-proliferative new bone [7,23]. Zoledronic acid also has anti-osteoclastic effects, and the ability to protect bone from resorption [8,15]. The present study indicates that denosumab promotes the deposition of new bone more effectively than zoledronic acid. Additionally, the optimal dosage and duration of zoledronic acid treatment in surgically unsalvageable GCTB remain unclear. At 18 months, the clinical benefits of both treatments were deemed satisfactory by trained physicians applying systematic assessment criteria. These results were in line with previous studies [7,8,15,23]. However, the group characteristics at baseline differed between groups (e.g., more males in the ZA group, more primary surgically unsalvageable tumors in the DB group). In consideration of these differences, the apparent clinical benefits of both treatments must be interpreted with caution.

Patients with zoledronic acid exhibited arthralgia, hypocalcemia, flu-like symptoms, hypophosphatemia, weight loss, hypokalemia, hypotension, and fever. Denosumab induced fatigue, back pain, and

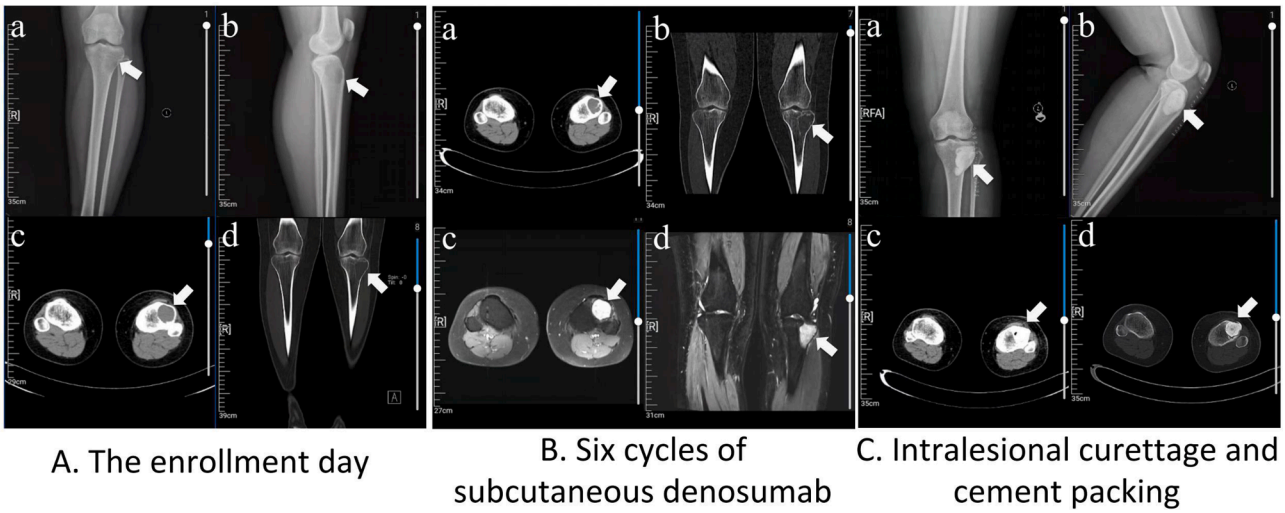

Fig. 4. Radiography and CT scan (Fig. 4A) revealed an expansive Campanacci grade II osteolytic lesion. Radiography and MRI revealed tumor shrinkage and osteosclerosis of the margins (Fig. 4B) after six cycles of denosumab. The lesion was filled with bone cement to restore the support of the lateral tibial plateau (Fig. 4C).

arthralgia as treatment-emergent adverse effects. Denosumab treatment has been consistently safe in advanced cancer, in line with the present study [17,24,26,27]. Because of the adverse effects reported here, zoledronic acid treatment was an additional burden for GCTB patients. During follow-up, the cost to control treatment-emergent toxic effects was higher for patients in the ZA versus DB group, but the total cost of denosumab treatment remained approximately 3-fold higher, as reported elsewhere [11,12]. Although denosumab showed advantages over zoledronic acid, in socioeconomic terms, denosumab is a costly alternative to zoledronic acid for GCTB patients. The average overall survival time was the same with denosumab and zoledronic acid treatment. These results are in line with previous studies [21,24]. Patients with solid tumors have shorter lives [21], and as neither denosumab nor zoledronic acid treatment demonstrated superiority in improving overall survival time, the use of one over the other in cases of surgically unsalvageable GCTB requires justification.

The limitations of this study included the relatively short follow-up period to check for local recurrence. As denosumab was administrated subcutaneously and zoledronic acid intravenously, patients were acknowledged in the grouping, and a double-blind design was not feasible. Furthermore, inter-and intra-observer variability were not evaluated, and tumor size reduction in bone was challenging to determine because RECIST criteria apply to soft tissue tumors [7]. Choi response criteria and modified European Organization for Research and Treatment of Cancer (EORTC) criteria for bone tumors were not applied in this study, since the utilization would have increased the evaluation costs.

5. Conclusion

The denosumab and zoledronic acid treatments led to marked reductions in GCTB, with relatively manageable adverse effects. As an antiresorptive agent, Denosumab is novel and more effective and safer–though costlier–than zoledronic acid for treating patients with surgically unsalvageable GCTB. There is a need for further double-blind studies with other antiresorptive agents to improve the overall survival of patients with this type of cancer.

6. Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

All authors had read and approved submission for publication. JY contributed to conceptualization and literature review of the study, the draft, and edited the manuscript for intellectual content. SL was project administrator contributed to the conceptualization and literature review of the study. WS contributed to the formal analysis, data curation, and literature review of the study. The authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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