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Clinical and pathological results of denosumab treatment for giant cell tumors of bone: Prospective study of 14 cases

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ABSTRACT

Objective: Giant cell tumor of bone (GCT) is a primary, osteolytic, benign tumor of the bone. Surgery is the commonly used treatment; however, recurrence remains a problem. Receptor activator of nuclear factor kappa B (RANKL) is responsible for the formation of osteoclastic cells. Discovery of RANKL and its human monoclonal antibody, denosumab, led to use of denosumab for treatment of GCT. The aim of this study was to evaluate clinical and pathological results of treatment of GCT with denosumab and to assess adverse effect profile and recurrence rate.

Methods: Thirteen patients with 14 lesions were enrolled in the study. Mean age was 38.3 years. Patients were given subcutaneous injections of denosumab (120 mg) every 4 weeks (with additional doses on days 0, 8 and 15 in cycle 1 only) and were radiologically evaluated for tumor response. Pain and functional status were measured using Visual Analog Score (VAS) and Musculoskeletal Tumor Society Score (MSTS). Adverse effects were analyzed after each cycle.

Results: Participants were 5 men and 8 women. Mean follow-up was 17 months. One lesion was Campanacci grade I, 8 were grade II, and 5 were grade III. Eight lesions were recurrent, and remaining were primary lesions. After average of 9 cycles (range: 4–17 cycles), all tumors underwent radiological regression. Ten lesions were removed surgically. More than 90% of giant cells were found to have regressed in all pathological specimens. On last follow-up, average VAS was 1 and MSTS was 87%. Fatigue and joint and muscle pain after injections was reported by 46% of patients, and mild hypocalcaemia was seen in 1 patient.

Conclusion: Denosumab has been shown to be a successful drug in treatment of GCT. Denosumab can be used as neoadjuvant for all recurrent lesions, grade II lesions with high surgical risk, grade III lesions, and metastatic cases of GCT.

Level of evidence: Level IV, Therapeutic study

Giant cell tumor (GCT) is an aggressive, benign bone tumor. GCT, which was first defined by Cooper and Travers, can produce pulmonary metastasis, albeit rarely (1–6%).[1,2] GCT constitutes 5% of primary bone tumors and 20% of benign bone tumors. Although GCT settles in metaphyseal area of long bones, particularly distal femur and proximal tibia, followed by distal radius and proximal humerus in 85% of cases, it is also seen in axial skeleton (10%) and in small bones of hands and feet (5%). GCT is common in third and fourth decades of life, and frequently emerges in women.[3]

Radiologically, GCT is lytic lesion without mineralization that often extends to subchondral area and is located eccentrically in metaphysoephyseal region. It has no sclerotic edge, but is separated from normal bone with narrow transition zone. It leads to cortical thinning, expansion, or cortex destruction, and soft tissue components may be found in more aggressive lesions. Pathological findings of GCT consist of osteoclast-like giant cells and proliferating mononuclear round stromal cells, which are responsible for neoplasia.[4] Although osteoclast-like giant cells control bone

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resorption, stromal cells direct monocytes by managing tumor pathology and ensure formation of giant cells.[5]

The classic treatment for GCT is surgery. Following aggressive curettage and high-speed burring, use of chemical adjuvants such as phenol, alcohol, hydrogen peroxide, and liquid nitrogen, as well as defect filling with grafts or bone cement are among most frequently used methods of treatment. Endoprosthetic reconstruction may also be used for grade III tumors with serious cortical destruction.[6] Recurrence rate ranges between 5% and 56%, depending on cement and chemical adjuvants used during surgery.[7] Recurrence still continues to be the major problem. In recurrent lesions, in lesions with wide soft tissue component, and in surgically difficult localizations like sacrum, spine, pelvis, and distal radius, methods such as embolization, radiotherapy, or bisphosphonates may be used.[8,9]

In the 1990s, effects of receptor activator of nuclear factor kappa B ligand (RANKL) and receptor activator of nuclear factor kappa B (RANK), members of the tumor necrosis factor (TNF) family, on formation of osteoclasts and bone resorption were demonstrated.[10,11] It was seen that RANKL expression in stromal cells caused neoplasia and stimulated both formation of osteoclast-like giant cells and bone resorption with activation of RANK.[12,13] Recognition of RANKL in pathogenesis led to investigations of potential curative effect of suppression of this molecule. The result was a human monoclonal immunoglobulin G2 antibody for RANKL, denosumab. It was initially shown to decrease bone resorption in postmenopausal osteoporosis and metastatic bone lesions.[14–16] Thomas et al reported successful clinical and radiological results with 120 mg denosumab dose in recurrent or inoperable GCT in a phase 2 study in 2010.[17] Denosumab was licensed for use in unresectable lesions and relapse tumors and in lesions for which resection would cause serious morbidity by the United States Food and Drug Administration in 2013 and the European Medicines Agency in 2014.[18]

The purpose of the present study was to evaluate clinical and pathological results of 120 mg subcutaneous denosumab treatment in patients with GCT and examine recurrence rate and adverse effect profile.

Patients and methods

Thirteen patients who were diagnosed as having GCT of bone between April 2011 and January 2015 in our clinic were included in this prospective study, conducted with permission from the Ministry of Health. Patient demographic data, tumor localization, and previous treatments were recorded. All patients were radiologically classified using Campanacci classification[19] after plain radiographies, bone scan, and computerized tomography (CT) of the lesion and thorax, and magnetic resonance imaging (MRI) of lesion. Grade I GCT is latent tumor in which the cortex is intact and its borders are clearly separated. Grade II GCT is an active tumor, whose borders can be separated, but there is no sclerotic edge; thinning is present with expansion in cortex. Grade III GCT is aggressive lesion that has ambiguous borders. Cortical destruction and soft tissue components are present. A closed-needle biopsy was performed on patients with primary tumors. Diagnoses were confirmed by re-evaluating paraffin-embedded blocks of recurrent lesions. One pathologist experienced in musculoskeletal system pathology undertook all pathological evaluations. Prior to drug use, calcium, phosphorus, and parathyroid hormone levels were measured in all patients. All measured levels were found to be normal.

All recurrent lesions, grade II lesions with high surgical risk, metastatic lesions, and grade III lesions were included in this study. Subcutaneous injections of denosumab (120 mg) were given every 4 weeks (with additional doses on days 0, 8 and 15 in cycle 1 only). Concomitantly, 1500 mg calcium carbonate+400 IU vitamin D were given daily.[17,20] The number of cycles was recorded. Adverse effect profile was examined after each dose.

Radiographs were used to evaluate lesion mineralization, septa formation, ossification of soft tissue component, and corticalization in each cycle of treatment, and CT in third month and at the end of treatment. Final status of lesion of patients who underwent surgery was examined with MRI after treatment. Postoperative patients were assessed in terms of recurrence using radiography, CT, and MRI every 3 months in the first year.

Curettage or resection material after treatment was classified using a 2-grade staging system developed for this study according to the tumor response. Grade 1 was grouped as fibrous tissue, inflammation, and a small amount of woven bone formation; Grade 2 was defined as woven bone, precancellous bone, and cancellous bone formation.

Pain relief was evaluated after treatment and at last follow-up. Pain scores of all patients were assessed using visual analog scale (VAS) ranging 0 to 10. Functional status was evaluated using Musculoskeletal Tumor Society (MSTS) Score at last follow-up.[21]

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences software version 16 (SPSS Inc., Chicago, IL, USA). Average and standard deviation were calculated for quantitative variables, and number of cases was calculated for categorical variables. Differences between pre- and post-treatment VAS scores were analyzed using t-test. P value less than 0.05 was considered significant.

Results

Fourteen lesions in 13 patients (5 men, 8 women; mean age: 38.3 years [range: 26–51 years]) diagnosed as GCT of bone and treated with denosumab were included in the study. Average length of follow-up was 17 months (range: 10–30 months). One patient had multifocal lesions in proximal and distal femur. One lesion was grade I (multifocal lesion with recurrent grade 2 lesion in distal femur), 8 were grade II, and 5 were grade III. Six lesions were primary, whereas 8 were recurrent. Two patients with recurrent lesions had lung metastasis; these patients had been under follow-up for GCT for more than 10 years. Demographic data, tumor localization, radiological grade, and previous treatments are shown in Table 1.

Due to availability of denosumab in our country, 4 patients received 1 × 120 mg (Xgeva; Amgen, CA, USA) and 9 patients had 2 × 60 mg (Prolia; Amgen, CA, USA). An average of 9 cycles (range: 4–17 cycles) were administered.

Ten lesions were surgically treated following denosumab administration, and resection/curettage specimens obtained were pathologically examined (Figs. 1 and 2). Pathological evaluation revealed that giant cells had regressed >90% in all cases. In 4 patients, 90% ossification of lytic area was seen radiologically with regression of pain; 3 of these patients continued follow-up without treatment and 1 continues to receive denosumab treatment for lung metastases. It was observed that lung lesions were regressing and remained stable (Fig. 3). For patients who underwent curettage, physical and chemical adjuvants such as high-speed burring, electrocauterization, phenol, alcohol, or hydrogen peroxide were used. Surgical treatments, number of treatment cycles, and pathological evaluation status are presented in Table 2. No recurrence has been observed in surgically-treated patients.

Average pre-treatment pain VAS of 7 (range: 3–10) was reduced to average of 2 after third cycle, and then 1 (range: 0–3) at last

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