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Systemic Adjuvant Therapies in the Management of Giant Cell Tumor of Bone: Current State of Understanding and Practice

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Abstract

GCT of bone is a locally aggressive bone-destroying tumor. The primary neoplastic tumor cell is a RANKL overexpressing cell that drives osteoclast recruitment and activation, ultimately leading to bone resorption at the site of the lesion. Osteoclast driven destruction in GCT may be ameliorated with the use of drugs such as Bisphophonates, which target Osteoclasts as well as the primary neoplastic stromal cells. Denusomab, is a monoclonal antibody against RANKL and it has a dramatic effect on Osteoclasts. Adjuvant therapies have reduced recurrence rates in GCT of bone, but uncertainties remain as to the optimum dose-intensity of the drugs and the duration of treatment.
Keywords: Tumor, bone destruction, Giant Cell Tumor of Bone.

Introduction

Giant cell tumor (GCT) of bone is a mesenchyme-derived neoplasm, in which its primary neoplastic cell (GCT stromal cell)originates from an osteoblastic lineage. The stromal cells of the GCT drive the recruitment and activation of the osteoclast-like giant cells that are the characteristic signature of this neoplasm. The osteoclast-like giant cells in turn are responsible for the aggressive osteoclastic resorption and the typical soap-bubble appearance of this tumor, in which cortical expansion eventually gives way to disruption and extension of the tumor beyond its bony confines. Local recurrence is one of the major problems associated particularly with intralesional treatment of this tumor. The rates of recurrence reported range from 3% to 33% when local adjuvants such as phenol and cement are used[1,2]. Cryosurgery has also been used to decrease local recurrence, yet 8–42% of patients will develop recurrence following cryotherapy and intralesional curettage, regardless of the method of reconstruction used [3,4]. Topical chemical adjuvants have failed to reduce local recurrence rates to clinically significant levels [5, 6], and in patients with soft tissue extension, aggressive wide resection, often with the sacrifice of the contiguous articulating end of the affected bone, remains a reasonable treatment option to reduce local recurrence. In the recent years, advances in the understanding of molecular signaling pathways and the development of specific drugs to target key cellular mechanisms have made a significant impact on the local control of this destructive neoplasm. These drugs may therefore extend the indications for intralesional curettage of the neoplasm, with joint preservation and significantly reduced rates of local recurrence.

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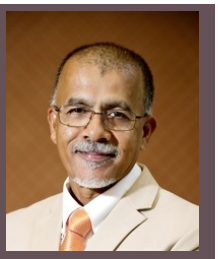

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Functional Biology of GCT of Bone

The receptor activator of nuclear factor kappa-B (RANK)/RANK ligand (RANKL) pathway(Fig.1) is the critical master regulator of bone remodeling. Physiological bone remodeling is controlled through the coupled interaction between osteoblasts and osteoclasts [7]. The dominant mechanism involves pre-osteoclast precursors, derived from hemopoetic stem cells, that are recruited through the release of cytokines such as the macrophage colony-stimulating factor and vascular endothelial growth factor, predominantly by cells of the osteoblast lineage. Mononuclear osteoclast precursors express RANK - a transmembrane receptor, which, when activated by interaction with its ligand, RANKL (expressed on the surface of osteoblastic cells) results in the activation of major genomic and synthetic actions eventually leading to the fusion of the mononuclear cells to bone resorbing osteoclasts. RANK [8] is an acronym for RANK. When activated RANK translocates (Fig. 2) from the cytoplasm to the nucleus of the mononuclear cell and activates a cascade of molecular interactions that drive gene expression, protein synthesis as well as cellular maturation, development, and proliferation. RANKL-RANK interaction is not unique to osteoclast development; it is major phenomenon in T-cell and lymphocyte maturation, and in the development of mammary glands. RANKL is a member of the superfamily of receptor-ligands called tumor necrosis factor (TNF); they have some common structural and functional elements and are involved in the regulation of several important cellular activities in a broad range of tissues. Osteoblastic cells also secrete osteoprotegerin (OPG) (Fig. 3).This is a decoy receptor that can bind to the surfaces well as soluble RANKL and prevents the interaction of the ligand with its receptor. OPG provides a negative feedback inhibition and can limit bone resorption by preventing the binding of RANKL to RANK [9]. The expression of OPG and RANKL is also controlled by several calcium-regulating hormones including parathyroid hormone

(PTH) and PTHRP among others. Thus, from a physiological standpoint, bone homeostasis and remodeling are finely controlled by the relative levels of OPG and RANKL. The interaction of these molecules is a paracrine or local phenomenon, and the ratio between RANKL and OPG determines the level of activation of RANK and the extent to which osteoclast formation is stimulated. RANKL interaction also activates newly formed osteoclast and stimulates the formation of acid-containing vesicles eventually critical for bone resorption. The GCT stromal cell is characterized by its dominant overexpression of RANKL in excess of OPG [10]. GCT of bone is best understood as a stromal cell-driven neoplasm in which RANKL-driven osteoclastic bone resorption is largely uncontrolled. Indeed, the multinucleated osteoclast-like giant cells in GCT of bone have the same physiological characteristics as bone-resorbingosteoclasts.

Osteoclast activity

The osteoclast is the only biological cell capable of dissolving the mineralized matrix of bone. Osteoclast-mediated bone resorption requires the attachment of the osteoclast to the bone surface. Hydrolytic collagenases initially dissolve the non-mineral (organic) matrix of bone and so enable the integrin-mediated attachment of the osteoclast to the bone surface. A strong acid (pH 2–2.5) is generated for the dissolution of the calcium-mineral complex in the bone. Given that the pH of normal human cells and tissue fluids is around 7.5, and the 5-log difference that is generated to create acid generating vesicles within the osteoclast requires high energy and a molecular synthetic apparatus with high capacity. The activated osteoclast is thus metabolically very active, requiring several nuclei to drive its synthetic functions, and therefore has a short half-life.The extracellular degradation products following the release of vesicles include organic and inorganic residues; these are internalized by the osteoclast through vesicular endocytosis. Each of these processes presents a potential target for the pharmacological regulation of bone resorption, particularly in patients with GCT of bone.

Bisphosphonates(BPs) in GCT of the Bone

Bps' have an affinity to the bone and have strong inhibitory effects on mature osteoclasts. Thus, they were among the first systemic adjuvants considered in the management of GCT. Since BPs have a chemical structure that is similar to the inorganic pyrophosphate molecule, they have a high affinity to hydroxyapatite in bone [11]. They are internalized by osteoclasts at sites of active bone resorption through a process of vesicular endocytosis [12]. The P-C-P bond in BPs' cannot be hydrolyzed and allows BPs to exert their pharmacological actions, specifically within osteoclasts. The non-nitrogen BPs' (clodronate and etidronate) are metabolized to ATP analogs, and essentially they block energy production within the cell leading to apoptosis. The nitrogen-containing BPs primarily affect the key enzyme farnesyl pyrophosphate synthetase, an enzyme that is required for the prenylation of key intracellular proteins necessary for osteoclast survival and function [13]. The action of BP's on GCT osteoclasts has been exploited clinically [14, 15, 16]. Reductions in local recurrence rates of GCTs have been reported in retrospective and prospective studies, but randomized clinical trials using bisphosphonates have yet to be reported. BPs were also shown to have an effect on the stromal cells of GCTinvitro. [17]. However, the inhibitory concentrations required are difficult to attain in clinical practice. It is therefore most likely that the reduction in local recurrences observed may relate more to the reduced osteoclastic activity, within the lesion, and less to the cytotoxic effects on the neoplastic stromal cells. There are several drawbacks with the clinical use of BPs in the management of GCTs of bone. Most Bps are rapidly eliminated from circulation through renal filtration. While 50% of the intravenous drug delivered is taken up by the skeleton, the rest is eliminated unaltered through the kidneys. The skeletal binding of the drug is difficult to determine, and most pharmacokinetic studies are also hampered by the technical difficulties of determining the concentration of the active drug in serum given its rapid renal clearance. Therefore, the optimal dose intensity of treatments has largely been left to empirical judgment. Currently, zoledronic acid is the most commonly used BP. It is administered intravenously; the common dosage being 4mg in 50–100 ml of saline and given over a 30-min period as a slow infusion. Most studies reported have used 1–2 doses at 2–4 weeks intervals before surgery. There are no reliable methods to determine the optimum effect of the drug on the tumor during treatments, and therefore, drug-dosing regimens have not been standardized to date. Reduction in bone resorption markers is perhaps the most reliable means of determining if the drug has had a significant impact on the tumor[18]. Increased mineral density within the lesion and a rind of calcification marginating the soft tissue limits of the tumor are well known, but unreliable and perhaps subjective means of judging response to treatments. Analysis of the tumor following BP treatment has shown significant apoptosis of the stromal cells and a reduction in the number of giant cells. Increased intralesional mineral deposition has been observed and may be a reactive response following apoptosis of the stromal cells. Concerns with the long-term effects of BPs in the skeleton are valid. Given that, these drugs remain in the skeleton for years and that small amounts will enter circulation with remodeling, their safety, particularly, in women of reproductive age is of concern, as the drug will cross the placental barrier. Long-term use of BPs may cause remodeling arrest and is responsible for adynamic bone fractures and dental complications including necrosis of the jaw bone [19]. Another significant concern is the use of the drug in patients with renal failure. Acute nephrotoxicity has been reported with zoledronicacid, and BPs must be used with caution in patients with renal impairment [20].

RANKL Antagonists

Given that, RANKL is a key player in bone remodeling in particular pathological bone resorption, and several anti-RANKL agents have been developed. A completely human monoclonal antibody specific to RANKL andwith very high selectivity and affinity to RANKL was eventually tested and found to be most promising, among all anti-RANKL

agents to date [21]. This molecule (denusomab) does not bind to the other members of the TNF superfamily (such as TRAIL) and given its small molecular mass has a longer half-life when compared with other agents such as synthetic OPG. Denusomab prevents RANKL from binding to its receptor RANK. Unlike BPs, which have to be internalized by osteoclast cells to be effective, denusomab does not require cellular uptake and has a much better dose-response relationship and a faster onset of action. Indeed, the first clinical studies with the use of denusomab in patients with GCT of bone showed excellent response to therapy in 86% of patients [22]. The definition for objective response was stringent, (more than 90% elimination of giant cells within the lesion), and a follow-up study showed that the drug arrested disease progression in 96% of surgically unresectable cases. The study further demonstrated that denusomab induced RANKL blockade also had an effect on the GCT stromal cells. Histological evaluation of the tumor showed a significant reduction in stromal cell population and a near complete disappearance of the osteoclast-like giant cells. Increased calcification within the lesion was consistently seen. While the drug is best recommended for non-salvageable cases of GCT, it has also been enthusiastically used as a neoadjuvant drug, particularly to facilitate surgery and to reduce the aggressive nature of the disease. Regrettably, however, there are no prospective randomized trials informing us of the optimal pre-operative doseintensity, the timing for surgery, the impact on reducing local recurrence, and the long-term consequences. In patients who have been given the drug in lieu of surgery, stopping treatments have led to local recurrence. This is not surprising, given that the drug does not have a direct effect of the neoplastic stromal cells. Denusomab is primarily a circulating antibody and has a half-life of about 26 days. In a separate study [23], it was shown that single subcutaneous dose of the drug, at the clinically significant level of 1mg/kg, resulted in significant lowering of bone resorption markers, 80% at 1 week and 59% at 6 months. Denusomab also caused a transient elevation in PTH; PTH levels were doubled 4 days after administration of the drug. The intermittent elevation in PTH may explain the dense mineralization that is often seen within the lesion. The current dosing regimen of denusomab in patients with large and non-resectable GCT of bone is recommended as 120 mg to be given subcutaneously, every 4 weeks; with an additional 120 mg on days 8 and 15 during the 1stmonth of therapy. Clinical remission is the only significant endpoint, but the cessation of treatment may result in local recurrences. Combination of adjuvant therapy and surgery seems the most logical, and perhaps, most effective means of reducing local recurrence following surgery. Such an approach has also enabled the development of minimally invasive approaches toward GCT treatments. This is of particular value in difficult to access locations such as the spine, pelvis, femoral neck, and talus. Neoadjuvant therapy enables preservation of the joint even in patients with pathological fractures. Current evidence suggests that denusomabis much more effective and has a faster onset of action than zoledronic acid and may be the preferred neoadjuvant drug. While the dosage recommendations from the manufacturer relate more to long-term use in non-operable patients, careful clinical, radiological, and biochemical monitoring may allow us to determine the optimal timing of surgery after a certain dose intensity of treatment has achieved the desired results in terms of reduction of resorption markers, increased mineralization within the lesion, and reduction of pain.

Conclusions

Adjuvant therapies have a major role to play in the management of GCT of bone. Surgery still remains the main mode of treatment, and reliance on drugs alone is limited to a small subset of patients, in which the risks of surgery far outweigh the benefits of medical management with drugs. Adjuvant therapies have resulted in reduced recurrence rates and have greatly reduced the indications for ablative surgeries in which the joint may be sacrificed. Multicenter randomized clinical trials in which the neoadjuvant utility and the optimal dose intensities of adjuvants are rigorously tested have not been done to date. Therefore, much of our clinical practice has been informed through a deeper understanding of mechanisms and through small cohorts of clinical case series.

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