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Review

Treatment of giant cell tumor of bone: focus on denosumab

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Abstract

Giant cell tumor of bone (GCTB) is a rare benign locally aggressive tumor of bone with malignant potential. Microscopically it is comprised of multinucleated giant cell rich osteoclastic cells. It typically occurs in the 2nd to 4th decade of life after skeletal maturity has been reached. Surgical intervention in the form of curettage with local adjuvant, marginal excision or enbloc resection was the only treatment modality in the past. However, an increasing understanding of the pathophysiology of the tumor and the role of receptor activator of nuclear factor kappa B ligand (RANKL) has shifted the management to a multidisciplinary approach with the consideration of using denosumab (a monoclonal antibody against RANKL) in advanced GCTB. Denosumab was approved for use in adults and skeletally mature adolescents by the US Food and Drug Administration in June 2013 for unresectable GCTB or where surgical resection would likely cause severe morbidity.

Key words: giant cell tumor of bone, denosumab, nuclear factor kappa B ligand, RANKL, RANK, osteoclastoma, GCT, GCTB

Introduction

Giant Cell Tumor of bone (GCTB) is a primary bone tumor which is generally considered "benign but locally aggressive", but can rarely be malignant. It was first described by Cooper and Travers et al in 1818 [1]. However not until 1940 was it recognized as a separate entity from other osteolytic tumors like aneurysmal bone cyst, non-ossifying fibroma etc. [2].

About 4-5% of all bone tumors are GCTB [3]. It comprises about 15-20% of all benign bone tumors [4, 5].Peak incidence is between 20-45 years of age. 10% of cases can occur in the second decade before skeletal maturity. In these cases there is an increased incidence of vertebral tumors and multicentricity [4, 6, 7] .The name "giant cell tumor" is on account of the abundant reactive multinucleated giant cells found in the tumor, which cause bone resorption. However, the actual neoplastic cells are believed to be the stromal cells that are responsible for the giant cell formation and orchestrate the pathogenesis of the tumor. Most common site of occurrence is the epiphyses of the long bones, however can occur in any other areas of the skeleton [8].

Surgical management is the definitive treatment. However, there is still a risk of local recurrence and metastasis. Often, very aggressive surgical interventions are needed to reduce risk of recurrence, which can lead to severe morbidity in young adults. Unresectable cases were mostly treated in the past with marginally effective treatments such as radiation and serial embolization, however any responses achieved with these procedures were generally not durable [9-11].

The maturation of the understanding of the role of the receptor activator of nuclear factor kappa B ligand (RANKL) in the pathogenesis of the disease, and the development and use of denosumab a RANKL inhibitor, has brought a paradigm shift in the treatment of this disease to a multidisciplinary approach, especially in cases which are advanced (with soft tissue extension, or with cortical break, joint invasion or pelvic location etc.)

or metastatic [12].

This review article discusses the current multidisciplinary approach in the treatment of GCTB with special emphasis on denosumab, its development, use, duration and concerns. It also discusses future directions in the treatment of this disease with increasing knowledge of its etiology and pathogenesis.

Clinical presentation and diagnosis

GCTB typically presents as a painful bone lesion. There can be swelling in the limb, and limitation of movement of the affected joint. Tumors affecting axial skeleton can cause neurologic symptoms. Sometimes GCTB can lead to pathologic fracture. It is generally believed to arise in the metaphyseal region, but may demonstrate epiphyseal extension in the majority of cases. It is often difficult to delineate the exact origin as this tumor occurs frequently in skeletally mature individuals where the growth plate has closed. Plain radiograph is the first step at diagnosing GCTB, where it appears as an eccentric radiolucent lesion with thinning and eventually perforation of the cortex. Remodeling of the bone generates an "expansile" cortical picture. One of the accepted grading systems to grade the tumor is the Campanacci system. Grade I shows lesions to be entirely within the bone, grade II includes lesions invading the cortex without perforating it. Lesions extending into soft tissue with perforation of the cortex are considered grade III [3, 13].

Computed Tomography (CT) scans can help better evaluate the extent of cortical thinning, and also rule out mineralization of the matrix which could indicate an alternate diagnosis such as giant cell rich osteosarcoma. Magnetic Resonance Imaging (MRI) is used for exact delineation of the bone and soft tissue extension of the tumor, neurovascular bundle involvement if any, and is helpful with surgical planning. As these tumors do have a rare metastatic potential, a CT chest is often done at presentation and is definitely indicated in the recurrent setting work up, where pulmonary metastasis is more common. Positron –emission tomography (PET) imaging, although not routinely indicated, when performed have shown the lesions to be fluorodeoxyglucose (FDG) avid likely due to the increased metabolic rate of the giant cells within the tumor [14,15]. Ultimately, a biopsy is needed for definitive diagnosis but one has to be aware of the fact that biopsy can be difficult to interpret, and results can be erroneous on account of the heterogeneity of these tumors [16].

Pathogenesis

Though originally named "Giant cell tumor" by Dr Bloodgood, a surgeon at John Hopkins in 1912, due to the abundant giant cells seen on microscopic evaluation, the giant cells are not believed to be the neoplastic cells [17]. Rather, the mesenchymal stromal cells found within the tumor are the true neoplastic cells; the giant cells are subsequently formed from interaction between stromal cells and recruited monocyte/macrophages from blood stream [18].The fact that the stromal cells are indeed the neoplastic and proliferative component in the pathogenesis of the tumor is supported by the evidence that only the stromal cell are capable of growing in cell cultures and forming tumors in mice [19-21]. On karyotypic analysis, the stromal cells are found to have various non-clonal alterations including insertions, deletions, translocations and other structural and numerical rearrangements. The most common cytogenetic finding in GCT is telomeric association found in over 70% of cases [22). Despite the above findings, no clear driver mutation had been detected. However, recent findings demonstrate a H3F3A mutation in the neoplastic stromal cells, not seen in normal mature or precursor osteoclasts. This is therefore thought to possibily be the driver mutation specific for GCTB, although further study will be needed to demonstrate this [23, 24]. Besides the above alterations, p53 is also commonly found to be mutated in these tumors. MDM2, which suppresses p53 by promoting its degradation by ubiquitination, is also found to be overexpressed in primary GCTB [22].

The identification and role of RANKL in the pathogenesis of the tumor has brought about a major change in the management of GCTB. RANKL was first discovered in mice thymoma cell lines EL40.5 in a bid to find tumor necrosis factor receptor (TNFR) homologues [25]. In 1997 an independent lab reported the finding of a new TNF family member expressed on T cells which was called TNF-related activation-induced cytokine (TRANCE; now called RANKL) [26].

Increased RANKL expression on the stromal cells together with secretion of stromal cell derived factor1 (SDF 1) and monocyte chemoattractant protein 1(MCP 1) leads to recruitment of monocyte precursors and formation of osteoclast like giant cells by fusion of the above. The monocytes have increased RANK expression which in turn is modulated by macrophage colony stimulating (M-CSF) factor again produced by the neoplastic stromal component of the tumor. However the event leading increased PTHrp in stromal cells in unclear. Further research regarding recent finding of H3F3A mutations may help shed light to the initial triggering event leading to the pathogenesis of GCTB [23, 24].

Local Treatment

Surgery is the only current definitive treatment option for GCTB. However, the type and extent of surgery depends on the location and extent of tumor. For tumors of the appendicular skeleton, one option is intralesional curettage followed by high-speed burring and adjuvant chemical intralesional treatment. Several adjuvant options

exist, including polymethyl methacrylate (PMMA), phenol, liquid nitrogen, hydrogen peroxide, and sterile water. These options have been all shown to reduce recurrence rate, but none has demonstrated significant advantage over the other in terms of reduction of recurence risk [3]. Since the adjuvants are equally effective in reducing recurrence, the risks and side effects of the choice of adjuvant, rather than the effectiveness, usually determines the choice of adjuvant by the surgeon. This procedure often gives acceptable functional outcome while offering a reasonable rate of local recurrence rates are approximately 30% with intralesional surgery and adjuvant therapy [29, 42-45]. The addition of an adjuvant is shown to be important, as intralesional curettage alone without adjuvant therapy can have a 50% or even higher risk of recurrence [28].

There are no randomized trials done to evaluate the efficacy of different adjuvant options, however PMMA (bone cement) is one of the only choices of adjuvant that confers some mechanical stability as well as reduction in recurrence rate, which in many cases may allow for early weight bearing. The adjuvant effect is believed to be due to the significant heat generated during the setting of the cement, which may induce tumor necrosis. The benefit of using bone cement as surgical adjuvant was shown in a retrospective study reported by the Scandinavian sarcoma group. Patients who had cement filling had a recurrence rate of 22% as opposed to 61% when bone graft was used to fill the cavity left tumor resection [29].

The second surgical option is wide resection of the tumor with the surrounding bone. Although this type of resection is demonstrated to lower recurrence rate to 0-12% [29,42-45], it generally comes with significant additional morbidity. Since these tumors generally extend to epiphyseal bone, wide resection usually means sacrificing the adjacent joint, which necessitates a large scale oncology-style joint reconstruction. Function with these types of reconstruction can be good [46], but is generally not as good as a standard or revision style reconstruction. Also, durability of these types of implants is significantly lower, in many cases necessitating revision for a variety of reasons within 10 years [47].

The highest risk of recurrence was noted when tumors had soft tissue extension [28]. For this reason, a reasonable algorithm used by many surgeons is that for Campanacci grade 1 and 2 tumors, without significant soft tissue extension, curettage and adjuvant is the first surgical consideration. For Campanacci grade 3 tumors, given increased risk of recurrence, many surgeons prior to the advent of denosumab would perform a resection and reconstruction as a first surgical procedure.

For tumors of the axial skeleton(predominantly sacrum and pelvis)intralesional curettage is most often done even when it is thought to be sub optimal with a high chance of residual tumor left behind because excision or en bloc resection would result in significant functional deficit for the patient. Adjuvants also may not be possible to use in these axial tumors due to the close proximity of the tumor to critical neurovascular structures, These factors in turn increase the local recurrence rate to as high as 50% in an axial skeletal location, stressing the need for additional treatment modality in such difficult anatomic locations.

Radiation therapy in unresectable cases, or cases in difficult surgical locations demonstrates adequate local control rates of around 80% but has significant risks [30]. A significant concern is that of secondary sarcoma at radiation site given that the disease affects mainly young adults [31]. With several reported cases of malignant transformation after radiation, although relatively effective, radiation is rarely used, and generally only considered for cases in which no other reasonable option exists. Given the lack of a reproducible and durable highly effective function-sparing definitive surgical treatment for these tumors, the alternative of a systemic treatment is very appealing, explaining the significant interest in the current understanding of the biologic mechanism of the disease.

Systemic treatment

Better understanding of the role of RANKL in the pathophysiology of GCT led to the development of meaningful systemic therapy in this disease. Denosumab is a fully human IgG2 monoclonal antibody against RANKL. It binds to both soluble and membrane bound RANKL. It prevents the binding of RANKL to RANK found on osteoclasts and osteoclast precursors [12].The ability of the antibody to inhibit the RANKL and RANK interaction led to its interest in GCTB where RANKL was known to play a key role in pathogenesis.

The first proof of concept study was an open label phase II study of denosumab in GCTB. In this study a total of 37 patients with recurrent or unresectable GCTB were enrolled and treated with monthly subcutaneous injection of 120 mg of denosumab after 3 weekly doses in the first month.35 out of 37 patients were evaluable and showed an 86%(95% CI , 70-95) tumor response rate which was predefined as either no progression by imaging of target lesion at week 25 (10 out of 15 patients assessed by imaging) or at least 90% elimination of giant cells by histology (20 of 20 patients that were evaluated by histology).The only grade 3 event thought to be related to treatment was the elevation in human chorionic gonadotropin in a non-pregnant patient. The other common side effects noted were headache (n=4), extremity pain (n=7) and back pain (n=4) [14].

The encouraging results of the above study led to an international open-label, phase 2 parallel group study in skeletally mature individuals with measurable tumor and

biopsy proven GCTB [32]. Subjects were above the age of 12 and weighed at least 45 kg. Patients were enrolled in 3 cohorts. The first cohort comprised of patients that had tumors not amenable to surgical resection.163 out of the total 170 subjects evaluable in this cohort (96%) had no disease progression after a median follow up of 13 months. Cohort 2 comprised of patients, in whom, tumor surgery if done upfront, would cause severe morbidity. 100 /101 patients were evaluable in this cohort, 74 out of the 100 patients did not have surgery. Of the 26 that had surgery 16 patients (62%) needed a less morbid surgery than thought initially. This cohort was followed for a median of 9.2 months. The remaining 11 patients were in cohort 3 and comprised of patients rolled over from the prior phase 2 denosumab study.

Common side effects noted were, joint pain (20%), headache (18%), nausea (17%), fatigue (16%), back pain (15%) Pain in extremity (15%). Grade 3,4,5 adverse event included hypophosphatemia (3%) and 1% in each of the following anemia, back pain, pain in extremity, arthralgia, depression, headache, musculoskeletal pain, osteomyelitis, osteonecrosis of jaw(ONJ) and weight gain. Adverse events of interest included ONJ 1%, hypocalcemia 5% (non- serious), serious infections 2% and new primary malignancy 1% [32]. This study led to the FDA approval of the drug on June 13th 2013 for skeletally mature individuals with GCTB that was surgically unresectable or surgery would cause severe morbidity.

Further reported complications include severe hypercalcemia reported in a patient 5 months after discontinuation of denosumab, which stresses on the importance of monitoring electrolytes even after discontinuation of denosumab therapy [33]. Data thus far on long term treatment (median of 12 months, ranging 6-45 months) suggests increased risk of ONJ (6%) and risk of recurrence on stopping denosumab at a median of about 8 months .However anecdotal data suggests response on re exposure to denosumab have been noted [34].

Bisphosphonates prevent osteoclastic bone resorption and hence is also a drug of interest in this disease. There are some in vitro reports suggesting the drugs ability to kill both stromal as well as osteoclast like cells in GCTB. There are clinical reports of improvement in symptom and disease control following its use in GCTB. However there was lack of eradication of giant cells in histologic exam. The role of bisphosphonates in GCTB needs to be explored further [11, 35- 38)

Discussion

The story of denosumab is the beginning of the era of molecularly targeted systemic therapy for this disease. In fact after the initial promising data from the two phase 2 studies many questions arise that need to be addressed in future clinical trials that will further clarify the use of denosumab e.g. duration of therapy in unresectable disease. The option and feasibility of interval therapy needs to be studied further. The risks and morbidity from long term and continuous treatment also needs further study. Given that denosumab indirectly affects GCTB by inhibiting RANKL and does not affect the neoplastic stromal cells directly, there is concern for increased risk of local recurrence should the macroscopic demarcation of the tumor disappear, often seen after prolonged treatment with denosumab neoadjuvantly. It may increases the risk of leaving residual tumor cells behind. Experts often believe that if intralesional curettage rather than en bloc resection is the goal following neoadjuvant therapy, then duration should not be longer than 3-4 months when a calcific rim develops around the tumor, however the tumor still remains clearly delineated [39-41]. As this is an important clinical scenario where the drug is used, a clinical trial addressing the question of duration of neoadjuvant therapy to reduce the risk of local recurrence after subsequent curettage is perhaps warranted. Given its promising role in the metastatic setting, studies to evaluate the benefit of denosumab in adjuvant setting to reduce recurrence is warranted. The role of bisphosphonates seen thus far calls for more studies including intralesional bisphosphonate or denosumab following intralesional curettage.

There is a need for further clarity in the understanding of the pathophysiology to help direct therapy towards the neoplastic cells. The recent knowledge of the H3F3A as a possible driver mutation in this tumor opens up avenues for potential new therapy approaches.

Conclusion

With the maturation of the use of denosumab in advanced cases of GCTB, the standard of care has essentially moved from a purely surgical approach to a multi-disciplinary approach. Neoadjuvant therapy with denosumab can now be considered the standard of care for all patients with GCTB who are not candidates for upfront curettage, to facilitate surgical removal with a less morbid procedure and have a better functional outcome. For unresectable and metastatic disease, denosumab is indicated for chronic use however exact interval, duration, long term side effects and goals are questions that still need clear answers. Denosumab has definitely revolutionized the treatment of GCTB. However much still remains to be achieved the current state of knowledge simply represents the end of the beginning of our understanding of this complex disease process.

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