

The Role of Denosumab in Patients with Giant Cell Tumor of Bone

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Abstract

Background and Purpose: Researches about the use of denosumab in patients with Giant Cell Tumor of Bone (GCTB) were springing up in the recent ten years. But most studies were case reports and the sample size of limited clinical trials was relatively small. The role of denosumab in GCTB patients still needs to be clarified.

Patients and Methods: A literature search of the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and the electronic databases of American Society of Clinical Oncology up-to-February 7, 2016, using the key word “Giant cell tumor” and “Denosumab”, was performed. Both controlled and non-controlled clinical trials evaluating the use of denosumab for the management of GCTB patients were included. Two independent authors evaluated studies using predetermined eligibility and exclusion criteria, and extracted data. The bias of studies was measured using the Cochrane Risk of Bias Tool.

Results: Four studies involving five hundred and fifty-eight patients were included. A summary 87.4% (95%CI 83.2%-91.7%) of patients undergo surgery without surgical upstaging after the treatment duration. The proportion of patients met any objective tumor response criteria on imaging was 74.8% (95%CI 65.8%-83.8%). The most commonly reported severe adverse event was hypophosphataemia with the incidence of 3.0% (95%CI 1.0%-4.0%). The combined incidence rate of four adverse events of interest was 0.7% (0.0%-1.5%), 4.2% (2.4%-5.9%), 6.9% (0.2%-13.6%) and 1.2% (0.1%- 2.4%) for osteonecrosis of jaw, hypocalcaemia, infections and new primary malignancy respectively.

Interpretation: The efficacy of denosumab in surgical downstaging and tumor response on imaging were supported. Adverse events were rare and can be monitored. Measurement of serum marker of infection, phosphate level and calcium level were recommended during denosumab therapy. However, a series of RCT studies were needed to strengthen the evidence of the efficacy and safety of denosumab.

Introduction

Giant Cell Tumor of Bone (GCTB) is a benign aggressive lesion that presents with significant local osteolysis which composing nearly 6% of the primary bone tumors [1]. Depending on the data from present researches, 80% of GCTBs have a benign course. But what cannot be ignored is that the local recurrence rate of GCTB range from 20% to 50% and about 10% undergo malignant transformation at recurrence. Even in cases of benign histology GCTB, pulmonary metastases can also occur in 1% to 4% of the patients [2]. So the management strategy of GCTB is

of significant importance. Surgery is the main treatment method of GCTB of the extremity [3]. Curettage of tumor is the mostly commonly used operative method which can effectively eliminate tumors as well as reserve the structure and function of joint. But as reported in several studies, the recurrence rate can be up to 12%-65% [4-8]. Local adjuvant treatment (e.g. phenol, liquid nitrogen, PMMA) after curettage was reported to be effective to reduce the risk of local recurrence [6]. For patients with local recurrence or metastasis, interferon or radiotherapy can be feasible alternative if complete resection of tumor is impossible or with severe functional impairment [9,10].

Histologically, GCTB consists of sheets of neoplastic ovoid mononuclear cells evenly interspersed with osteoclast-like giant cells [11]. These cellular components interact with various factors and play a significant role in the osteolytic process, leading to bone destruction. The osteoclast-like giant cells and their precursors express the receptor of activator of nuclear factor-kappa B (RANK), and some of the stromal cells express RANK Ligand (RANKL) [12]. The receptor of activator of nuclear factor-kappa B (RANK), RANK ligand (RANKL) and Osteoprotegerin (OPG) are major components of RANK pathway. It is a key signaling pathway of bone remodeling, and it plays a critical role in differentiation of precursors into multinucleated osteoclasts and activation of osteoclasts leading to bone absorption [13]. It is possible that the aggressive osteolytic activity of GCTB is related with RANK pathway. Denosumab is a fully human monoclonal antibody to the RANKL. The development and function of osteoclasts can be inhibited by its role in blocking RANKL. Therefore, decreasing bone resorption and increasing bone density [14]. Based on its pharmacological mechanism, the usage of denosumab to treat osteoporosis was noted in several studies. It has also been reported to be effective in preventing skeletal events in patients with bone metastases from solid tumors and treating hypercalcemia of malignancy [15,16]. There were rarely adverse events reported in recent studies, and in a long-term extension of one phase 2 study, the most frequent side effects included upper respiratory tract infections (13.5%) or arthralgia (11.5%) and back pain (9.0%) [17]. Researches about the use of denosumab as a treating method in patients with GCTB were springing in the recent ten years. Significant results were found and denosumab was approved by the US Food and Drug Administration (FDA) for use in patients with recurrent or unresectable or metastatic GCTB for patients in whom surgery would be morbid [18].

However, most studies are case reports. And the sample size of limited clinical trials was relatively small. In addition, the application scope approved by USFDA for denosumab was restricted to unresectable GCTB patients. The role as a pre-operative therapy for resectable GCTB patients or a first choice treatment instead of surgery still requires clarification. To understand and synthesize the available evidence, we conducted a systematic review to evaluate the efficacy and safety of denosumab in the management of GCTB. Specifically, we asked: (1) Does denosumab lead to less morbid operative method? (2) What proportion of patients met objective tumor response criteria on imaging after denosumab treatment? (3) Does denosumab result in the occurrence of severe adverse events or adverse events of interest?

Materials and Methods

Database Search

We performed a systematic literature search of the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and the electronic databases of American Society of Clinical Oncology, using the key words “Giant cell tumor” and “Denosumab”. Only articles published in the English language were included. We

searched all databases from their earliest record to February 2016.

Eligibility and Exclusion Criteria

Both controlled and non-controlled clinical trials evaluating the use of denosumab for the management of GCTB patients were included. Studies published with available full text were included and there was no restriction on study design. The patient inclusion criteria were not under consideration. Patients were treated with denosumab irrespective of dosage and schedule. Abstracts of the conference proceedings with adequate data were included if the journal article for the corresponding studies have not been published. Reviews and case reports were excluded. Only the latest version of the publications in different stages of the same study was included. The studies of basic medicine or clinical trials focused on pathological or radiological result rather than clinical response were excluded.

Study Selection

The titles and abstracts of obtained studies identified by the already thought-out searching strategy were screened by two independent reviewers (HY, JT) to remove duplicates. Full texts of probable relevant articles were achieved for detailed review. The studies were then assessed for final selection using predetermined eligibility and exclusion criteria. Discussions were carried out in our team when disagreements occurred until consensus was achieved.

Data Extraction

Two authors (ZH, JS) independently extracted data from the included studies. The following data were extracted: (1) characteristics of patients, including patient inclusion criteria, sample size, median age of patients; (2) study design; (3) dose and schedule of denosumab; (4) treatment median duration; (5) tumor response on imaging; (7) clinical benefits; (8) adverse events; (9) other significant results.

Bias Assessment

Each article that met eligibility criteria was independently assessed by two reviewers (YW, YC) for quality using the Cochrane Risk of Bias Tool. Each items were graded as low risk, high risk and unable to determine [19].

Statistical Analysis

All outcomes were summarized using RevMan software (version 5.3). It can be estimated that the heterogeneity may be high due to the design and included patients in each study were discrepant. So we used random-effects models for meta-analysis to synthesize the data. The incidences of events or proportion of patients were used for synthesis. All summary estimates were reported with point estimates and corresponding 95% CI. We estimated heterogeneity between studies with Cochran's Q (reported as χ^2 and p values) and the I^2 statistic [19]. Where there were no appropriate data extracted for meta-analysis, a narrative method was carried out for summarizing of results.

Results

Selected Articles

The initial database searching identified 96 articles. After removal of duplicates, 86 articles were included for further assessment. 13 articles were selected for full-text evaluation after screening of titles and abstracts on the basis of eligibility and exclusion criteria. The articles were examined carefully and discussions were performed, 4 publications [20-23] were deemed appropriate for inclusion in this systematic review and meta-analysis (Figure 1).

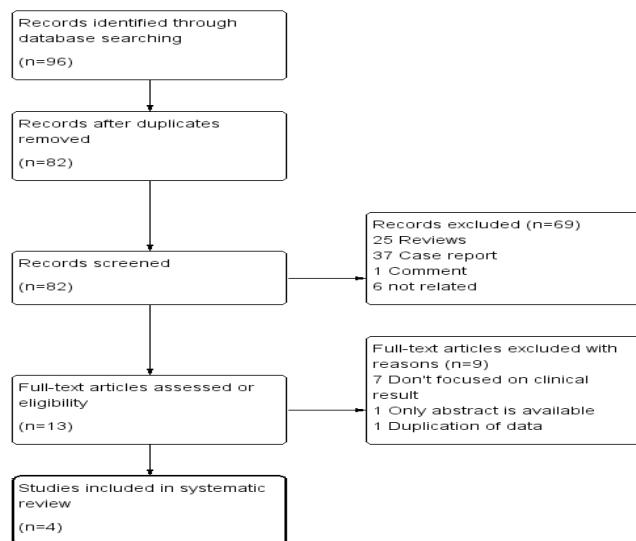


Figure 1: The flow diagram of study selection process.

Study Characteristics

The four included studies were all open-label, phase 2 study funded by industry. They were non-controlled study. The number of enrolled patients ranged from 17 to 282. The year of publication ranged from 2010 to 2015 (Table 1).

Author; year	Thomas, et al. 2010 [20]	Chawla, et al. 2013 [21]
Study design information	Open-label, phase II study; single-group	Open-label, phase II study, Parallel-group; Cohort1:surgically unsalvageable, Cohort2: salvageable with severe morbidity, Cohort3: transferred from a previous study of denosumab
Sample size	37	282
Median age (year)	30	Cohort1:33, Cohort2:34, Cohort3:30

Patient inclusion criteria	Recurrent or unresectable histologically confirmed GCTB; measurable by radiology	Histologically confirmed GCTB; radiographically measurable active disease; Karnofsky performance status of 50% or greater
Intervention	DB SQ 120 mg Q4W; loading doses on days 8 and 15	Cohort1/2:DB SQ 120 mg Q4W; loading doses on days 8 and 15; Cohort3:DB SQ 120 mg Q4W
Treatment median duration	NR	10.4 months
Continued		
Author; year	Ueda et al; 2015 [23]	Rutkowsk et al; 2015 [22]
Study design information	Open-label, phase II study; multicenter	Open-label, Phase II study
Sample size	17	222
Median age (year)	30	34
Patient inclusion criteria	Histologically confirmed GCTB; measurable by radiology; Karnofsky performance status of 50% or greater	GCTB patients; initially planned surgery was associated with functional compromise or morbidity
Intervention	DB SQ 120 mg Q4W; loading doses on days 8 and 15	DB SQ 120 mg Q4W; loading doses on days 8 and 15
Treatment median duration	13.1 months	15.3 months

GCTB: Giant Cell Tumor of Bone; DB: Denosumab; SQ: Subcutaneous Injection; NR: Not Reported.

Table 1: Overview of characteristics of included studies.

Patient Characteristics

In total, 558 patients from 4 studies were included. There were 281 primary GCTB, 277 recurrent GCTB. Both lesions of appendicular and axis skeleton were involved. There were both resectable and unresectable patients. Across the trials, the mean age of patients ranged from 30 to 34 years, the percentage of female patients ranged from 52.9% to 58.2% (Table 1).

Bias Assessment

All the four full-text articles were available for risk of bias assessment. Based on Cochrane Risk of Bias Tool, all of them were judged to have high risk of selection bias due to sequence generation and allocation concealment, performance bias due to blinding of participants and detection bias due to blinding of outcome assessment.

Intervention

In all the four included studies, 120 mg denosumab was injected subcutaneous every four weeks with loading doses on days eight and fifteen. Daily supplements containing 500 mg calcium or more and 400 IU vitamin D or more were taken by patients. The

median treatment duration ranged from 10.4 to 15.3 months.

Efficacy and Safety

Operative Method: Operative method with preoperative denosumab usage was evaluated in two studies [21,22]. A summary 87.4% (95%CI 83.2%-91.7%) of patients undergo surgery without surgical upstaging after the treatment duration. And the heterogeneity was low ($I^2 = 24.8\%$). A summary 60.7% (95%CI 34.9%-86.5%) of patients undergo surgery with less morbid operative method than planned. And the heterogeneity was high ($I^2 = 97.4\%$) (Figure 2). The proportion of patients underwent as planned and more morbid surgical method were also analyzed (Figure 3,4, See Supplementary Data).

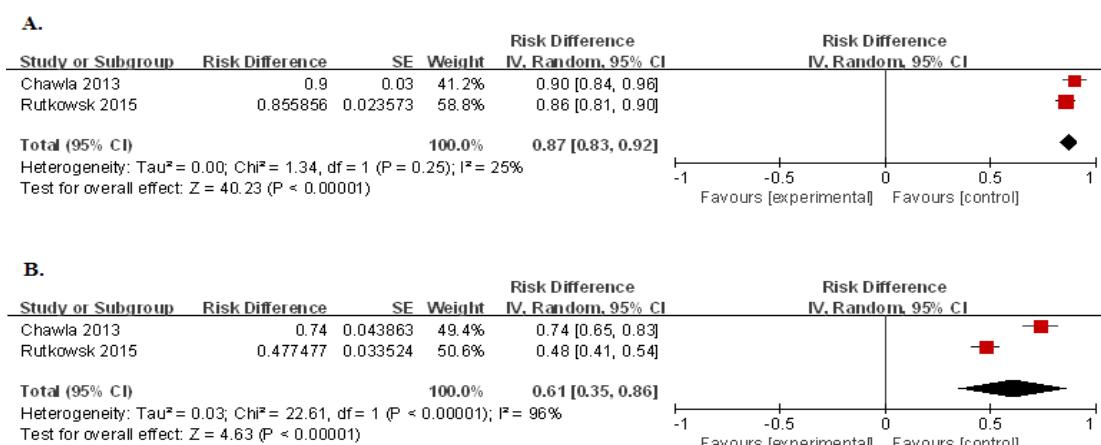


Figure 2: A: The forrest spots for the proportion of patients underwent surgery without surgical upstaging. B: The forrest spots for the proportion of patients underwent less morbid operative method.

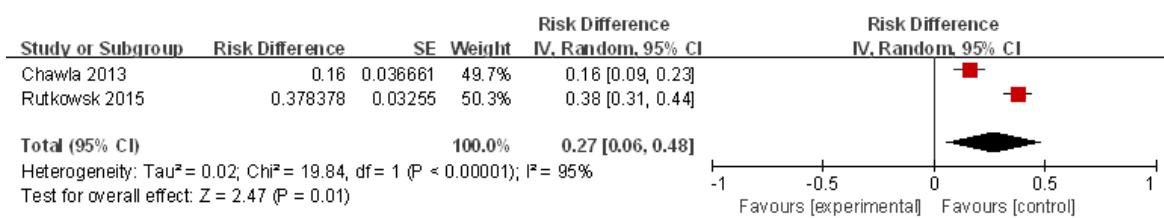


Figure 3: The forrest spots for the proportion of patients underwent operative method as planned.

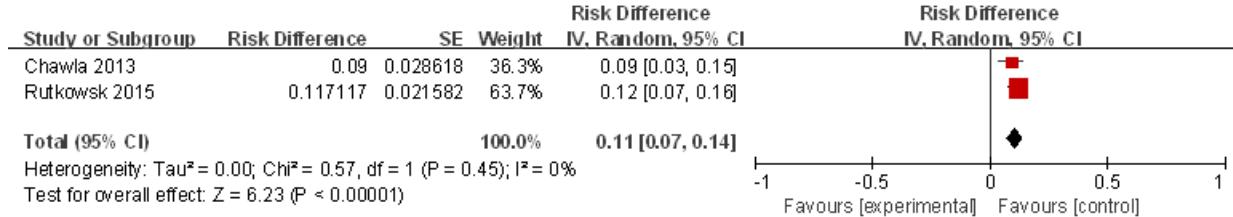


Figure 4: The forrest spots for the proportion of patients underwent more morbid operative method.

Tumor response on imaging: Evaluation of tumor response on imaging by three commonly used objective tumor response criteria were taken in two studies [21,23]. The criteria included modified Response Evaluation Criteria in Solid Tumors (RECIST) [24], modified European Organization for Research and Treatment criteria (EORTC) [25] and inverse Choi criteria [26]. Briefly, the three criteria are judged by the size, density or FDG uptake of tumor, based on the medical imaging result, including CT, MRI or PET. As there was available data of the proportion of patients undergo objective tumor response, meta-analysis of these outcomes was carried out (Figure 5, See Supplementary Data). The summary proportion of patients met any one of the three objective tumor response criteria mentioned above was 74.8% (95%CI 65.8%-83.8%). Statistical heterogeneity, as measured by I^2 , was low (27.3%) (Figure 6). The approximately median time to objective tumor response (months) was 3 months.

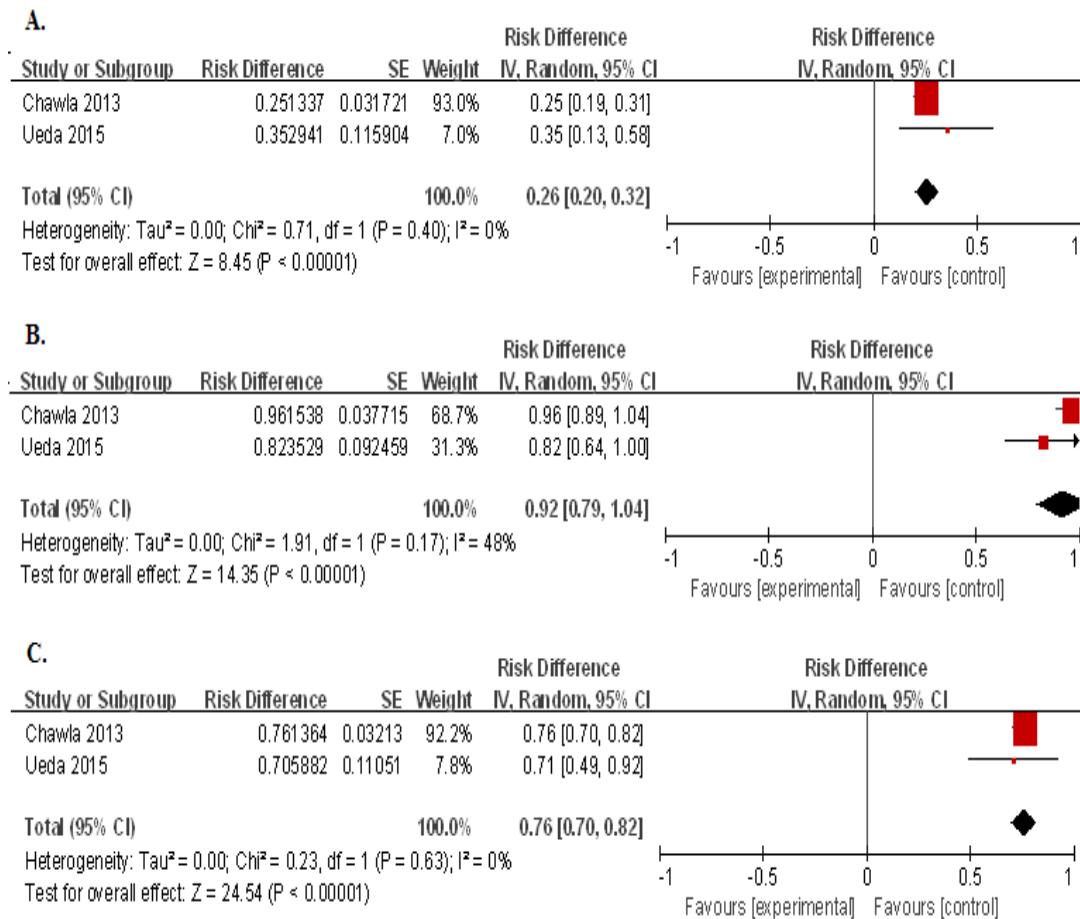


Figure 5: **A:** The forest spots for the proportion of patients met Modified RECIST criteria. **B:** The forest spots for the proportion of patients met Modified EORTC criteria. **C:** The forest spots for the proportion of patients met Inverse Choi criteria.

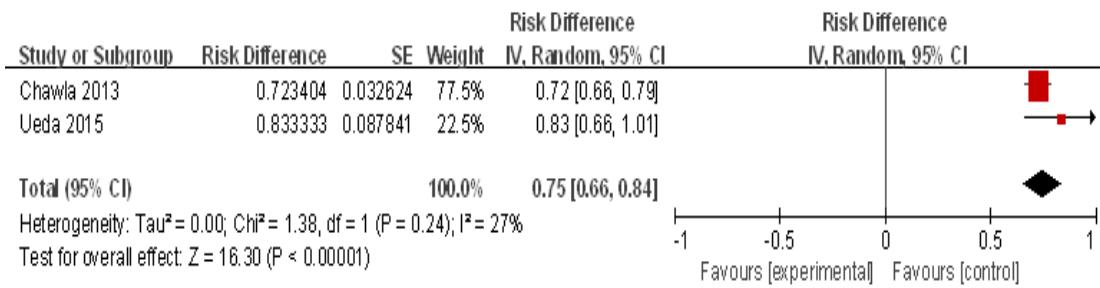


Figure 6: The forest plots for the proportion of patients met any one of the three objective tumor response criterias on imaging.

Adverse events: Analysis of adverse events was included in all the four studies. These four studies reported 479 adverse events in 558 patients. The most commonly noted adverse event were nasopharyngitis 29.4%(5/17), pain in an extremity 18.9% (7/37), arthralgia 19.6% (55/281) and arthralgia 24.8% in Ueda, Thomas, Chawla and Rutkowsk study respectively (Table 2).

Study	Thomas, et al.; 2010 [20]		Chawla, et al.; 2013 [21]	
Adverse events	Pain in an Extremity	7/37 (18.9%)	Arthralgia	55/281 (19.6%)
	Back pain	4/37 (10.8%)	Headache	51/281 (18.1%)
	Headache	5/37 (13.5%)	Nausea	48/281 (17.1%)
	Null	Null	Fatigue	45/281 (16.0%)
	Null	Null	Back pain	42/281 (14.9%)

continued

Study	Ueda, et al.; 2015 [23]		Rutkowsk, et al.; 2015 [22]	
Adverse events	Nasopharyngitis	5/17 (29.4%)	Arthralgia	55/222 (24.8%)
	Dental caries	4/17 (23.5%)	Fatigue	46/222 (20.7%)
	Influenza	4/17 (23.5%)	Pain in extremity	43/222 (19.4%)
	Injection site reaction	4/17 (23.5%)	Headache	42/222 (18.9%)
	Malaise	4/17 (23.5%)	Nausea	40/222 (18.0%)

Table 2. The summary of the adverse events frequently reported in the included studies.

Severity of adverse events was classified by Common Terminology Criteria for Adverse Event (CTCAE) in the included studies. Adverse events of grade 3 or higher were thought to be severe ones. Ueda study reported severe adverse events in 23.5% (4/17) of the patients. In Chawla study, severe adverse events included hypophosphataemia 3.2%(9/281), pain in extremity 1.1% (3/281), anaemia 1.1% (3/281) and back pain 1.1% (3/281). In Rutkowsk study, severe adverse events included hypophosphatemia 2.7 % (6/222) and pain in extremity 1.4 % (3/222). As the most commonly reported severe adverse event, a summary of 3.0% (95%CI 1.0%-4%) patients suffered from hypophosphatemia. And the heterogeneity was low ($I^2 =0\%$) (Figure 7, See Supplementary Data).

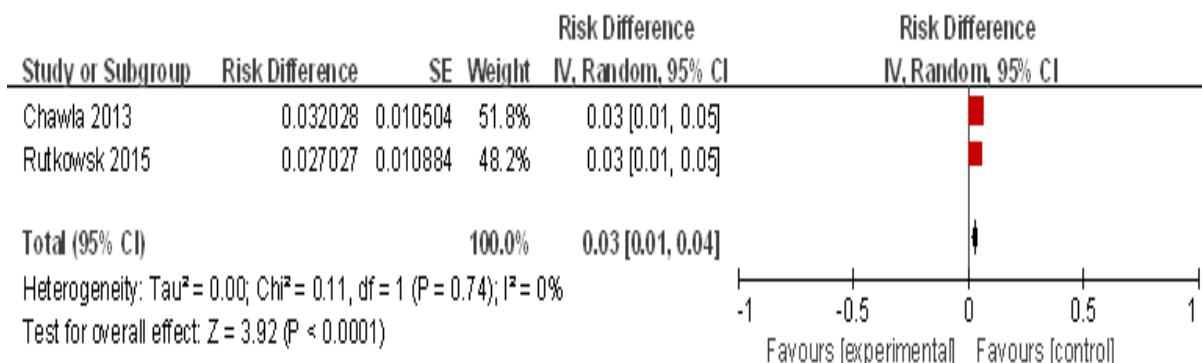


Figure 7: The meta-analysis result of severe adverse event hypophosphatemia. (Showing in supplementary data)

Adverse events of interest based on Medical Dictionary for Regulatory Activities and Common Terminology Criteria for Adverse Events were noted. The combined incidence rate and 95% convince interval of adjudicated positive osteonecrosis of jaw(ONJ), hypocalcaemia, infections and new primary malignancy was 0.7% (0.0%-1.5%), 4.2% (2.4%-5.9%), 6.9% (0.2%-13.6%) and 1.2% (0.1%-2.4%) respectively. The heterogeneity was low except in the synthesis of outcomes of infections (Figure 8).

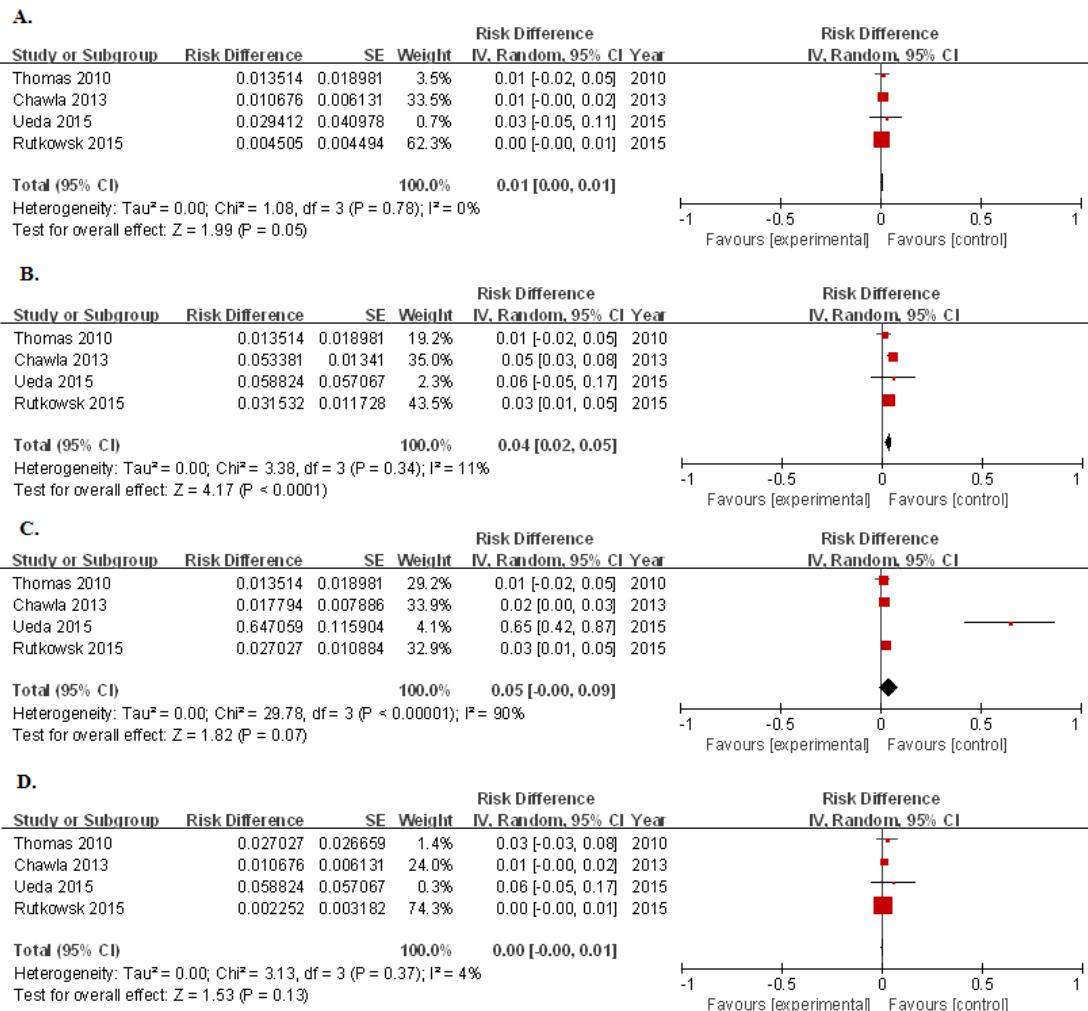


Figure 8: The meta-analysis result of four adverse events of interest. **A:** The meta-analysis result of adjudicated positive osteonecrosis of the jaw. **B:** The meta-analysis result of hypocalcaemia. **C:** The meta-analysis result of infections. **D:** The meta-analysis result of new primary malignancy.

Discussion

The principal regulators of bone resorption are the RANKL, RANK and OPG. The agents work by influencing osteoclast differentiation and activity. RANKL is a transmembrane soluble cytokine from the superfamily of the tumor necrosis factor receptors, highly expressed by the osteoblasts. Its receptor, RANK, is located on the cell membrane of osteoclast and pre-osteoclasts. RANKL/RANK binding stimulate the differentiation activity and survival of osteoclasts, resulting in increased bone resorption [27]. By binding RANKL and preventing RANK/RANKL interaction acting like a decoy receptor, OPG inhibits bone resorption and encourages bone formation [28]. Denosumab is a fully human monoclonal antibody to RANKL that has been designed to imitate the inhibiting actions of OPG over RANKL. By binding RANKL with high affinity and specificity, denosumab prevents RANKL and RANK interaction in a similar way to OPG, decreasing bone resorption [29]. It has been

used to treat osteoporosis, bone metastases from solid tumors, hypercalcemia of malignancy and unresectable GCTB.

In this systematic review, we analyze the efficacy and safety of denosumab for patients with GCTB. Five hundred and fifty-eight patients were included. In all the four included studies, 120 mg denosumab was injected subcutaneous every four weeks with loading doses on days eight and fifteen. Based on Cochrane Risk of Bias Tool, all of the four studies were judged to have high risk of selection bias, performance bias and detection bias mostly because of the lack of blind and comparision. As the role of denosumab in GCTB is still under investigation and there is recently no RCTs, it is acceptable for us to include these four studies in our systematic review under the circumstance of carefully evaluating the design of them. After the treatment duration, most patients undergo surgery without surgical upstaging, in detail over half of the patients taken less morbid operative method than planned. It

shows that denosumab can be significant in the adjuvant therapy before surgery, at least has a low risk at making a later surgical procedure more extensive.

In our work, we got the conclusion that a summary of 74.8% (95% CI 65.8%-83.8%) patients met any of the three objective tumor response criteria judged by the size, density or FDG uptake of tumor, based on result of CT, MRI or PET. The result gave prove to the usage of denosumab in treatment of primary lesion of GCTB. Our review included both resectable and unresectable GCTB patients. We may estimate that the indication of denosumab may be expanded to resectable GCTB patients, but more trials still need to be completed. When it comes to the safety of denosumab, based on researches from basic medicine, increased risk of infection, cancer, and dermatologic reactions has been a concern, as RANKL and RANK are expressed by a wide variety of cells, including T lymphocytes, B cells, and dendritic cells. However, there were no significant differences in the overall incidences of adverse events between patients who received denosumab and those who received placebo or alendronate in any of the phase 2, phase 3, or extension studies [30].

Based on our work, the occurrences of pain in either extremity or joint were not rare which can be noted in nearly twenty percent of the patients. But the incidence of pain over grade 3 was only one percent and normally would not result in the changing of treatment plan. In the clinical practice, we may not distinguish treatment-related or disease-related pain. Based on the facts above, the relatively high incidence of extremity or joint pain cannot be the obstacle of denosumab usage. Hypophosphataemia was the mostly commonly reported severe adverse event with the incidence around three percent based on results from two studies. So we recommend routinely measurement of serum phosphate level during denosumab therapy. Adjudicated positive ONJ, hypocalcaemia, infections, and new primary malignancy were thought to be adverse events of interest. Based on the accessed information and meta-analysis, the incidence of them was not high but still existed. Due to the high treatment-related effect, these adverse events cannot be ignored. The signs and symptom of ONJ and infection need to be carefully checked. The serum calcium level should be monitored. Routinely whole body CT scanning is beneficial to exclude the possibility of new primary malignancy.

Limitations of The Analysis

To our knowledge, no systematic review has analyzed the safety and efficacy of denosumab in GCTB patients. It's unfortunately that there were no proper data for analyzing of duration of therapy and recurrence rate during long time follow-up visit of denosumab treatment. The heterogeneity of meta-analysis seemed to be high. To our knowledge, no RCT were searched by source we got and only six trials with different design. As giant cell tumor of bone is a low overall incidence and invasive behavior. RCT cannot be possible in this early stage because the sample is limited and the treatment strategy of giant cell tumor of bone nowadays is proved to benefit most of the patients. Although the design was different between trials, but individually, each study

was of fairly good quality. Although the heterogeneity was high to some extent, the conclusion we got were still meaningful.

Conclusion

In this systematic review and meta-analysis of studies of GCTB and denosumab, the efficacy in operative method and tumor response on imaging were noted. Adverse events were rare and can be monitored. Measurement of serum marker of infection, phosphate level and calcium level were recommended during denosumab therapy. However, a series of RCT studies were needed to strengthen the evidence of the efficacy and safety of denosumab. Duration of denosumab therapy and recurrence rate during long time follow-up visit should be emphasized in further studies.

Conflict of Interest Statement

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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