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Review Article

Intra-Tumoral Denosumab for Giant Cell Tumor of Bone (GCT): A Case Report

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Abstract

Background: Denosumab has emerged as an effective therapy for managing giant cell tumor of the bone (GCT). However, its use is limited by the osteonecrosis of the jaw (ONJ). **Case presentation:** We describe a Caucasian woman with GCT of the 3rd middle phalange who developed ONJ after several years of denosumab therapy requiring cessation of treatment. As an alternative to amputation, intra-tumoral denosumab provided durable and complete tumour regression without causing recurrence of ONJ. **Conclusion:** Intra-tumoral administration of denosumab constitutes an effective and durable method of drug delivery and should be considered for patients or who develop ONJ while receiving denosumab or whose dentition places them at high risk of ONJ.

Keywords: Giant cell tumor of bone, Denosumab, Intra-tumoral injection, Osteonecrosis of Jaw; ONJ

List of Abbreviations

GCT: Giant cell tumor of bone; i.t: Intra-tumoral; NF-κB: Nuclear factor kappa beta; OPG: Osteoprotegerin; RANKL: Ligand for Receptor Activator of Nuclear Factor Kappa beta; s.c.: Subcutaneous; TNFSF11: Tumor Necrosis factor (ligand) Superfamily Member 11 gene

Background

Giant cell tumor (GCT) is a benign bone neoplasm most commonly affecting the metaphyseal or epiphyseal regions of the tibia, femur, humerus, wrist, hands, feet, patella, or sacrum [1]. Disease onset usually occurs between ages 20 to 40 years with a slight female predominance [2]. GCT tends to recur and has the potential for locally aggressive behaviour, disability, and pain [3]. Despite its classification as a benign disease, GCT has 1 to 5% risk of lung metastases [3].

Pathogenetically, GCT emanates from stromal cells of osteoblastic lineage which induce osteoclasts to drive osteolytic destruction. In these tumors, the ligand for receptor activator of nuclear factor κB (RANKL) coded for by TNFSF11 expression is highly expressed, and its inhibitor, osteoprotegerin (OPG), is low or minimally expressed, [4,5] subsequently, triggering the tumorigenic program of NF-κB transcription factors. This seminal observation led to targeting RANKL with denosumab, a RANKL monoclonal antibody, which became a standard of care for managing GCT [6]. However, the benefit of denosumab is countered by risk of osteonecrosis of the jaw (ONJ) when given subcutaneously. Here we report the efficacy of intra-tumoral (i.t.) injection of denosumab in a patient who developed ONJ during long-term anti-RANKL therapy.

Case Report

A 46-year-old Caucasian female pianist with GCT involving the left 3rd finger middle phalange was initially treated with surgical resection and reconstruction in 2013 consisting of intralesional curettage, polymethylmethacrylate cement, and bone grafting from the right hip. Local recurrence ensued after eight months that was unresectable. Thereafter, she received denosumab 120 mg subcutaneously (s.c.) at 4 to 6-week intervals for more than 6 years associated with waxing and waning of the middle finger tumor that provided a clinically acceptable partial response but incomplete disease control. Complete disease regression was never identified from the s.c. denosumab administration. Subsequently, the patient developed severe ONJ necessitating discontinuation of denosumab. The tumor progressed and the patient was advised to undergo amputation.

As an alternative to amputation, i.t. administration of denosumab was proposed. Accordingly, the standard subcutaneous dosage of denosumab 120 mg diluted in 1 mL sterile water was injected with a 27-gauge needle into the tumor using a 4-quadrant technique. Within days, complete tumor regression surpassing the response to s.c. denosumab was observed (Figure 1). The response persisted for 6 months before the need for a repeat i.t. injection. Because of pain associated with the first i.t. injection, the subsequent injection was administered after a lidocaine nerve block was given and this was much better tolerated. No recurrence of ONJ or other toxicity occurred after the i.t. injections.

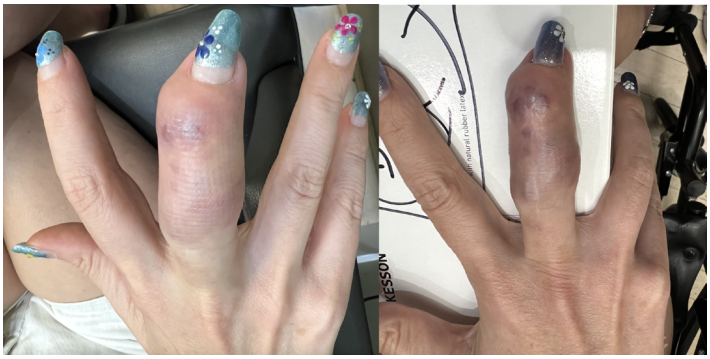

Figure 1a: Baseline

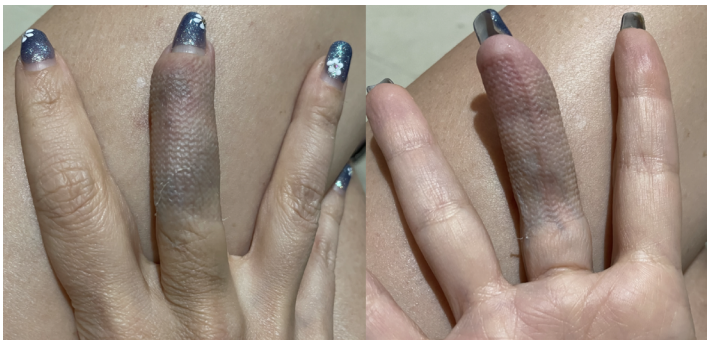

Figure 1b: 1 week after injection

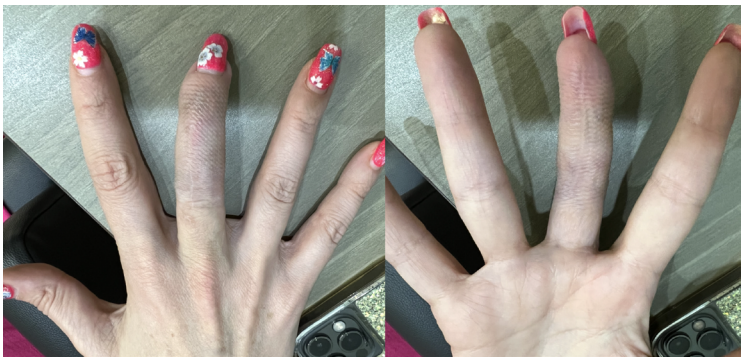

Figure 1c: 5 weeks after injection.

Figure 1a-1c: Serial photographs before and after intra-tumoral injection of denosumab.

Discussion

Denosumab is an indispensable and usually well-tolerated treatment for patients with osteoporosis, metastatic bone disease, and GCT. However, the utility of this treatment is limited by ONJ, an uncommon but clinically significant complication of anti-RANKL therapy that may lead to necrotic bone exposure, intraoral or extraoral fistulae, and possibly tooth extraction [7,8]. Poor dentition and history of prior dental extraction predispose to ONJ and severe periodontal disease is a contraindication to denosumab therapy leading to delays or interruption of treatment. The patient in this case report lacked antecedent dental history or symptoms prior to development of ONJ, possibly indicating that even subclinical periodontal disease should be a routine subject of clinical concern during denosumab therapy.

Intra-tumoral administration of denosumab appears to represent a highly effective and potentially safer approach that merits consideration for GCT patients, especially those with ONJ or poor dentition. Additionally, the impressive magnitude of tumor regression and prolonged duration of benefit makes intratumoral injection a more cost-effective method of drug delivery which could improve access to the drug in resource-limited economies. The superiority of i.t. over s.c. administration for this patient suggests that local injection may overcome barriers to drug delivery caused by pharmacokinetic and pharmacodynamic issues and could be considered as a strategy for monoclonal antibody agents in general. Phase 2 studies are warranted to confirm the superiority and safety of i.t. versus s.c. denosumab therapy.

Conclusion

Intra-tumoral administration of denosumab constitutes an effective and durable method of drug delivery and should be considered for patients or who develop ONJ while receiving denosumab or whose dentition places them at high risk of ONJ.

Declarations

Ethics approval and consent to participate: Not applicable since this was not a study.

Consent for publication: The patient provided written consent for publication.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study. The supporting data for the case report is contained in the photographs that are included with the case report and in the patient's medical record where availability is restricted by law.

Competing Interests: The authors have no conflict of interests.

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Authors' Contributions: MC Drafted the report, SC conceived the therapy, EG drafted and edited the report. All authors reviewed and approved the report.

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