Local Administration of Zoledronic Acid for Giant Cell Tumor of Bone

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abstract

Giant cell tumor of bone is a locally aggressive tumor with a high local recurrence rate. Several adjuvant therapies have been employed to reduce the recurrence rate, but their effectiveness remains controversial. The authors attempted local administration of zoledronic acid, a nitrogen-containing bisphosphonate that strongly inhibits bone resorption, as an adjuvant treatment for histologically proven giant cell tumor of bone in 5 patients at their institution. After biopsy, 4 patients were treated with local administration of zoledronic acid with artificial bone and 1 was treated with zoledronic acid without artificial bone. Histologic response to the treatment was evaluated with surgically resected specimens. The 4 patients treated with artificial bone showed local control, with histologic tumor necrosis rates of 90%, 90%, 50%, and 10%. Magnetic resonance imaging showed poor gadolinium enhancement, and histologic examination after local zoledronic acid treatment showed tumor necrosis. One patient without artificial bone showed no histologic tumor necrosis and had local recurrence in soft tissue 18 months after tumor resection. A 3-week waiting period between biopsy and zoledronic acid treatment appears reasonable from the histological study. Complication of this therapy was delayed wound healing and it occurred in 2 cases. Taken together, this case series suggests that local administration of zoledronic acid with artificial bone is a potential adjuvant therapy for giant cell tumor of bone. On the other hand, effective local administration of zoledronic acid requires some bone matrix, including artificial bone. Campanacci’s grading is important for predicting the effect of local administration of zoledronic acid. [Orthopedics. 2015; 38(1):e25-e30.]
Giant cell tumor of bone is a relatively rare benign but locally aggressive tumor. The standard treatment is curettage and bone grafting. However, intralesional curettage alone has a high local recurrence rate of 18% to 50%.

Although several adjuvant therapies, including phenol, liquid nitrogen, bone cement, high-speed burr debridement, and argon beam cauterization, have been used to reduce the recurrence rate, their effectiveness is controversial. In particular, complete resection of giant cell tumor of bone in the pelvis and spine is difficult. Thus, a new adjuvant therapy is required for giant cell tumor of bone.

Bisphosphonates have a characteristic chemical structure that leads to selective accumulation in bone. They are selectively taken up by osteoclasts and strongly inhibit bone resorption by inducing apoptosis. Furthermore, they have been widely and successfully used in the treatment of several disorders of increased bone resorption, including bone metastasis. Nitrogen-containing bisphosphonates, including zoledronic acid, have been reported to promote apoptosis of not only osteoclasts but also tumor cells by inhibiting the action of the enzyme farnesyl pyrophosphate synthase in the mevalonate pathway.

Some reports have shown that intravenous administration of bisphosphonates reduces local recurrence of giant cell tumor of bone. Although bisphosphonates are generally well tolerated and rarely induce severe side effects, intravenous use has been reported to carry risks of significant complications, including osteonecrosis of the jaw. Because bisphosphonates have low bioavailability because of their poor lipophilicity and negative charge, the authors previously reported the potential use of zoledronic acid for local treatment of giant cell tumor of bone to reduce the risk of side effects and increase the bioavailability of bisphosphonates.

The goal of this study was to evaluate the effectiveness of locally administered zoledronic acid for giant cell tumor of bone as well as to provide a brief review of the literature.

**MATERIALS AND METHODS**

Written informed consent was obtained from patients with giant cell tumor of bone, and the treatment protocol was approved by the ethics committee of Tokushima University. Five patients (4 men and 1 woman) treated with local administration of zoledronic acid for histologically proven giant cell tumor of bone at the authors’ institution from 2008 to 2013 were included in this study (Table). Mean age was 44 years (range, 22-66 years), and mean follow-up was 19 months (range, 3-38 months). Tumors were localized to the proximal tibia, distal fibula, proximal radius, and pelvis, respectively. According to the Campagnacci grading system, 2 tumors were classified as grade II and 3 were classified as grade III.

The authors’ strategy is shown in Figure 1. After intraoperative or definitive pathologic diagnosis was obtained by open biopsy, zoledronic acid was locally administered

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex/Age, y</th>
<th>Location</th>
<th>Grade</th>
<th>Follow-up, mo</th>
<th>Zoledronic Acid Dosing</th>
<th>Waiting Period, wk</th>
<th>Definitive Surgery</th>
<th>Local Necrosis Rate, %</th>
<th>Histologic Complication After Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/43</td>
<td>Fossa ilei</td>
<td>III</td>
<td>10</td>
<td>4.4</td>
<td>18</td>
<td>No</td>
<td>No</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>M/33</td>
<td>Distal radius</td>
<td>III</td>
<td>38</td>
<td>6</td>
<td>10</td>
<td>No</td>
<td>No</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>M/66</td>
<td>Proximal tibia</td>
<td>II</td>
<td>90</td>
<td>3</td>
<td>10</td>
<td>Delays healing</td>
<td>No</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>M/33</td>
<td>Proximal fibula</td>
<td>II</td>
<td>50</td>
<td>1</td>
<td>10</td>
<td>Curettage and bone grafting</td>
<td>No</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>M/56</td>
<td>Ischium</td>
<td>III</td>
<td>15</td>
<td>3</td>
<td>10</td>
<td>Curettage and bone grafting</td>
<td>No</td>
<td>90</td>
</tr>
</tbody>
</table>
to the lesion. Definitive surgery, such as curettage or en bloc resection, was performed after a waiting period to achieve the full drug effect. Histologic sections obtained by definitive surgery were evaluated to confirm the effect of local zoledronic acid treatment.

Open biopsy was performed in all patients. After intraoperative diagnosis, 4 patients were treated with local administration of zoledronic acid with artificial bone (hydroxyapatite, Neobone, MMT Co Ltd, Osaka, Japan, in cases 2, 3, and 4; and beta-tricalcium, Superpore, Pentax, Tokyo, Japan, in case 1) (Figure 2). The remaining patient (case 5) was treated with local administration of zoledronic acid without artificial bone after definitive histologic diagnosis because a malignant bone tumor was suspected based on radiologic findings (Figure 3).

Initially, the authors used zoledronic acid (4 mg) for local administration, according to the standard for intravenous zoledronic acid use.\(^{20,21}\) In case 5, an additional 4 mg zoledronic acid was administered because no effect of the initial 4 mg zoledronic acid was observed on preoperative needle biopsy. To minimize the risk of side effects, a lower dose of zoledronic acid was used for cases 3 and 4, based on clinical experience.

The waiting period from open biopsy to definitive surgery was 10 weeks, 3 weeks, 1 week, 3 weeks, and 6 weeks for cases 1 to 5, respectively. In case 1, the authors used a waiting period of 10 weeks to ensure effective treatment with zoledronic acid.\(^{19}\) Thereafter, the authors changed the standard waiting period to 3 weeks for intravenous zoledronic acid administration in patients with bone metastasis.\(^{20,21}\) In case 3, definitive surgery was performed before the end of the waiting period because of peroneal nerve palsy.

For definitive surgery, 3 patients (cases 1, 2, and 4) underwent curettage and debridement with a high-speed burr and bone grafting. Artificial bone was used in cases 1 and 2, and autograft bone was used in case 4. En bloc resection was performed for the other 2 patients (cases 3 and 5). In case 5, the patient had a huge pelvic tumor that was reconstructed with polymethylmethacrylate followed by en bloc resection of the ischium and extended curettage of the acetabular lesion with a high-speed burr after cementing.

Four patients underwent gadolinium-enhanced magnetic resonance imaging (MRI) during the waiting period. Only 1 patient (case 3), who had a fibular head tumor, did not undergo MRI because of peroneal nerve palsy that required emergent surgery. The necrosis rate for giant cell tumor of bone was evaluated based on histologic findings.
ologic specimens stained with hematoxylin and eosin.

**RESULTS**

Two types of artificial bone material, hydroxyapatite and beta-tricalcium phosphate, were used as the zoledronic acid carrier in 4 patients (cases 1-4). However, no apparent differences were noted between these 2 types of artificial bone with regard to the effectiveness of local zoledronic acid administration. Three patients (cases 1, 2, and 4) showed poor gadolinium enhancement on MRI after local administration of zoledronic acid. Cases 1 and 2, classified as Campanacci grade II, showed a 90% histologic tumor necrosis rate. Cases 3 and 4, classified as Campanacci grade III, showed a 50% and 10% histologic tumor necrosis rate, respectively. These 4 patients were disease-free during the follow-up period.

Case 5, classified as Campanacci grade III, was an exception in this case series (Figure 3). Because preoperative radiologic findings suggested malignancy, the patient underwent only tissue extraction by open biopsy and no local zoledronic acid administration. Between open biopsy and definitive surgery, the patient was administered zoledronic acid locally with a syringe at the outpatient clinic. An additional 4 mg zoledronic acid was administered because no tumor necrosis was apparent on preoperative needle biopsy after initial administration of 4 mg zoledronic acid. However, gadolinium-enhanced MRI before definitive surgery showed no significant changes. Despite administration of a double dose, no histologic tumor necrosis was observed. Further, a postoperative pubic fracture occurred 5 months after the definitive operation, resulting in nonunion. The patient had local recurrence in soft tissue that required recurrence 18 months later.

Delayed wound healing after biopsy occurred in 2 patients and was controlled with antibiotics and debridement (Figure 4). Because the peroneal palsy in case 3 occurred just before open biopsy, the authors believe that there was no connection between nerve palsy and zoledronic acid treatment. No other complications were observed during treatment.

**DISCUSSION**

The mechanisms of bone destruction in giant cell tumor of bone are similar to those of bone metastasis in carcinoma. Two different cell types are involved in giant cell tumor of bone, osteoclast-like giant cells and fibroblast-like stromal tumor cells. Osteoclast-like giant cells mainly destroy bone, and fibroblast-like stromal cells behave similarly to neoplastic cells and activate these giant cells through expressing receptor activator of nuclear factor kappa-B ligand. Several studies of the use of bisphosphonates to prevent local recurrence or for systemic treatment of giant cell tumor of bone have been reported. When local administration of bisphosphonates for giant cell tumor of bone is possible, bioavailability is greater than with intravenous administration. A case of giant cell tumor of bone that was treated successfully with local bisphosphonates is described.
administration of zoledronic acid was reported.19

In this case series, the rate of local control was 80%; only 1 patient did not achieve control. Artificial bone is considered necessary for zoledronic acid to be effective because it accumulates in the bone matrix to exhibit its effect. In an animal study by Kumar et al.26 pamidronate mixed with saline produced inconsistent bone uptake and therefore was not used. For the same reason, Campanacci grading is important to predict the effect of local zoledronic acid administration.2

In case 5, local recurrence occurred in soft tissue, and zoledronic acid is known to have a high affinity for mineralized bone. Its concentration declines rapidly in plasma and noncalcified tissue when administered intravenously.27 Locally administered zoledronic acid may accumulate strongly in the bone matrix and poorly in soft tissue. The characteristics of zoledronic acid may be a reason for soft tissue recurrence.

The optimal waiting period has not been elucidated. From the authors’ experience, the different waiting periods in case 1 (10 weeks) and case 2 (3 weeks) had no effect on the histologic necrosis rate. Furthermore, the histologic necrosis rate was 50% in case 3, with a waiting period of only 1 week. Therefore, a waiting period of as little as 2 weeks may be sufficient. In addition, intravenous zoledronic acid for bone metastasis is administered once every 3 to 4 weeks as standard therapy.20,21 Taken together, a 3-week waiting period between biopsy and zoledronic acid treatment appears reasonable.

In 2 cases, delayed wound healing occurred. Several studies reported that zoledronic acid inhibits angiogenesis,28-30 and Kobayashi et al11 showed that zoledronic acid delays wound healing of the tooth extraction socket, inhibits oral epithelial cell migration, and promotes proliferation. Therefore, a certain degree of technique is needed to prevent leakage of zoledronic acid into soft tissue. Because the direct effect of zoledronic acid on nerve tissue is unclear, local administration is likely unsuitable for lesions at sites such as the sacrum.

**References**


24. Kim Y, Nizami S, Goto H, Lee FY. Modern


