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REVIEW

Giant-cell tumor of bone, anti-RANKL therapy

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Giant-cell tumor of bone (GCTB) is a rare osteolytic tumor of the bone. Although classified as a benign tumor, GCTB is characterized by local aggressiveness and risk of local recurrence. In addition, GTCB can in some cases lead to the development of so-called 'benign' chest metastases. Surgical resection by intralesional curettage with high-speed burring and polymethylmethacrylate cement is the standard treatment for resectable tumors. In cases of metastatic or unresectable disease (when planned surgical procedure is impossible or would result in severe morbidity), medical treatments such as cytotoxic chemotherapy or interferon-α have limited efficacy. Bisphosphonates have been proposed as a therapeutic option to reduce osteoclast activity. In bone, various pathological states may result from an imbalance in the RANK (receptor activator of nuclear factor kappa-B)/RANKL (receptor activator of nuclear factor kappa-B ligand)/OPG (osteoprotegerin) pathway. Involvement of the RANKL pathway in pathogenesis of GCTB was first proposed in 2000. Denosumab is a fully human monoclonal antibody that binds and inhibits RANKL, thereby preventing the activation of the RANK pathway. As it showed the possibility to counteract osteoclast activation in GCTB and prevent the known physiopathological role of RANKL, denosumab has been under evaluation in the clinic as a treatment for GCTB since 2005. Results of a first Phase II trial demonstrate the therapeutic potential of denosumab to inhibit progressive bone destruction and metastatic progression in patients with unsalvageable giant-cell tumor (GCT), and have also provided key insights into the biology of GCT. Denosumab is currently a therapeutic option for patients with unresectable GCTB but its place in the global therapeutic strategy has not yet been defined.

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Introduction

Giant-cell tumor of bone (GCTB) is a rare tumor of the bone representing 4–10% of primary bone tumors (20% in China), and 20% of benign bone tumors. [1] It was described as a separate entity at the beginning of the last century.[2] Several studies comprised of hundreds of patients led to a better description of the features of this tumor.[3–7]

Table 1 describes clinical characteristics of GCTB from the largest studies published in the last 5 years. GCTB usually occurs in patients aged 20–40 years with the same frequency among male and female patients. It typically develops in the epiphyses of long bones, most frequently in the distal end of the femur, the proximal end of the tibia, and the proximal end of the humerus. GCTB are rarely multifocal. Extension to the articular space, ligaments or synovial membrane is possible, as well as transarticular extention to adjacent bone through the joint. These tumors have the unusual capacity to develop at distant sites, with slow-growing or even stagnant metatases. No risk factors have been identified for GCTB. Familial clustering of the Paget's disease and GCTB has been reported.[8,9]

Clinical Presentation

Usually, the disease is discovered after a patient presents with bone pain. In more rare cases, the diagnosis is based on a palpable mass or pathological fracture. Even more rarely, the disease is discovered radiographically in the absence of symptoms; this method can detect either the bone tumor site or benign pulmonary metastases.

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Table 1 Clinical characteristics of GCTB from the largest studies published during the last 5 years

Author, year	Kivioja, 2008	Balke, 2008	Gupta, 2008	Errani, 2010	Niu, 2012
Number of patients	294	214	470	349	621
Sex ratio male/female	156/138	97/117	268/202	172/177	359/262
Mean age at diagnosis (years)	35	33	21–30	32	31.4
Location (lower ext/upper ext/axis)	208/86/0	135/20/59	262/148/60	270/79/0	

Abbreviation: GCTB, giant-cell tumor of bone.

Diagnosis and Staging

Diagnosis and staging are based on radiologic imaging features. The most important radiographic findings regarding giant-cell tumor are the location of the tumor, its lytic nature and the lack of a host response. Typically, giant-cell tumors are expansible, osteolytic, radiolucent lesions without sclerotic margins and usually without a periosteal reaction. **Figure 1** shows a typical radiographic appearance of GCTB in the left femur of a 40-year-old man (**a**) and in the right distal femur of a 37-year-old man (**b**).

Computed tomography scans may provide more complete diagnostic information than standard radiography but are most useful in surgical planning. Magnetic resonance imaging supplements essential information found via radiography by detecting soft-tissue changes, intra-articular extension and marrow changes. It is the best imaging method for assessing subchondral breakthrough and the extension of tumor into an adjacent joint. GCTB generally exhibits enhanced fluorodeoxyglucose (^{18}F-FDG) uptake, mainly attributable to an enhanced vascular fraction and increased ^{18}F-FDG transport.[10] This examination is not part of the routine assessment of GCTB. Complete staging must also include chest imaging (X-ray and/or computed tomography scan) to evaluate the possible presence of pulmonary metastasis.

Overall, complete staging to plan surgery of newly diagnosed GCTB should include radiographics, computed tomography scan and magnetic resonance imaging of the tumor site, as well as a chest X-ray.

Staging. The most commonly used staging is that reported by Campanacci[11] based on the Enneking classification system.[12] It was established to stage musculoskeletal sarcoma and consists of three grades corresponding to radiological extent. A Grade I tumor has a well-marginated border of a thin rim of mature bone, and the cortex is intact or slightly thinned but not deformed. A Grade II tumor has relatively well-defined margins but no radiopaque rim; the combined cortex and rim of reactive bone is rather thin and moderately expanded but still present. Grade III designates a tumor with fuzzy borders, suggesting a rapid and possibly permeative growth; the tumor bulges into soft tissue, but the soft tissue mass does not follow the contour of the bone and is not limited by an apparent shell of reactive bone.

Histology

Macroscopically, GCTB presents as a hemorrhagic, soft, lobulated mass, which erodes the bone. It is usually bound by a thin and often incomplete shell of reactive bone. Although the tumor frequently erodes the subchondral bone to reach the deep surface of the articular cartilage, it seldom penetrates it.

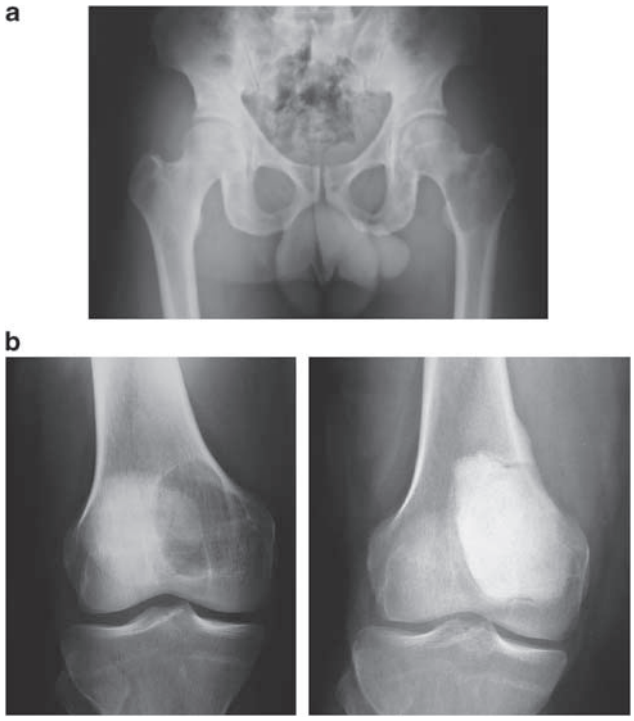

Figure 1 Typical radiographic appearance of giant-cell tumor of bone (CGTB) with expansile, osteolytic and radiolucent lesions. (**a**) GCTB of left femur in a 40 years old man. (**b**) GCTB of right distal femur in a 37 years old man before and after surgical treatment with high speed buring and cement (we see on right picture that cementoplasty is lined with a thin border of osteolysis encircled by osteosclerosis corresponding to the adaptive response of the residual bone).

Microscopically, it has long been known that multinucleated giant cells (containing 50–100 nuclei) are not neoplastic and constitute only part of the tumor's cellular composition. The GCTB is also made up of round to oval polygonal or elongated mononuclear 'stromal' cells, which represent the neoplastic component. Their nuclei are very similar to those of the osteoclasts, having an open chromatin pattern and one or two small nucleoli. The cytoplasm is ill-defined and there is little intercellular collagen. Mitotic figures are invariably present from 2 to 20 per 10 high-power fields. Atypical mitoses are not seen and their presence may suggest malignant transformation. Mononuclear cells are thought to arise from primitive mesenchymal stromal cells. The proliferatively active neoplastic tumor cells, which are also described as 'giant-cell tumor stromal cells', represent various proportions of the tumoral tissue. They do not arise from the monocytic-histiocytic lineages.[13] Owing to the complex histological composition of GCTB, differential diagnosis is required to exclude the diagnosis of other lesions also containing giant cells, such as variants of aneurysmal bone cysts, fibrous metaphyseal defects, chrondroblastoma, brown tumor in

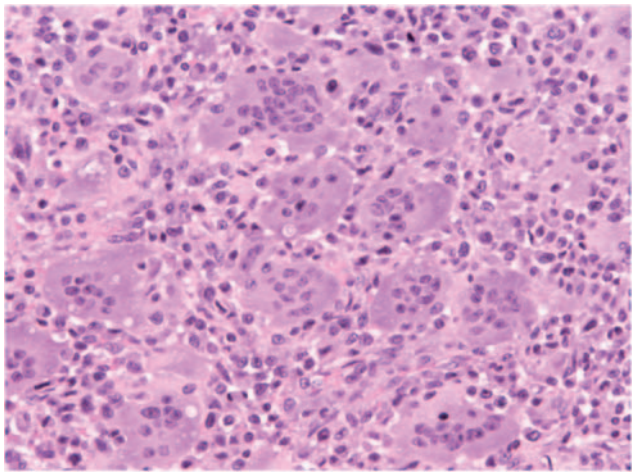

Figure 2 Typical appearance of giant-cell tumor of bone with multinucleated large giant cells and uniform ovoid mononuclear cells (100×).

hyperparathyroidism, as well as giant-cell-rich variants of osteosarcoma. **Figure 2** presents the typical appearance with large osteoclasts and uniform ovoid mononuclear cells.

To confirm the diagnosis, immunohistochemical analysis may be performed. Giant cells constantly express CD68, an antigen expressed by both macrophages and osteoclasts, as well as p63. However, although sensitive to detection, p63 is not specific and can be expressed in other giant-cell-containing lesions of bone, specifically primary aneurismal bone cysts, chondroblastomas, giant-cell reparative granulomas and some osteosarcomas.[14–16] Analysis of gene and protein expression within the tumor leads to an exploration of the mechanisms of interaction between the two cellular components. Multinucleated giant cells present osteoclast profile (expression of receptor activator of nuclear factor kappa-B (RANK)) and are sensitive to osteoclast differentiation signals expressed by stromal cells, which present osteoblast profile (expression of osteoclast differentiation factor, receptor activator of nuclear factor kappa-B ligand (RANKL), and osteoprotegerin (OPG)).[1]

Benign metastasis? One unusual characteristic of these benign-classified tumors is the development of so-called 'benign' chest metastases, which show histologic features identical to those of a benign tumor. The mean interval between primary diagnosis and the onset of lung metastasis is about 4 years. Local recurrence is a major risk factor for the occurrence of lung metastasis. As mentioned above, medical treatment has limited efficacy. Surgical resection of such metastases, iterative if necessary, may improve survival.[17–19]

Malignant GCTB. Malignant GCTB (MGCTB) have been reviewed by Bertoni *et al.*[20] who distinguished (1) primary MGCTB (PMGCTB) occurring simultaneously with benign GCTB and (2) secondary MGCTB (SMGCTB) occurring at the site of previously treated GCTB, typically after irradiation. Among five PMGCTB, there were four osteosarcoma and one malignant fibrous histiocytoma; among twelve SMGCTB there were nine osteosarcoma, two fibrosarcoma and one malignant fibrous histiocytoma. While SMGCTB is usually easy to diagnose upon malignant clinicoradiographic presentation, PMGCTB often mimics giant-cell tumors both clinically and radiographically. Their prognosis is overall poor, with the worst outcome associated with postradiation SMGCTB.[20]

Local Treatment

Surgery. Surgery is the mainstay treatment of GCTB. Although a benign tumor, local aggressiveness and recurrence risk of GCTB, as well as its rarity, make it mandatory that the disease be managed by a team with experience and a high level of expertize in bone tumors.

The type of surgical excision depends on the local tumoral staging (bone, articular, and soft tissue involvement); methods used include intralesional excision with tumoral curettage, marginal excision and wide/radical excision. No randomized trials to evaluate the best management methods for this rare tumor have been conducted. Two large retrospective studies provide information on recurrence rate according to surgical procedures. Among 327 patients and 331 surgical procedures, Campanacci *et al.*[11] reported no recurrence in cases of radical/wide excision, 8% recurrence in cases of marginal excision and 30% in cases of intralesional excision.

Several strategies have been tested in addition to intralesional curettage with the aim to decrease the recurrence rate: these include local injection of polymethylmethacrylate (PMMA), PMMA after phenolization, phenolization and cryotherapy.[21–24] The injection of PMMA cement into the tumor cavity is reported to be the best method, reducing the recurrence rate from 29.7% without cement to 14.3% with cement after intralesional curettage among 330 patients.[25] In multivariate analysis, both the stage of disease the and use of cement were independent significant factors associated with local recurrence in this study. However, the use of cement was associated with a higher risk of subsequent need for joint replacement, in case of local recurrence, as well as without recurrence. More recently, Balke *et al.*[27] reported similar results for recurrent GCTB: the use of adjuvant cement after curettage was found to decrease the risk of subsequent recurrence (58.8–21.7%) in a retrospective study.

The results of a meta-analysis evaluating 'high-speed burring' after intralesional management of GCTB were published in 2010.[27] The authors systematically identified all studies in the literature reporting recurrence rates in GCTB following intralesional curettage and high-speed burring with a comparison group of the same cohort who underwent the same procedure plus a chemical or thermal adjuvant (recurrence rate: 23% and 20%, respectively, among 387 patients). They conclude that meticulous surgical technique including high-speed burring is the most important step in reducing recurrence rates. **Table 2** presents the recurrence rate of GCTB according to the type of surgery and the use of adjuvant in case of intralesional excision.

In view of the present literature, surgical management of resectable GCTB should include intralesional curettage with high-speed burring and PMMA cement.

Radiotherapy. When tumor location and/or locoregional extension precludes any complete resection with acceptable morbidity, surgical resection is contra-indicated. Several treatments can then be discussed. Radiotherapy may improve local control in two main settings: in case of unresectable disease or as adjuvant treatment in case of positive margins after surgical resection. **Table 3** presents the efficacy of radiotherapy in GCTB.[28–31] Five-year disease-free survival rates vary from one of these retrospective studies to another, but it is evident that long-term

Table 2 Recurrence rate of resectable GCTB increases with less-aggressive surgical technique (intralesional excision) but decreases with the addition of adjuvant therapy

Author, year	*Number of cases*	*Recurrence rate according to local treatment*			
		Wide/radical excision (%)	*Marginal excision (%)*	*Intralesionnal excision (%)*	*Use of adjuvant after intralesional excision*
Campanacci, 1987	327	0	8	27	
Becker, 2008	384			49	22% (PMMA) 27% (PMMA + phenol) 15% (phenol)
Klenke, 2009	118	5		25	15% (PMMA + phenol) 34% (phenol)
Lackmar, 2005	63				6% (burring + PMMA + phenol)
Oh, 2006	42				9.5% (burring + phenol)
Gaston, 2011	330			29.7	14.3% (cement)
Blake, 2009	66 recurrent tumors	0	58.8		21.7% (PMMA + burring)
Algawahmed, 2010 (meta-analysis)	387			20	20% (high-speed burring + adjuvant), 15% (high-speed burring)

Abbreviations: GCTB, giant-cell tumor of bone; PMMA, polymethylmethacrylate.

Table 3 Results of largest studies evaluating the efficacy of radiotherapy in GCTB in its two main indications: RT alone for unresectable tumors and postoperative RT for non-*in-sano*-resected tumors. Local control can be achieved for a substantial proportion of patients

Author, year		Caudell, 2003	Feigenberg, 2003	Bhatia, 2011	Kriz, 2012
Number of patients		25	24	58	35
Treatment context	RT alone	14	15	58	19
	Post-op RT	11	11		16
Dose (Gy)		25–65	35–55	20–65	35–60
Recurrence rate (%)		60	23	15	41
RT-induced sarcoma		2	1	1	0

Abbreviations: GCTB, giant-cell tumor of bone; RT, radiotherapy.

local control can be achieved for a substantial proportion of patients. Although rare, especially since the use of megavoltage radiotherapy, the most serious complication associated with radiotherapy is the development of sarcoma, which may occur in 2–3% of patients given the present published data.

Therefore, radiotherapy can lead to prolonged local control in patients whose tumor is unresectable or in case of marginal surgical resection with acceptable toxicity.

Systemic Treatment

The use of medical treatments such as cytotoxic chemotherapy or interferon-α has been reported. No randomized clinical trials to precisely define their efficacy are available. The number of cases of patients treated with chemotherapy reported in literature is very low, and activity seems modest.[17–19] In addition, a few case reports have shown interferon-α to have antitumor activity at the cost of increased toxicity.[32,33]

There is a preclinical and clinical rationale for the use of bisphosphonates in GCTB. Bisphosphonates prevent bone resorption by inhibiting osteoclast activity and promoting osteoclast apoptosis. In 2004, *in vitro* and *in vivo* experiments reported efficacy on GCTB of several bisphosphonates such as zoledronate, pamidronate and alendronate; these compounds were shown to induce apoptosis in both osteoclast-like giant cells and stromal cells.[34,35] Local administration of zoledronic acid directly into the tumor lesion also leads to massive tumor cell death, observable by histology.[36] In clinical practice, bisphosphonates seem to improve disease control with symptom relief. Balke *et al.*[37] reported the largest series evaluating the efficacy of bisphosphonates, which consisted of 25 patients with aggressive primary, recurrent or metastatic GCTB. All patients had several episodes of recurrence before they received study treatment, which was zoledronic acid in most cases. The majority of patients presented radiologically stable disease with symptom relief. Among 25 patients, 22 presented stable disease after a median follow-up of 24 months (3 patients had disease progression at 3, 12 and 60 months, respectively).[37] The role of bisphosphonates in the adjuvant setting could also be interesting. A retrospective case–control study including 44 patients reported a lower local recurrence rate, especially in Stage III tumors, with the use of bisphosphonates administered peri-operatively.[38]

Bisphosphonates may be useful to control the evolution of inoperable GCTB. Their role in the adjuvant setting remains to be clearly defined.

The Role of RANKL in the Pathogenesis of GCTB

Bone is a rigid organ in appearance that is continuously remodeled. Osteoblasts deposit new bone while osteoclasts govern the resorption of the matrix of the bone. The regulation of the activity of osteoblasts and osteoclasts ensures the balance between resorption and synthesis and provide normal bone tissue. Osteoclasts are derived from hematopoietic stem cells and osteoblasts are derived from the mesenchymal stem cell line. Osteoclast differentiation and activation requires RANK ligand and CSF-1 (for colony-stimulating factor -1). RANKL is a TNF-related cytokine produced by osteoblasts, T-cells and stromal cells. CSF-1 is a polypeptide growth factor produced by osteoblasts and marrow stromal cells. These two hematopoietic factors are both necessary and sufficient for osteoclastogenesis,[39]

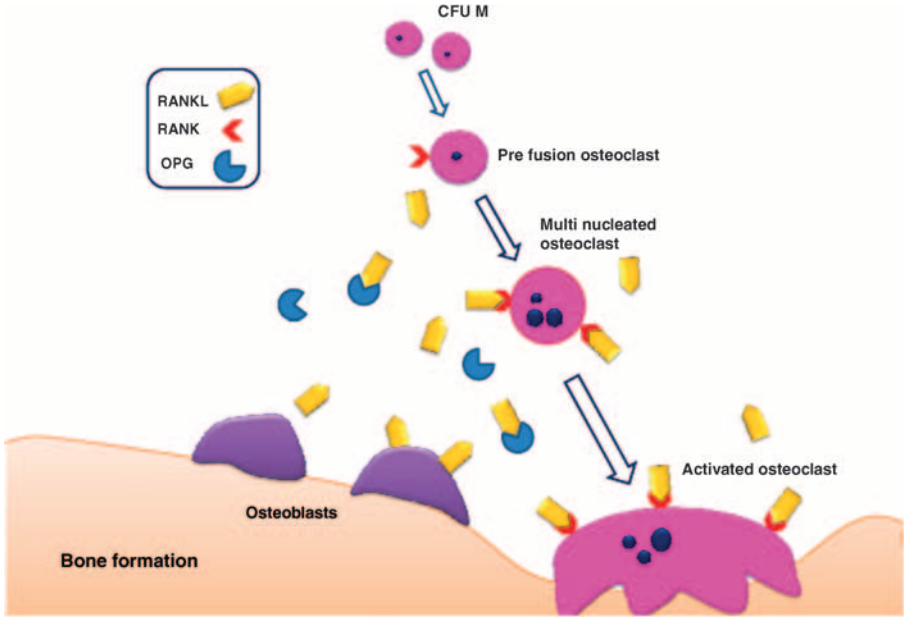

Figure 3 RANK/RANKL/OPG (receptor activator of nuclear factor kappa-B)/receptor activator of nuclear factor kappa-B ligand/osteoprotegerin) pathway of osteoclastogenesis. Stimulation of osteoclast precursor involves multiple cells. Primary stimulator of precursors is osteoblast through expression of RANK ligand (RANKL). Osteoblast can also release osteoprotegerin (OPG), which binds RANK ligand and inactivates it.

binding their receptor, RANK, and c-fms/CSF1R, respectively. Binding initiates multiple intracellular signaling pathways leading to the expression of osteoclast-specific genes, leading to mature osteoclast phenotype in the case of RANKL and to proliferation and survival of osteoclast precursor in the case of CSF-1.[40]

OPG was discovered in 1997.[41] Its possible involvement in tumor-cell-induced osteoclast-like cell formation was first described by Huang in 2000.[42] It acts as a soluble decoy receptor by blocking RANKL binding to its cellular receptor RANK.[43] OPG is a member of the TNF receptor super family and is produced by osteoblasts. Expression of RANKL and OPG is therefore coordinated to regulate bone resorption and density by controlling the activation state of RANK on osteoclasts.

Various pathological states are derived from the imbalance of this RANK/RANKL/OPG pathway. Increased osteoclastic activity is seen in osteoporosis. Bone resorption facilitates the progression of primary and secondary bone malignancies; on the other hand, impaired osteoclast activity leads to osteopetrosis.[44]

Involvement of the RANKL pathway in GCTs was first proposed in 2000 when two teams described the detection of RANKL and RANK mRNA in GCTs using reverse transcriptase-PCR and *in-situ* hybridization.[42,45] RANKL was also detected by immunofluorescence in cultured cells derived from GCTs. In 2002, Roux *et al.*[46] provided the first immunohistochemical evidence that RANK and RANKL were expressed in these tumors at the protein level, with RANK being expressed by osteoclast-like cells, and RANKL by the mononuclear cells that form the mesenchymal component of GCTs. These findings were consistent with the involvement of RANKL and RANK expression in the pathogenesis of GCTs, as the overexpression of RANKL by tumor stromal cells could be responsible for the formation of numerous osteoclasts within the tumor. **Figure 3** presents the RANK/RANKL/OPG pathway.

Clinical Activity of Denosumab

Denosumab is a fully human monoclonal antibody that binds to RANKL and thereby inhibits its binding to RANK, preventing RANK activation. Thereby, it inhibits the maturation of osteoclasts. It therefore mimics the endogenous effects of OPG, reducing the effects of RANKL on RANK and helping to modulate bone resorption.

Denosumab in osteoporosis and bone metastases. Denosumab was first developed for treatment of osteoporosis, and the results of a Phase I study evaluating resorption activity and the safety of denosumab were published in 2004.[47] The drug was administered vs a placebo to 49 postmenopausal women; patients received six separate doses of denosumab via subcutaneous injection. The authors report a dose-dependent rapid and sustained decrease in bone turnover as measured by urinary and serum N-telopeptide and serum bone-specific alkaline phosphatase. The Phase III trial FREEDOM showed a significant decrease in fracture rate among 7868 patients with osteoporosis.[48] The tolerance was excellent. Its efficacy in cancer was first tested in 1468 non-metastatic prostate cancer patients receiving hormone-deprivation therapy. Patients were randomized to receive either denosumab or a placebo every 6 months over a 36-month period. All patients also received calcium and vitamin D supplements. Of those in the placebo arm, 3.9% experienced bone fractures during the 36 months, compared with 1.5% of those who received denosumab (relative risk 0.38; 95% CI ; $P=0.006$).[49] Denosumab demonstrated similar efficacy with bone mineral density increasing by 5.5% and 7.6% at 12 and 24 months, respectively in a study conducted in non-metastatic breast cancer patients treated with aromatase inhibitors.[50] Based on these findings, denosumab was approved by the Food and Drug Administration and European Medicines Agency at the dose of 60 mg subcutaneously every 6 months for the treatment of postmenopausal women with osteoporosis at

high risk for fracture, as well as for patients at high risk of bone fracture, including patients undergoing androgen deprivation therapy for non-metastatic prostate cancer or on adjuvant aromatase inhibitor therapy for breast cancer.

Following these encouraging results, denosumab was compared with zoledronic acid and approved for the treatment of bone metastases from solid tumors.[51,52] At the dose of 120 mg every 4 weeks, it delayed the time to first skeletal-related events. Furthermore, in men with non-metastatic castration-resistant prostate cancer at high risk of bone metastasis, denosumab increased bone-metastasis-free survival (median 29.5 vs 25.2 m; hazard ratio 0.85; $P = 0.028$) and time to first bone metastasis (median 33.2 vs 29.5 m; hazard ratio 0.84; $P = 0.032$) compared with placebo; however, this effect did not translate into a survival advantage.[53]

By inhibition of osteoclast activity, bisphosphonates and denosumab are associated with osteonecrosis of the jaw (ONJ), especially in the presence of comorbodities such as diabetes, infection, trauma and coagulation disorders. In the arm of patients treated with denosumab in these three studies,[51–53] the occurrence rate of ONJ was 2%, 1.1% and 5% in 1026, 886 and 716 patients, respectively. This rate was not statistically higher than that observed in the zoledronic acid arm;[51,52] no case of ONJ was reported in the placebo arm.[53] These rates should be carefully followed in the future to ensure they do not increase further, especially due to the knowledge that ONJ may occur after a long duration of antiresorptive treatment and sometimes even after cessation of therapy. The development and approval of denosumab in patients with osteoporosis or bone metastasis taught us to adopt measures to prevent ONJ, which is a potential concern for patients.

Denosumab in GCTB. The presence of osteoclast activation in GCTBs and the role of RANKL led to work, which assessed the effectiveness of denosumab against these tumors. Results of the first study were published in *Lancet Oncol* in March 2010.[54] This Phase II trial was multicentric and multinational and included 37 patients with recurrent or unresectable giant-cell tumor (GCT). Patients received subcutaneous injections of 120 mg of denosumab every 28 days, with additional loading doses on days 8 and 15 of the first month. Treatment was well tolerated in 33 of the 37 patients. Adverse events of any grade were reported, and five patients reported grade 3–5 adverse events. Of these five, only one adverse event was deemed to be treatment-related.

Of the 37 patients, 2 were not evaluable for efficacy due to insufficient histologic or radiologic data. Twenty patients were assessable by histology, and all of these patients presented tumor response with 90% or greater reduction of giant cells. Histological examination of the tissue samples of these patients showed the spindle-shaped cell-dense stroma replaced with a less cellular stroma, with embedded new osteoid formation lined by RANKL-expressing cells, particularly in the central area of the resected tumors. Peripheral to the areas of osteoid formation, there was a progressive transition to areas of irregular small woven bone trabeculae. These trabeculae were lined with a smaller number of osteoblast-like RANKL-expressing cells. At the peripheral margin of the resected tumor, woven bone transitioning to normal lamellar bone was observed.

Among the 15 patients assessable by radiology, 10 presented tumor response. FDG-positron emission tomography evaluation showed reduction in FDG uptake, suggesting that positron emission tomography may be a sensitive early detection method for clinical response in GCT of bone. Overall, 84% of patients experienced clinical benefit (that is, reduced pain or improvement in functional status) and 29% exhibited bone repair. This study shows the therapeutic potential of denosumab to inhibit progressive bone destruction and metastatic progression in patients with unsalvageable GCT, and also provides key insights into the biology of GCT. **Figure 4** shows radiographic aspects of chest metastases of GCTB before and after 6 months of denosumab treatment.

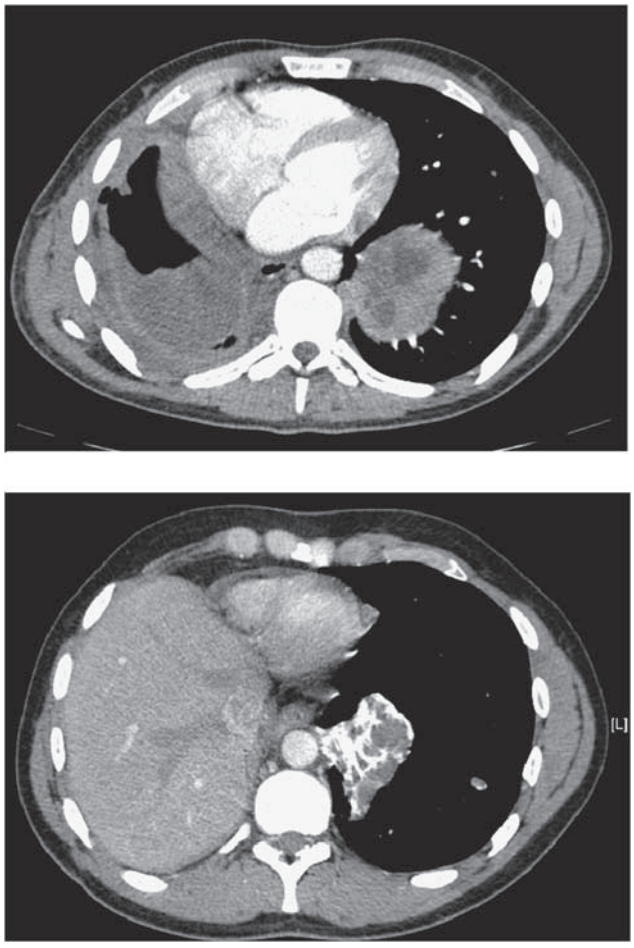

Figure 4 Chest metastasis of giant-cell tumor of bone histologically proven before and after 6 months of denosumab treatment.

Denosumab is a new efficient therapeutic option to treat unresectable and metastatic GCTB.

Pending its official approval, patients should be enrolled in clinical trials to benefit from the drug. A Phase II multinational study is currently in the process of recruiting 250 patients: subjects with surgically unsalvageable GCTB (that is, sacral, spinal GCTB or multiple lesions including pulmonary metastases) or subjects whose planned surgery includes surgical procedure resulting in severe morbidity (NCT00680992, AMGEN 20062004). Preliminary results on safety were reported last year and confirmed a good tolerance for the drug (abstract no. 10034 ASCO 2011). Definitive results should provide insight regarding the benefit of pre-operative denosumab in reducing morbidity associated with resection surgery.

Several questions remain unresolved regarding the precise strategy of treatment for patients with GCTB treated with denosumab. How long should the treatment be given? What side effects will present in the long term? When should secondary surgical resection be proposed? What is the risk of relapse following interruption of therapy? Will denosumab be still efficient if reintroduced after a break?

It would also be prudent to perform clinical trials to assess denosumab in an adjuvant setting in patients with high risk of relapse or who previously progressed. A study is being considered within the Soft Tissue and Bone Sarcoma Group of the European Organisation for Research and Treatment of Cancer, with the support of the EuroSarc FP7 grant.

Conclusion

Although benign, the management of GCTB remains challenging due to its symptomatic characteristics, its locoregional aggressiveness and its high potential to recur (locally or with distant 'benign metastases'). Recent advances in the understanding of the biological mechanisms of this complex disease have led to the use of targeted therapy with undeniable efficacy. Once more, a better knowledge of carcinogenesis of a tumor allows the physician to choose the most beneficial treatment for the patient. Denosumab is a new therapeutic option for patients with unresectable GCTB, but many questions remain to be answered to precisely define its place in the global therapeutic strategy.

Conflict of Interest

The authors declare no conflict of interest.

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