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REVIEW ARTICLE

How safe and effective is denosumab for bone giant cell tumour?

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Abstract Recent clinical studies have suggested that denosumab is associated with beneficial tumour response, surgical down-staging, and reduced surgical morbidity in patients with giant cell tumour of bone. However, these studies reported results of patients still on denosumab treatment, or patients after denosumab treatment but with a short follow-up. Other studies reported that the new osseous tumour matrix and thickened cortical bone that develop with denosumab treatment does not allow the surgeon to delineate the true extent of the tumour, and probably increases the risk for local recurrence. A study showed that cell proliferation is only diminished by denosumab; the cells continue to proliferate in vitro, albeit at a slower rate. More importantly, nine cases of malignant transformation of GCT during denosumab therapy without previous radiation exposure have been reported; inhibition of RANKL may increase the risk of new malignancies due to immunosuppression. With these concerns in mind, this article is an attempt to put essential information in one place, creating a comprehensive review that the curious reader would find interesting and informative.

Keywords Denosumab · Giant cell tumour of bone · Malignant transformation · Sarcoma

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Editorial

The treatment of giant cell tumour (GCT) remains controversial [1]. Surgical treatment options include intralesional surgery (curettage) using a high-speed burr or resection [2]. Curettage has a higher recurrence rate, but preserves adjacent joint function. Resection with wide margins minimises tumour recurrence; however, it is associated with worse functional results [3]. Some authors recommend the use of local adjuvants combined with curettage to reduce the risk of recurrence [4–6], while according to others, local adjuvants do not improve the outcome to local recurrence [7, 8]. On 13 June 2013, the Food and Drug Administration (FDA) approved denosumab (Xgeva®, subcutaneous injection; Amgen, Thousand Oaks, CA, USA), a monoclonal antibody that binds receptor activation of nuclear factor kappa-β ligand (RANKL), for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity [9–11].

Recent clinical studies have suggested that denosumab is associated with beneficial tumour response [9–12], surgical down-staging [11–13] and reduced surgical morbidity in patients with GCT [9–13]. However, these studies reported results of patients still on denosumab treatment, or patients after denosumab treatment but with a short follow-up (median, 13 months; range, 4–13 months) [11, 13]. Thomas et al. [10] reported the first open-label phase II study showing clinical benefits of denosumab treatment in 37 patients with GCT; however, only a small minority of the patients in that series underwent intralesional surgery after denosumab. Chawla et al. [11], in a similar open-label phase II study in 282 patients with GCT, confirmed the safety and efficacy of denosumab, including a capacity of reducing the need for morbid surgery [11]. As in the study of Thomas et al. [10], the study of Chawla et al. [11] reported results of patients still on

denosumab treatment or patients that underwent surgery after denosumab treatment with a short follow-up (median, 9.2 months). Another open-label phase II study evaluated reduction of surgical morbidity after denosumab treatment in patients with resectable GCT [13]. Overall, 222 patients were evaluable for surgical down-staging. Of the 115 patients who had surgical treatment, local recurrence occurred in 17 patients (15%). The median postoperative follow-up for all patients who had surgical treatment was 13.0 months (range, 8.5–17.9 months). The median post-operative time until local recurrence was 13.6 months (range, 10.5–15.7 months). It is obvious that the median post-operative follow-up was shorter than the median post-operative time until local recurrence. Therefore, as the authors reported, because of the discrepancy and short-term follow-up, these results must be interpreted with caution [13].

Traub et al. [14] reported the results of a prospective non-randomised study of patients with GCT who received denosumab for six to 11 months pre-operatively; all patients underwent intralesional surgery. Local recurrence occurred in 3/18 patients (17%), at ten, 12 and 25 months post-operatively. The median follow-up after surgical treatment was 30 months (range, 20–45 months). The authors reported that the new osseous tumour matrix and thickened cortical bone that develop with denosumab treatment raises a new surgical challenge by not allowing the surgeon to delineate the true extent of the tumour [14]. In fact, tumour cells can "hide" within the thickened cortex and subchondral bone, which could unfavourably increase the risk of local recurrence.

Other authors confirmed these data, reporting a local recurrence rate of 8.3% in 12 patients with GCT treated by curettage after denosumab treatment, and emphasised on the same conclusions: tumour cells can remain in the newly-formed bone induced by denosumab and the stiff newly formed bone makes intralesional surgery more difficult [15]. Rekhi et al. [16] reported a local recurrence rate of 18.5% in 27 patients with GCT treated by surgery and denosumab therapy at a median follow-up of 18 months. Intralesional surgery was undertaken on 15 patients and resection on 12 patients. Unfortunately, the authors did not differentiate the two groups of patients with respect to local recurrence, and it is not possible to know the real local recurrence rate after curettage following denosumab treatment. Moreover, the follow-up was again too short for important conclusions to be drawn regarding the local recurrence rate.

Goldschlager et al. [17] reported no local recurrence in two patients with GCT of the spine treated with denosumab and en bloc vertebrectomy. Müller et al. [15] reported that five patients had resection after denosumab treatment without any local recurrence [15]. Therefore, resection following denosumab therapy seems to decrease local recurrence compared to resection only. Probably, denosumab improves subchondral and cortical bone by reconstituting a peripheral rim that allows for easier resection (Table 1) [9, 14, 15, 17, 18].

Table 1 Summary of published studies on surgery of GCT after denosumab treatment

Study	Patients (n)	Surgery (Patients, n)	Post-operative follow-up (months)	Local recurrence (Patients, n)	Post-operative time until local recurrence (months)	Duration of denosumab treatment (months)		
						Pre-operative	Post-operative	Total
Thomas et al. [10]	7	Resection (7)	NR	NR	NR	Range, 3–7	None	Range, 3–7
Chawla et al. [11]	25	Curettage (16) Resection (9)	Median 9.2 (IQR, 4.2–12.9)	0% (0/16) 0% (0/9)	None	Median, 24	None	Median, 24
Rutkowski et al. [13]	115	Curettage (80) Resection (35)	Median 13.0 (IQR, 8.5–17.9)	17.5% (14/80) 8.6% (3/35)	Median 13.6 (IQR, 10.5–15.7)	8	6	Median, 14.2; IQR 12.0–17.7
Goldschlager et al. [17]	4	Curettage (2) Resection (2)	Mean 12 (range, 4.5–26)	0% (0/2) 0% (0/2)	None	Mean, 6; range, 5–7	None	Mean, 6; range 5–7
Traub et al. [14]	18	Curettage (18)	Median 30 (range, 20–45)	17% (3/18)	NR	Range, 6–11	None	Range, 6–11
Müller et al. [15]	18	Curettage (12) Resection (6)	Mean 23 (range, 9–49)	8.3% (1/12) 0% (0/6)	7	Mean, 3.9; range 3–6	6	9.9
Rekhi et al. [16]	27	Curettage (15) Resection (12)	Mean 17.6 (range, 7–27)	18.5% (5/27)	Mean 13.2 (range, 9–18)	Mean, 2.5	None	Mean, 2.5

NR not reported, *IQR* interquartile range

Table 2 Summary of published studies reporting on cases with sarcomatous transformation of GCT after denosumab treatment

Study	Patients (*n*)	Age/ gender	Site	Treatment	Outcome (follow-up)	LP (years)/ histology of sarcoma	Time of sarcomatous transformation[a] (months)	Time of denosumab treatment (months)
Thomas et al. [10]	2	NR	Upper extremity	Resection	NR	NR	Range 3–7	Range, 3–7
		NR	Lungs	Resection	DOD (NR)	NR	Range 11–15	Range, 3–7
Chawla et al. [11]	2	NR	NR	NR	NR	NR	NR	NR
Rutkowski et al. [13]	2	NR	Pelvis and sacrum	NR	NR	NR	8.5	8.5
Apote-Tino et al. [20]	1	20/F	Proximal tibia	Amputation	CDF (6 months)	5/high-grade pleomorphic sarcoma	13	13
Broehm et al. [21]	2	59/M	Ischium	Chemotherapy	AWD-M(NR)	13/osteosarcoma	31	30
		56/M	Distal femur	Wide resection + CMT	DOD (4 months)	7/osteosarcoma	6	6

LP latent period between diagnosis of benign GCT and diagnosis of sarcomatous transformation of GCT, *NR* not reported, *CDF* continuous disease free, *AWD-M* alive with disease (metastasis), *DOD* death of disease, *CMT* chemotherapy

[a] Time interval between the start of denosumab treatment and diagnosis of sarcomatous transformation of GCT

A recent in vitro study examined the viability and osteoclastogenic capabilities of neoplastic stromal cells of GCT [19]. This study showed that cell proliferation is only diminished by denosumab; the cells continue to proliferate in vitro, albeit at a slower rate. These data show that denosumab appears to be biologically active in inhibiting osteoclastogenesis. However, although the stromal cells are quiescent during denosumab treatment, the neoplastic cells remain proliferative once the microenvironment is free of denosumab [19]. Although generally considered benign, rarely GCT can metastasise despite maintaining a benign histology [2]. In this setting, nine cases of malignant transformation of GCT during denosumab therapy without previous radiation exposure have been reported (Table 2) [10, 11, 13, 20, 21]. In the study of Thomas et al. [10], two patients developed new sarcomas; one patient developed a high-grade sarcoma in the upper extremity during denosumab treatment and another patient developed a malignant GCT with lung metastases eight months after discontinuing denosumab. Similarly, in the study of Chawla et al. [11], two patients developed new sarcomas; in the first patient, the sarcoma was retrospectively suspected to be present at baseline, and in the second patient, the sarcoma was thought to be a malignant transformation [11]. In the study of 222 patients with GCT of Rutkowski et al. [13], the GCT lesions in two patients developed malignant transformation under denosumab treatment. These authors considered the diagnosis of primary malignant GCT that was missed by sampling error at the time of the initial core biopsy [13]. Aponte-Tinao et al. [20] reported a patient with a recurrent GCT who developed a bone sarcoma while receiving denosumab treatment. Broehm et al. [21] reported two patients with malignant transformation of their GCT to osteosarcoma while receiving denosumab treatment [21]. All patients in these series reported a clinical benefit to denosumab treatment until the occurrence of malignant transformation, while none of these patients had undergone previous radiation therapy. The expression of RANKL plays an important role in B- and T-cell differentiation and dendritic cell survival; its inhibition of bone destruction could eventually increase the risk of new malignancies due to immunosuppression [22–24].

We have a concern regarding the ability to perform a complete curettage of GCT after denosumab treatment. The rim of new bone may contain neoplastic cells that may reactivate once denosumab treatment is finished. Therefore, if curettage is feasible, we do not suggest denosumab administration for the treatment of GCT. In addition, as the present literature review has summarised, the scientific community and treating physicians should be aware of the possible association of denosumab treatment with malignant transformation of GCT or occurrence of new malignancies.

Compliance with ethical standards

Conflict of interest No benefits have been or will be received from a commercial party related directed or indirectly to the subject matter of this article.

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