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The dilemma of denosumab: Salvage of a femoral head giant cell tumour

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ABSTRACT

INTRODUCTION: Denosumab is a monoclonal RANKL antibody which has been shown to be highly effective in treating giant cell tumour (GCT) of bone. We report on its use as a neo-adjuvant agent to avoid morbid surgery for an adolescent.
PRESENTATION OF CASE: We report a case of a15-year old female with a Campanacci 3 GCT involving the femoral head and neck.
DISCUSSION: To preserve bone stock and avoid an outright hip replacement, the patient was given denosumab pre-operatively to consolidate the tumour. After receiving 6 months of treatment, a rim of cortical bone had developed to allow an extended curettage of the tumour to be performed without fear of collapse of the articular surface.
CONCLUSION: This is the first reported case of the use of denosumab in GCT of the femoral head and neck. We describe our experience in the neo-adjuvant use of denosumab and offer suggestions for future use. Further studies will be needed to see if denosumab has a role in conventional GCT and whether it can lead to a lowering of local recurrence rates.

1. Introduction

Receptor activator of nuclear factor kappa-B ligand (RANKL) drives osteoclast formation, function and survival and an excess of RANKL causes an increase in bone destruction. In giant cell tumour of bone (GCT) RANKL is secreted by neoplastic ovoid cells as well as monocytoid cells and drives the formation of RANK positive non-neoplastic osteoclast like cells, which mediate bone destruction in GCT.[1,2]

Denosumab is a human monoclonal RANKL antibody currently licenced in the UK for the treatment of resistant osteoporosis and metastatic bone disease.[3,4] By disruption of RANK–RANKL interaction denosumab inhibits osteoclast mediated bone destruction in this osteolytic bone tumour. It has also been shown to be highly effective in giant cell tumours (GCT), with a 96% response rate recently reported in a Phase 2 clinical trial when used in patients with either inoperable GCT or where surgery would be associated with major morbidity.[5,6] In the reported trial, 90% of patients who were planned to have major surgery and who received denosumab either avoided surgery or had less morbid surgery. As a result of this trial denosumab was approved for use in the USA for unresectable GCT or where surgical resection was likely to result in severe morbidity by the FDA in June 2013.[7]

Denosumab is given monthly by subcutaneous injections of 120 mg and the principal side effects include osteonecrosis of the jaw and hypocalcamia.[6] It is contraindicated in anyone with pre-existing dental sepsis or hypocalcaemia and in children who are still growing. Any female of child bearing age must use appropriate contraception as denosumab crosses the placental membrane and has been associated with increase stillbirth and decreased growth/development in infants in animal studies.[8] There is evidence that if denosumab is stopped without the lesion being surgically removed, that recurrence is probably inevitable (personal communication). This may mean that in inoperable tumours denosumab will need to be continued indefinitely.

We report on the use of densoumab in a 15 year old female to demonstrate how less morbid surgery can be performed using this as a neoadjuvant agent. The report was prepared in accordance with ethical standards and written informed consent was obtained.

2. Presentation of case

A 15 years old female presented with progressive left groin pain and difficulty in walking. Plain radiographs showed a lytic lesion involving the left femoral head and neck (Fig. 1). MRI scans demonstrate the involvement of >50% of the head and neck of the femur with a cortical breach. CT-guided biopsy showed the typical appearance of a giant cell tumour of bone rich in osteoclast-like giant cells scattered within densely packed plump to slightly spindled mononuclear cells (Fig. 4A). The CT also demonstrated the almost

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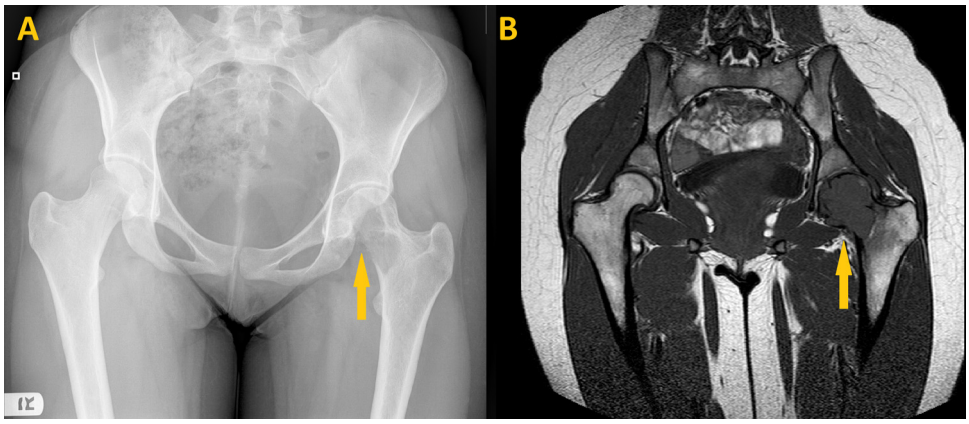

Fig. 1. (A) Plain AP radiograph of the pelvis showing a giant cell tumour of bone within the left femoral head and neck (arrow). (B) T1-weighted MRI scan demonstrating the extent of the tumour within the femoral head and neck and corresponding cortical breach (arrow).

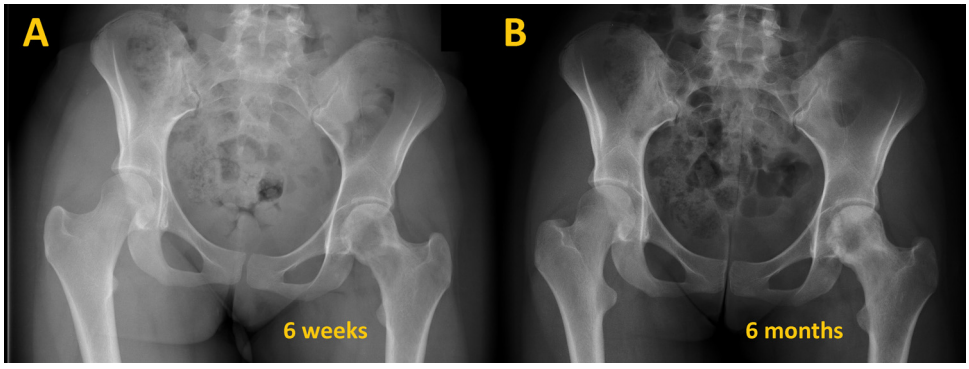

Fig. 2. Serial radiographs showing response to treatment with denosumab. (A) Radiographs after 6 weeks of starting denosumab illustrating reformation of the cortical rim of bone around the head and neck of the left femur. (B) Further ossification of the femoral head and neck after 6 months of treatment.

complete absence of any bone supporting the articular surface. An extended curettage, even with grafting, would lead to almost certain collapse of the femoral head given the extent of the tumour and leave no other option for reconstruction other than a hip replacement. To avoid an outright joint replacement in a teenager, we opted to give denosumab, to see if this would consolidate the tumour and the surrounding bone.

After obtaining informed written consent, denosumab was approved for use in this case by the host institution and was given 120 mg subcutaneously monthly for 6 months with additional doses at day 8 and 15 of the first month as previously described.[6] Calcium and vitamin D supplementation was provided with regular monitoring for signs of hypocalcemia and osteonecrosis. Within six weeks her hip symptoms resolved and the patient was pain free. Serial radiographs and CT showed the development of a good rim of cortical bone with clinical improvement in pain and ability to walk (Fig. 2).

After six months of denosumab, the patient underwent an extended curettage of her femoral head. Through a lateral approach to the hip, a cortical window was made over the lateral cortex to allow access to the femoral head and neck as previously described.[9] The curettage was performed with various angled curettes and a high-speed burr under image intensifier control to map out the extent of the tumour and ensure a complete curettage (Fig. 3). An ipsilateral fibular graft was harvested and placed as a strut supporting the articular surface and the remainer of the cavity packed with femoral head autograft.

Curettings taken following denosumab treatment showed striking morphological changes to classical GCT appearances as described previously.[10] The majority of the tumour area was occupied by long spindle cells with bland nuclei within a densely collagenised matrix (Fig. 4C). There were cellular nodules of residual mononuclear cells also with smaller nuclei with condensed chromatin (Fig. 4B). Residual osteoclast-like giant cells were not found. Newly formed woven bone was also seen (Fig. 4D).

3. Discussion

Giant cell tumours of the femoral head and neck are rare lesions that often present a surgical dilemma to the treating orthopaedic oncologist. Although intralesional curettage is the standard treatment for Campanacci 1 and 2 tumours of femoral head and neck,[11–13] this treatment strategy is often not possible in Campanacci 3 tumours. Due to limited bone stock and high rates of local recurrence, primary excision and reconstruction with a hip arthoplasty or endoprosthetic replacement has been advocated. Khan et al. reported on 12 patients with Campanacci 3 GCT of the proximal femur which were adequately treated with endoprosthetic replacements without local recurrences.[14] Tibrewal reported on four cases treated primarily with curettage, all developing local recurrence, and suggested the possibility of hip arthroplasty as primary treatment.[15] Given the patient's young age, avoidance of a joint replacement is of utmost importance, especially in the setting of a benign neoplasm.

The decision to use denosumab was based on the senior author's experience of contributing patients to the Phase 2 trial and the observation that denosumab produces a rim of firm bone around a residual central cavity at the site of the tumour. Maximal radiological response is usually seen within 26 weeks. In some cases there is complete consolidation of the previous GCT