ORIGINAL ARTICLE

Calcitonin use in giant cell bone tumors

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Accepted: 21 March 2011

Summary

Introduction: As osteoclast, giant cell tumors express calcitonin receptors. The aim of this paper is to assess treatment using salmon calcitonin after curettage.

Material and methods: We retrospectively reviewed 25 patients with giant cell tumor of the appendicular skeleton treated with a single protocol of calcitonin administration following curettage in order to assess the effectiveness of calcitonin in reducing the rate of local recurrence.

Results: The mean duration follow-up was 68 months. Thirteen patients (52%) had local recurrence. Eight of them were treated successfully after repeated curettage and calcitonin. Four patients had bone resection and one patient had curettage and cement filling. All patients with cavity left empty had ossified and the functional score as assessed by the MSTS score was 28.02/30.

Conclusion: This study suggests that the use of calcitonin as adjuvant is not effective and that filling agents are not required after curettage of giant cell tumors.

Level of evidence: Level 4.
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Introduction

Giant cell tumors (GCTs) represent approximately 15–20% of nonmalignant bone lesions and are described as stage 2 or 3 lesions, benign but locally aggressive, with a typical recurrence rate after curettage alone approaching 50% [1–4]. Over the years, many different adjuvant therapies have been suggested, ranging from mechanical, chemical, to thermal, biologic, injection, and embolization treatments. The purpose of these modalities is the control of microscopic disease in the reactive zone after curettage has removed the gross tumor.

It has been demonstrated that giant cells express calcitonin receptors. Nicholson et al. [5] and Flanagan et al. [6], in an immunohistochemical study using osteoclast-specific monoclonal antibodies, were the first to demonstrate that giant cells in chronic giant cell granulomas (CGCGs) are osteoclasts. Therefore, giant cells are directly inhibited in their function by calcitonin, which causes an increasing influx of calcium into the bones and, thus, functions antagonistically to parathormone.

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1877-0568/$ - see front matter © 2011 Published by Elsevier Masson SAS.
doi:10.1016/j.otsr.2011.03.019

The aim of this paper is to report the results of the treatment of GCT of bone with a single protocol of salmon calcitonin after curettage.

Material and method

We retrospectively reviewed the charts of 25 patients with a GCT of the appendicular skeleton treated at our institution between 1990 and 2007 by a single protocol of curettage and calcitonin. Clinical, radiological and histological data were reviewed and the outcome was assessed with a minimum follow up of 3 years.

The GCTs were graded radiologically according to the system described by Campanacci et al. [7]. The percentage of the epiphysis occupied by the tumor was calculated basing on plane radiographs and CT scan. Histological diagnosis was confirmed by biopsy before any therapeutic procedure. All the cases were benign GCTs. The therapeutic protocol is composed of four successive steps which were applied for all patients:

- First step is curettage: a cortical fenestration was made with an osteotome. The tumor was removed with curettes of different sizes. Then the cavity was irrigated with sterile saline, injected with 100 to 200 IU of calcitonin and was not filled in.
- Second step: postoperatively, patients received intra muscular injection of 100 IU of calcitonin each day for 15 days.
- Third step: after healing of the operative scar, we performed intralesional injection of 100 IU of calcitonin each day for one month.
- Fourth step: for 2 months, patients received intra muscular injection of 100 IU of calcitonin each day.

Patients with a lesion on the lower limb used no weight for not more than 3 months after the operation. Patients were followed once a month until the reossification of the cavity was confirmed, then each 3 months the first year then twice a year for 5 years. At each check up, clinical examination, plain radiograph of the involved bone and the chest were obtained. MRI or CT examinations were made at 6- or 12-month intervals to evaluate bone formation and detect local recurrence for 2 years. No CT scan of the lung was performed.

Local recurrence was suspected radiologically then confirmed histologically. The mean follow up was 67.8 ± 30.57 months (median: 60, range 36 to 180). The Musculo Skeletal Tumor Society score developed by Enneking et al. [8] was used to assess the functional score.

Statistical Analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software version 17.0 (SPSS Inc., Chicago, USA). Yates’ corrected x2-test and Kaplan-Meier survival analysis by log-rank test were performed. A p value < 0.05 was considered significant.

Results

There were five males and 20 females (sex ratio: 1/4). The mean age was 31.8 ± 12.7 years (range 13 to 73). The most common site was about the knee with 40% occurring in the proximal tibia and 28% in the distal femur (Table 1). The Campanacci grades were I in 4 cases, II in 18 cases and III in 3 cases. Seven patients had pathological fracture at presentation (case 1). Three of them were managed nonoperatively and 4 were stabilised by external fixation.

On plan radiographs the lesions began to show bone formation at 1 month after curettage (case 2). On CT scan, we observed that the cavity tended to heal by thickening of the cortex and then by development of septae running across the defect that gradually became radiopaque, although complete bone filling of all cavities was not achieved (case 3). In one case, we performed a biopsy at the radiolucent areas (Fig. 1C). Histological examination revealed a fibrous tissue. The cortical defect performed for exposure was visible for a long time but with no mechanical consequences (Fig. 2D). At the last follow up, all the patients with a cavity left empty (20 patients) healed. The average time to bone healing, as judged by allowing weight bearing, was 10 weeks (range 6 to 12). Although there was a trend for larger cysts (over 50% of the epiphysis) to take slightly longer to heal, this was not statistically significant. Five patients had degenerative changes on articular cartilage (Fig. 3C).

The overall rate of local recurrence was 52% (13 patients). Local recurrences occurred by a mean time of 10.7 ± 15.9 months (median 5 months). Sixty one percent of

Table 1 Descriptive characteristics.

<table>
<thead>
<tr>
<th>Age</th>
<th>31.8 ± 12.7 (13–70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M/F: 5/20</td>
</tr>
<tr>
<td>Location: nb (%)</td>
<td>PT: 10 (40) DF: 7 (28) DR: 3 (12) PH: 2 (8) PU: 1 (4) PF: 1 (4) DT: 1 (4)</td>
</tr>
<tr>
<td>Campanacci grade</td>
<td>G1: 4 (16%) GII: 18 (72%) GIII: 3 (12%)</td>
</tr>
<tr>
<td>Tumor size</td>
<td>&lt; 50%: 7 (28%) &gt; 50%: 15 (60%) &gt; 100%: 3 (12%)</td>
</tr>
<tr>
<td>Pathological fracture</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Time to recurrence (month)</td>
<td>40.5 ± 41.6 (range: 2–180)</td>
</tr>
<tr>
<td>M: male; F: female; PT: proximal tibia; DF: distal femur; DR: distal radius; PH: proximal humerus; PU: proximal ulna; PF: proximal femur; DT: distal tibia.</td>
<td></td>
</tr>
</tbody>
</table>
Calcitonin use in giant cell bone tumors

Figure 1  Case 1. A: A 28-year-old woman with grade II GCT of the distal femur revealed by a pathological fracture. The lesion was treated with curettage and Calcitonin. The fracture was managed nonoperatively by a plaster. B: At 6 months, we note an excellent reossification of the lesion. C: CT scan of the knee showing the reossification of the lesion. The nonreossified areas are filled with a fibrous tissue but not a residual tumor which was confirmed in this case by a biopsy.

them occurred within the first 6 months. The longest local recurrence occurred after 5 years (Fig. 4).

The local recurrence rate varied significantly with Campanacci grade, being 25% in grade I, 50% in grade II and 100% in grade III ($p=0.005$). Neither the size of the tumor nor pathologic fracture did correlate with local recurrence.

The first local recurrence was treated by the same protocol in 11 patients. One patient had wide resection of the fibula head and one patient was treated by curettage and cement filling for a tumor of the proximal tibia.

The success rate of the second protocol was 7 to 11 (63.6%). The patients with additional local recurrences were treated by wide resection and arthrodesis in three cases and one patient healed after repeated curettage and calcitonin.

Therefore, 20 patients (80%) were treated successfully by our protocol: twelve after one course of treatment, 7 after 2 courses and one after four courses.

None of the patients developed a postoperative infection and none of them was reoperated for a mechanical failure unless a local recurrence occurred.

The Enneking functional score was documented in these 20 patients with a mean score of 28.02/30 (93.4%).

Discussion

The therapeutic concept for administration of calcitonin in the treatment of GCT is based on an immunohistochemical study that demonstrated that giant cells in GCT are osteoclasts [6]. This was suspected from the in vitro reaction of giant cells to calcitonin and the behaviour of giant cells in cortical bone causing bone excavation similarly to osteoclasts [6,9]. Later on, it was demonstrated that giant cells are directly inhibited in their function by calcitonin [10].

In 1993, Harris [11] was the first to report the use of human calcitonin as a therapy for central giant cell granuloma (CGCG) of the mandible. The successful use of human calcitonin in the treatment of CGCG of the jaw has also been demonstrated by others [12–14]. At present, only salmon calcitonin is commercially available. Theoretically, the effect of salmon calcitonin is stronger than the effect of human synthetic calcitonin: 50 IU of salmon calcitonin appears to be equipotent with 75 to 90 IU of HC [15]. An in vitro study showed that there is no difference in the effect of human or salmon calcitonin on the inhibition of osteoclastic bone resorption [16].

The effectiveness of calcitonin on GCT remains unclear. Only one double-blind placebo-controlled clinical trial to evaluate the effect of salmon calcitonin was published [17]. The results of this study showed a variable response of the patients to the calcitonin therapy. During the 3-month placebo-controlled period and at the end of treatment/follow up, no significant differences in tumor size reduction were observed between the groups. Overall, considerable reductions in tumor size were seen in half of the patients at 6 months follow-up. However, complete remissions were not observed. Because of the limited number of patients enrolled in this study and the relatively small effect of calcitonin, the power of the study is restricted.

To our knowledge, this is the first report of the use of calcitonin as adjuvant after curettage of GCT of skeletal bones. Our rate of local recurrence of 52% is one of the highest reported in literature and concurred with that of old series using curettage alone without adjuvants [18,7,19,20]. In recent series, this rate ranges from 0 to 20% [21–26] (Table 2). Many authors advocate the role of adjuvants in reducing the rate of local recurrence. In 2008, a collective group studied local recurrence after intralesional treatment...
with and without adjuvants, covering several adjuvants, in both primary and recurrent lesions in 384 procedures [20].

The results showed a rate of recurrence of 50% without adjuvants, and a range of 15–27% with adjuvants. Another study of 214 patients concluded that adjuvant therapy (with burring, hydrogen peroxide and cementation) is recommended over curettage alone; 12% compared with 65% recurrence [27].

However, evidences provided concerning the real effect of these different adjuvants are debated, since the majority of large series involved heterogeneous groups of patients treated by different modalities over long periods of time. And there were never any prospective randomized studies published. Turcott et al. [23] reported a series of 148 patients who had curettage and could not identify any significant statistical effect on local recurrence by any adjuvant therapy including phenol, nitrogen and cement. In a recent study, Errani et al. [21] reviewed the experience of the Rizzoli institute. Two hundred patients underwent curettage of the lesion and in 64 of these cases, three local adjuvants, such as phenol, alcohol and cement, were employed. The local recurrence was 12.5% in patients treated by intraluminal surgery and three local adjuvants. Conversely, it was higher in the second group of patients with an incidence of 18% of cases. However, the authors were unable to prove the putative value of single adjuvants.

With increasing understanding of the biology of GCT come novel and unique treatment options. The stromal cells in GCT produce RANK ligand, the factor that stimulates the activation of the osteoclast, causing bone resorption [28]. It is this mechanism, also seen in metastatic disease and osteoporosis, that is targeted by the bisphosphonates. In a recent retrospective case-control study by Tse et al. [29] patients with GCT were treated with curettage, burring and cementation, with one group receiving bisphosphonates. There were 20 control patients compared to the 24 trial patients who received both preoperative and postoperative intravenous bisphosphonates, with 3 months of oral treatment thereafter. There was a 4.2% recurrence rate compared with 30% in the control group. The antagonist to RANK ligand in osteoclast activation is osteoprotegrin (OPG), and the selective estrogen receptor modulator reloxifene has been shown

Figure 2  Case 2. A: A 32-year-old woman with a GCT of the proximal tibia. B: plan radiographs one month after curettage and calcitonine protocol. C: after 2 months, we note a progressive reossification of the lesion. D: The lesion healed after 3 months. The radiolucency seen on the lateral view corresponds to the cortical window resected for exposure. E: at 2 years, we note a good reossification of the lesion without local recurrence neither cartilaginous change.

Figure 3  Case 3. A: A 47-year-old woman with grade II GCT of the proximal tibia, treated with curettage and Calcitonin. B: there was a local recurrence and progression of the lesion to grade III at 3 months, treated with a second course. C: At 7 years, there was no local recurrence, remodelling of the cavity was excellent and the patient developed osteoarthritis. D: CT scan of the recurrence showing the destruction of the epiphysis and the extra osseous extension of the tumor. E: at the end of the second course, thickening of the cortex. F: at the last follow-up, excellent bone formation.

Table 2  Reported rates of recurrence after primary curettage.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Number</th>
<th>Additional treatments</th>
<th>Recurrence (%)</th>
</tr>
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<tbody>
<tr>
<td>Campanacci [19]</td>
<td>1987</td>
<td>106</td>
<td>None</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phenol</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nitrogen</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cement</td>
<td>0</td>
</tr>
<tr>
<td>Capanna et al. [20]</td>
<td>1990</td>
<td>280</td>
<td>None</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cement</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phenol</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nitrogen</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cement + phenol</td>
<td>3</td>
</tr>
<tr>
<td>Masui et al. [18]</td>
<td>1998</td>
<td>17</td>
<td>None</td>
<td>47</td>
</tr>
<tr>
<td>Blackley et al. [27]</td>
<td>1999</td>
<td>59</td>
<td>Bone graft</td>
<td>12</td>
</tr>
<tr>
<td>Gherli et al. [26]</td>
<td>2002</td>
<td>47</td>
<td>Cement + phenol or electrocautery</td>
<td>13</td>
</tr>
<tr>
<td>Ward and Li [25]</td>
<td>2002</td>
<td>24</td>
<td>H2O2, phenol, electrocautery, cement</td>
<td>8</td>
</tr>
<tr>
<td>Turcotte et al. [24]</td>
<td>2002</td>
<td>120</td>
<td>None, cement, phenol, liquid nitrogen</td>
<td>12</td>
</tr>
<tr>
<td>Prosser et al. [23]</td>
<td>2005</td>
<td>137</td>
<td>None</td>
<td>19</td>
</tr>
<tr>
<td>Errani et al. [22]</td>
<td>2010</td>
<td>200</td>
<td>Phenol, alcohol, cement, bone graft</td>
<td>12</td>
</tr>
<tr>
<td>Present series</td>
<td>2010</td>
<td>25</td>
<td>Calcitonin</td>
<td>52</td>
</tr>
</tbody>
</table>

wider exposure necessary for phenolization. Trieb et al. [32] reported no benefit of using phenol and advocated thorough removal of the tumor. More recently in 2010, Al Gawahamed et al. [33] reviewed systematically the literature and have retained six studies evaluating adult patients diagnosed with primary or recurrent GCT of bone treated with curettage and high speed burr with or without a local adjuvant. Adjuvant modalities were phenol, bone cement and liquid nitrogen. They demonstrated that adjuvants are not necessary to reduce recurrence rates and concluded that meticulous surgical technique including high speed burring is the most important step in reducing recurrence rates in GCT of bones.

The reasons for filling the defect after curettage of a GCT are to increase final bone strength and to reduce the risk of local recurrence. Like others [22,34,35], we think that this is not necessary since spontaneous reossification of the cavity is possible. Some experimental data showed that bone defects that are left empty, heal just as well as when filled with a bone substitution [36,37]. Clinical studies including ours demonstrated the natural ability of the cavity to fill after curettage as the sole treatment in benign bony lesions [22,34,35]. Moreover keeping the cavity empty avoids disadvantages of filling material such as mechanical problems, cost, infection and availability. Hirn et al. [34] think that apart from bone cement, most substances that are used to fill defects have no inherent strength and rely upon bone in growth for strength. Thus these patients will be as much at the same risk of fracture or collapse of the joint surface as those without any filling until the bone has consolidated.

Conclusion

The current study is a retrospective review of patients from one institution. Although it is limited by the single protocol with no attempt to randomize cases, the effect of calcitonin on preventing local recurrence seems to be very limited. Therefore, we suggest that filling agents are not required after curettage of GCT.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


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