

Radiological Evaluation of the Efficacy of Denosumab as a Treatment for Giant-cell Tumour of Bone with Histopathological Correlation

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ABSTRACT

Objective: To evaluate the efficacy of denosumab as a treatment for giant-cell tumour of bone (GCTB) with histopathological correlation.

Methods: This was a single-centre retrospective study of patients with histologically proven GCTB. Clinical data of all patients treated with neoadjuvant and adjuvant denosumab according to a standardised protocol were reviewed. Duration of follow-up from the time of diagnosis ranged from 4 to 30 months. Clinical response in terms of pain reduction or functional improvement and major adverse drug effects were documented. Pre- and post-treatment tumour responses were evaluated using available radiographs, computed tomography (CT) and magnetic resonance imaging (MRI) images taken at irregular intervals. Concomitant histopathological evaluations of tissue samples were also conducted to assess the percentage of giant cells and de novo bone matrix.

Results: A total of 12 patients received denosumab treatment for GCTB from 20 July 2012 to 5 June 2015. Among them, 10 (83.3%) patients had no tumour recurrence before September 2016; and 11 (91.6%) patients reported reduced pain or functional improvement with no major treatment complications. Excellent treatment response was achieved for 10 (90.9%) of 11 patients who underwent radiographic assessment and four (100%) of four patients who underwent CT assessment. Serial MRI assessments demonstrated tumour recurrence in two (18.2%) of 11 patients. Histopathological tumour response was observed in all patients.

Conclusion: Denosumab is an efficacious treatment for GCTB in terms of clinical, radiological, and histopathological response, with no major complications documented in the present study. Radiography and CT are useful tools for clinical evaluations of the efficacy of denosumab treatment for GCTB.

Key Words: Denosumab; Giant cell tumor of bone

中文摘要

以放射學評估Denosumab對骨巨細胞瘤的療效和其組織病理相關性

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目的：評估denosumab治療骨巨細胞瘤的療效及其組織病理相關性。

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方法：這項單中心回顧研究針對經組織學證實的骨巨細胞瘤（GCTB）患者，回顧根據標準化方案以新輔助和佐劑denosumab治療所有患者的臨床數據。診斷後的隨訪期為4至30個月。本研究記錄患者疼痛減輕或功能改善和主要藥物不良反應，並利用不規則間隔拍攝的X線片、CT和MRI評估治療前後的腫瘤反應，以及進行組織樣本病理評估以評估巨細胞與骨基質的百分比以及新骨生成。

結果：2012年7月20日至2015年6月5日期間共12名患者接受denosumab治療GCTB，其中10例（83.3%）患者在2016年9月前無腫瘤復發；11例（91.6%）患者報告疼痛減輕或功能改善，沒有因治療引發的嚴重併發症。在接受放射學評估的11名患者和接受CT評估的4名患者中，分別有10名（90.9%）和4名（100%）顯示極佳治療反應。連續MRI評估顯示11例患者中有2例（18.2%）腫瘤復發。所有患者皆顯示組織病理學腫瘤療效。

結論：在臨床、放射學和組織病理學反應方面皆顯示denosumab為治療GCTB的有效方法。本研究未有發現重要併發症。X線片和CT是用於臨床評估denosumab對GCTB療效的有用工具。

INTRODUCTION

Giant-cell tumour of bone (GCTB) is a primary bone tumour that presents as an eccentric osteolytic lesion frequently affecting the epiphyseal or subarticular region of long bones, the spine, or the sacrum. GCTB, a type of giant cell-rich lesion of bone, is generally benign; however, atypical GCTB may be associated with multiple local recurrences, multicentricity, pulmonary metastases, or lesions that cannot be removed surgically without causing substantial morbidity. The World Health Organization therefore classifies GCTB as “an aggressive, potentially malignant lesion”.¹

GCTB accounts for approximately 5% of all primary bone tumours and approximately 20% of all benign bone tumours. It is also known for its locally aggressive behaviour and high recurrence rates of 15% to 50% after usual curettage only and 2.3% to 20% after curettage with adjuvant treatment (ie, further debridement with a high-speed burr, cryotherapy with liquid nitrogen, chemical debridement with phenol, or bone cementing). When treating GCTB non-surgically with agents such as denosumab, a major concern is that it can be difficult to histologically distinguish between GCTB and giant-cell rich osteosarcoma at initial presentation based on biopsy specimens. Therefore, incomplete surgical excision can be extremely problematic in some cases. Therefore, new developments in therapy for aggressive GCTB have been sought.²

GCTB is characterised by osteoclast-like giant cells and their precursors that express receptor activator of nuclear factor- κ B (RANK), and mononuclear stromal cells that express RANK ligand (RANKL), a key mediator of osteoclast activation. Mononuclear stromal cells are

therefore responsible for the aggressive osteolytic nature of GCTB. Denosumab is a monoclonal antibody that inhibits RANKL, thereby preventing RANK-RANKL interactions and GCTB-induced bone destruction³ (Figure 1⁴). On 13 June 2013, the Food and Drug Administration of the United States approved denosumab (Xgeva injection, for subcutaneous use, Amgen Inc.) for the treatment of adults and skeletally mature adolescents with GCTB that is unresectable or where surgical resection is likely to result in severe morbidity. Non-surgical treatment also allows better functional capability. Denosumab's approval was based on demonstration of durable objective responses observed in two multicentre open-label trials enrolling adult and skeletally mature adolescents with histologically confirmed, measurable GCTB.⁵

The present study aimed to perform radiological evaluation of the efficacy of denosumab as a treatment for GCTB with histopathological correlation. There have been no similar studies performed in Hong Kong, and few such studies have been published internationally.

METHODS

The present study was a single-centre, retrospective study. Denosumab treatment for GCTB has been offered in our hospital since 2012. All consenting patients with histological confirmation of GCTB were treated with denosumab, after excluding pregnant patients and those with hypocalcaemia. The range of follow-up from diagnosis was 4 to 30 months. The denosumab treatment followed the protocol employed by two multicentre open-label trials. Patients received 120 mg neoadjuvant denosumab subcutaneously every 4 weeks with additional loading doses on day 8 and day 15 of the first

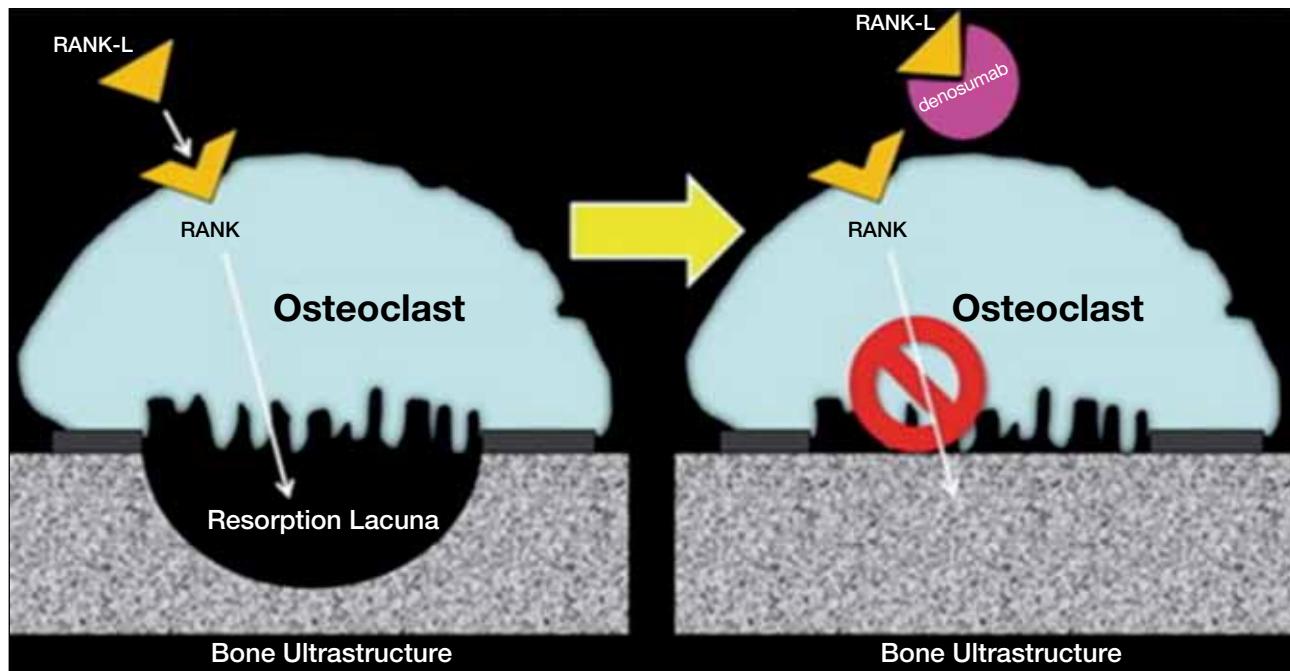


Figure 1. Illustrative diagram explaining how denosumab works as a monoclonal antibody that inhibits RANK-L against giant-cell tumour of bone, thereby decreasing bone resorption. Reprint with permission: The Radiological Society of North America
Abbreviation: RANK-L = receptor activator of nuclear factor- κ B ligand.

month, then one to four adjuvant doses.^{6,7} Regular renal function tests were performed for monitoring of blood calcium and phosphate levels. Calcium and vitamin D supplements were also prescribed.

The major adverse drug effects of denosumab include hypocalcaemia, serious infections, suppression of bone turnover including osteonecrosis of the jaw, and atypical femoral fractures. Any treatment-related and dermatologic adverse events were recorded if present.

Serial computed tomography (CT) and magnetic resonance imaging (MRI) assessments were made for the available radiographs for pre- and post-treatment changes. These radiological assessments were made at irregular intervals, subject to clinical judgement by orthopaedic surgeons.

Radiographs and CT results were used to assess changes in tumour size (maximal length, width, and depth) and presence of osteosclerosis by visual inspection. MRI results were used to assess changes in actual tumour size (maximal length, width and depth), presence of an extraosseous soft tissue component, and enhancing tumour area by visual assessment. All factors assessed were categorised as 'decrease', 'no change', or 'increase'.

A retrospective determination of radiological response was performed by radiologists who had received accredited training in musculoskeletal imaging and had 1 to 7 years of experience.

Concomitant histopathological comparisons of the pre- and post-treatment specimens were performed to evaluate the effects of denosumab treatment on overall tumour morphology. The specimens, obtained under fluoroscopic guidance with 14G Murphy coaxial needle and the bone biopsy set, were stained with haematoxylin and eosin and assessed by a consultant pathologist with more than 20 years of experience. Evaluation included the extent of the tumour section composed of mononuclear tumour stromal cells and giant cells and de novo bone matrix.

Tumour response was assessed based on the constellation of findings concluded by the pathologist. When tumour response was deemed adequate, curettage was performed.

RESULTS

A total of 12 patients received denosumab treatment for GCTB from 20 July 2012 to 5 June 2015. The mean age of the patients was 40 (median, 38; range, 21-66) years. After having received four neoadjuvant and one to

Table. Treatment response in terms of radiological, clinical, and histopathological entities. Assessment parameters suggestive of treatment response are listed and categorised as decrease, no change, or increase.

	Clinical (n = 12)	Radiographs (n = 11)	CT (n = 4)	MRI (n = 11)	Histopathological (n = 12)
Tumour size		No change: 11 (100%)	No change: 4 (100%)	No change: 9 (82%) Increase: 2 (18%)	
Osteosclerosis		Increase: 10 (90.9%)	Increase: 4 (100%)	Suboptimal for assessment	
Tumour enhancement				No change: 9 (82%) Increase: 2 (18%)	
Soft tissue component				No change: 9 (82%) Increase: 2 (18%)	
Multinucleated osteoclast-like giant cells					Decrease: 12 (100%)
New bone matrix					Increase: 12 (100%)
Pain/function	Improved: 11 (92%)				

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging.

four adjuvant doses of denosumab, 10 (83.3%) patients had no tumour recurrence by September 2016. The remaining two (16.7%) patients developed histologically proven tumour recurrence. Both patients with recurrent tumours received four neoadjuvant and four adjuvant denosumab doses. These two patients presented with clinical discomfort or pain over the affected area and subsequent MRI results demonstrated recurrence of soft tissue component which was not suspicious on radiographs. Histologically or radiographically, they showed no clear difference with other cases in terms of initial treatment response (Table).

Clinical Parameters

Although formal assessment of pain and quality of life was not mandated in this study, data collected from 11 (92%) patients reported at least reduced pain or subjective functional improvement. Through regular monitoring of renal function and prescription of calcium and vitamin D supplements, no episode of hypocalcaemia was detected. The denosumab treatment was also generally well tolerated, with no major or minor treatment-related adverse events reported.

Radiological Response

Serial radiographs at baseline and after denosumab treatment were available for 91.7% of patients; CT and MRI results were available for 33.3% and 91.7% of patients, respectively.

Serial radiographic assessments demonstrated treatment response with evidence of osteosclerosis for 10 out of 11 (90.9%) patients. None of the lesions showed definite interval change in size. The earliest case showing

osteosclerotic changes was 1 month after the first dose of denosumab. The extent of osteosclerosis showed interval progression in serial analysis. From the first dose of denosumab treatment to the surgery date (a few months), the mean number of radiographs taken was three (range, two to four). Typical examples are shown in Figures 2 and 3.

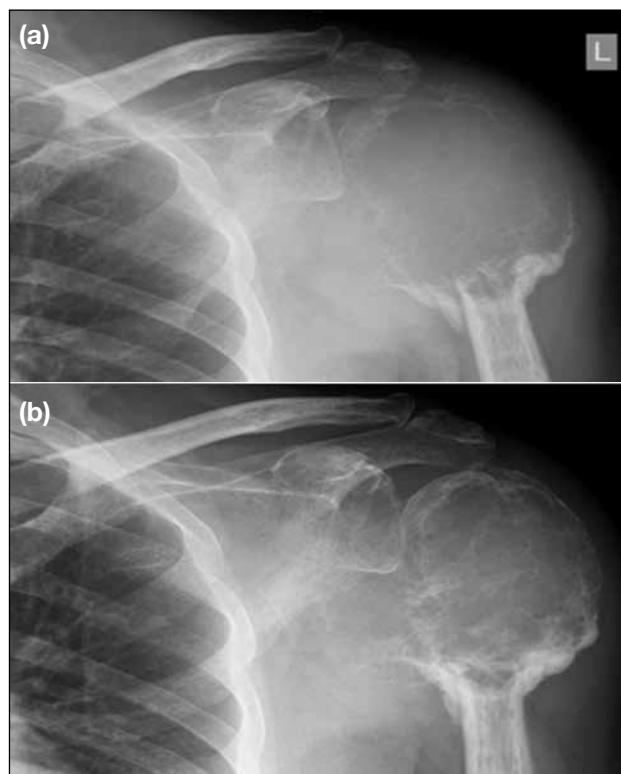


Figure 2. Frontal radiographs of the left humerus showing a giant-cell tumour of the humeral head with typical subarticular involvement. (a) Before and (b) after 3 months of denosumab treatment, markedly increased osteosclerosis in the previous lytic area is demonstrated. The size of the lesion remained unchanged.



Figure 3. (a) Lateral radiograph of the lumbosacral spine showing a lytic lesion in the posterior aspect of the L5 vertebral body with lower endplate destruction and involvement of the posterior elements. Subsequent biopsy revealed giant-cell tumour of bone. (b) Radiograph after 2.5 months of denosumab treatment, demonstrating increased osteosclerosis of the tumour with partial restoration of the lower endplate. Reduction of L5/S1 disc space is projectional.



Figure 4. Computed tomographic images of knee showing a giant-cell tumour of the distal femur with typical involvement of the subarticular region. (a) Before and (b) after 3 months of denosumab treatment, demonstrating markedly increased osteosclerosis and new bone trabeculae formation, especially in the subarticular lytic area of the lesion. The size of the lesion remained unchanged.

Serial CT assessments demonstrated changes similar to those shown on radiographs, with evidence of bone repair with increased osteosclerosis in four out of four (100%) patients. An example is shown in Figure 4. Again, none of the lesions showed definite interval change in size.

Serial MRI assessments demonstrated no definite interval change in terms of overall size of tumour, enhancement characteristics, and extent of soft tissue component in nine out of 11 (82%) patients before and after treatment. An example is shown in Figure 5. Osteosclerosis was

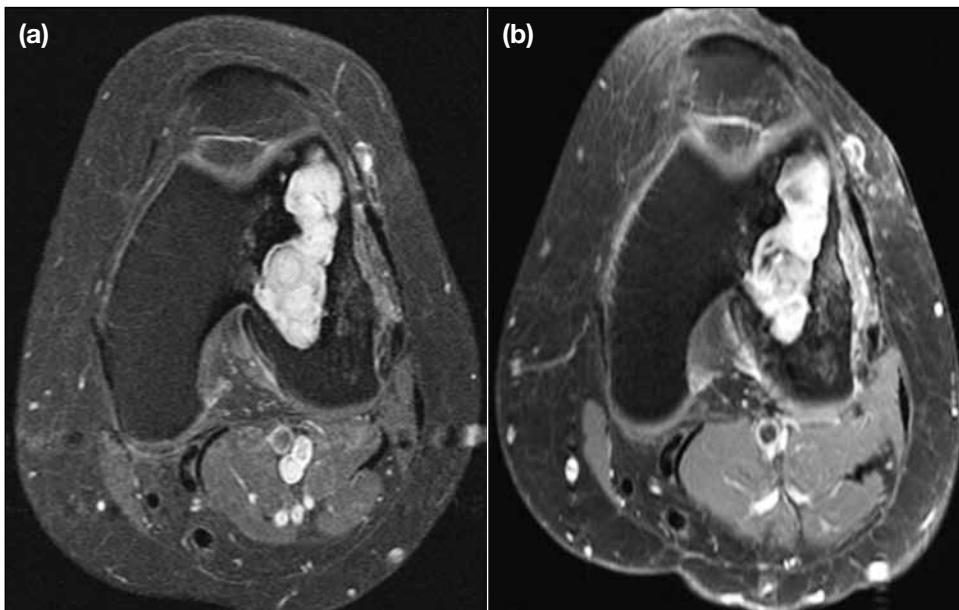


Figure 5. Axial T1-weighted fat-suppressed post-contrast magnetic resonance image of the knee showing a giant-cell tumour involving the lateral femoral condyle with lobulated contrast enhancement. (a) Before and (b) after 4 months of denosumab treatment, showing no interval change in size or appearance.



Figure 6. (a) Follow-up radiograph of the knee 6 months after curettage procedure with bone cementation and internal nail fixation for giant-cell tumour of the proximal tibia. Bony cortex was smooth with no definite radiolucent lesion identified. (b) Subsequent follow-up magnetic resonance image revealing a clear rim of enhancing soft tissue around the bone cement. Biopsy confirmed tumour recurrence.

not assessed by MRI, as the changes in our patients were subtle and do not correspond well to the extent of osteosclerosis that we see on radiographs or CT.

Tumour Recurrence

Two out of 11 (18%) patients developed soft tissue tumour recurrence 6 and 9 months postoperatively. Both patients reported vague discomfort and underwent MRI. The tumours were poorly visible on follow-up

radiographs but were clearly seen on MRI (Figure 6). Both of these patients had a positive initial tumour response radiologically (in terms of osteosclerosis) and histologically (disappearance of giant cells). They both underwent lesion curettage, as did the remaining nine patients.

Histopathological Response

The pretreatment biopsied samples and post-treatment

resected specimens were available for all patients for histopathological comparison. All patients assessed by histology had an excellent tumour response with marked reduction or complete disappearance of multinucleated osteoclast-like giant cells together with evidence of de novo bone matrix or new bone formation. A typical example is shown in Figure 7.

DISCUSSION

Because RANKL is a key mediator of osteoclast activation, the RANK-RANKL interaction in GCTB is thought to participate in the growth of the tumour cells, possibly as a result of the production of growth factors by osteoclast-like giant cells through a paracrine loop.⁸ The inactivation of osteoclasts by denosumab, a human monoclonal antibody that specifically inhibits RANKL, disturbs the bone destruction in patients with osteoporosis⁹ and in malignant bone tumours, such as metastatic bone tumours¹⁰ and multiple myelomas.¹¹ Considering its mechanism of action, clinical efficacy of denosumab for GCTB had been expected.

In this single-centre retrospective review of denosumab treatment for GCTB, radiological and histopathological assessments yielded initial promising results with high rates of positive tumour response without major adverse drug reactions. Only two cases of tumour recurrence were detected, in which the underlying cause or mechanism of drug resistance was not determined. Our comparative observational analysis demonstrates that the marked osteosclerosis shown by radiographs and CT images reflects the devitalisation of giant cells and reactive bone formation. The radiographs have excellent sensitivity in assessing tumour response to denosumab treatment, which can explain the low number of CT examinations. Conversely, the findings obtained by contrast-enhanced MRI in pre- and post-treatment phases were similar, presenting similar enhancement patterns, extraosseous soft tissue components and tumour sizes. Contrast-enhanced MRI, owing to its poor ability to delineate bony structures, is typically less useful than radiographs or CT in evaluating the osteosclerotic response of denosumab treatment for GCTB. A previous single case report on such a comparative approach also arrived at a similar conclusion.² In the present study, both cases of tumour recurrence were detected by MRI owing to the increased extraosseous soft tissue component, suggesting a pivotal role for MRI in tumour assessment after denosumab treatment and operation. Histological assessment of the lesion, despite the potential difficulty in excluding giant-cell rich osteosarcoma, remains the gold standard for assessing tumour response and for confirmatory diagnosis of the lesion before commencement of treatment.

To date, there have been few studies on concomitant evaluation of radiological and histopathological response to denosumab, and none of these studies were in Hong Kong. This concomitant assessment clarifies the strengths and weaknesses of each imaging modality in assessing tumour response. Two cases of tumour recurrence occurred despite initial good tumour response, emphasising the importance of continued tumour surveillance.

Limitation

This study has several limitations. First, denosumab has only recently come into clinical use for treatment of GCTB. As such, the study population is limited. Second, this was a single-arm study with no control group for comparison; it is difficult to determine whether the apparent improvement in tumour characteristics was due to natural disease progression or due to genuine

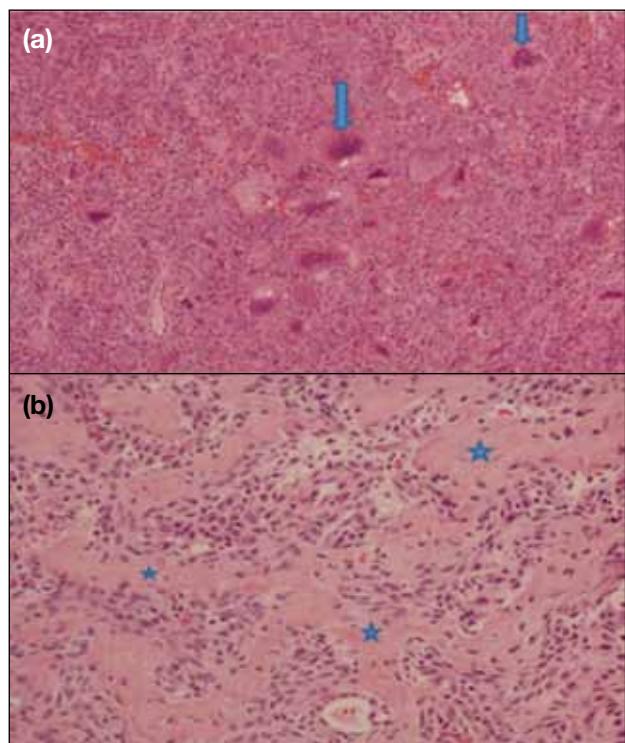


Figure 7. (a) Typical histology of giant-cell tumour of bone before treatment. Note the numerous osteoclast-like giant cells (arrows) [haematoxylin and eosin, $\times 20$]. (b) Histological features after denosumab treatment. Note the complete absence of giant cells and the oesinophilic osteoid-like matrix (asterisks), which may be mistaken as osteosarcoma (haematoxylin and eosin, $\times 40$).

improvement with denosumab. This would be solved if there were a control group receiving placebo treatment but this would be technically difficult due to the limited available study population. A double-blind randomised controlled trial with a larger patient cohort should be considered for future study. Third, core biopsies used for assessment of treatment response may not always provide representative specimens. However, this study establishes the therapeutic potential of denosumab to inhibit progressive bone destruction in patients with GCTB and also provides key insights into its biology.

Future Direction

Questions remain concerning the use of denosumab drug for treating GCTB. Denosumab is useful in the neoadjuvant setting, but the optimal duration and dose of neoadjuvant and adjuvant treatment remains to be refined via robust clinical trials. Moreover, the long-term effects of denosumab therapy on patients with normal bone density are unknown. Although patients with osteoporosis have been treated for many years, this situation is different from patients with bony metastases and GCTB, who generally have normal bone densities. Just as with any other clinical treatment option, the importance of clinical vigilance must be emphasised.

CONCLUSION

Denosumab is an efficacious treatment for GCTB in terms of clinical, radiological, and histopathological response with no recognisable complications, and this is confirmed by the present study conducted in Hong Kong. Radiographs and CT were helpful for evaluating

the efficacy of denosumab treatment, whereas MRI was more useful for postoperative tumour surveillance.

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