Denosumab May Increase the Risk of Local Recurrence in Patients with Giant-Cell Tumor of Bone Treated with Curettage

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Background: Recent clinical studies have suggested that denosumab is associated with tumor response and reduced surgical morbidity in patients with giant-cell tumor of bone (GCTB). We therefore evaluated the recurrence-free survival rate of patients who had GCTB in an extremity and were treated with surgery and denosumab, to determine the influence of denosumab and clinical factors on the risk of local recurrence.

Methods: We retrospectively reviewed the medical records of 408 patients treated for GCTB in an extremity in a single institution from 1990 through 2013. Two hundred and forty-seven patients underwent curettage (intralesional surgery) with a high-speed burr, and 161 underwent resection. Phenol adjuvant was used in 221 of the 247 patients who had curettage. We also reviewed the medical records of 30 patients treated surgically (25 with curettage and 5 with resection) and with denosumab from 2010 through 2013 and compared their clinical results with 378 historical control subjects. The overall minimum duration of follow-up was 24 months.

Results: The local recurrence rates were 60% (15) of 25 patients treated with curettage and denosumab and 16% (36) of 222 patients treated with curettage alone. The joint preservation rates were 80% (20) of 25 patients treated with curettage and denosumab and 94% (209) of 222 patients treated with curettage alone. Univariate and multivariable analyses showed that denosumab was the only independent factor associated with a poor prognosis when recurrence-free survival and joint preservation were considered. The overall median duration of follow-up was 85.6 months (interquartile range, 54.3 to 125.1 months). Viable tumor was present in all 30 specimens from patients treated with denosumab.

Conclusions: There was a higher rate of recurrence in the cohort exposed to denosumab. Because there were substantial differences in the cohorts and randomization was not applied, however, causation could not be evaluated.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Giant-cell tumor of bone (GCTB), a rare primary benign bone tumor, accounts for approximately 5% of all primary bone tumors[1]. Treatment of GCTB remains controversial[2]. Surgical options include intralesional surgery (curettage) using a high-speed burr or resection. Curettage, which preserves adjacent joint function, is associated with a higher recurrence rate, whereas resection with wide margins minimizes tumor recurrence but is associated with worse functional results[3]. Clinical studies recently have suggested that denosumab—a monoclonal antibody that binds RANKL (receptor activation of nuclear factor-kappa β ligand)—is associated with tumor response and reduced surgical morbidity in patients with GCTB[4-7]. Denosumab also has been reported to result in beneficial surgical downstaging[6-8]; however, the results were from patients who remained on denosumab or in whom it had been discontinued but who had been followed only a median of 13 months[6,8].

We therefore evaluated the recurrence-free survival rate of patients with GCTB in an extremity who underwent both surgery and denosumab treatment of the tumor and who had a long follow-up. We determined the influence of several factors on the risk of recurrence after surgery, including denosumab administration, local tumor presentation, and demographic

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characteristics. We hypothesized that denosumab contributes to a lower rate of local recurrence after surgery.

Materials and Methods

We retrospectively reviewed the medical records of 412 patients diagnosed with histologically confirmed GCTB in an extremity from January 1990 to December 2013 and with a minimum follow-up of 24 months. A total of 247 patients underwent curettage, and 161 had resection. Four patients who required amputation were excluded from the study because they were at no risk of local recurrence.

The clinical characteristics of the 247 patients treated with curettage are summarized in Table I. The median age of the patients was 29.2 years (interquartile range [IQR], 23.0 to 38.5 years). We divided the patients into 2 groups according to the location of the tumor because it was reported that the distal radial site was associated with a higher local recurrence rate[9]. Thus, 1 group comprised patients with GCTB in the distal end of the radius, and the other comprised patients with GCTB at other sites.

TABLE I Association of Denosumab Administration with Clinical Variables in the Patients Treated with Curettage

Variable (N = 247)	No. (%) of Patients	Denosumab Administration *(no. [%])*		P Value
		Yes	No	
Age in yr				<0.0001*
<30	130 (52.6)	4 (16.0)	126 (56.8)	
≥30	117 (47.4)	21 (84.0)	96 (43.2)	
Sex				0.121
Male	112 (45.3)	15 (60.0)	97 (43.7)	
Female	135 (54.7)	10 (40.0)	125 (56.3)	
Site				0.001*†‡
Distal end of radius	14 (5.7)	6 (24.0)	8 (3.6)	
Proximal part of femur	12 (4.9)	0 (0)	12 (5.4%)	
Distal end of femur	88 (35.6)	4 (16.0)	84 (37.8)	
Proximal part of tibia	80 (32.4)	5 (20.0)	75 (33.8)	
Distal end of tibia	16 (6.5)	3 (12.0)	13 (5.9)	
Proximal part of humerus	11 (4.5)	4 (16.0)	7 (3.2)	
Others	26 (10.5)	3 (12.0)	23 (10.4)	
Campanacci classification				0.053†§
Stage I	6 (2.4)	0 (0)	6 (2.7)	
Stage II	189 (76.5)	16 (64.0)	173 (77.9)	
Stage III	52 (21.1)	9 (36.0)	43 (19.4)	
Previous operations				0.189†
None	218 (88.3)	20 (80.0)	198 (89.2)	
1	29 (11.7)	5 (20.0)	24 (10.8)	
Surgery				0.598
Curettage without cement	60 (24.3)	5 (20.0)	55 (24.8)	
Curettage with cement	187 (75.7)	20 (80.0)	167 (75.2)	
Phenol adjuvant				<0.0001*†
Yes	221 (89.5)	15 (60.0)	206 (92.8)	
No	26 (10.5)	10 (40.0)	16 (7.2)	
Recurrence				<0.0001*
None	196 (79.4)	10 (40.0)	186 (83.8)	
≥1	51 (20.6)	15 (60.0)	36 (16.2)	
Joint replacement				0.024*†
None	229 (92.7)	20 (80.0)	209 (94.1)	
1	18 (7.3)	5 (20.0)	13 (5.9)	

*The difference was significant. †The Fisher exact test was used. ‡Comparison of distal end of the radius and the others. §Comparison of Campanacci stage I with stages II and III.

TABLE II Univariate Analysis of Recurrence-Free Survival in the Patients Treated with Curettage

Variable	No. of Patients	Five-Year Recurrence-Free Survival (95% Confidence Interval) *(%)*	P Value
Age in yr			0.946
<30	130	80.5 (72.4-86.6)	
≥30	117	78.6 (70.0-85.3)	
Sex			0.670
Male	112	77.3 (68.2-84.4)	
Female	135	81.5 (73.8-87.3)	
Site			0.093
Distal end of radius	14	64.3 (37.6-84.3)	
Others	233	80.5 (74.7-85.8)	
Campanacci classification			0.021*
Stage I or II	195	82.0 (75.7-87.0)	
Stage III	52	70.7 (56.9-81.6)	
Previous operations			0.595
None	218	79.9 (73.8-84.8)	
1	29	76.8 (56.1-89.6)	
Surgery			0.055
Curettage without cement	60	74.7 (62.2-84.2)	
Curettage with cement	187	81.2 (74.7-86.4)	
Denosumab administration			<0.0001*
Yes	25	39.0 (22.0-59.1)	
No	222	84.2 (78.6-88.6)	
Phenol adjuvant			0.001*
Yes	221	82.2 (76.3-86.9)	
No	26	57.7 (38.5-74.8)	

*The difference was significant.

Previous clinical studies have suggested that denosumab was associated with tumor response and reduced surgical morbidity in patients with GCTB[5]. Therefore, we identified 30 patients (25 treated with curettage and 5 treated with resection) from an open-label, parallel group in a Phase-II trial (AMG20062004 [ClinicalTrials.gov identifier: NCT00680992]), conducted from 2010 to 2013, or who had received denosumab on an off-label basis, and included them in the study. Denosumab was used particularly in patients with GCTB in the distal end of the radius (for downstaging the tumor) because tumors at this site are aggressive and their resection is associated with worse functional results[9,10]. Preoperatively, denosumab (120 mg) was given subcutaneously once a week for 1 month and then once a month for 6 to 12 months. Postoperatively, it was given at the same dose once a month for 3 to 7 months[11]. The patients also took daily calcium (2,500 mg) and vitamin D (≥400 IU) supplements.

After following the preoperative denosumab regimen, all patients had remaining tumor and therefore underwent surgery, usually 1 month after the final denosumab injection. To

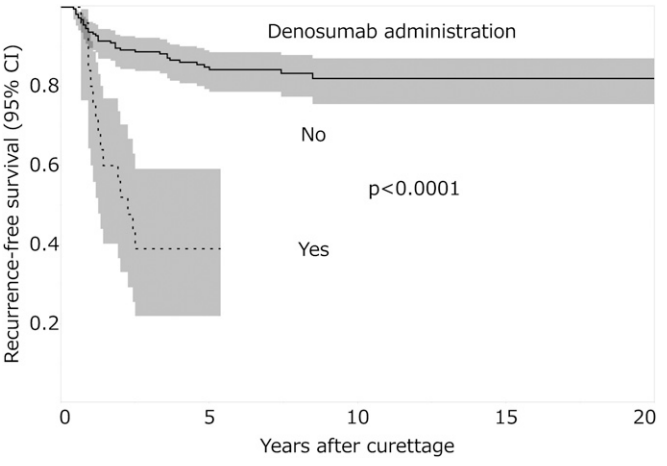

Fig. 1

Kaplan-Meier analysis of local recurrence-free survival in 247 patients with GCTB who were treated with curettage with or without denosumab administration. The shading surrounding the curves represents the 95% confidence interval (CI).

TABLE III Multivariable Cox Regression Analysis of Recurrence-Free Survival in the Patients Treated with Curettage

Variable	Hazard Ratio (95% Confidence Interval)	P Value
Campanacci classification		
Stage III versus stage I or II	1.73 (0.95-3.15)	0.075
Denosumab administration		
Yes versus no	4.78 (2.45-9.35)	<0.0001*
Phenol adjuvant		
Yes versus no	0.56 (0.28-1.16)	0.117

*The difference was significant.

assess the effect of denosumab, radiographic images made just before denosumab administration were compared with those made just before surgery to determine the best response as measured with modified inverse Choi (density/size) criteria[6,7,12]. Adverse events and laboratory abnormalities were assessed using Common Terminology Criteria for Adverse Events (CTCAE; version 4.0)[13].

The patients were managed surgically with curettage or with resection, which was indicated for large tumors with soft-tissue extension, pathological fractures with joint invasion or an unstable fracture pattern, multiple recurrences, or involvement of expendable bones (head of the fibula or distal end of the ulna)[10]. Curettage was performed through a large cortical bone window using curets of different sizes that enabled removal of all visible tumor. The cavity was then cleaned with a high-speed burr and was washed in an attempt to remove all pathological tissue[10]. In 221 of the 247 patients who had curettage, phenol was applied to the border of the cavity with cotton-tipped applicators and then was neutralized with alcohol. The tumor cavity was left alone or packed with bone allografts, cement, or cement with bone allografts. Cement and bone allograft reconstruction was performed in 2 steps. First, the cavity was filled with cement after bone chip allografts were placed in a subchondral area to protect the articular surface

TABLE IV Univariate Analysis of Joint Preservation Survival in the Patients Treated with Curettage

Variable	No. of Patients	Five-Year Joint Preservation (95% Confidence Interval) *(%)*	P Value
Age in yr			0.965
<30	130	93.0 (87.1-96.3)	
≥30	117	93.7 (87.3-97.0)	
Sex			0.719
Male	112	94.3 (87.9-97.4)	
Female	135	92.6 (86.7-95.9)	
Site			0.935
Distal end of radius	14	92.9 (63.0-99.0)	
Others	233	93.4 (89.3-96.0)	
Campanacci classification			0.739
Stage I or II	195	93.7 (89.2-96.4)	
Stage III	52	92.3 (81.2-97.1)	
Previous operations			0.987
None	218	93.4 (89.2-96.1)	
1	29	93.1 (76.2-98.3)	
Surgery			0.960
Curettage without cement	60	93.3 (83.4-97.5)	
Curettage with cement	187	93.4 (88.7-96.2)	
Denosumab administration			0.002*
Yes	25	79.8 (59.7-91.3)	
No	222	94.9 (91.1-97.2)	
Phenol adjuvant			0.057
Yes	221	94.4 (90.4-96.8)	
No	26	84.6 (65.5-94.1)	

*The difference was significant.

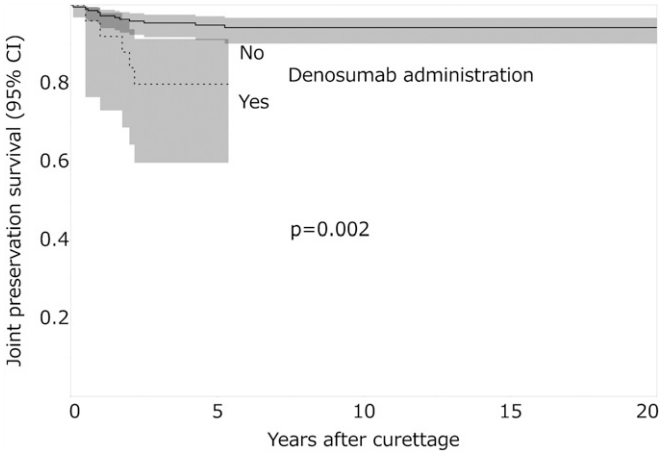

Fig. 2

Kaplan-Meier analysis of joint preservation survival in 247 patients with GCTB who underwent curettage with or without denosumab administration. The shading surrounding the curves represents the 95% confidence interval (CI).

from the thermal effect of cement. Second, the cavity was filled with cement and cortical bone allografts to support the articular surface mechanically[10,14]. Prophylactic surgical stabilization with internal fixation was also performed in 5 patients at high risk of a pathological fracture.

Patients who had undergone resection had reconstruction using a modular prosthesis, massive bone allografts, or allograft composite prostheses. The only exceptions were patients whose tumors were in the proximal part of the fibula or the distal end of the ulna. They did not undergo reconstruction.

Finally, the results of the 30 tumor samples from diagnostic biopsies and curettage or resection procedures done after denosumab administration were analyzed and compared histologically.

Routine follow-up included a clinical examination and conventional radiography. The Musculoskeletal Tumor Society (MSTS) score, developed by Enneking et al., was used to assess functional results[15].

Recurrence-free survival was defined as the interval between the first surgery and the manifestation of local recurrence discovered by radiographic imaging during follow-up. Joint preservation survival was defined as the interval between the first curettage and joint replacement for the local recurrence.

The chi-square test or Fisher exact test was used to evaluate the association between 2 variables, as appropriate. Recurrence-free survival and joint preservation were estimated using the Kaplan-Meier method. The log-rank test was used to evaluate differences between the survival curves. Cox proportional hazards regression analysis was conducted to estimate the hazard ratios for risk factors for recurrence and joint replacement. The difference between 2 independent samples was statistically analyzed using the Mann-Whitney U test for nonparametric analyses. Significance was defined as $p < 0.05$. All analyses were performed with IBM SPSS (version 21.0; IBM) and JMP 11 (SAS Institute).

The independent ethics committee of our institution approved the study, which was registered with ClinicalTrials.gov (identifier NCT02996734).

Results

Univariate analysis revealed that Campanacci stage III ($p = 0.021$) and denosumab administration ($p < 0.0001$) had a significant association with unfavorable recurrence-free survival in the 247 patients treated with curettage (Table II, Fig. 1)[16]. Phenol adjuvant, in contrast, showed a significant association with favorable recurrence-free survival ($p = 0.001$) (Table II). A multivariable analysis that was conducted with clinical variables related to unfavorable recurrence-free survival revealed that denosumab administration was the only independent prognostic factor for poor recurrence-free survival ($p < 0.0001$) (Table III). Univariate analysis revealed that denosumab administration showed a significant association with unfavorable joint preservation in the 247 patients treated with curettage ($p = 0.002$) (Table IV, Fig. 2). A multivariable analysis was conducted only with clinical variables that were related to local recurrence in previous reports. The multivariable analysis revealed that denosumab administration was the only independent prognostic factor associated with poor joint preservation ($p = 0.018$) (Table V).

Wide resection was associated with a significantly ($p = 0.049$) lower recurrence rate than intralesional surgery (curettage): 13% (21 of 161 patients) compared with 21% (51 of 247 patients), respectively. Lung metastases occurred in 4.9% (20) of all 408 patients. The median follow-up was 85.6 months (IQR, 54.3 to 125.1 months). Three patients were followed up for the minimum of 24 months.

TABLE V Multivariable Cox Regression Analysis of Joint Preservation Survival in the Patients Treated with Curettage

Variable	Hazard Ratio (95% Confidence Interval)	P Value
Site		
Distal end of radius versus other sites	0.43 (0.05-4.09)	0.466
Campanacci classification		
Stage III versus stage I or II	1.13 (0.34-3.68)	0.846
Surgery		
With cement versus without cement	0.94 (0.30-2.94)	0.919
Denosumab administration		
Yes versus no	4.12 (1.27-13.35)	0.018*
Phenol adjuvant		
Yes versus no	0.50 (0.15-1.72)	0.272

*The difference was significant.

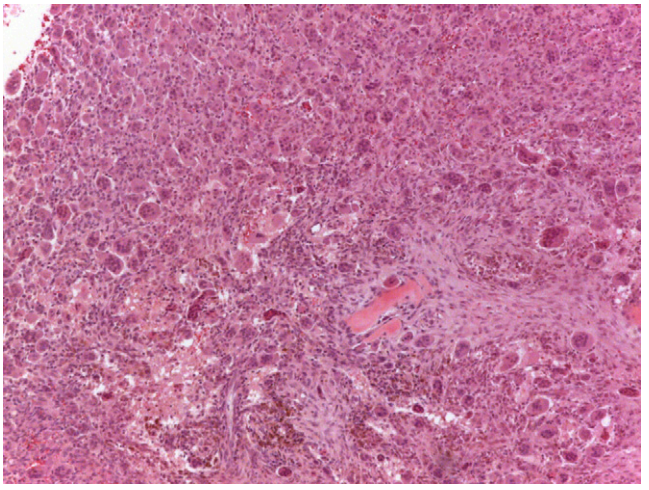

Fig. 3-A

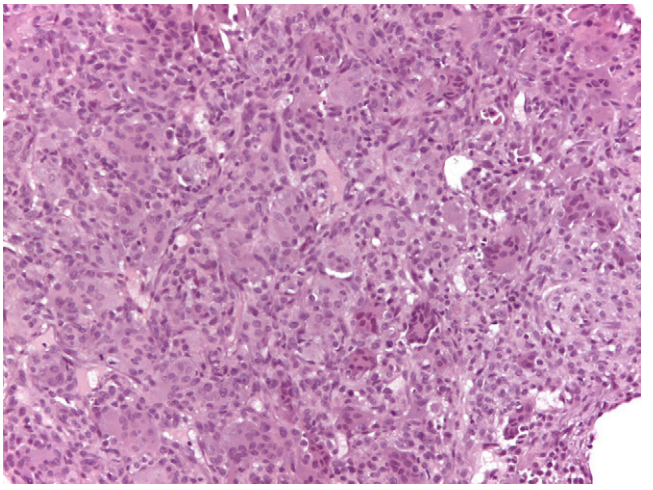

Fig. 3-B

Figs. 3-A and 3-B Tumor biopsy specimen after hematoxylin and eosin staining reveals that the GCTB is composed of an admixture of neoplastic mononuclear cells and numerous, evenly distributed, osteoclast-type giant cells associated with hemosiderin deposits and focal reactive bone formation. **Fig. 3-A** Magnification, ×100. **Fig. 3-B** Magnification, ×200.

Denosumab was more frequently administered in patients who were ≥30 years old ($p < 0.0001$) and who had GCTB in the distal end of the radius ($p = 0.001$) (Table I). Phenol was used less frequently in patients who received denosumab than in those who did not receive denosumab ($p < 0.0001$) (Table I). Phenol was used less frequently at the distal radial site than at other sites: 64.3% (9 of 14 patients) compared with 91.0% (212 of 233 patients) ($p = 0.009$), respectively. There was a significant association between denosumab administration and both local recurrence ($p < 0.0001$) and joint replacement ($p = 0.024$) (Table I). In 25 patients treated with curettage and denosumab, the use of phenol adjuvant was not associated with age, sex, tumor site, Campanacci stage, previous surgery, or the use of cement. 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). Ten patients remained disease-free, and 15 had no evidence of disease after treatment of a local recurrence. The local recurrence rate was 60% (15 patients), and the median interval between the first surgical treatment and local recurrence was 15.0 months (IQR, 11.0 to 24.0 months). The joint preservation rate was 80% (20 patients), and the median interval between the first surgical treatment and joint replacement was 21.0 months (IQR, 9.0 to 25.0 months).

For the 222 patients who underwent curettage with a high-speed burr without denosumab, the median follow-up

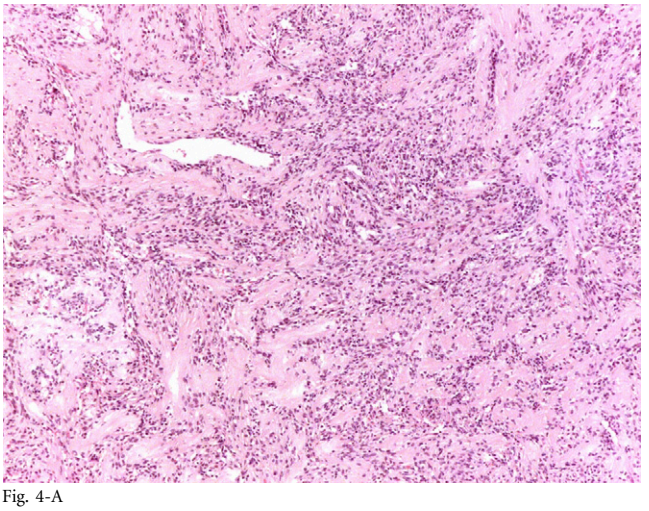

Fig. 4-A

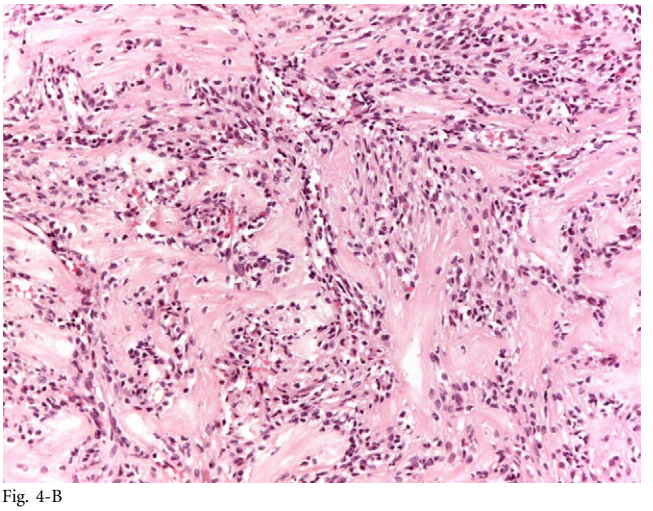

Fig. 4-B

Figs. 4-A and 4-B Hematoxylin and eosin staining of GCTB after denosumab treatment reveals that the residual tumor is composed of bland-appearing spindle cells organized in short fascicles with a storiform pattern, associated with collagen matrix production. This matrix appears either as thin bands or as thicker connected trabecular structures with a honeycomb appearance **Fig. 4-A** Magnification, ×100. **Fig. 4-B** Magnification, ×200.

was 88.4 months (IQR, 57.1 to 123.9 months). With respect to the oncologic results, 182 patients remained disease-free, and 36 had no evidence of disease after treatment of a local recurrence. One patient had no evidence of disease after treatment of lung metastasis, and 2 patients were alive with lung metastases. One patient died of another disease. The local recurrence rate was 16% (36 patients), and the median interval between the first surgical treatment and local recurrence was 15.0 months (IQR, 9.0 to 43.0 months). The joint preservation rate was 94% (209 patients), and the median interval between the first surgical treatment and joint replacement was 42.0 months (IQR, 7.0 to 46.0 months). Lung metastases occurred in 3 patients (1.4%). The median interval between the primary disease diagnosis and lung metastasis was 49.6 months (IQR, 36.5 to 52.4 months).

The median MSTS score was 96.7 (IQR, 85 to 100) for the 25 patients receiving denosumab and 96.7 (IQR, 90 to 100) for the 222 patients who did not receive denosumab. Hence, there was no significant difference among the 247 patients who had curettage ($p = 0.372$). For the 161 patients who had resection, univariate analysis revealed that denosumab administration was not associated with recurrence-free survival ($p = 0.425$).

With regard to tumor response and adverse events among the 30 patients treated with denosumab, 6 (24%) of 25 patients managed with curettage had stable disease and 19 (76%) had a partial response. Of the 5 patients who underwent resection, 2 had stable disease and 3 had a partial response. During denosumab treatment, 2 patients (7%) reported grade-III adverse events and were unable to continue denosumab therapy after surgery. One patient had a periapical abscess, and the other had grade-III periodontal disease. None of the other patients experienced adverse events during denosumab therapy and so completed the regimen.

Histopathological examination of the diagnostic tumor biopsy specimens confirmed morphology typical of GCTB in all cases (Figs. 3-A and 3-B): an admixture of neoplastic mononuclear cells and numerous, evenly distributed osteoclast-type giant cells associated with hemosiderin deposits and focal reactive bone formation on hematoxylin-eosin staining. Following denosumab treatment, all samples showed pronounced changes and viable tumor (Figs. 4-A and 4-B): osteoclast-like giant cells had disappeared. Cellular areas characterized by sheets of round-ovoid tumor cells or spindle cells had formed in a storiform pattern with little or no extracellular matrix. Other areas were characterized by an abundant fibrillary extracellular matrix organized in trabecular structures or with increased honeycomb-pattern bone. These histological patterns were not haphazardly distributed in resected specimens but tended toward a "zonal" distribution, with more cellular areas in the central portion of the tumor and matrix-rich areas in the periphery. At the periphery of the tumor, the osteoid-like matrix seemed to merge with host bone.

Discussion

This study of GCTB in an extremity showed that denosumab administration apparently increased the rate of local recurrence and the need for joint replacement after curettage. Similar to findings in previous studies[1,10,16-19], there was a significantly lower risk of recurrence after wide resection than after curettage. Some authors have recommended local adjuvants combined with curettage to reduce the risk of recurrence[18-20], whereas others consider it unnecessary[21,22]. Prosser et al.[21] reported a low overall recurrence rate (19%) for 137 patients who underwent curettage alone. Turcotte et al.[22] reported that the nature of the cement filling had no significant impact on the risk of recurrence in 148 patients treated with curettage, including 64 who had cement filling. In our study, the use of phenol adjuvant (but not cement) significantly decreased the risk of local recurrence.

The U.S. Food and Drug Administration approved the use of denosumab for treating adults and skeletally mature adolescents with unresectable GCTB or when resection is likely to result in severe morbidity[6]. Thomas et al.[5] reported an open-label Phase-II study in which they showed clinical benefit when treating GCTB with denosumab. In 86% (30) of 35 patients, there was a tumor response to denosumab, as assessed by histological and radiographic evaluations. Only a small number of these patients, however, underwent intralesional surgery after denosumab. Thus, it remains unknown whether the local recurrence rate was affected by denosumab in that study.

Chawla et al.[6] confirmed the efficacy (which included reduction in the need for morbid surgery) and the safety of denosumab in 282 patients affected by GCTB. As in the investigation by Thomas et al.[5], they studied patients still on denosumab treatment and 25 patients who underwent surgery after denosumab treatment with a median follow-up of only 9.2 months, which is inadequate for definitive conclusions.

Another open-label Phase-II study evaluated reduced surgical invasiveness after denosumab treatment in 222 patients with resectable GCTB that was able to be evaluated for surgical downstaging[8]. Of the 115 patients who had surgery, 17 (15%) experienced local recurrence during a median follow-up of 13.0 months (IQR, 8.5 to 17.9 months). The median time to recurrence was 13.6 months (IQR, 10.5 to 15.7 months) postoperatively. For the 99 patients who underwent surgery but had no local recurrence, the median postoperative follow-up was 12.9 months (IQR, 7.8 to 18.0 months). The authors warned that these results must be interpreted with caution because of the short follow-up time.

Traub et al.[23], in a prospective nonrandomized study of patients with GCTB who received denosumab for 6 to 11 months preoperatively, reported that all patients underwent intralesional surgery, with local recurrence in 3 of the 18 patients at 10, 12, and 25 months postoperatively; the median follow-up was 30 months (range, 20 to 45 months). The local control rate was comparable with those in other studies in which denosumab was not used before curettage[10,21,22]. Hence, these data do not indicate that denosumab improved local control of GCTB. The authors reported that the new osseous tumor matrix and the thickened cortical bone that developed following denosumab treatment raise a new surgical challenge by not allowing the surgeon to delineate the true extent of the

tumor. They theorized that tumor cells can "hide" within the thickened cortex and subchondral bone, which could increase the risk of local recurrence.

Our data showed an unacceptably large increase in local recurrence in patients treated with denosumab and without phenol. Further investigation of the role of denosumab and phenol as adjuvant treatments is warranted. In the present report, we describe the results for 25 patients with GCTB who underwent curettage following denosumab with a median follow-up of 42.1 months. The local recurrence rate was 60% (15 patients). Follow-up for these patients was longer than in previous studies, which may explain the higher local recurrence rate.

A recent in vitro study that assessed the viability and osteoclastogenic capabilities of neoplastic stromal cells of GCTB[24] showed that cell proliferation is only diminished by denosumab. Thus, the cells continue to proliferate in vitro, albeit at a slower rate. These data suggested that denosumab actively inhibits osteoclastogenesis biologically. Although the stromal cells were quiescent during drug exposure, the neoplastic cells again proliferated once the microenvironment was free of denosumab[24]. We also observed residual neoplastic stromal cells following denosumab administration.

With the very small numbers available, we were not able to show an effect of denosumab administration on local recurrence in patients with resected GCTB. Several authors reported that denosumab seems to improve subchondral and cortical bone by reconstituting a peripheral rim, allowing easier resection[4,23,25-27].

An objective tumor response (defined by modified inverse Choi criteria as a partial or complete response) was noted in 22 (73%) of 30 patients. Chawla et al.[6] reported that 76% of 176 patients had an objective tumor response by the same criteria. Ueda et al.[7] reported that 71% of 17 patients showed an objective tumor response. Objective tumor responses in our study were similar to those described in the latter 2 studies.

The present study has several limitations. First, it is retrospective, and the patients given denosumab treatment were compared with 378 historical control subjects, including patients treated by different surgeons over a 24-year period and with different techniques. Second, the patients treated with curettage and denosumab differed considerably from those who underwent curettage alone. The group treated with denosumab were older, had more tumors in the distal end of the radius (which are associated with a higher rate of local recurrence), and had more Campanacci stage-III tumors. Phenol was used less frequently in the denosumab group. Even though multivariable analysis was used to correct the influence of confounding factors, it might not have been able to correct the influence of the major differences in the 2 groups, which is a limitation. Third, although the total sample size is relatively large, the number of patients in the denosumab group and the number of joint replacements in the curettage group are relatively small. Finally, we enrolled only patients treated at our institution.

There was a higher rate of recurrence in the cohort exposed to denosumab. Because there were substantial differences in the cohorts and randomization was not applied, however, causation could not be evaluated.

The ability to perform curettage correctly after denosumab treatment is a concern because the rim of new bone may contain tumor cells that could reactivate once denosumab treatment is completed[4]. We strongly recommend collaborative studies involving clinical trials and rigorous data collection to identify the optimum indications for using denosumab to treat GCTB of the extremities. ■

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