DERLEME REVIEW

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The Efficacy and Safety of Denosumab for Treating Giant Cell Tumor of Bone: A Systematic Review and Meta-Analysis

Kemiğin Dev Hücreli Tümörünün Tedavisinde Denosumabın Etkililiği ve Güvenliliği: Sistematik Bir Derleme ve Meta-Analiz

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ABSTRACT The adjuvant treatment of denosumab for the management of giant cell tumor of bone (GCTB) has been widely investigated. However, the inconclusive findings were observed. Therefore, our study aimed to assess the efficacy of denosumab for the adjuvant therapy in the management of GCTB. We conducted a meta-analysis study during the period of February-August. Article search was conducted in PubMed, ScienceDirect, and Cochrane library. The predictor was denosumab administration, and the outcomes measures were local recurrence, blood loss, Musculoskeletal Tumor Society (MSTS) score, lung metastase, and malignant transformation. Data were analyzed using Z test to evaluate the association. We included 11 papers, consisting of 253 cases and 1,145 controls. The quality of the included article was evaluated using the Newcastle-Ottawa scale (NOS). Our results identified that denosumab administration was associated with lower blood loss and improved MSTS score compared to those without denosumab administration in patients with GCTB. However, GCTB patients with and without denosumab administration shared similar findings in the context of local recurrence, lung metastase, and malignant transformation. Our study has verified that denosumab administration as an adjuvant treatment for the management of GCTB is associated with lower blood loss during surgical procedure and improved MSTS score.

Keywords: Giant cell tumor of bone; denosumab; blood loss; local recurrence; Musculoskeletal Tumor Society score

ÖZET Kemiğin dev hücreli tümörünün (KDHT) yönetiminde denosumab ile adjuvan tedavi geniş olarak araştırılmıştır. Fakat birbiriyle uyuşmayan sonuçlar gözlenmiştir. Bu nedenle çalışmamızda KDHT'nin yönetiminde adjuvan tedavi için denosumabın etkinliğinin değerlendirilmesi amaçlanmıştır. Şubat-Ağustos döneminde bir meta-analiz çalışması gerçekleştirdik. PubMed, ScienceDirect ve Cochrane kütüphanesinde makale araştırması yapıldı. Ön gördürücü denosumab uygulaması idi ve sonuç ölçümleri lokal nüks, kan kaybı, Kas-iskelet Tümörleri Derneği (Musculoskeletal Tumor Society -MSTS) skoru, akciğer metastazı ve malign transformasyon idi. Veriler ilişkiyi değerlendirmek için Z testi ile incelendi. Toplam 253 olgu ve 1.145 kontrol içeren 11 yazıyı aldık. Dahil edilen makalenin kalitesi Newcastle-Ottawa ölçeği (NOS) kullanılarak değerlendirildi. Bulgularımız denosumab uygulamasının KDHT olan ve denosumab uygulanmayan hastalar göre daha az kan kaybı ve daha iyi MSTS skoru ile ilişkili olduğunu göstermiştir. Fakat denosumab uygulanan ve uygulanmayan hastalar lokal nüks, akciğer metastazı ve malign transformasyon bakımından benzer sonuçlara sahipti. Çalışmamız KDHT yönetiminde adjuvan tedavi olarak denosumab uygulamasının cerrahi işlem sırasında daha az kan kaybı ile ve daha iyi MSTS skoru ile ilişkili olduğunu doğrulamıştır.

Anahtar Kelimeler: Kemiğin dev hücreli tümörü; denosumab; kan kaybı; lokal nüks; Kas-iskelet Tümörleri Derneği skoru

Giant cell tumor of bone (GCTB) is a benign tumor of bone and is considered as a local aggressive tumor of bone.[1-7] The variation incidence of GCTB was reported between 1.03 and 1.66 per 1,000,000 population.[8] Among them, the mortality rate was 23%.[9] Currently, the management of GCTB was conflicting, and the surgical management is the widest treatment used, such as: wide resection and curratage.[4,10-12] The wide

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resection procedure was reported having low incidence of local recurrence, however, massive destruction of bone and joint which is associated with poor functional outcome was observed. On the other hand, while curretage was associated with low incidence of joint destruction, the higher rate of GCTB recurrence was observed.[3,10,11,13-16] Therefore, in effort to decrease the local recurrence and decrease morbidity, the adjuvant treatments were warranted. The choice of adjuvant therapies were liquid nitrogen, cryotherapy and filling with bone cement, polymethylmethacrylate, phenol, alcohol, high-speed burr, denosumab, and biphosphonate zoledronic acid.[1,3,14,17] Of those, denosumab was considered the promising treatment for the adjuvant therapy in patients with GCTB.[16,18]

Denosumab is a monoclonal antibody in human, and a number of previous studies revealed that denosumab inhibited osteoclastogenesis by disturbing the interaction between RANKL-positive stromal cells and RANK-positive osteoclast like giant cells.[4,19-23] Denosumab was first introduced in 2006, and initially it was used for treating severe osteoporosis.[24,25] Furthermore, denosumab was used for the management of some diseases, such as: osteoporosis in postmenopausal women, breast cancer or prostate cancer which prevent pathological fracture caused by lack of androgen hormone, and other metastatic bone diseases. In 2013, denosumab was approved by the U.S. Food and Drug Administration to use for treating GCTB in mature adolescence when the tumor is unresectable or the surgery procedure tends to lead severe morbidity.[3,5,26] Moreover, the investigations had been performed to assess the efficacy of denosumab for treating GCTB in United States, Australia, Europe, and China.[3,16,27] However, inconclusive findings were observed across the studies. Therefore, the aims of our present study were to assess the efficacy of denosumab for the management of GCTB using meta-analysis approach. Our current study might provide the answer of conflicting findings on the use of denosumab for the management of GCTB.

MATERIAL AND METHODS

STUDY DESIGN

Our current study conducted a systematic review and meta-analysis to evaluate the efficacy of denosumab for treating GCTB and to evaluate the potential complication of denosumab in patients with GCTB. Those potential efficacies involved decreased blood loss during operation and Musculoskeletal Tumor Society (MSTS) score. The potential complications included lung metastasis, local recurrence, and malignant transformation. To obtain the adequate data for the calculation of the combination of odd ratios (ORs) and 95% confidence intervals (95% CIs), a systematic search was performed in PubMed, Cochrane, and ScienceDirect. The protocols for the systematic review and meta-analysis were performed according to the checklist outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[28]

INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria were: 1) Evaluating the efficacy of denosumab for treating GCTB; 2) The study design were observational studies (case-control or cohort or cross-sectional) and randomized controlled trials (RCTs); 3) Providing sufficient data for the calculation effect estimates in double arm model; 4) The articles were written in English. Studies were excluded if they were review articles, animal or cell experiments, having insufficient data presentation, and duplicate publications. The data from each study was extracted using a pilot form: 1) Author name; 2) Publication year; 3) Study location; 4) Study design; 5) Sample size of patients treated with denosumab and without denosumab; 6) Dosage of denosumab; 7) Effect estimate between patients treated with denosumab and without denosumab.

SEARCH STRATEGY

We searched comprehensively, using English language only, from major scientific databases (PubMed, Cochrane, ScienceDirect) up to February 12, 2021. The following keywords were used in literature search: (“Giant Cell Tumor” OR “Giant Cell Tumor of Bone” OR “GCTB”) and (“Denosumab” OR “Recurrence” OR “Metastasis”) and (“Efficacy” OR “Safety”). We also conducted the searching strategy in the reference list of the potential article to obtain the additional papers.

ASSESSMENT OF THE METHODOLOGICAL QUALITY

Before including the studies, we performed the evaluation of potential articles using Newcastle-Ottawa Scale (NOS), to assess the methodological quality of the potential article. This evaluation might interprete the study having low, moderate, or high quality. Articles with moderate to high quality were included in our analysis.[29] Two independent investigators (CAD and AS) performed assessment of the study using a standardized pilot form.

STUDY MEASURE

The predictor of our study was denosumab treatment. The outcome measures were local recurrence, reduced blood loss, lung metastasis, malignant transformation, and MSTS score. Local recurrence is defined as new-onset of pain, swelling, and disturbance in range of motion during post-operative period and there was evidence by magnetic resonance imaging that new lesion was appeared.[19] Blood loss was presented by the amount of intraoperative blood loss.[16,19,30] Malignant transformation was defined as secondary tumor recurrence and confirmed by post-operative pathological examination.[4,30,31] Lung metastasis was presented by computed tomography scan of the chest.[19,32] We evaluated functional outcomes based on MSTS score. MSTS score is a questionarre which is developed by Enneking et al. for measuring functional outcome in neoplasm patients.[33]

STATISTICAL ANALYSIS

Review Manager version 5.3 (Revman Cochrane, London, United Kingdom) was used for analyzing the data. The association between denosumab administration and the efficacy (potential reduced blood loss during surgery and increase MSTS score) and safety (prevent recurrence, malignant transformation, and lung metastasis) in patients with GCTB was evaluated by the calculation of the effect estimate (a pooled OR and 95% CI). The combination of effect estimates was conceived in forest plot. We used Z test for determining the significance of the pooled ORs ($p<0.05$ was classified in statistically significant). Heterogeneity across the studies was analyzed with Q test. A random effect model will be adopted if heterogeneity existed ($p<0.10$). If the studies did not have heterogeneity ($p>0.10$), the fixed effect model was adopted. Publication bias among the included studies was assessed by performing an analysis using Egger's test and presented in a funnel plot ($p<0.05$ was indicated potential publication bias existed).

RESULTS

ELIGIBLE STUDIES

We obtained 1,121 qualifying studies and we excluded 750 studies after assessing the abstracts. Furthermore, we performed an assessment of the full text for 50 potential studies. Additionally, we excluded 39 studies (15 review articles, 5 meta-analyses, 3 articles with low NOS quality, and 16 papers having insufficient data). Totally, we only included a total of 11 studies in our meta-analysis.[4,10,16,19,30,31,34-37] We summarize the paper selection in Figure 1. We describe the baseline characteristics of our studies in Table 1.

THE EFFICACY OF DENOSUMAB FOR TREATING GCTB

From our data synthesis, we assessed blood loss, local recurrence, MSTS score, lung metastase, and malignant transformation. Of them, we found that reduced blood loss [mean difference (MD): -0.59; CI: -0.89, -0.28] was observed in patients receiving denosumab compared to those without denosumab administration (Figure 2). We also found that patients treated with denosumab had better MSTS score compared to those without denosumab administration (MD: 0.27; CI: 0.00, 0.54) (Figure 3). On the other hand, we found that patients treated with and without denosumab administration had similar risk to develop local recurrence (OR: 1.85; CI: 0.89, 3.84) (Figure 4). While, we failed to clarify the association between denosumab administration and the risk of lung metastase (OR: 1.01; CI: 1.01, 0.33) and malignant transformation (OR: 2.07; CI: 0.11, 40.03) (Table 2).

SOURCE OF HETEROGENEITY

Local recurrence and malignant transformation showed evidence of heterogeneity. Therefore, we ap-

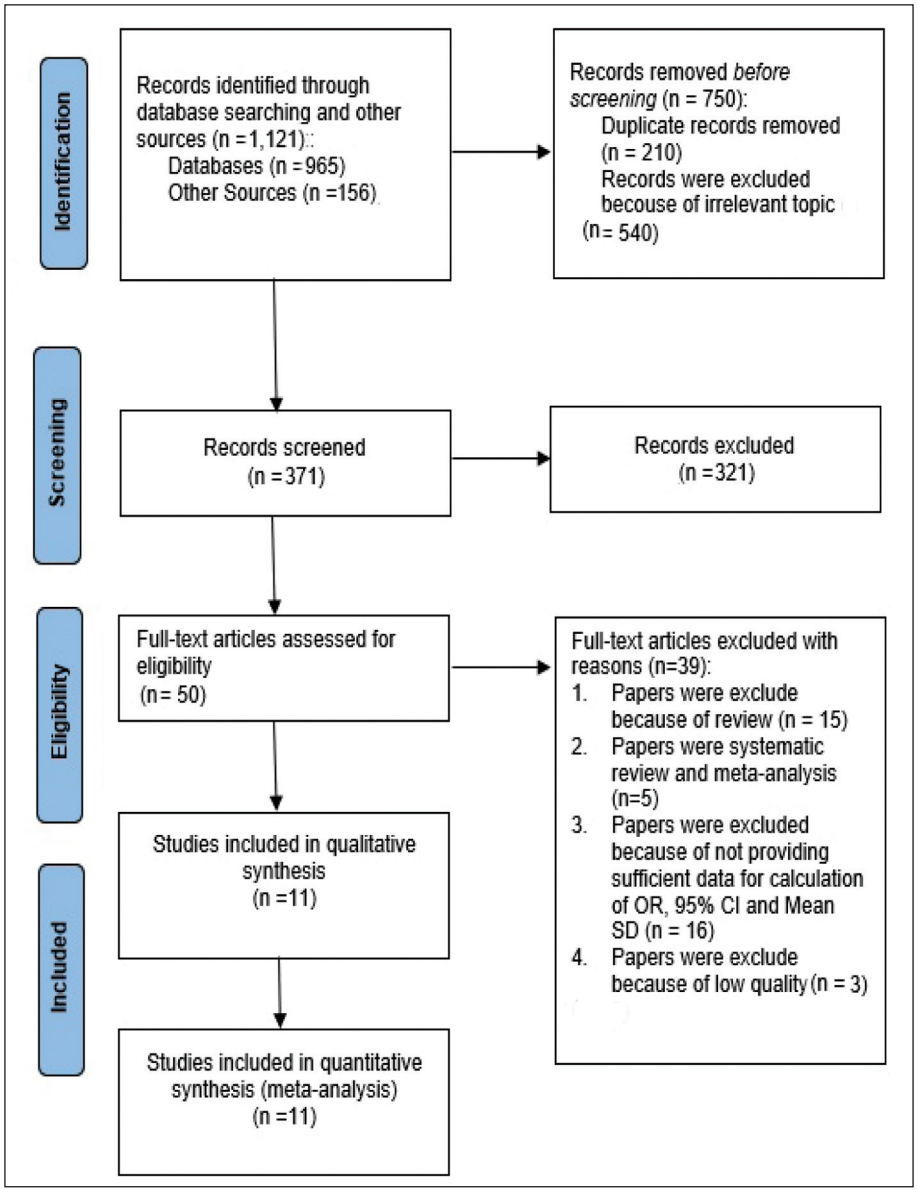

FIGURE 1: A flowchart of paper selection in our study. OR: Odd ratio; CI: Confidence interval; SD: Standard deviation.

plied the random effect model to assess the data. On the other hand, the fixed effect model was applied to assess the data on reduced blood loss, lung metastasis, and MSTS score, because no evidence of heterogeneity was observed.

POTENTIAL PUBLICATION BIAS

We evaluated the probability of publication bias among studies using Egger's test. Our evaluation showed that publication bias ($p<0.05$) was only found in lung metastasis covariate.

DISCUSSION

Our findings revealed that denosumab was associated with reduced blood loss during operation and increased functional outcome in patients with GCTB. Previous systematic review in this context had been performed, and our findings were consistent with previous systematic review. They also found that denosumab was proven having good effectivity for reducing tumor size, pain, and morbidity of surgical procedure in patients with GCTB. Moreover, they

TABLE 1: Baseline characteristics of studies included in our analysis.

Author & year	Country of origin	Study design	Sample size		Dosage	Quality assessment
			Case	Control		
Chen et al. 2018[4]	China	Retrospective cohort	20	10	Denosumab 120 mg by subcutaneous injection every four weeks.	Good quality
Chinder et al. 2019[19]	India	Retrospective cohort	42	81	120 mg denosumab was administered subcutaneously once every 4 weeks, with booster doses on day 7 and day 15 of the first month.	Good quality
Errani et al. 2018[10]	Italy	Retrospective cohort	25	222	Preoperatively, denosumab 120 mg was given subcutaneously once a week for 1 months and then once a month for 6 to 12 months. Postoperatively, the denosumab was given at the same dossage once a month for 3 to 7 months.	Good quality
Lim et al. 2020[30]	China	Retrospective cohort	25	37	Preoperative, denosumab 120 mg was given by subcutaneously on days 1, 8, 15, and on day 28 and after that every four weeks before surgery. Postoperative, denosumab was given monthly.	Good quality
Murphy et al. 2020[31]	Australia	Retrospective cohort	21	133	Denosumab 120 mg was given subcutaously on days 1, 8, and 15 of the first month. After that denosumab 120 mg was given monthly for 3-6 months.	Moderate quality
Sano et al. 2020[34]	Japan	Retrospective cohort	24	54	Not reported	Good quality
Scoccianti et al. 2018[35]	Italy	Retrospective cohort	12	9	120 mg denosumab was given every week subcutaneously for 3 week and then onthly for 3 months.	Good quality
Tsukamoto et al. 2018[32]	Japan	Retrospective cohort	30	381	Preoperatively, denosumab was administered subcutaneously 120 mg once a week for 1 month and then once a month for 6 to nine monthhs. Post-operatively, denosumab was given with same dossage for 3 and 7 months.	Good quality
Urakawa et al. 2018[36]	Japan	Retrospective cohort	40	158	Not reported	Moderate quality
Yang et al. 2018[16]	China	Case control studies	6	10	120 mg of denosumab was given subcutaneously every 4 weeks with additional dossage administered on days 8 and 15 during the first month.	Good quality
Zou et al. 2018[37]	China	Retrospective cohort	8	50	Preoperatively, denosumab was given subcutaneously at dosage of 120 mg on day 1, day 8, day 15 and day 29 as the loading dosage for the first month. 120 mg per four weeks thereafter.	Good quality

also found no correlation between denosumab administration and lung metastase, local recurrence, and malignant transformation.[38] However, a study by Chen et al. provided a contrast to our findings.[39] They found that denosumab administration had higher risk to develop local recurrence, especially if denosumab was given pre-operatively. However, their studies had several important limitations. Their studies were systematic review only and involved several case reports, suggesting that the findings might have high

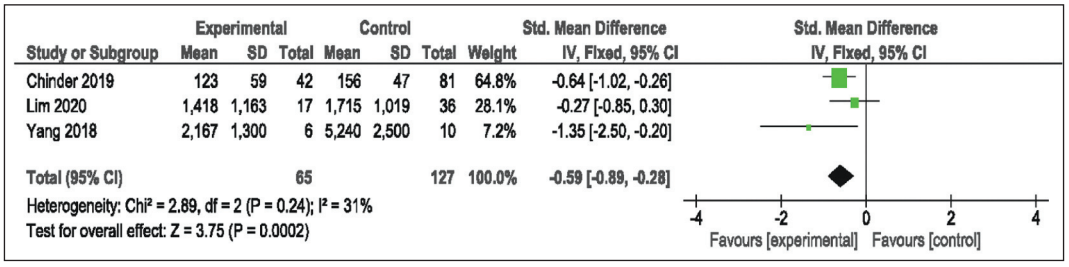

FIGURE 2: A forest plot of the association between denosumab can reduce blood loss in patients with giant cell tumor of bone. SD: Standard deviation; CI: Confidence interval; df: Degree of freedom; IV: Inverse variance.

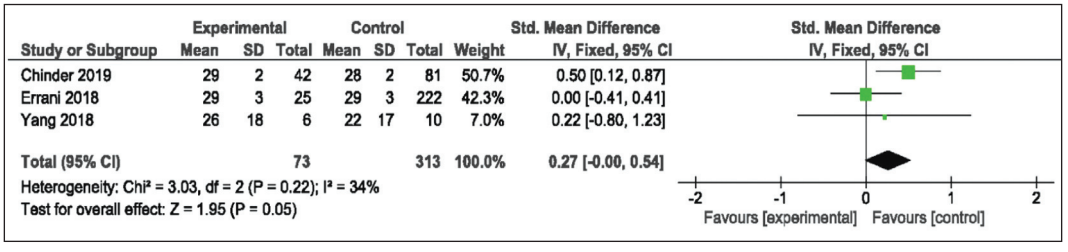

FIGURE 3: A forest plot of the association between denosumab and functional outcome based on Musculoskeletal Tumor Society score in patients with giant cell tumor of bone. SD: Standard deviation; CI: Confidence interval; df: Degree of freedom; IV: Inverse variance.

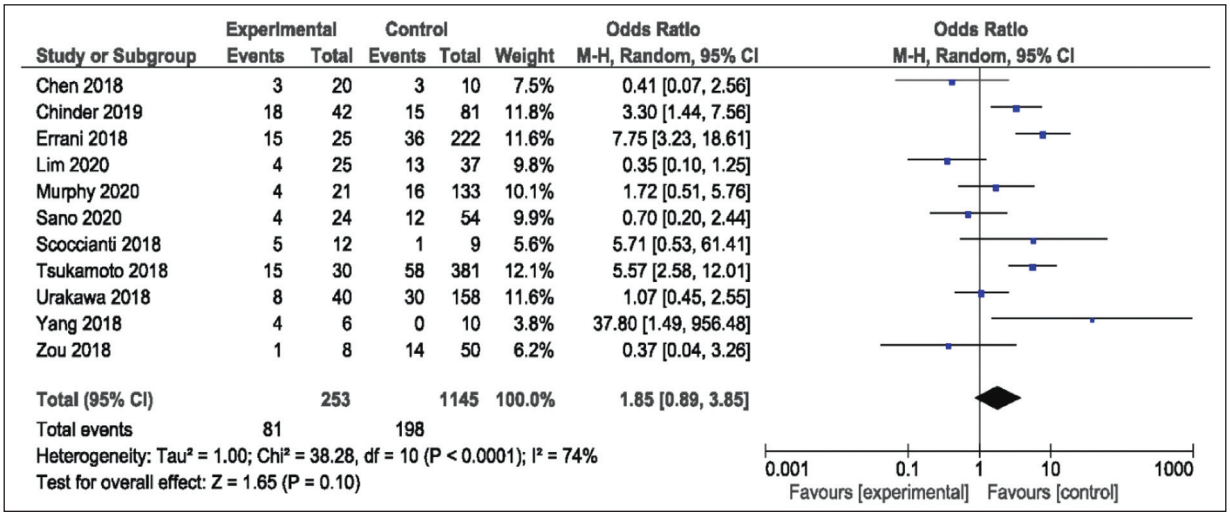

FIGURE 4: A forest plot of the association between denosumab and local recurrence in patients with giant cell tumor of bone.
CI: Confidence interval; df: Degree of freedom.

risk of bias due to no risk calculation. Moreover, our present study had a larger sample size. Previous study only involved 169 cases and 913 controls. Our present study included 253 cases and 1,145 controls. Therefore, our present study might provide better evidence on the efficacy of denosumab for treating patients with GCTB.

The theory underlying our findings between reduced both blood loss and better MSTS score and denosumab administration remained debatable. However, some possible reasons might be proposed. First, denosumab might reduce the angiogenesis of GCTB.[12,16,40] Briefly, denosumab is a monoclonal antibody which may inhibit osteoclastogenesis by dis-

TABLE 2: Summary of the efficacy and potential risk of denosumab for treating GCTB.

Outcomes	Model	NS	Denosumab	Control	Effect size	95% CI	pHet	pE	p value
Local reccurence	Random	11	32.01	17.29	1.85	0.89-3.84	0.0000	0.9950	0.0970
Reduced blood loss	Fixed	3	1236.0±1034.1	2370.3±2604.6	-0.599	-0.91-(-0.29)	0.1910	0.2540	0.0000
Lung metastasis	Fixed	3	4.12	3.80	1.01	1.01-0.33	0.9130	0.0000	0.9870
Malignant transformation	Random	3	4.54	1.11	2.07	0.11-40.03	0.0600	2.1020	0.6300
MSTS score	Fixed	3	28.0±1.7	26.3±3.8	0.27	0.01-0.54	0.2160	0.1900	0.0500

Note, data were presented in mean±standard deviation or n (%); GCTB: Giant cell tumor of bone; NS: Number of studies; pE: p Egger; pHet: p Heterogenity; OR: Odd ratio; CI: Confidence interval; MSTS: Musculoskeletal Tumor Society.

turbing the interactions between RANKL-positive stromal cells and RANK-positive osteoclast like giant cells. In this process, denosumab may bind to RANKL, and as a result, osteoclast-like giant cells may not be formed.[3,19,21,27] Furthermore, a study also revealed that denosumab administration was associated with decreased GCTB which is represented by proliferation of tumor stromal cells to woven bone, mature bone and non-proliferative osteoid bone matrix.[21,30,41,42] This transformation was proposed to reduce angiogenesis, and therefore might reduce blood loss.[24,40] Second, denosumab administration might be associated with the shrinking and calcifying the tumor cell. This mechanism might lead the formation of pseudocapsule on the rim of tumor, and therefore it might cause the surgeon easy for resection.[42] Therefore, it was reliable that, in our study, denosumab administration was associated with reduced blood loss and better MSTS score among patients with GCTB.

In our present meta-analysis, we emphasized that denosumab administration had a good efficacy to reduce blood loss and improve the MSTS score in patients with GCTB. Our current findings might support the previous evidence that the use of denosumab had a good efficacy for treating patients with GCTB. Moreover, interestingly, our finding might break the previous opinion that denosumab was associated with increased risk of local recurrence. In our findings, the evidence in the context of association between denosumab administration and the risk of local recurrence was failed to clarify. However, further investigations with holistic designs are warranted to elucidate the real efficacy of denosumab for treating GCTB.

We had several limitations in our meta-analysis. First, the period and duration of denosumab treatment was undefined properly in each study. Therefore, we could not perform a sub group analysis in the context of time-dependent. Second, the dosage of denosumab administration varied in each study, and therefore, this discrepancy might contribute to the risk of bias. Third, the surgery method varied in each study, and this variation might also lead the potency of false positive findings. Fourth, a limited investigation on the role of denosumab in the case of GCTB had made us to recruit the limited number of sample size. Therefore, an interpretation with caution should be applied. Fifth, most of our included papers were non-randomized controlled trials. Therefore, to achieve the better levels of evidence, the up-coming studies only involved randomized controlled trial studies might be required.

CONCLUSION

Our current study has identified that denosumab administration has a good efficacy to reduce blood loss and improve the MSTS score for treating patients with GCTB. We also find that the potential complications including local recurrence, lung metastase, and malignant transformation were failed to verify after denosumab administration. However, further studies are required to elucidate the optimal dosage, treatment period, route of administration, and the method of surgery.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that pro-

vides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Chairul Arby Desiyanto;* ***Design:*** *Chairul Arby Desiyanto;* ***Control/Supervision:*** *Chairul Arby Desiyanto, Jonny Karunia Fajar;* ***Data Collection and/or Processing:*** *Chairul Arby Desiyanto, Astri Soetanto, Jonny Karunia Fajar;* ***Analysis and/or Interpretation:*** *Chairul Arby Desiyanto, Rady Dwipayana, Rieva Ermawan, Iwan Sutanto, Jonny Karunia Fajar;* ***Literature Review:*** *Chairul Arby Desiyanto, Rady Dwipayana, Rieva Ermawan, Iwan Sutanto;* ***Writing the Article:*** *Chairul Arby Desiyanto, Rady Dwipayana, Rieva Ermawan, Iwan Sutanto, Astri Soetanto, Jonny Karunia Fajar;* ***Critical Review:*** *Chairul Arby Desiyanto, Rady Dwipayana, Rieva Ermawan, Iwan Sutanto, Astri Soetanto, Jonny Karunia Fajar;* ***References and Fundings:*** *Chairul Arby Desiyanto, Rady Dwipayana, Rieva Ermawan, Iwan Sutanto, Astri Soetanto, Jonny Karunia Fajar.*

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