Denosumab in Patients with Giant Cell Tumor and Its Recurrence: A Systematic Review

Running title: Giant Cell Tumor and Denosumab

Abstract:

Recent studies regarding drug treatment with Denosumab suggest that this drug reduces the size of tumor, and therefore make surgery easier with lower morbidity. However, some studies have reported several complications associated with this drug. So, we decided to do systematic review .This study reviews the literature to determine the effectiveness and safety of Denosumab in reducing activity bone destructions in giant cell tumor and skeletal- related events in patients with giant cell tumor of bone and its recurrence.

We explored studies in PubMed, and Cochrane Collaboration Library. For this purpose, articles of various levels were retrieved until October 22, 2016. Two reviewers assessed articles independently based on predefined criteria to extract the relevant data. Primary outcomes associated with skeletal-related event (SRE), overall survival, and secondary outcomes such as pain, quality of life and adverse events were evaluated and analyzed.

The total population of this meta-analysis consisted of 686 patients. Of this population, only 55% had primary giant cell tumor of bone and the remaining 45% had giant cell tumor recurrence, with 2% experiencing secondary recurrence.

The results showed the effectiveness of Denosumab in reducing the tumor size due to inhibiting the Osteoclastogenesis. Denosumab did not show any effect on reducing tumor recurrence, but in cases where complete tumor surgery is not possible and tumor residuals may remain, Denosumab can be helpful. Also, the clinician should consider that risk benefit of Denosumab.

Key words:Giant Cell Tumor of Bone, Recurrence,Denosumab, Systematic Review, Meta-Analysis

Abbreviations:

Giant cell tumor of bone (GCTB)

Skeletal-related event (SRE)

Osteonecrosisof the jaw (ONJ)

Introduction:

As we know, giant cell tumor is considered as a benign aggressive tumor, though their recurrence rate varies from 0 to 65% depending on the type of treatment and tumor location (1). Secondary malignant transformations in a typical pathological form of giant cell tumor without radiotherapy are rare (occurring in less than one percent of patients) (2). It is highly improbable to emerge malignantly in initial biopsy (3). Tumor recurrence usually occurs in most cases thatreceived radiotherapy or have multiple cysts lesion in the range of 1.4 to 6.6% (4, 5, 6).

The giant cell tumor treatment is highly controversial. Surgical treatment options include curettage using high-speed burr or resection. Curettage has a high recurrence rate, but maintains the adjacent joint function. Resection with a wide margin reduces tumor recurrence but correlates with worse functional outcomes.

In 2013, the FDA approved Denosumab as a monoclonal antibody that activates nuclear RANKL to treat adults and adolescents with giant cell tumors in cases where surgical resection has considerable side effects or is unresectable.(7)

What matters is that the giant cell tumor is considered as biphenotypic cell pathology, with the interaction of mesenchymal spindle-like stromal cells that express the RANKL and osteoclast giant cells that activated with RANKL, so resulting in bone resorption (8). In general, it can be said that giant cell tumor of bone with primary behavior is benign, which is traditionally treated with surgery. But the disease can recur even after the best surgical intervention. In addition, it can develop in places where surgery will be difficult and risky. Therefore, understanding the role of active ligand receptors Factor- κB in the pathophysiology of giant cell tumors of bone can lead to the application of Denosumab.

Denosumab is a monoclonal antibody that binds with RANKL and inhibits osteoclastogenesis directly. It has been shown to cause objective changes in tumors with clinical response in patients with non-removable tumors or huge recurrences (9).Recently, Denosumab has been reported to destroy RANKL expression almost completely, with pathologic assessment demonstrating the absence of giant cells but the persistence of stromal neoplastic cells (10).

A host of questions such as the efficacy of Denosumab in treating giant cell tumors of bone have been raised. Accordingly, this paper seeks to review studies about the effectiveness of

Denosumab on giant cell tumor of bone and how to manage giant cell tumor of bone (GCTB) under these conditions and evaluated the skeletal-related complication.
In this study, the Denosumab effectiveness was considered as size decreasing of the tumor and prevention of recurrence and growing of tumor residual.

Method:

Sources and search strategies:

We searched all English articles in PubMed, and Cochrane collaboration Library Databases on October 22, 2016. The references of articles were also reviewed manually. The search strategy is shown in Figure 1.

Selection of studies:

The titles and abstracts of all articles and their citations were reviewed by two independent reviewers (an orthopedic oncologist and a Master of Medical Education) and possible disagreements were resolved through negotiation and discussion.

Inclusion criteria:

All studies about the effectiveness of Denosumab (at any dose or frequency) for the treatment of patients with giant cell tumor of bone and recurrent GCTB were investigated and those possessing at least one of the measures under study such as occurrence of SRE, overall survival, overall progression of disease or adverse effects were included.
The abstracts presented at conferences, which had been printed in the conference booklet but their full text was not published in any journal, were also included in the study. All papers in which the study population had tumors other than GCTB or children with this condition were excluded from the study.
It is worth noting that research articles were only considered in this meta-analysis.

Data extraction

Primary outcomes of the study included: 1. Skeletal-related event (SRE): This is as a pathological fracture, bone radiotherapy.2. Overall survival: which covered the period of entering the study until the death of participants. 3. Histopathologic results: This referred to the absence of more than 80% of osteoclastic giant cells. 4. Radiological results: an improvement of more than 60% in the size or shape of the tumor in radiological images.

Secondary outcomesincluded: 1.pain: which referred to deteriorated or improved condition or enhanced physical activity of the patient. The pain was measured by any valid means or using visual analogue scale

2. Hypocalcemia: it defined as marked or unmarked serum calcium below 8 mg /dl. 3. Osteonecrosis of the jaw (ONJ): Bone necrosisin the oral cavity. 4. Infection

Quality assessment:

For each article, the eligibility criteria were assessed by two authors in accordance with Cochrane collaboration's risk of bias tool for studies included in the meta-analysis (11). Two researchers performed the evaluation of studies independently and differences were resolved through discussion. (Table 1)

All outcomes were analyzed with comprehensive meta analysis software. The dichotomous results of single group including values and their ratios were computed at 95% confidence intervals. Mean and standard deviation of demographic information were calculated and reported. In cases in which meanhad not been reported, the median was used.

Results:

925 studies were evaluated out of which only 1 cohort study and 9 case series were included in the meta-analysis and 11 case reports were also reported separately. The inter-reviewer agreement was 98.5%.

Characteristics of studies and subjects:

The information of 10 studies included in the meta-analysis is given in the following table 2. The study population consisted of 686 people with an average age of 31.5± 2.8 years out of whom 55% with primary giant cell tumor of bone, and 45% withrecurrencewere enrolled in the study.

Outcomes:

SRE: All studies did not indicate the occurrence of SRE during or after the treatment of patients

Overall survival: None of the studies had considered overall survival, and only mortality of patients had been reported. As such, one case of dearth was reported in RELEHI and another in CHAWLA, which was causedby respiratory failure and thus irrelevant to denosumab treatment related.

Histopathologic results: in eight studies, biopsy was performed after treatment examine histopathology and the reports had been expressed qualitatively with patients lacking more than 80% of osteoclastic giant cells were regarded as receiving positive response from the treatment. Details are given in Figure 2.

Radiological results: Five studies reporting more than 60% improvement in size or shape of the tumor in radiological images including PET, CT scan, MRI or X-ray after treatment were studied and the results are as follows. (Figure 3).

Pain:it was referred to the deteriorated or improved condition of the patient or enhanced physical activity. In papers under study, pain had been referred to as a condition. In Figure 4, the severity of post-treatment pain has been reported, which was either caused by disease or it persisted throughout the treatment.

Hypocalcemia: The papers under study had not reported the numerical value of hypocalcemia serum in patients and only the number of patients with or without hypocalcemia after treatment had been reported.
These values are shown in Figure 5.
None of the studies had reported symptoms of the ONJ, the only exception was the study of Chawalain which 2 cases of ONJ and 7 cases of infection were reported.
Given the large population of this study and the prolonged duration of treatment with denosumab, it could be argued that these symptoms only appear in long-term treatment. Therefore, further studies are required to verify the results.
Recurrence: Of all subjects of the study, only 2% had experienced recurrence.

Case reports:
Nearly 11 studies in form of case reports had mentioned the treatment of giant cell tumors or its recurrence with denosumab. Hakozaki in 2014 reported the neoadjuvant treatment of denosumab in a 20-year old man with giant tumor cell of bone in femur. PET images revealed reduced uptake of tumor and histologic results showed fibrosis of histiocytoma-like

features and disappearance of bone mononuclear stromal cellsand multinuclear osteoclast-like giant cell (21). Vaishya in 2015 reported that use of denosumab therapy in three patients who could not be operated due to improper location of the tumor or its small size. The results of follow-up radiology showed the positive response of the tumor to the treatment (22). Diagnosis in Oncology Group released a report in 2013 about a 10-year-oldfirl with giant cell tumor in the knee and a nodule in the lungs, who had been treated with denosumab after surgery for 4 months after which she no longer needed to use pain medications and was able to walk without the use of wheelchair (23).

In 2015, Stadler reported the case of a 20-year-old woman with secondary recurrences of tumor, which had led to the removal of her upper knee, and the results of sarcoma biopsy in which the patient had been treated with denosumab after surgery without any signs of recurrence or complications after two years (24).

In 2014, Akaike discussed the case of a 28-year-old man with third recurrences of tumor in the distal femur. In this case, denosumab treatment had been applied before surgery in the third recurrence and given that the patient had not demonstrated any certain side effects during denosumab treatment and the tumor had shrank in size, the conditions were favorable for the surgery of patient (25).

In another study in 2014, Isabella treated two patients with neoadjuvant denosumab and four other patients without denosumab, with the results of follow-up after six months revealing that side effects were not present in both groups, though postoperative complications had reduced in patients treated with denosumab (26). In 2016, Kajiwara reported the case of a 43-year old man who had lost all symptoms after two –month treatment with denosumab so that no signs of tumor recurrence were detected in CT scan (27).

In 2016, Yamagishi reported the case of a 19-year-old boy with giant cell tumor at the sacrum and a nodule in the lung who was under treatment with denosumab. After 8 months, nodule shrank and patient was operated to remove tumor in sacrum and nodule in long. In this case, no sign of recurrence was observed (28).

In another study, a 41 year-old male with giant cell tumor in Ischium, which was inoperable due to largeness of tumors, was treated with denosumab for 3 months, after which he was operated without any side effect (29).

In a study in 2014, 22-year old women with a lesion in the C2 vertebral body and odentoid process were treated with denosumab every three weeks. After 16 months, radiologic images showed complete disappearance of osteolytic process (30).

In 2013, the case of a 27-year-old patient were reported, who was subject to radiotherapy after first recurrence of the tumor. However, the tumor grew larger and therefore the patient was treated with denosumab. The operation was carried out after three months and Denosumab treatment continued postoperatively without any symptoms of recurrence in follow-ups (31).

As these studies show, it seems that the use of denosumab helps the treatment or smooth the surgery. However, the exact duration of using this drug medicine is an issue that calls for further research.

Discussion:

The results of this study showed that the giant cell tumors are more likely to develop in the third decade of life, especially in women. Bone resorption follows the tumor activation via direct osteoclast activated with RANKL(this precursors being derived from monocytes/macrophage cell line residing in bone)(32).

Tumoral giant cell are activatedosteoclasts through indirect effect on osteoblasts and stromal cell with presence of a stimulating factor (RANKL) increases the overall process of osteoclasts formation and activation, so increases bone resorption. (figure6)

To differentiate at the level of osteoclasts, RANK receptors have to interact with RANKL. There is a theory that this interaction is inhibited in the presence of Denosumab (the monoclonal antibody that band with RANKL)(32 & 1). Moreover, we know that surgery is a typical treatment of giant cell tumor of bone with a recurrence rate of 15-45% (33 and 34) and when in intralesionalsurgery by high speed burr and allograft bone-cement is done this rate dropping to 2-14% (35 & 1).

With regard to local recurrence of treatment such as repeated intralesionalcurettageorwide surgical resection, mutilating procedure should be avoided. It is posited that compared to intralesional surgery, massive removal of tumor was accompanied with lower risk of recurrence (5% vs. 25%), which intensified the problems of reconstruction (1).

Many studies suggest that denosumabis a suitable treatment alternative for giant cell tumor of bone, when function-sparing surgery is not an option, or tumor is placed in an improper location or surgery is highly risky due to large size of tumor (33).

The medical treatment of giant cell tumor of bone is experimental and based on broad theories regarding the cause of the disease. The present study showed a recurrence rate

of 2% in the case of using denosumab. However, other studies reported a local recurrence rate of 2.4% in the case of bisphosphonate therapy due to the effect of antibodies (36).
The present study consistent with other studies showed that diet before standard surgery for the use of denosumab over a six-month period can improve the treatment of certain cases of giant cell tumor of bone and its recurrence.The results of this study suggest that the use of denosumab can slightly reduce surgical complications and it can act be helpful in complex cases or in patients resistant to pain killers (37). The long-term use of denosumab can increase concerns over its toxicity.
Recent studies regarding drug treatment with Denosumab suggest that this drug reduces the size of tumor, and therefore make surgery easier with lower morbidity. However, some studies have reported several complications associated with this drug.

Denosumab makes surgery easier because it reduces the stage of the tumor and improves treatment in cases when there are recurrence or tumor residuals after surgery. However, in patients who have been initially treated with surgery, it has been shown that the use of denzumab does not prevent relapse.

Complications such as arthralgia, headache, nausea, fatigue, pain, anemia, hypercalcemia and osteonecrosis in jaw have been reported (12, 6, and 32). The present study also showed similar complications. However, denosumab can be used as a helpful alternative along with surgery or in cases where surgery is not an option or it would be complex and difficult.

In general, there are still several questions unanswered about the use of denosumab in the treatment of giant cell tumor of bone. It is clear that this drug is useful in neoadjuvantsettings, but its optimal treatment duration is still unknown. The authors of this study, based on results, believe that in any situation, depending on the location, the presence of fracture and surgical skills, the tumor aggressiveness and the size of tumor. As a result, clinical judgment should be determining the course of treatment for this disease, and follow-up is especially important to determine the long-term effects of this drug.

In Thomas (20) and Chawla's studies (7) reported that four patients developed new sarcoma.There have been reports of atypical femoral fracture in osteoporotic patients with metastatic bone disease treated by Denosumab. Despite the complications of denosumab, it can be used in cases where recurrence is possible or complete resection is not an option. Therefore, clinicians should be aware of the clinical problem. (38).

Considering that none of studies were clinicaltrials, the necessity of conducting such studies to make more accurate decisions regarding the use of this drug and its effectiveness is felt.

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