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GFFCC-ESTRO COOPERATION

The Management of Breast and Colorectal Cancer
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16-18 November 2019
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**Abstract**

Giant cell tumor of bone (GCTB) is a biologically benign osteolytic tumor that affects the metaphyseal/epiphyseal portions of bones. Histologically, GCTB is composed of osteoclast–like multinucleated giant cells that express receptor activator of nuclear factor kappa B (RANK), and neoplastic mesenchymal stromal cells that express RANK ligand (RANKL). The pathogenesis of GCTB is primarily attributable to the RANK–RANKL interaction, resulting in the activation of osteoclasts and the resultant osteolytic phenotype. Denosumab is a monoclonal antibody targeted against RANKL. In 2013, it was approved by the United States Food and Drug Administration (FDA) for the treatment of adults and skeletally mature adolescents with GCTB that is inoperable, or initial surgery is expected to culminate in substantial morbidity. The aim of this study is to narratively review the current literature on the role of preoperative denosumab followed by surgery in the management of patients with GCTB. In brief, caution should be exercised in the interpretation of existing data on preoperative denosumab in the management of GCTB patients, owing to some critical limitations, for example, short follow-up and only a minority of patients have undergone intralesional surgery following denosumab therapy. All in all, administration of preoperative denosumab is associated with clinical, radiological, and histopathological therapeutic benefits. It is also associated with tolerability, safety, surgical downstaging and less morbid salvageable procedures. Preoperative denosumab does not seem to reduce the likelihood of local recurrence after intralesional therapy; a planned randomized phase III clinical trial (JCOG 1610) will holistically address this concern. Furthermore, more than ten cases of denosumab–related malignant transformation of GCTB have been reported in literature. Lastly, large–sized phase III randomized clinical trials with long–term follow–up data are warranted to withdraw concrete conclusions and recommendations.

**Keywords:** preoperative; denosumab; surgery; giant cell tumor of bone; curettage

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**Introduction**

Giant cell tumor of bone (GCTB), also known as osteoclastoma, is a biologically benign osteolytic tumor that affects the metaphyseal/epiphyseal portions of bones. Histologically, GCTB is composed of osteoclast–like multinucleated giant cells that express receptor activator of nuclear factor kappa B (RANK), and neoplastic mesenchymal stromal cells that express RANK ligand (RANKL). The pathogenesis of GCTB is primarily attributable to the RANK–RANKL interaction, resulting in the activation of osteoclasts and the resultant osteolytic phenotype. Despite the benign nature of GCTB, it can present with primary local aggressiveness, causing severe bone destruction and invasion into adjacent soft tissues.
has a low metastatic potential, and the rate of distant metastasis has been estimated to range from 1–3%, with the lungs being the most frequent sites. Generally, the optimal treatment of GCTB remains widely debatable. However, surgery stands out as the gold standard, and it provides the definitive therapy whenever technically possible. Surgical intervention may be associated with considerable morbidity, and recurrence rates range from as low as 0% to as high as 75%, depending on the size and site of the lesion, as well as type of the surgical intervention. Surgical treatment options typically comprise intralesional surgery (curettage) and en bloc resection. Intralesional surgery (with or without local adjuvants) is conservative in nature and largely preserves the joint function. However, it is associated with higher recurrence rates. On the other hand, en bloc resection with wide margins is debulking in nature. Furthermore, although it is associated with lower recurrence rates, it is accompanied by worse postoperative functional outcomes. Indeed, local recurrence of GCTB continues to be a major problem in the clinical management.

Unfortunately, at the time of clinical diagnosis, approximately 80% of GCTB patients present with primary locally advanced tumors that are not potentially feasible for surgical intervention. Besides, in such patients, initial surgery will be associated with potential severe morbidity (for example: joint resection, limb amputation and graft reconstruction). This subset of patients presents substantial challenges in clinical management. An optimal approach should be directed towards: [i] inducing preoperative beneficial tumor response (clinically, radiologically and histologically), [ii] prompting surgical downstaging, [iii] minimizing surgery–related procedural morbidity, and [iv] reducing the rate of local recurrence.

Denosumab (Xgeva®, subcutaneous injection; Amgen, Thousand Oaks, CA, USA) is a monoclonal antibody targeted against RANKL. In 2013, it was approved by the United States Food and Drug Administration (FDA) for the treatment of adults and skeletally mature adolescents with GCTB that is inoperable, or initial surgery is expected to culminate in substantial morbidity.

The aim of this study is to narratively review the current literature on the role of preoperative (neoadjuvant) denosumab followed by surgery in the management of patients with GCTB.

**Literature Review**

Several clinical trials, case series and case reports have demonstrated that preoperative denosumab is associated with favorable outcomes. Such favorable outcomes include: delayed tumor progression, therapeutic clinical imaging/histopathological response, tumor downstaging, decreased surgical morbidity, satisfactory drug tolerability and acceptable drug toxicity profile in patients with GCTB. PubMed® database was searched until October 31st, 2018 using the following keywords: “denosumab” and “giant cell tumor of bone”. Additional references from published articles were also screened for potential additional studies. Only studies that examined preoperative denosumab plus successive surgery were included in this narrative review. Exclusion criteria included studies with preoperative and postoperative denosumab, only postoperative denosumab, or preoperative denosumab without successive surgery.

One of the earliest studies that suggested therapeutic benefits of denosumab was reported in 2010 by Thomas et al. The research team conducted an open–label, phase II study examining the role of preoperative denosumab in 37 patients with recurrent or inoperable GCTB. The primary endpoint of study was tumor response, defined as: [i] eradication of ≥90% of giant cells based on histopathology, or [ii] no evidence of tumor progression up to 6.25 months based on radiology. The duration of denosumab therapy ranged from 3 to 7 months. Two patients were excluded from study analysis because they were unevaluable for the study’s primary point. Twenty (n=20) out of 20 patients (100%) evaluated by histopathology exhibited tumor response. Also, 10 out of 15 patients (66.7%) evaluated by imaging exhibited tumor response. Thus, overall, a total of 30 out of 35 patients exhibited tumor response. Adverse events occurred in 33 out of 37 patients, and the most commonly encountered adverse events were extremity pain (n=7), headache (n=4) and backache (n=4). Grade–II increased human chorionic gonadotropin (hCG) level occurred in only one patient, and was most likely attributable to denosumab therapy. In this study, only seven patients underwent successive surgery (resection), however, the study did not report any data regarding local recurrence. The study concluded that denosumab appeared to exhibit therapeutic benefits clinically and histopathologically, and was advocated as a potential therapy in the management of inoperable GCTB. Furthermore, authors demanded further studies on the potential role of preoperative denosumab in improving surgical outcomes in patients with unresectable or locally advanced GCTB.

In 2013, Chawla and colleagues (interim analysis of an international, multicenter, open–label, parallel–group, phase II study) reported provisional safety and efficacy of preoperative denosumab in 100 patients with potentially resectable GCTB for which initial surgery was associated with severe morbidity. The median duration on denosumab therapy was 24 months. The median
90% viable tumor cells. The mean duration of follow-up response to denosumab as demonstrated by more than one patient (25%) failed to exhibit a histopathological had positive imaging response to denosumab. Only were managed with resection. All patients (100%) intralesional curettage whereas the remaining 2 patients months (range: 5–7). Two patients were managed with denosumab followed by surgery in 4 patients with spine prospective series) examined the role of preoperative surgical downstaging (no surgery or less morbid surgery) advantages, decreased local recurrence and reduced morbid surgical procedures in patients with potentially resectable GCTB.

In 2015, Rutkowski and partners (open–label phase II study) examined the impact of surgical downstaging induced by preoperative denosumab in 222 patients with primary locally advanced (unresectable) or recurrent GCTB for which initial surgery was associated with potential undesirable functional morbidity. A total of 106 patients (48%) did not undergo surgery, and the median time on denosumab therapy was 19.5 months (range: 12.4–28.6). On the other hand, a total of 116 patients (52%) underwent surgery as follows: intralesional curettage and resection in 80 and 36 patients, respectively. Compared to initial planned surgery, less morbid surgery post denosumab was observed in 84 patients (72.4%, n=84/116), and local recurrence took place in 17 patients (6%, n=17/116). Specifically, local recurrence happened in 14 and 3 patients treated with intralesional curettage and resection, respectively. The median duration of postoperative time until recurrence in the 17 patients who experienced local recurrence was 13.6 months (range: 10.5–15.7). The median duration on denosumab was 8 months. Only for patients who had complete tumor resection (n=36), denosumab therapy continued for six additional doses after resection. Overall, the drug was well–tolerated. The study concluded that for patients with unresectable or potentially resectable GCTB, preoperative denosumab therapy was associated with favorable surgical downstaging (no surgery or less morbid surgery) and fairly low recurrence rate.

In 2015, Goldschlager and associates (multicentre prospective series) examined the role of preoperative denosumab followed by surgery in 4 patients with spine GCTB. The average duration of denosumab was 6 months (range: 5–7). Two patients were managed with intralesional curettage whereas the remaining 2 patients were managed with resection. All patients (100%) had positive imaging response to denosumab. Only one patient (25%) failed to exhibit a histopathological response to denosumab as demonstrated by more than 90% viable tumor cells. The mean duration of follow-up was 12 months (range: 4–26). There were no reported denosumab–related side effects or local recurrence. The study concluded that preoperative denosumab was clinically advantageous at imaging and histopathological levels, despite longer follow–up of patients was deemed essential.

In 2016, Muller and friends (case series from Italy) evaluated the role of preoperative denosumab plus surgery in 7 patients with GCTB. The average duration of denosumab was 4 months (range: 3–6). All patients (n=7) were treated afterwards with surgery as follows: 5 patients with intralesional curettage and 2 patients with resection. Drug response was observed in 6 patients (85.7%) and surgical downstaging occurred in 3 patients (42.9%). Local recurrence was identified in only one patient who was treated with intralesional curettage (14.3%). The mean postoperative follow–up was 23 months (range: 9–49). The study concluded that preoperative denosumab was fairly effective in surgical downstaging in patients with GCTB.

In 2016, Traub and companions (prospective nonrandomized study from Canada) investigated the efficacy of preoperative denosumab in joint preservation for 20 patients with GCTB. The median duration of denosumab therapy ranged from 6 to 11 months. A total of 18 patients exhibited tumor response to denosumab according to imaging findings, and subsequently underwent intralesional curettage surgery. Histopathological analysis demonstrated barely identifiable osteoclast–like giant cells in the resected specimens, in addition to decreased RANKL positivity of the neoplastic stromal cells. Only three patients (16.7%, n=3/18) developed local recurrence at a median follow–up of roughly 30 months (range: 20–45). The study concluded that preoperative denosumab was therapeutically effective according to clinical, imaging and histological parameters. Moreover, it enabled less morbid surgery, particularly joint preservation in patients with GCTB.

In 2016, Borkowska et al. (retrospective case series from Poland) studied the role of preoperative denosumab in 35 patients with locally advanced inoperable GCTB. These patients did not participate in previous clinical trials. Denosumab therapy was administered and continued until complete tumor resection was achievable, or tumor progression or intolerable drug–related side effects took place. Only 17 patients underwent successive surgical surgery, as follows: 6 patients with intralesional curettage without prosthesis implantation, and 11 patients with wide en–bloc resection with prosthesis implantation. Tumor progression (local recurrence) occurred in only 2 patients who were treated with intralesional curettage without prosthesis implantation (11.8%, n=2/17). Histopathological examination of en–bloc resected
specimens exhibited absence of giant cells, reduced neoplastic stromal cells and augmented bone formation. The mean duration of denosumab was 7 months (range: 5–12). The duration of postoperative follow-up was not reported. The study concluded that preoperative denosumab offered therapeutic benefits in patients with locally advanced and inoperable GCTB.

In 2016, Dubory and partners (prospective case series from France) analyzed the role of preoperative denosumab in 4 patients with spinal GCTB. All patients received denosumab at least 6 months before surgery. A total of 3 and 1 patient(s) underwent intralesional curettage and en-bloc resection, respectively. Systematic computed tomography scan at 6 months prior to surgery showed decreased tumor size and bone consolidation. Intraoperative histologic analysis of surgical specimens showed absence of giant cells and ≤10% of alive tumor cells. The mean postoperative follow-up was 19.3 months (range: 3.2–52.4). Back pain and neurologic deficit improved for all patients. No drug-related adverse events occurred. No data on local recurrence were reported. The study concluded that preoperative denosumab was helpful in surgical downstaging, inducing bone formation in the periphery of tumor, and enabling less aggressive surgical procedure in patients with spinal GCTB.

In 2017, McCarthy and colleagues (case series from United Kingdom) examined the role of preoperative 3–month course of denosumab in the management of GCTB of the distal radius/ulna in 5 patients. The denosumab course was followed by intralesional curettage and cementation in all patients. The average follow-up duration was 37 months (range: 17–54). All patients experienced favorable improvement in wrist pain and function according to the modified Mayo Wrist Score (MMWS). Imaging assessment displayed tumor response according to pre-specified criteria. Histopathological evaluation exhibited absence of osteoclasts and enhanced formation of fibro-osseous tissue. Preoperative denosumab enabled surgical downstaging and performance of salvage therapy in all patients. Only one patient (20%) developed local recurrence, which occurred 2 months after surgery. The study concluded that a short-term schedule of preoperative denosumab was effective clinically, radiologically and histopathologically in patients with distal forearm GCTB, and provided a capacity to perform salvage surgery with less morbidity.

In 2017, Rekhi and associates (case series from India) explored the role of preoperative denosumab in the management of 27 patients with GCTB. The preoperative course was followed by intralesional curettage in 15 patients and surgical resection in 12 patients. The mean duration of denosumab therapy was 2.5 months. Around 55% of resected specimens exhibited disappearance of osteoclast–like giant cells on histopathological examination. The median follow-up duration after surgery was 18 months (range: 7–27), and follow-up data were only available for 25 patients. Among those, 20 patients (81.5%) were disease-free whereas 5 patients (18.5%) developed local recurrences at a median duration of 14 months (range: 12–19). The study concluded that preoperative denosumab was clinically useful in the management of patients with GCTB. Furthermore, it reduced severe surgery–related morbidity, and increased elimination of tumorigenic osteoclast–like giant cells on histopathological examination.

In 2017, Boye et al conducted a nationwide study from Norway on the role of pre/postoperative denosumab in 18 patients with GCTB. Only one patient was treated with preoperative denosumab for a duration of 7 months and followed by a sequential resection surgery without postoperative administration of denosumab. The patient was a 39–year–old female with a tumor involving the trapezium bone. Although the patient did not develop local recurrence (follow-up time was not reported), the patient did not experience a less morbid surgery than initially planned. The study concluded that preoperative denosumab reduced local recurrence without favorable impact on reducing surgical morbidity. Also, the study concluded that denosumab should not be advocated for use as a postoperative therapy in patients with GCTB.

In 2017, Deveci et al (prospective case series from Turkey) examined the role of preoperative denosumab followed by surgery in 10 patients with GCTB. The mean duration of denosumab therapy was 9 months (range: 4–17). A total of 6 and 4 patients underwent successive intralesional curettage and resection, respectively. Histologic analysis of surgery specimens displayed more than 90% regression of neoplastic giant cells. The average postoperative follow-up was 17 months (range: 10–30), and no patient developed local recurrence. On last follow-up, the mean Visual Analog Score (VAS) and Musculoskeletal Tumor Society Score (MSTS) were 1 and 87%, respectively. Drug–related joint/muscle pain after injections was reported by 46% of patients. Overall, the drug was well–tolerated and only 1 patient developed mild hypocalcaemia. The study concluded that administration of preoperative denosumab was associated with clinical and histological benefits in patients with primary locally advanced or recurrent GCTB.

In 2018, Chen and associates (retrospective series from China) explored the role of preoperative denosumab in 11 patients with sacral GCTB. Among them, 10 patients received postoperative denosumab therapy after surgery. Only one patient received preoperative denosumab.
followed by intralesional curettage. The patient was a 14-year-old teenager and developed recurrence 9 months after surgery. The mean duration of preoperative denosumab was 4 months (range: 1–11), although the exact duration for the teenager was not specified. The study concluded the need for more research on the role of preoperative denosumab combined with surgery on the long-term recurrence rate of GCTB.

In 2018, Rutkowski and partners (retrospective multicenter analysis outside clinical trial) evaluated 89 patients with unresectable GCTB who underwent surgery after preoperative denosumab. The median time on denosumab was roughly 6 months (range: 0.5–20.8). Almost all patients (98%) had therapy-related clinical benefits. A total of 39 patients (44%) underwent wide en-block resection, and local recurrence happened in 3 patients. Conversely, a total of 50 patients (56%) underwent intralesional curettage, and local recurrence happened in 16 patients. The median postoperative follow-up was 23 months (range: 6–55). The 2-year event-free survival was statistically and significantly higher in the wide en-block resection group than the intralesional curettage group (93% vs. 55%, p=0.006). For all patients, the 2-year progression-free survival was 81%. Overall, the chemotherapy toxicity profile was endurable; only one patient developed jaw osteonecrosis in addition to 2 cases of therapy-related grade—III adverse events. A total of 17 patients received postoperatively denosumab up to 6 months after histological confirmation of partial or complete response. The study concluded that preoperative denosumab was associated with therapeutic benefit, tolerability, safety, surgical downstaging and less morbid procedure in patients with locally advanced GCTB. Additionally, neoadjuvant denosumab with wide en—block resection was associated with better recurrence—free rates.

In 2018, Urakawa et al (national questionnaire survey from Japan) explored the clinical outcomes of preoperative denosumab and successive intralesional curettage in 21 patients with primary GCTB. The median duration of denosumab therapy was 6 months (range: 2–41). Local recurrence occurred in 6 patients (28.6%). Administration of more than 5 times of preoperative denosumab (3-month course) was substantially correlated with a

<table>
<thead>
<tr>
<th>Reference</th>
<th>Authors</th>
<th>Year</th>
<th>Study Type</th>
<th>Total Patients (n)</th>
<th>Surgery type (Patients, n)</th>
<th>Local recurrence (Patients, n)</th>
<th>Duration of postoperative follow-up (months)</th>
<th>Duration of preoperative denosumab therapy (months)</th>
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<td>(3)</td>
<td>Thomas et al</td>
<td>2010</td>
<td>Open—label phase II trial</td>
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<td>Not reported</td>
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<td>Chawla et al</td>
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<td>Open—label, parallel—group, phase II</td>
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<td>Median: 9</td>
<td>Median: 24</td>
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<td>Goldschlager et al</td>
<td>2015</td>
<td>Multicenter, prospective series</td>
<td>4</td>
<td>Curettage (2)</td>
<td>0% (0/2)</td>
<td>Mean: 12 (range: 4–26)</td>
<td>Mean: 6 (range: 5–7)</td>
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<td>Muller et al</td>
<td>2016</td>
<td>Case series (Italy)</td>
<td>7</td>
<td>Curettage (5)</td>
<td>20% (1/5)</td>
<td>Mean: 23 (range: 9–49)</td>
<td>Mean: 4 (range: 3–6)</td>
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<td>(12)</td>
<td>Traub et al</td>
<td>2016</td>
<td>Prospective non—randomized series (Canada)</td>
<td>18</td>
<td>Curettage (18)</td>
<td>16.7% (3/18)</td>
<td>Median: 30 (range: 20–45)</td>
<td>Range: 6–11</td>
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<td>(13)</td>
<td>Borkowska et al</td>
<td>2016</td>
<td>Retrospective case series (Poland)</td>
<td>17</td>
<td>Curettage (6)</td>
<td>33.3% (2/6)</td>
<td>Not reported</td>
<td>Mean: 7 (range: 5–12)</td>
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<td>(14)</td>
<td>Dubory et al</td>
<td>2016</td>
<td>Prospective case series (France)</td>
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<td>Curettage (3)</td>
<td>Not reported</td>
<td>Mean: 19.3 (range: 3.2–52.4)</td>
<td>Mean: 6</td>
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<td>(15)</td>
<td>McCarthy et al</td>
<td>2017</td>
<td>Retrospective case series (United Kingdom)</td>
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<td>Curettage (5)</td>
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<td>Mean: 37 (range: 17–54)</td>
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<td>(16)</td>
<td>Rekhi et al</td>
<td>2017</td>
<td>Retrospective case series (India)</td>
<td>27</td>
<td>Curettage (15)</td>
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<td>Median: 18 (range: 7–27)</td>
<td>Mean: 2.5</td>
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<td>Boye et al</td>
<td>2017</td>
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<td>7</td>
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<td>(18)</td>
<td>Deveci et al</td>
<td>2017</td>
<td>Prospective case series (Turkey)</td>
<td>10</td>
<td>Curettage (6)</td>
<td>0% (0/6)</td>
<td>Mean: 17 (range: 10–30)</td>
<td>Mean: 9 (range: 4–17)</td>
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<td>(19)</td>
<td>Chen et al</td>
<td>2018</td>
<td>Retrospective series (China)</td>
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<td>Curettage (1)</td>
<td>100% (1/1)</td>
<td>9</td>
<td>Not reported</td>
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<td>(21)</td>
<td>Urakawa et al</td>
<td>2018</td>
<td>National survey (Japan) to plan JCOG1610</td>
<td>21</td>
<td>Curettage (21)</td>
<td>28.5% (6/21)</td>
<td>Not reported</td>
<td>Median: 6 (range: 2–41)</td>
</tr>
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</table>

Table 1. A summary of published studies (clinical trials and case series) on the role of preoperative denosumab followed by surgery

JCOG 1610: Japan Clinical Oncology Group, phase III clinical trial; * Two patients were lost during follow—up
Preoperative denosumab plus surgery in GCTB, Ahmed Abu–Zaid et. al.,

reduced incidence of local recurrence after intralesional curettage (p<0.001). No data were reported on the duration of follow-up. The study concluded the need for a randomized phase III clinical trial (JCOG 1610) to evaluate the clinical efficacy of preoperative denosumab with curettage for GCTB.\(^{(21)}\)

Table 1 displays a summary of published studies (clinical trials and case series) on the role of preoperative denosumab followed by surgery.

Several isolated case reports have demonstrated therapeutic benefits of preoperative denosumab in surgical downstaging, and thus enabling salvageable surgery in patients with locally advanced GCTB.\(^{(22–35)}\) Table 2 shows a selected summary of case reports in which patients received preoperative denosumab and surgery without postoperative denosumab.\(^{(22, 25, 28, 33, 35)}\)

### Table 2. A selected summary of case reports in which patients received preoperative denosumab and surgery without postoperative denosumab therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Authors</th>
<th>Year</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Duration of pre-operative denosumab therapy (months)</th>
<th>Surgery type</th>
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<td>(25)</td>
<td>Hakozaki et al</td>
<td>2014</td>
<td>Male</td>
<td>20</td>
<td>6</td>
<td>Intralesional curettage</td>
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<td>(22)</td>
<td>Von Borstel et al</td>
<td>2017</td>
<td>Male</td>
<td>29</td>
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<td>(28)</td>
<td>Kumar et al</td>
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</table>

### Discussion

All in all, administration of preoperative denosumab was associated with clinical/radiological/histopathological therapeutic benefits, tolerability, safety, low local recurrence rate, surgical downstaging and less morbid salvageable procedures in patients with unresectable or locally advanced GCTB for which initial surgery would be associated with substantial morbidity. However, this conclusion should not be solidly taken for granted, especially for the rate of local recurrence. Rather, this conclusion should be interpreted with caution due to the small number of patients who underwent successive surgery (intralesional curettage or resection) after preoperative denosumab treatment. The mean number of patients in this narrative review was roughly 11 patients (range: 1–27).

To counteract the limitation of small sample size, there is a planned randomized phase III clinical trial (JCOG 1610, registration ID: UMIN000029451) that aims primarily to explore the efficacy and local recurrence rate of preoperative denosumab in a large number of patients with GCTB which can be treated with successive intralesional curettage.\(^{(21)}\) The study will investigate the true recurrence rate after intralesional curettage. Additional (secondary) aims include data on joint–preserved survival, surgical and postoperative complications, local relapse–free survival, metastasis–free survival, overall survival, discontinuation of denosumab, side effects and serious high–grade adverse events.

A major limitation of the published studies is the relatively short time of postoperative follow-up which hindered definitive conclusions to be withdrawn, particularly for rates of local recurrence and side effects. Long–term data on the toxicity profile of denosumab are deficient. Palmerini et al studied the safety of preoperative denosumab in 97 patients with GCTB.\(^{(36)}\) A total of 54 patients did not undergo surgery, and the median time on denosumab was 54 months (range: 9–115). On the other hand, the remaining 43 patients underwent surgical resection, and the median time on denosumab was 12 months (range: 6–45). Overall, a sum of 6 patients developed osteonecrosis of the jaw, as follows: 5 (9%) and 1 (2%) patient(s) in the unresectable and resectable groups, respectively. Furthermore, only the unresectable patients with prolonged denosumab treatment (n=54) developed higher rates of toxicity–related adverse events as follows (in an ascending order): hypophosphatemia (n=2, 4%), atypical femoral fracture (n=2, 4%), skin rash (n=5, 9%) and mild peripheral neuropathy (n=6, 11%). Generally speaking, all patients on denosumab therapy should be advised to take daily supplements of ≥500 mg calcium and ≥400 IU vitamin D.

The FDA approval did not specify a dose or treatment duration of preoperative denosumab for treatment of GCTB. However, the most frequently employed schedule in clinical trials and case series was denosumab 120 mg subcutaneously every 28 days, with 2 additional loading doses on days 8 and 15 of the first month only.
At the present time, the optimal duration of preoperative denosumab is not yet established. This is because the timing of surgery is often scheduled according to the level of observed radiological improvement that permits potential salvage surgery with less morbidity. On average, patients are generally treated for about 3–6 months preoperatively. Long–term pretreatment with denosumab should be avoided (because of dose–dependent toxicity profile), and it should limited to the minimum needed to conduct an operable salvage surgery. Also, it should be noted that abrupt cessation of denosumab will result in tumor relapse. Hence, preoperative denosumab therapy should be continued until definitive surgical treatment becomes feasible.

A recently published systematic review by Jamshidi et al concluded that denosumab decreases tumor size, but it does not reduce the likelihood of recurrence. Preoperative denosumab treatment is associated with formation of calcified rim, condensed osseous–matrix and thickened cortical bone. Tumor cells can hide and remain in the newly formed bone. This in turn increases the risk of local recurrence after surgery. This holds particularly true for intralesional curettage surgery, and hence the surgical procedure should shift from gentle to more aggressive in order to reduce the risk of high local recurrence. Conversely, en–bloc resection after preoperative denosumab does not seem to give rise to an increased risk of local recurrence.

Exposure to radiation therapy has been established as a potential risk factor for occurrence of malignant transformation of GCTB. In very rare occasional cases, true spontaneous malignant transformation of GCTB under denosumab therapy can take place, without exposure to radiation therapy. To the best of our knowledge, around 13 cases of malignant transformation of GCTB during denosumab therapy have been described in patients without previous exposure to radiation therapy. This is one of the limitations that may restrict the use of long–term denosumab in the preoperative setting. Wojcik et al. showed that denosumab–treated GCTB displays some degree of morphologic overlap with malignant GCTB. However, dissimilar to malignant GCTB, denosumab–treated GCTB lack substantial nuclear atypia, mitotic activity, and infiltration of preexisting bone. Furthermore, denosumab–treated GCTB display a special configuration of intralesional bone deposition. Most importantly, since denosumab–treated GCTB exhibit slight similarity to their pre–treated GCTB counterparts, vigilant care to history of denosumab administration is essential to prevent a misdiagnosis of malignant GCTB.

Conclusion

Administration of preoperative denosumab (monoclonal antibody targeted against RANKL) is associated with clinical, radiological, and histopathological therapeutic benefits. It is also associated with tolerability, safety, surgical downstaging and less morbid salvageable procedures in patients with unresectable or locally advanced GCTB for which initial surgery will be associated with considerable morbidity. However, caution should be exercised in the interpretation of existing data on preoperative denosumab in the management of GCTB patients, owing to some critical limitations, for example, short follow–up and only a minority of patients have undergone intralesional surgery following denosumab therapy.

Preoperative denosumab does not seem to reduce the likelihood of local recurrence after intralesional therapy; a planned randomized phase III clinical trial (JCOG 1610) will holistically better address this concern. Preoperative denosumab treatment is associated with formation of calcified rim, condensed osseous–matrix and thickened cortical bone. Tumor cells can hide and remain in the newly formed bone. This in turn increases the risk of local recurrence after intralesional curettage surgery as opposed to en–bloc resection surgery. In case an intralesional curettage surgery will be performed after administration of preoperative denosumab, then surgery should shift from gentle to more aggressive in order to reduce the risk of high local recurrence. Although rare, cases of malignant transformation of GCTB while receiving preoperative denosumab therapy have been reported (~ n=13).

Lastly, large–sized phase III randomized clinical trials with long–term follow–up data are warranted to withdraw concrete conclusions and recommendations.

References

Preoperative denosumab plus surgery in GCTB, Ahmed Abu--Zaid et. al.,


