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Denosumab Treatment for Patients with GCTB

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Current clinical trials of denosumab for patients with giant cell tumor of bone (GCTB) have shown safety and efficacy (1, 2). Denosumab treatment can achieve beneficial tumor response, surgical downstaging, and decreased surgical morbidity in patients with GCTB (3). Thus, denosumab is considered a promising neoadjuvant treatment for this disease.

Previous research on denosumab focused on adverse events such as osteonecrosis of the jaw, hypophosphatemia, or hypocalcemia. Although some scholars have expressed concern that this drug may cause local recurrence or malignant transformation, no study to date has proved that hypothesis. In this *JBJS* study, Errani et al. explore the role of denosumab treatment on local recurrence among GCTB patients, with a median follow-up of 85.6 months. These authors found that the local recurrence rate (60%) in 25 patients treated with curettage and denosumab was significantly higher than that (16%) in 222 patients treated with curettage alone, indicating that denosumab may be a risk factor for local recurrence in patients with GCTB. Errani et al. suggest that shorter follow-up times may explain why previous researchers did not get this result (1, 2, 4). However, in a relatively long follow-up study (median 30 months), Traub et al. (5) found that denosumab may not affect the local recurrence rate for resected GCTB.

Errani et al. discussed the main limitation of their study, namely that they could not evaluate causation between denosumab usage and local recurrence, due to substantial differences in the cohorts and lack of a randomized trial design. However, in addition to the risk factors explored in this study, there are other risk factors that should be carefully considered when conducting similar studies. For example, denosumab is usually used in patients with advanced GCTB, and they often have soft-tissue extension, cortical destruction, or joint involvement (5, 6). The clinical and radiological performance of these patients is worse than that of less severely affected patients, and advanced GCTB may contribute to the increased risk of local recurrence.

The presence of pathological fracture, the size of soft-tissue extension, and the degree of joint involvement should be balanced in the cohorts when investigating this question. Tumor size is a very important nonsurgical factor for local recurrence in most tumors, including GCTB (7). The size of tumors before and after denosumab treatment would be a very interesting question to investigate. Additionally, the optimal duration, interval, and dosing of denosumab treatment remain unknown. Different protocols may lead to different results. Therefore, it is necessary to standardize the use of this drug in future GCTB studies, especially when conducting multicenter studies.

In summary, this study was not able to confirm a cause-and-effect relationship between denosumab treatment and local recurrence in GCTB patients following curettage. However, it reminds us that we should better understand the optimum indication for denosumab in GCTB and use this medication with caution. The clinical effects of denosumab on GCTB must be evaluated thoroughly, and a well-controlled randomized clinical trial is especially needed to determine the effect of denosumab treatment on local recurrence in patients with resected GCTB.

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Conflict of Interest: None Declared

Article Author Response

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Article Author(s) to Letter Writer(s)

We thank Wang et al. for their letter. Our study showed that for the 25 patients treated with curettage and denosumab, the median duration of follow-up was 42.1 months (IQR, 37.4 to 50.8 months). The duration of follow-up in our study was longer than the duration that Traub et al. reported, which may explain the higher local recurrence rate in the denosumab group.

Regarding the comment by Wang et al. that advanced GCTB may contribute to the increased risk of local recurrence, >21% of the tumors we studied were Campanacci stage III, so we included information about tumors with soft-tissue extension, cortical destruction, or joint involvement.

Regarding the comment by Wang et al. about tumor size and denosumab dosing, we would like to investigate the association between tumor size and local recurrence in the future. We did report the tumor response (the size of tumors before and after denosumab) in this study. We agree that the optimal duration, interval, and dosing of denosumab treatment should be further investigated in more cases with multicenter

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studies.

Finally, we completely agree with Wang et al. that “a well-controlled randomized clinical trial is especially needed to determine the effect of denosumab treatment on local recurrence in patients with resected GCTB.”