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The Role of Denosumab in the Treatment of Primary Tumors of Bone

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Abstract

Many hand surgeons treat benign bone tumors without referral to orthopaedic oncologists. However, there have been considerable advances in the medical therapy for some of these tumors with which hand surgeons may not be as familiar. This Current Concepts Review focuses on the mechanism and uses of Denosumab in the treatment of benign tumors of bone. While the hand surgeon may not be directly prescribing this therapy, they are often the only physician treating the patient for these conditions. As such, awareness regarding the utility of this therapy in reducing pain, decreasing tumor volume, and treatment of potential lung metastases is critical to those taking on these cases without the support of an orthopaedic oncologist. This article aims to familiarize hand surgeons with Denosumab to help to promote a knowledge of this therapeutic option and the potential role of this medication in the treatment of primary bone tumors in the hand.

Denosumab has been employed in the treatment of many tumors of bone including giant cell tumor of bone, multiple myeloma, aneurysmal bone cyst, and osteoblastoma, as it impacts the shared downstream pathway activation of osteoclasts by the neoplastic cells. It is also FDA approved for the treatment of giant cell tumor of bone. The mechanism of action of this relatively new medication, potential uses in hand surgery, and its associated side effects are reviewed in this article.

The dynamic balance between bone resorption and bone formation is carefully regulated by the receptor activator of NF-κB and receptor activator of NF-κB ligand pathway. The NF-κB pathways mediate RANK ligand-induced differentiation of monocytes/macrophages into the bone-resorbing osteoclasts.[1] In the setting of primary bone tumors, bone resorption may be stimulated by the overproduction of RANKL by pathologic cells. In osseous neoplasms,

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excess RANKL leads to an “imbalance” that favors bone resorption. The body’s effort to respond leads to a process of bony expansion – osteoblasts trying to respond at the periphery, resulting in an expansile, lytic lesion that leaves the bone prone to pathologic fractures. Denosumab is a human monoclonal antibody that inhibits bone resorption by binding RANKL and preventing its activation of RANK.

OPG-RANK-RANKL pathway review

The tumor necrosis factor (TNF) and TNF receptor (TNFR) superfamily family plays a crucial role in the development and function of the human immune system.[1] RANK is a TNFR homologue and its cognate binding partner on the surface of various cells is RANKL. RANKL are type II transmembrane proteins that contain a small N-terminal intracellular domain, a transmembrane region, and a C-terminal extracellular domain, which is characteristic of the TNF family (Figure 1).

A negative bone balance results when bone loss outpaces bone formation. Bone resorption and matrix deposition are closely linked through the bone mineral unit (BMU). Osteocytes, osteoblasts, and osteoclasts are the main cells of the BMU. Osteocytes form an interconnected network of cells that occupy lacunae and are derived from osteoblasts, which are bone-forming cells. They direct the process of bone resorption by releasing RANKL. RANKL binds to osteoclasts and osteoclast precursors, which promote bone resorption. Conversely, osteoblasts produce osteoprotegrin (OPG), which prevents the interaction between RANK and RANKL by binding to RANKL, suppressing bone turnover. As such, the balance between OPG and RANKL production plays a major role in controlling bone remodeling.

A negative bone balance can result from an increase in RANKL secretion by osteoblasts and osteocytes, which increases activation of osteoclasts precursors and mature osteoclasts. Negative bone balance commonly occurs in oncologic processes, as the RANKL pathway has been shown to play a key role in the pathogenesis of bone tumors. RANKL can be produced directly by cancer cells and not only aids in the recruitment of monocyte precursors but also activates and prolongs the survival of mature osteoclasts, resulting in bone loss.

Denosumab

History of Denosumab

Denosumab is a fully human monoclonal antibody that inhibits RANK ligand (RANKL) via binding with great affinity and specificity.[2,3] Denosumab was previously approved by the Food and Drug Administration (FDA) as well as the European Medical Agency (EMA) for use in the treatment of osteoporosis and management of skeletal related events in bone metastases from solid tumors in adults.[4,5] The FDA subsequently approved Denosumab for neoadjuvant use in advanced and/or surgically unresectable giant cell tumor of bone in June 2013 and it remains the only medication approved for this purpose based on multiple open-label, Phase II trials.[2,6-8] Denosumab is administered under the brand names Prolia (Amgen; Thousand Oaks, CA) and Xgeva (Amgen; Thousand Oaks, CA).

Mechanism of Action

By binding the RANKL with higher affinity than that of RANK, Denosumab effectively interrupts the RANK-RANKL pathway thereby preventing the neoplastic mononuclear stromal cells of Giant Cell Tumor of Bone (GCTB) from activating osteoclast-like giant cells.[8,9] This lack of giant cell recruitment prevents the osteolysis characteristic of GCTB.[2] Accordingly, a response to Denosumab can be identified radiologically with the formation of a calcified rim of bone around the tumor and/or a decrease in size of the lesion.[2,10] It is important to note that Denosumab prevents the recruitment of osteoclast-like giant cells but does not target the neoplastic stromal cells. This mechanism likely contributes to the unchanged recurrence rate after preoperative treatment with Denosumab.

Histologic analysis pre- and post-treatment with Denosumab in a Phase II study of 20 patients treated with Denosumab with patients receiving 120 mg every 28 days with additional doses on days 8 and 15, demonstrates a reduction of RANKL stromal cells with increased fibro-osseous tissue and/or new bone.[11] Giant-cell density was reduced by 90% or more in all 20 samples. Traub *et al* confirmed these findings in a prospective, non-randomized trial of patients receiving neoadjuvant Denosumab, demonstrating rare osteoclast-like giant cells with an increase in osteoid and woven bone post-treatment.[12]

While Denosumab interrupts the RANK-RANKL pathway, there are concerns of local recurrence with discontinuation of Denosumab.[2,3,5,7] Tsukamoto et al performed a systematic review of 619 patients treated with curettage, 127 of whom received Denosumab preoperatively. The authors noted a higher rate of local recurrence in the group that received Denosumab.[3] This association has also been reported in a meta-analysis.[8] The high recurrence rate after curettage is an anatomical issue – rather than a single cavity, Denosumab creates multiple cavities because its leads to haphazard bone formation (Figure 2). This results in multiple cavitary defects with associated neoplastic cells. Neoplastic cells may reside within the calcified rim of bone which, if not adequately treated at the time of surgery, leaves residual tumor cells which may lead to late re-activation with Denosumab discontinuation.[3,7,8,12]

Responsive Tumor Biology

Giant Cell Tumor of Bone

Giant cell tumor of bone is a primary bone tumor that is rich in RANKL and for which surgery is currently the only curative treatment option. Denosumab has been increasingly adopted in the treatment of these lesions. In a small (n = 37) open-label Phase II study of Denosumab, a tumor response was observed in 86% of evaluable patients.[13] Similar results were seen in a second study that enrolled both adult and adolescent patients. In a prespecified interim analysis, 99% of evaluable patients (72 out of 73) with surgically unsalvageable disease experienced no disease progression after 12 months of Denosumab treatment, and Denosumab treatment allowed for delay in surgery in 65% of patients (15 out of 23).[14]

Literature in the field of hand surgery has reflected a higher recurrence rate among giant cell tumors in the hand than in other locations with rates cited up to 80% after intralesional

procedures.[15,16] Additionally, lesions in the hand demonstrate a higher rate of metastases to the lung at 14%[15] than do giant cell tumors in other locations, which are commonly reported with metastatic disease in 1-5%.[7,17] However, some authors suggest that this phenomenon is secondary to insufficient access windows rather than a difference in tumor biology.[18]

Aneurysmal Bone Cysts

Aneurysmal bone cysts (ABC) are benign tumors, accounting for roughly 3% of all bone tumors in the hand.[19] ABC present as primary tumors in roughly 70% of cases, usually associated with chromosomal rearrangements resulting in the upregulation of USP6 gene, or can be secondary to another primary tumor, such as osteoblastoma, giant cell tumor of bone, chondroblastoma, fibrous dysplasia or low-grade osteosarcoma. Tissue specimens from ABCs demonstrate increased RANKL and RANK expression in the fibroblast-like stromal cells and osteoclastic multinucleated giant cells.[20,21] Given the increased activity of this pathway, clinicians have reported off label use of Denosumab in the treatment of ABCs.[22] Patients have reported improvement of pain with this measure, and tumors exhibited radiographic improvements in roughly 86% of patients.[23] However, side effects of this treatment include possible rebound hyper- and hypocalcemia in about 6-22% of patients. Additionally, when patients were taken off Denosumab, roughly 40-50% demonstrate subsequent radiographic progression.

Uses

Neoadjuvant treatment - Tumor control prior to surgical resection

Denosumab has been proposed as neoadjuvant therapy or as an alternative to surgery in some cases.[24] In a recent open-label Phase II trial, Rutkowski *et al* reported on 222 patients who underwent Denosumab treatment prior to a planned surgical resection.[10] At their final follow-up at a median of 9.2 months, 38% had avoided surgery altogether and 48% underwent a less extensive procedure than that which was originally planned. However, understanding the effects of Denosumab is critical in using the drug in this fashion. While Denosumab blocks receptor activator of nuclear factor kappa-B ligand (RANKL) activation, it does not specifically target the pathogenic cells in primary tumors of bone. As such, Denosumab results in the solidification of these tumors but not a true reduction in volume. Many authors suggest that Denosumab should primarily be considered in those tumors with substantial soft tissue extension or in those through which pathologic fracture has occurred as Denosumab helps to better define the bounds of soft tissue extension in these tumors should wide resection be endeavored.[5,25]

While Denosumab may halt growth of tumor, it does not reduce size of tumor nor change resectability, and studies have not shown improvement in recurrence rates with neoadjuvant treatment. Clinical studies have demonstrated that Denosumab does not alter recurrence rates and may even result in an increased rate of recurrence secondary to the development of multiple cavitary niduses of tumor.[26] Many recurrences will arise within 7–9 months of stopping treatment.[3,7,8,12] In their study of 222 patients treated with Denosumab for GCTB, they detected a 15% recurrence rate surgery, which is comparable to recurrence rates in

literature.[10] It is also not clear whether a rechallenge of Denosumab in case of secondary progression can achieve a long-term clinical response.

Definitive treatment

While infrequent in the hand and wrist, Denosumab use has been advocated for in the setting of unresectable disease.[12,14] Further, in the upper extremity, patients with advanced, Campanacci III GCTB may refuse resection if amputation is recommended. If resection is unacceptable to the patient for concern of functional or cosmetic impairment, then definitive treatment with Denosumab may be attempted.

In the setting of long-term treatment with Denosumab, controversy exists regarding the length of Denosumab treatment, as the side effects of long-term treatment are poorly understood. While prolonged treatment with Denosumab has sustained activity in GCTB, there is an associated dose-dependent toxicity.[27] Recent studies have suggested careful and strict monitoring of patients who need prolonged treatment and potential for decreased dose-intensity schedules for maintenance. It is important to note that there is concern that Denosumab withdrawal is associated with a high rate of subsequent tumor recurrence. Mak *et al.* demonstrated that Denosumab only partially addresses the therapeutic need of patients with a giant cell tumor by eliminating the osteoclasts, but it does not eradicate proliferative neoplastic stromal cells.[28] Thus, if long term treatment is pursued drug withdrawal requires close surveillance (Figure 3).

Treatment of Lung Metastases

Should a patient with a primary giant cell tumor of bone in the hand develop pulmonary metastatic disease, Denosumab can be used as an effective option for systemic disease control. This should be weighed against appropriate surgical resection such as metastasectomy, wedge resection or lobectomy. The metastases of GCTB are usually slower growing than traditional metastases in keeping with the slow growth of GCTB. This is a relatively rare occurrence overall at roughly 5% and usually seen in the setting of recurrence; however, has been identified at a rate of up to 14% in the hand.[15] Besides the lung, other sites of metastatic deposits have been documented for GCTB.[17,29] We recommend the involvement of medical and thoracic oncology upon the identification of metastatic lung disease.

Complications and Limitations of Denosumab Use

Adverse effects associated with Denosumab include nausea, headaches, extremity pain, arthralgia, and back pain, as well as more serious events such as alterations in serum calcium levels and in the case of GCTB, malignant transformation.[10,12,13] Patients are required to supplement with calcium and vitamin D and undergo routine electrolyte monitoring as well as dental examinations while on therapy. Thomas et al report adverse events in 33 of 37 patients in their open label, single group study.[13] An increased risk of multiple spontaneous vertebral fractures after discontinuation of Denosumab after two doses has also been reported.[30] Traub et al cite 30% of their 222 patients reporting adverse events including fatigue, headache, nausea and arthralgia.[12] A Phase II clinical trial report on safety

and efficacy results in 282 patients in three cohorts noted osteonecrosis of the jaw (1%), hypocalcemia (5%), hypophosphatemia (3%), back pain (1%), anemia (1%) and extremity pain (1%) and two cases of sarcoma.[5,14,31] Though significant recent improvements have been made in this regard, prior lack of standard treatment regimens for use of Denosumab in a clinical setting has highlighted concerns regarding the safety profile. There is ongoing concern about long-term use for controlling unresectable disease.[2,5]

Hypercalcemia

Alterations in bone turnover levels can be seen with starting as well as discontinuing Denosumab. These changes can alter blood calcium levels. Discontinuation of Denosumab has been associated with hypercalcemia, thought secondary to rebound osteoclast activity.[2,4] Hypercalcemia causes fatigue, bone pain, headaches, nausea, constipation and can be life-threatening if untreated. Hypocalcemia, associated with use of Denosumab, secondary to inhibition of osteoclast-mediated skeletal calcium release was reported to occur in Phase II trials.[4,12-14] Traub et al treated two patients on Denosumab with hypocalcemia with oral calcium and vitamin D alone.[12]

Pediatric Population

Similarly, by affecting bone turnover rates, theoretical concerns regarding bone development, including dentition, have been raised in the pediatric population.[32] There have been no reports of abnormal growth or bone shape and no adverse effects on dentition although these are limited by lack of large pediatric groups.[4] Effects of Denosumab on the unborn fetus are not defined.[2]

Malignant Transformation

Since its approval by the FDA in 2013, some reports suggest that Denosumab might be related to sarcomatous transformation of GCTB. The association between the medication and malignant transformation is not well defined, however physicians should be aware of this possibility.[33] It is not clear that these occurrences are secondary to Denosumab treatment as opposed to natural history or a result of the incorrect initial diagnosis, likely secondary to lesional sampling error.[2,6,8,34] Primary malignant GCTB is thought to occur in less than one percent of cases while secondary malignant transformation has classically been attributed to prior use of radiotherapy or less commonly prior surgery.[8,34] As of 2020, 18 cases of malignant transformation were reported during Denosumab treatment.[8] Location information was not reported in all series; however, for those available, two of eleven sites of malignant transformation were specific to the upper extremity.[8] As a question of biology, risk of malignant transformation is thought to be a risk of denosumab treatment independent of tumor location. Transformation to fibrosarcoma, osteosarcoma and undifferentiated pleomorphic sarcoma have all been reported in GCTB.[4,8,10,14,31,34] Unfortunately, the lack of randomized controlled trials makes it difficult to directly associate the use of Denosumab with development of sarcoma, however multiple pathophysiologic mechanisms have been suggested including immunosuppression secondary to RANKL inhibition; increased susceptibility to nuclear oncogenes in osteosarcoma; or aberrant osteoblast differentiation in osteosarcoma secondary to RANKL inhibition - all mechanisms by which oncogenic changes may occur.[8] Given the preponderance of giant cell tumors

in many types of tumors – including malignant tumors – some argue that GCT is often misdiagnosed and later “transformation” may be an issue with initial diagnostic accuracy. Further studies are critical to determining the true risk of sarcomatous transformation of GCTB during treatment with Denosumab.

Conclusions

Evidence continues to evolve regarding the role for the use of Denosumab in the treatment of primary tumors of bone in the hand and wrist. Though less commonly indicated for so-called unresectable disease, as in the case of spinopelvic locations, there is evidence for neoadjuvant use of Denosumab for consolidating high-risk GTCB with extension to soft tissue to facilitate less morbid surgical procedures or to potentially hasten progression or avoid surgery altogether in the setting of a patient who may not be amenable to surgical intervention. Denosumab may be of utility in the setting of aggressive giant-cell rich lesions with soft tissue extension and may significantly aid the technical ease of surgical excision or resection. Finally, Denosumab is an important consideration in the treatment of patients with lung metastases, which may be more common in the setting of GCTB in the hand. However, Denosumab treatment carries risks of hypocalcemia during treatment or hypercalcemia upon medical withdrawal and malignant transformation without improvement in recurrence rate. Additionally, the duration of Denosumab use as well as the long-term risks of Denosumab treatment are unknown, particularly in skeletally immature patients. The use of Denosumab should be carefully considered in each patient and should be discussed with an interdisciplinary care team, including a medical oncologist who is familiar with administration of this medication.

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References

1. Lacey DL, Boyle WJ, Simonet WS, et al. Bench to bedside: Elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. Nat Rev Drug Discov. 2012;11(5):401–419. doi:10.1038/nrd3705 [PubMed: 22543469]
2. van der Heijden L, Dijkstra PDS, Blay J-Y, Gelderblom H, Giant cell tumour of bone in the denosumab era. Eur J Cancer. 2017;77(75):83.
3. Tsukamoto S, Tanaka Y, Mavrogenis AF, Kido A, Kawaguchi M, Errani C. Is Treatment with Denosumab Associated with Local Recurrence in Patients with Giant Cell Tumor of Bone Treated with Curettage? A Systematic Review. Clin Orthop Relat Res. 2020;478(5):1076–1085. doi:10.1097/CORR.0000000000001074 [PubMed: 31794487]
4. Pan KS, Boyce AM. Denosumab Treatment for Giant Cell Tumors, Aneurysmal Bone Cysts, and Fibrous Dysplasia—Risks and Benefits. Curr Osteoporos Rep. 2021;19(2):141–150. doi:10.1007/s11914-021-00657-z [PubMed: 33616817]
5. Gaston CL, Grimer RJ, Parry M, et al. Current status and unanswered questions on the use of Denosumab in giant cell tumor of bone. Clin Sarcoma Res. 2016;6(1):13–18. doi:10.1186/s13569-016-0056-0 [PubMed: 27482375]
6. Palmerini E, Staals EL, Jones LB, Donati DM, Longhi A, Randall RL. Role of (Neo)adjuvant Denosumab for Giant Cell Tumor of Bone. Curr Treat Options Oncol. 2020;21(8). doi:10.1007/s11864-020-00766-4

7. Errani C, Ruggieri P, Asenzio MAN, et al. Giant cell tumor of the extremity: A review of 349 cases from a single institution. Cancer Treat Rev. 2010;36(1):1–7. doi:10.1016/j.ctrv.2009.09.002 [PubMed: 19879054]
8. Li H, Gao J, Gao Y, Lin N, Zheng M, Ye Z. Denosumab in Giant Cell Tumor of Bone: Current Status and Pitfalls. Front Oncol. 2020;10(October):1–10. doi:10.3389/fonc.2020.580605 [PubMed: 32076595]
9. Jamshidi K, Gharehdaghi M, Hajialiloo SS, Mirkazemi M, Ghaffarzadehgan K, Izanloo A. Denosumab in patients with giant cell tumor and its recurrence: A systematic review. Arch Bone Jt Surg. 2018;6(4):260–268. doi:10.22038/abjs.2018.25254.1665 [PubMed: 30175172]
10. Rutkowski P, Ferrari S, Grimer RJ, et al. Surgical Downstaging in an Open-Label Phase II Trial of Denosumab in Patients with Giant Cell Tumor of Bone. Ann Surg Oncol. 2015;22(9):2860–2868. doi:10.1245/s10434-015-4634-9 [PubMed: 26033180]
11. Branstetter DG, Nelson SD, Manivel JC, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. Clin Cancer Res. 2012;18(16):4415–4424. doi:10.1158/1078-0432.CCR-12-0578 [PubMed: 22711702]
12. Traub F, Singh J, Dickson BC, et al. Efficacy of denosumab in joint preservation for patients with giant cell tumour of the bone. Eur J Cancer. 2016;59:1–12. [PubMed: 26990281]
13. Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. Lancet Oncol. 2010;11(3):275–280. [PubMed: 20149736]
14. Chawla S, Henshaw R, Seeger L, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol. 2013;14(9):901–908. [PubMed: 23867211]
15. Athanasian EA, Wold LE, Amadio PC. Giant cell tumors of the bones of the hand. J Hand Surg Am. 1997;22(1):91–98. doi:10.1016/S0363-5023(05)80187-X [PubMed: 9018620]
16. Averill RM, Smith RJ, Campbell CJ. Giant-cell tumors of the bones of the hand. J Hand Surg Am. 1980;5(1):39–50. doi:10.1016/S0363-5023(80)80042-6 [PubMed: 7365216]
17. Xu R, Choong PFM. Metastatic giant cell tumour of bone: a narrative review of management options and approaches. ANZ J Surg. 2022;92(4):691–696. doi:10.1111/ans.17520 [PubMed: 35143093]
18. Kremen TJ, Bernthal NM, Eckardt MA, Eckardt JJ. Giant cell tumor of bone: Are we stratifying results appropriately? Clin Orthop Relat Res. 2012;470(3):677–683. doi:10.1007/s11999-011-2172-8 [PubMed: 22125240]
19. Fuhs SE, Herndon JH. Aneurysmal bone cyst involving the hand: A review and report of two cases. J Hand Surg Am. 1979;4(2):152–159. doi:10.1016/S0363-5023(79)80132-X [PubMed: 370188]
20. Pelle DW, Ringler JW, Peacock JD, et al. Targeting receptor-activator of nuclear kappaB ligand in aneurysmal bone cysts: verification of target and therapeutic response. Transl Res J Lab Clin Med. 2014;164(2):139–148.
21. Yamagishi T, Kawashima H, Ogose A, et al. Receptor-activator of nuclear kappaB ligand expression as a new therapeutic target in primary bone tumors. PLoS One. 2016;11(5):1–11. doi:10.1371/journal.pone.0154680
22. Wong K, Chantharasamee J, Nelson S, et al. Aggressive osteoblastoma with a secondary aneurysmal bone cyst treated with denosumab. Rare Tumors. 2021;13. doi:10.1177/20363613211034710
23. Dubory A, Missenard G, Domont J, Court C. Interest of denosumab for the treatment of giant-cells tumors and aneurysmal bone cysts of the spine. About nine cases. Spine (Phila Pa 1976). 2016;41(11):E654–E660. doi:10.1097/BRS.0000000000001350 [PubMed: 27244112]
24. Borkowska A, Goryń T, Pieńkowski A, et al. Denosumab treatment of inoperable or locally advanced giant cell tumor of bone. Oncol Lett. 2016;12(6):4312–4318. doi:10.3892/ol.2016.5246 [PubMed: 28101196]
25. Gerrand CH, Bell RS, Wunder JS, et al. The influence of anatomic location on outcome in patients with soft tissue sarcoma of the extremity. Cancer. 2003;97(2):485–492. doi:10.1002/cncr.11076 [PubMed: 12518373]

26. Errani C, Tsukamoto S, Leone G, et al. Denosumab may increase the risk of local recurrence in patients with giant-cell tumor of bone treated with curettage. J Bone Jt Surg - Am Vol. 2018;100(6):496–504. doi:10.2106/JBJS.17.00057
27. Palmerini E, Chawla NS, Ferrari S, et al. Denosumab in advanced/unresectable giant-cell tumour of bone (GCTB): For how long? Eur J Cancer. 2017;76:118–124. [PubMed: 28324746]
28. Mak IWY, Evaniew N, Popovic S, Tozer R, Ghert M. A translational study of the neoplastic cells of giant cell tumor of bone following neoadjuvant denosumab. J Bone Jt Surg. 2014;96(15):e127(1). doi:10.2106/JBJS.M.01332
29. Thomas DM. RANKL, denosumab, and giant cell tumor of bone. Curr Opin Oncol. 2012;24(4):397–403. doi:10.1097/CCO.0b013e328354c129 [PubMed: 22581354]
30. Lamy O, Stoll D, Aubry-Rozier B, Rodriguez EG. Stopping Denosumab. Curr Osteoporos Rep. 2019;17(1):8–15. doi:10.1007/s11914-019-00502-4 [PubMed: 30659428]
31. Broehm CJ, Garbrecht EL, Wood J, Bocklage T. Two cases of sarcoma arising in giant cell tumor of bone treated with denosumab. Case Rep Med. 2015;2015. doi:10.1155/2015/767198
32. Federman N, Brien EW, Narasimhan V, Dry SM, Sodhi M, Chawla SP. Giant cell tumor of bone in childhood: Clinical aspects and novel therapeutic targets. Pediatr Drugs. 2014;16(1):21–28. doi:10.1007/s40272-013-0051-3
33. Errani C, Tsukamoto S, Mavrogenis AF. How safe and effective is denosumab for bone giant cell tumour? Int Orthop. 2017;41(11):2397–2400. doi:10.1007/s00264-017-3536-9 [PubMed: 28646421]
34. Aponte-Tinao LA, Piuzzi NS, Roitman P, Farfalli GL. A High-grade Sarcoma Arising in a Patient With Recurrent Benign Giant Cell Tumor of the Proximal Tibia While Receiving Treatment With Denosumab. Clin Orthop Relat Res. 2015;473(9):3050–3055. doi:10.1007/s11999-015-4249-2 [PubMed: 25758379]

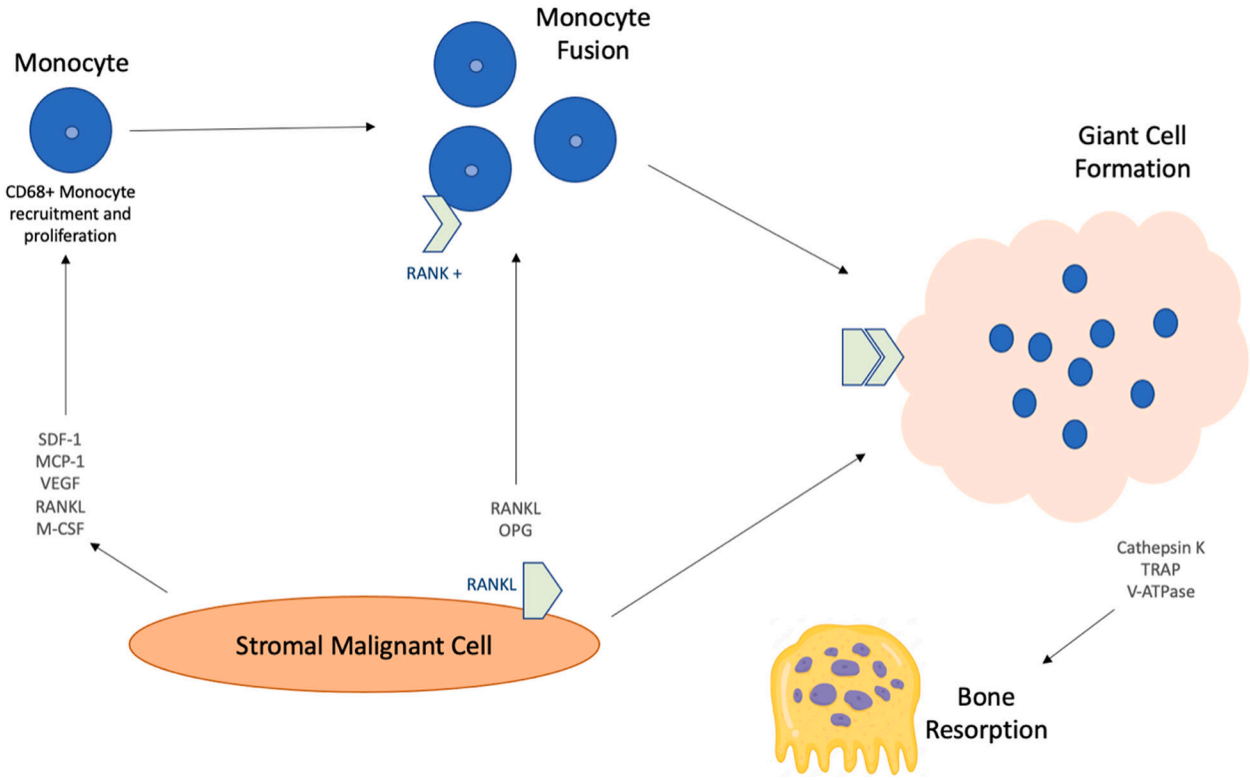

Figure 1.
Illustration of OPG-RANK-RANKL pathway

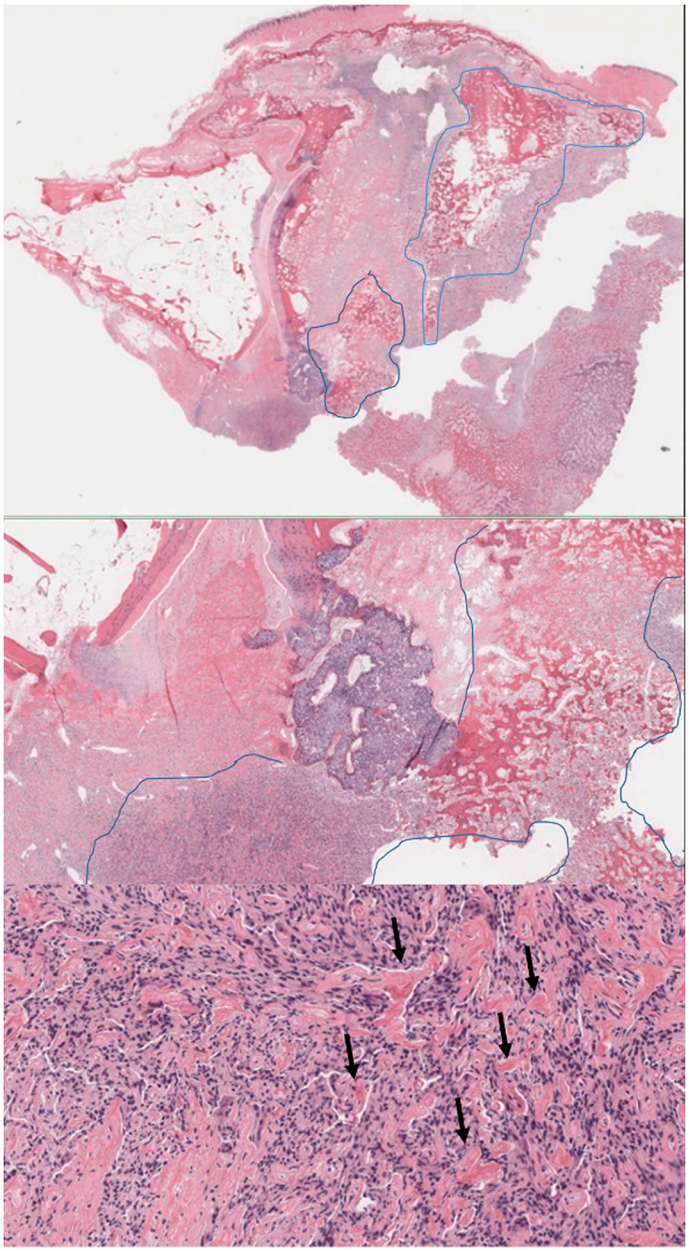

Figure 2.

Pathology from a clinical example of a 25-year-old female with giant cell tumor of the index proximal phalanx with soft tissue extension treated with preoperative denosumab (same patient shown in Figure 3). Low- through high-power magnification histologic slide demonstrating haphazard bone formation replacing tumor in patient treated with Denosumab. The areas within the blue lines are all areas of ossification. High magnification panel demonstrates random patterns of trabecula are immature bone in pink, some of which is mineralizing.

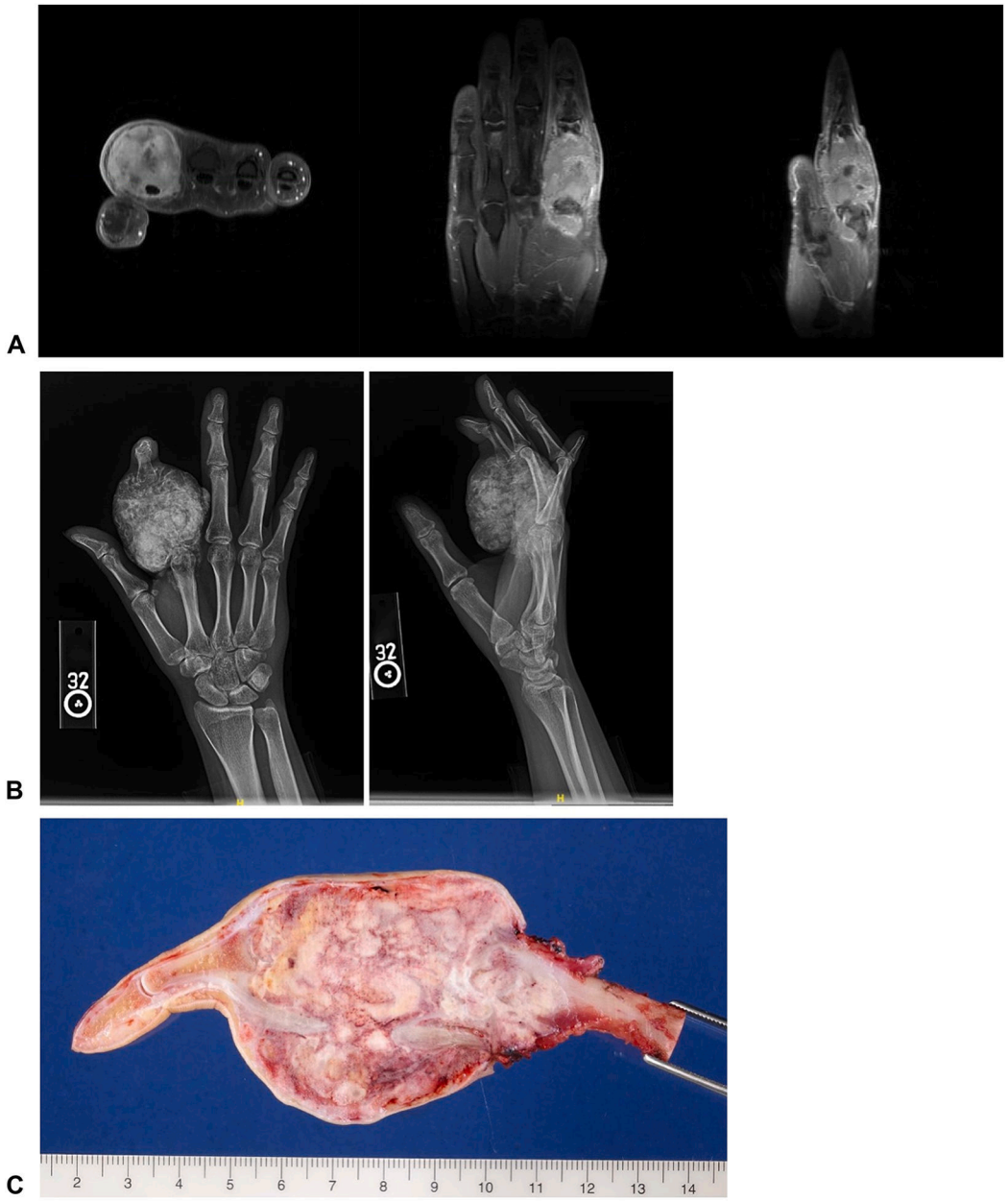

Figure 3.

Radiographs from a clinical example of a 25-year-old female with giant cell tumor of the index proximal phalanx with soft tissue extension treated with preoperative denosumab (same patient shown in Figure 2). A) MRI of patient's finger, pre-denosumab treatment. B) Radiographs demonstrating a patient with giant cell tumor of bone, treated with Denosumab, demonstrating the development of haphazard deposition of bone with multiple septations. C) Gross section of the tumor specimen after ray resection, note the soft tissue extension raising concern for risk of local recurrence if not resected widely.