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THERAPY IN PRACTICE

Giant Cell Tumor of Bone in Childhood: Clinical Aspects and Novel Therapeutic Targets

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Abstract Giant cell tumor of bone (GCTB) is a rare primary bone tumor that primarily affects young adults, but can be seen in children. The primary modality of treatment is surgical resection; however, this is not always possible given the location and extent of the neoplasm. Recent developments in the understanding of the underlying molecular pathogenesis of disease have pointed to interactions between the stromal component producing receptor activator of nuclear factor-kappaB (RANK) and RANK-ligand (RANKL) causing the formation of osteoclast-like giant cells that drive bone destruction. The development of a monoclonal humanized antibody to RANKL, denosumab, has been shown to reduce skeletal-related events from osteoporosis and from bony metastases from solid tumors. Recent phase II clinical trials with denosumab in skeletally mature adolescents over age 12 years and adults with GCTB, have shown both safety and efficacy, leading to its accelerated US FDA approval on 13 June 2013. In children who are skeletally immature, safety and efficacy has not been established, and there has been only published anecdotal use.

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1 Introduction

Giant cell tumor of bone (GCTB) is a rare, generally benign though locally aggressive primary neoplasm of bone, characteristically showing osteolytic activity [1]. The definitive therapy for GCTB is surgery; however, only about 80 % of GCTB are treated with surgical excision and this may be associated with morbidity and recurrence [2]. Though primarily seen in adults (subjects >18 years old who have reached skeletal maturity), GCTB can be seen in children and adolescents, posing additional problems in those patients who have yet to reach skeletal maturity [3]. This review summarizes the available data on GCTB in skeletally mature children and adolescents, our current understanding derived from the treatment of adult GCTB, molecular pathogenesis of disease, novel therapeutic targets (i.e. denosumab), and summarizes the clinical trials that have led to the recent US Food and Drug Administration (FDA) approval of denosumab in the treatment of this disease.

2 Epidemiology

GCTB makes up about 5 % of all primary bone tumors in the USA. In Asia, GCTB is considerably more common, representing approximately 20 % of all primary bone tumors [4]. The reason for this increase in incidence in the Asian population is not known. GCTB is a tumor of young

adults, presenting between 20 and 40 years of age. The most common sites of presentation in adults are at the epiphyses of long bones. In the pediatric population, GCTB is not as common, making up roughly 2–5 % of all reported GCTB cases [5, 6] and predominates in adolescence (age 13–19 years). In children, the most common site of disease is in the proximal tibia, followed by axial skeletal lesions such as in the vertebrae and pelvis [7] and originate more commonly from a metaphyseal location rather than an epiphyseal one as seen in older subjects. Younger patients also have a higher incidence of multicentric disease. In childhood and adolescence, GCTB seems to have a higher female to male incidence [6, 7]. Although speculative, this might be as a result of females reaching skeletal maturity on average 2 years before males.

3 Clinical Presentation, Radiographic, and Pathologic Features

The most common presenting symptom of GCTB in the appendicular skeleton is pain accompanied by swelling, deformity, and limited range of motion at the affected extremity. In axial primary tumors, patients may present with pain and neurological signs and symptoms from nerve compression. Pathologic fracture is not uncommon at the time of presentation; however, this is more frequently seen in adults than in children [8].

Imaging is crucial for aiding in diagnosis and for evaluating extent of disease. Plain film radiography can show either a geographic or permeative lytic lesion involving the epi-metaphyseal region with cortical thinning and usually lacking a sclerotic rim. Expansion of the bone may occur if a secondary aneurysmal bone cyst is present; this is seen in approximately 20–30 % of GCTB. Aggressive periosteal reaction is seldom seen (Fig. 1). As mentioned, a pathologic fracture may also be present [9]. Gross pathology generally shows a hemorrhagic, lobulated mass eroding bone. Histologically, GCTB is a heterogeneous tumor composed of stromal cells and multinucleated giant cells (Fig. 2) that express CD68, CD163 and other markers consistent with true mature osteoclasts such as receptor activator of nuclear factor-kappaB (RANK), the calcitonin receptor, and $\alpha(v)\beta(3)$ integrin [10, 11].

4 Molecular Pathogenesis of Disease

Over the last 2 decades there has been great progress made in the overall understanding of the molecular pathogenesis of GCTB, primarily due to the discovery of RANK ligand (RANKL). RANKL is a membrane-bound member of the tumor necrosis factor (TNF) family; it is required for osteoclast formation, mediates osteoclast activation, and is highly expressed by the stromal cells of GCTB [12]. It is thus thought that the stromal cellular component and not the giant cell component is the true influence on neoplastic growth. RANKL, which is highly expressed on stromal cells, binds to RANK, which is highly expressed on monocytes, promoting cellular fusion of the monocytes, osteoclastogenesis, and formation of giant cells that are capable of bone resorption (Fig. 3) [13]. However, the underlying etiology of increased RANKL expression in stromal cells leading to giant cell formation and bone resorption is not completely understood.

Other factors that have been implicated in the pathogenesis of GCTB suggest a role for chemotaxis, hypoxia, and angiogenesis. Stromal cell-derived factor (SDF)-1, hypoxia inducible factor (HIF)-1-alpha, and vascular endothelial growth factor (VEGF) are expressed by the stromal cellular component of GCTB and appear to also be drivers of monocyte recruitment, osteoclast formation, and bone resorption in GCTB [13, 14].

5 Therapeutic Management

The gold standard of GCTB management is surgery. This can be accomplished via en bloc excision with reconstruction or extended intralesional curettage followed by filling the defect with a bone substitute (i.e. bone cement or bone graft) (Fig. 1). Mechanical, chemical, and thermal adjuvants are often used in combination with intralesional procedures to reduce the risk of local recurrence [15–17]. The recurrence rates, though variable across published data, are generally lower for wide local resection than for intralesional surgery; in one larger study, recurrence rates were 5 vs. 25 %, respectively, with an improvement with the addition of polymethylmethacrylate to the intralesional curettage group [18].

Clearly, the surgical approach depends on the site of disease, proximity to the joint space, the presence of soft tissue extension, pathologic facture and potential long-term functional deficits. This is particularly true in children who may not have reached skeletal maturity where en bloc excision can be associated with long-term skeletal developmental problems and functional deficits. Furthermore, in children, the higher incidence of axial skeletal primaries increases the likelihood of tumors that are not amenable to en bloc excision or intralesional curettage.

Radiation has been used as a means of local control, primarily in adult patients with GCTB that are not resectable, without significant morbidity [19]. The local control rates have been favorable, averaging about 75 % across series; however, there is a small though not insignificant long-term risk of development of a radiation-associated

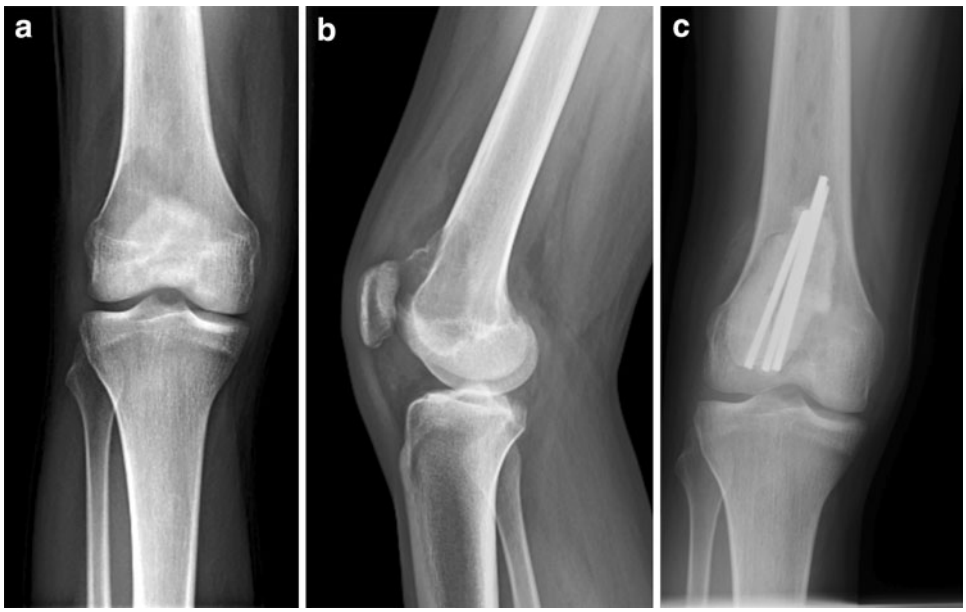

Fig. 1 Plain film radiographic appearance of GCTB in the distal femur of an 18 year old shows **a** AP view and **b** lateral view showing a subarticular geographic destructive process in the distal femur with expanded, thinned, and irregular cortex with adjacent soft tissue edema. **c** AP view post-curettage, polymethylmethacrylate bone cementing, and rod placement. *AP* anteroposterior, *GCTB* giant cell tumor of bone

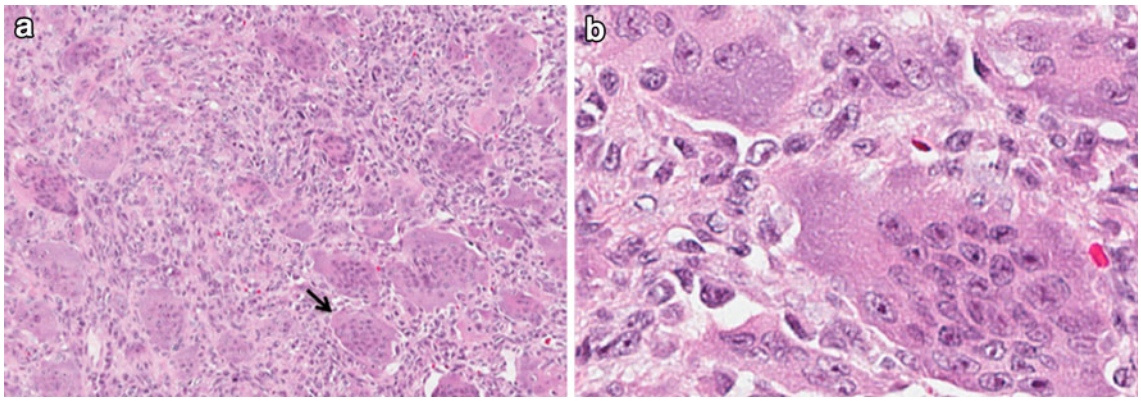

Fig. 2 **a** Histology sections show abundant multinucleated giant cells (*arrow*) and admixed ovoid stromal cells. The stromal cells are uniform, with scattered typical mitoses. **b** Characteristic multinucleated giant cell in giant cell tumor of bone containing >30 nuclei

sarcoma [20, 21]. The standard for radiation treatment is now with intensity modulated radiation therapy, but newer modalities such as proton therapy and stereotactic beam radiotherapy may improve the outcomes while limiting radiation doses to normal tissues. In children, radiation therapy as a means of local control of GCTB is generally not used unless other modes are impossible or have failed. This is because of the long-term risks from radiation, particularly in the pediatric population.

In children, the sacrum and spine are special sites of GCTB that bear separate discussion, as these sites may not be amenable to complete surgical excision. Generally, these sites are approached with intralesional curretage with polymethylmethacrylate cementing and cryotherapy, though historically these sites carry high recurrence rates [22, 23]. Serial sacral artery embolization is a local control method that can be successful and is gaining wider use for these larger sacral primary tumors [24, 25].

Systemic chemotherapy, primarily with anthracycline/alkylating agent bone and soft tissue sarcoma-based regimens, have been used in GCTB, particularly malignant GCTB [26, 27]. However, the utility of systemic chemotherapy in unresectable GCTB is really unproven and clearly has significant toxicity. Other systemic therapies such as interferon and bisphosphonates have been administered with some reports of disease stability and pain relief, though again these therapies are not considered standard [28, 29].

6 Novel Therapeutics

The above-mentioned finding of increased RANKL expression in the stromal cellular compartment of GCTB, and the hypothesis that this is the driving factor behind RANK-expressing osteoclast-like giant cells in GCTB,

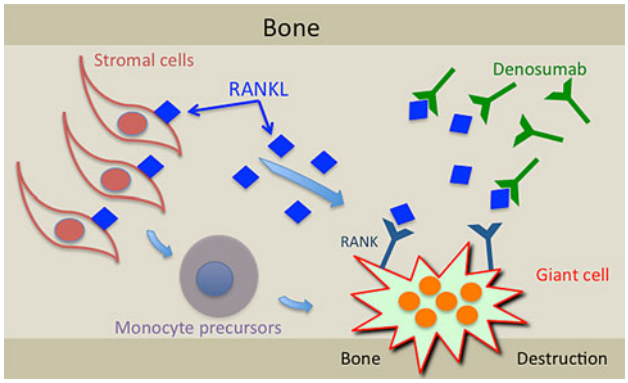

Fig. 3 Putative molecular pathogenesis of giant cell tumor of bone and mechanism of action of denosumab. RANKL, which is highly expressed on stromal cells binds to RANK, which is highly expressed on monocyte precursors, promoting cellular fusion of the monocyte precursors, osteoclastogenesis, and formation of giant cells that are capable of bone resorption. Denosumab, a humanized (Ig)G2 monoclonal antibody to RANKL competitively binds to RANKL, and thereby inhibits the formation and bone destructive activity of the osteoclast-like giant cells. *IG* immunoglobulin, *RANK* receptor activator of nuclear factor-kappaB, *RANKL* RANK-ligand

made way for potential therapeutics targeted to RANKL. Further supporting the targeting of RANKL in GCTB was that this strategy was used successfully in other conditions with increased bone destruction, namely osteoporosis and bone metastases [30]. The fully humanized immunoglobulin (Ig)G2 monoclonal antibody against RANKL, denosumab (Amgen), was shown to reduce skeletal-related events from bone metastases in breast cancer, prostate cancer, multiple myeloma, and other cancers [31–33]. Denosumab was approved by the US FDA for postmenopausal osteoporosis in June 2010 under the brandname Prolia® given every 6 months, and subsequently approved under the name Xgeva® for the prevention of skeletal-related events in patients with bone metastases from solid tumors, where 120 mg is administered subcutaneously every 4 weeks [34].

It was thus thought that denosumab could inhibit osteoclast-like giant cells in GCTB and reduce bone resorption in a similar fashion (see Fig. 3 for putative mechanism of action in GCTB). This set the stage for an open-label, single-arm, proof-of-concept phase II trial of denosumab in patients with GCTB conducted by Thomas et al. [35] and described here. In this multicenter, international trial, 37 adult patients (age >18 years) with unresectable or recurrent GCTB were enrolled to receive denosumab 120 mg subcutaneously every 28 days with additional loading doses at day 8 and 15 in the first month of treatment. The primary endpoint of this study was tumor response, measured by elimination of >90 % of the giant cells on post-treatment biopsy pathology or no radiological progression at 25 weeks. Of the 35 subjects, 30 (86 %) had a tumor response (two subjects were excluded for insufficient data). Although the study was not designed to evaluate pain and quality of life, >80 % of patients did report improvement in symptoms or overall function. Histopathologically, all of the 20 patients who had post-treatment tumor biopsies had >90 % reduction of tumor RANK-positive giant cells and RANKL stromal cells. Of the 20 patient histopathological samples, 13 also showed new bone formation and/or dense fibro-osseous tissue replacing the proliferative RANKL stromal component [36]. In this phase II clinical trial, denosumab was well tolerated. There were five serious adverse events reported, but none were deemed related to the drug. Of note, there were no reported cases of osteonecrosis of the jaw (ONJ); however, the smaller sample size and low incidence rate of ONJ with denosumab (1–2 %) may explain the absence of reported cases in this trial. The potential ramifications of ONJ in childhood are particularly important, so extensive counseling prior to treatment, with a careful dental exam and recommendations for oral hygiene with appropriate preventive dentistry, should be performed [37].

From this small proof-of-concept trial, denosumab was heralded as a potential breakthrough in GCTB; however, criticisms included the short follow-up period in the afore-mentioned phase II trial (25 weeks), the lack of primary surgical local control information on the recurrent cases, and the subjective nature of the inclusion criteria definition of 'unresectable' disease [38]. That said, RANKL inhibition by denosumab was clearly a promising systemic strategy in adult patients with recurrent or unresectable GCTB. In many ways, the phase II trial raised many more questions than it answered about the appropriate use of denosumab in GCTB.

This afore-mentioned trial set the stage for the largest therapeutic study of GCTB to date, an open-label, multicenter, phase II study of denosumab in subjects with GCTB (NCT00680992), which has been completed. Here the age inclusion criteria was extended to include skeletally mature adolescents (>12 years old, weight ≥45 kg) and adults. Skeletal maturity was defined as at least one long bone with a closed epiphyseal growth plate. In this clinical trial, patients with GCTB were stratified into two primary arms with a third extension arm: Cohort 1 included those patients with unresectable GCTB; Cohort 2 included resectable GCTB where salvage surgery was planned; and Cohort 3 an open-label extension of the patients transferring over from the previous phase II trial (NCT00396279). The primary objective for this study was to continue to examine the safety profile of denosumab with secondary objectives of time to disease progression in cohort 1, and the proportion of subjects who did not have any surgery at 6 months from treatment start in cohort 2. The dosing of denosumab was consistent with the prior phase II study, with subcutaneous denosumab 120 mg every 28 days with

additional loading doses at day 8 and 15 of the first month of treatment [39, 40].

In the recently published interim results of this trial, 282 patients (ages 13–83 years) have been enrolled and the results are striking. Denosumab was well tolerated overall, with commonly reported non-serious adverse events: arthralgia, headache, nausea, and musculoskeletal pain. Hypocalcemia deemed to be non-serious was also reported in 5 % of patients. Three patients (1 %) did have ONJ, which is in keeping with current estimates of the incidence of ONJ with denosumab. Of 169 patients in cohort 1, 163 (96 %) had no disease progression. In cohort 2, 71 of the 100 subjects had surgery planned at baseline, 64 (90 %) of these patients did not undergo surgery at the 6-month evaluation point, and at the analysis cut-off, 74 % had still had no surgery and 16 % had undergone a less morbid procedure than planned upfront [39].

Clinical benefit with improved mobility and function was seen in about 20 % of cohort 1 (those who were deemed unresectable) and 30 % of cohort 2 (resectable with planned surgery) [35]. Pain and analgesic use was also studied in this trial. Interestingly, 31 % of subjects reported meaningful improvement of pain within the first week of receiving denosumab, and 42 % of the patients with moderate to severe pain at baseline improved to no or mild pain; about 20 % had worsening pain through the course of the study. Of note, several patients also decreased analgesic use from strong opioids to no or low analgesic use [41].

Objective responses as defined by modified Response Evaluation Criteria in Solid Tumors (RECIST), inverse Choi criteria, and European Organisation for Research and Treatment of Cancer (EORTC) criteria were seen in 72 % of patients; 25 patients had a complete response (eight in cohort 1 and 17 in cohort 2). Median time to objective tumor response was 3 months, and about half of the patients had a response duration of >8 months, with two patients going on to progression of disease after an initial response [39].

Safety data from both phase II clinical trials of denosumab in GCTB showed that, in the 304 adolescent and adult patients, the most common adverse events reported in >10 % were headaches, arthralgia, fatigue, and back and extremity pain. Serious adverse events, ONJ, and osteomyelitis were reported in 0.7 % and resulted in discontinuation of the drug. Both moderate hypocalcemia (2.6 %) and severe hypophosphatemia (9.5 %) were not uncommon laboratory findings [35, 37]. Of the six evaluable skeletally mature adolescents who were enrolled on the trial, two had an objective response by RECIST criteria [37]. As an example, in one 13-year-old patient with a large recurrent cervical GCTB who was enrolled in the phase II denosumab clinical trial, imaging pre and post 3 years of denosumab treatment has shown dramatic osseous mineralization of the C6–7 vertebra at the original site of the tumor (see Fig. 4). The toxicity profile appeared similar in the ten skeletally mature pediatric patients; however, the small sample size makes it hard to assess its overall safety and pharmacokinetics.

Because denosumab is only recently FDA approved in skeletally mature adolescents with GCTB, its published use in the skeletally immature pediatric population is limited to case reports and small case series. Denosumab has been administered in children with osteogenesis imperfecta type VI (OI-VI). The rational for denosumab use in this population is that mutations in SERPINF1 in OI-VI lead to activation of osteoclasts via the RANK/RANKL pathway. Denosumab was administered to four children with OI-VI in doses of 1 mg/kg subcutaneously every 3 months. Although a small case series, the drug was well tolerated and showed reversible inhibition of bone resorption [42]. Denosumab (0.13 and 0.27 mg/kg subcutaneously) has also been reported to reduce severe hypercalcemia in two young children post-hematopoietic stem cell transplantation for

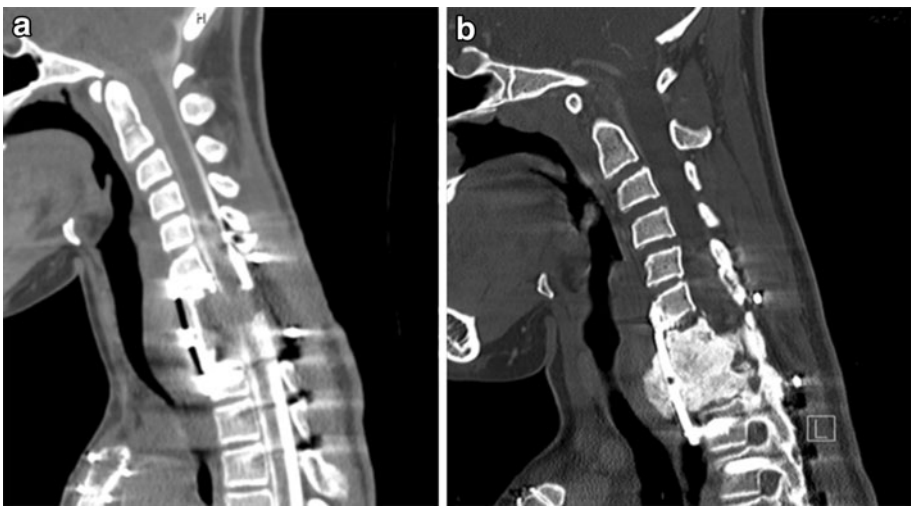

Fig. 4 Imaging response to denosumab in a 13-year-old female with recurrent cervical GCTB. **a** Computed tomography images pre-denosumab and **b** post-denosumab therapy shows extensive osseous mineralization at the site of the GCTB in the C6–7 vertebrae. *GCTB* giant cell tumor of bone

osteopetrosis [43]. Finally, denosumab has been reported with benefit in children with extensive fibrous dysplasia of bone and recurrent vertebral aneurysmal bone cysts [44, 45]. Still, there is a dearth of safety, efficacy, and toxicity information in the skeletally immature pediatric population.

In childhood skeletally immature GCTB, a case was reported of a 10-year-old girl with metastatic GCTB (patella primary with lung and subcutaneous metastases) who was treated with denosumab per the phase II trial dosing by Thomas et al. Similar to the adolescent and adult patients in the phase II trial, she had a dramatic improvement in pain and quality of life. Pathology from the patellar resection post-treatment showed a paucity of giant cells and new bone production. This patient did require vitamin D, calcium, and phosphorus supplementation for the development of hypocalcemia and hypophosphatemia secondary to denosumab treatment. As an interesting caveat in treating the skeletally immature, this patient did have normal growth velocity during treatment, though developed increased total bone mineral density perhaps as an adverse effect to denosumab as it portends an increased risk of potential later fracture [46].

Obviously, there is relatively little that can be inferred from these single case reports except that more systematic exploration of denosumab in children in the context of clinical trials should be performed. However, larger questions continue to exist and will likely remain unanswered in the near future regarding the duration of denosumab treatment, optimal dose schedule, late effects of therapy, and whether its use really can facilitate surgical local control. These same questions exist in the pediatric population, as do the more worrisome issues of acute toxicities to skeletal development and overall growth as well as late effects on the skeleton and other organs. Denosumab in utero exposure in monkeys resulted in marked developmental defects such as absence of some lymph node chains, bone defects, tooth mal-alignment, and hematopoietic abnormalities [37]. Moreover, in small children, the pharmacodynamics and pharmacokinetics of denosumab are not known. Because of the risk of hypocalcemia in adults with denosumab, current prescribing information from the manufacturer recommends concomitant calcium 1 g and vitamin D 4,000 μ daily. Recommendations for calcium and vitamin D supplementation in smaller children receiving denosumab should be straightforward, but guidelines will also need to be established.

7 Conclusion

GCTB is a rare and aggressive bone tumor that is most often seen in young adults and has metastatic potential. In children, GCTB predominates in later adolescence though can be seen in the skeletally immature. In children, treatment for GCTB has primarily been surgical, but axial skeletal locations, primarily in the sacrum and pelvis, can make surgery impossible; moreover, significant morbidity and local recurrences after intralesional excisions are not uncommon. A variety of other local and systemic therapies have been utilized, but with varying degrees of success. More recently, there has been elucidation of the underlying molecular pathogenesis of disease in GCTB involving RANK/RANKL driving the osteoclast-like giant cell proliferation and aggressive bony destruction associated with this disease. Denosumab, a human monoclonal antibody that is a competitive RANKL antagonist has had remarkable results in recent phase II trials, resulting in US FDA approval as of 13 June 2013 in adults and skeletally mature adolescents with GCTB that is unresectable or where surgical resection is likely to result in severe morbidity. In this capacity, denosumab can and should be used now, both in those patients with unresectable GCTB and in those in whom neoadjuvant use may avoid surgery altogether or make surgical resection more feasible and potentially less morbid. Looking forward, hopefully we can extend this therapy to younger GCTB patients with few options for management. Larger questions do remain about the long-term effects of denosumab therapy in children regarding skeletal development, risk of ONJ, and other potentially unforeseen late complications. Clearly, the results from the recent trials of denosumab in GCTB warrant further systematic investigation in clinical trials in the pediatric population, particularly in the skeletally immature.

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