Effect of zoledronic acid on metastatic hormone-refractory prostate cancer resistant to taxane, estramustine, carboplatin, and dexamethasone

Nobuyuki Kikuno MD PhD, Department of Urology, Shimane University School of Medicine, Izumo, Japan

Abstract: This case report demonstrates the effect of zoledronic acid (ZA) on a patient with bone metastatic hormone-refractory prostate cancer (HRPC) resistant to taxane, estramustine phosphate, carboplatin, and dexamethasone. The pathogenesis, diagnosis, and management of bone metastasis on HRPC are also reviewed.

Key words: dexamethasone, hormone-refractory prostate cancer, taxane, zoledronic acid.

Introduction

Bisphosphonate has demonstrated efficacy for preventing skeletal complications and decreasing bone pain in patients with hormone-refractory prostate cancer (HRPC). We report a case of taxane and dexamethasone resistant metastatic HRPC in which the serum prostate-specific antigen (PSA) levels were dramatically decreased and the measurable disease displayed a partial response to the administration of 4 mg zoledronic acid (ZA) every 3 weeks.

Case report

A 66-year-old man presented complaining of lumbago. On examination, the serum PSA was increased to 110 ng/mL and transrectal ultrasonography revealed no zonal anatomy in the prostate. Poorly differentiated adenocarcinoma (Gleason’s score: 4+5=9) was confirmed from all cores with a systematic sextant prostatic needle biopsy. A bone scintigraphy showed multiple bone metastases.

Although the PSA decreased to 0.2 ng/mL 6 months after androgen deprivation therapy, the patient ultimately entered a state of HRPC 28 months after the treatment. A combined treatment of docetaxel (30 mg/m² per week), estramustine phosphate (10 mg/kg per day), and carboplatin (area under the curve [AUC] 6/month) (DEC) was initiated as a first line chemotherapy treatment. During this combined chemotherapy course, dexamethasone (8 mg/week) was also intravenously administered to suppress the inflammatory side-effects of taxane. The treatment was to be discontinued if at any time the patient displayed unacceptable toxicity or evidence of progressive disease. The PSA continued to decrease and reached 4.3 ng/mL (from 60.5 ng/mL) at 4 months, and the PSA levels did not increase significantly for 5 months thereafter. However, at 13 months the PSA levels increased again to 61.9 ng/mL and progressive bone metastasis was detected.

The PSA level continued to gradually increase after a second line chemotherapy treatment was commenced that consisted of paclitaxel (100 mg/m² per week) instead of docetaxel (PEC); therefore, from 16 months an intermediate-dose of dexamethasone (4 mg/day) was begun in combination with the incadronate (10 mg/every 2 weeks). The PSA continued to increase and the patient began to feel severe lumbar bone pain at 21 months. For that reason, a diagnosis of DEC/PEC- and dexamethasone-resistive HRPC was made.

Following institutional review board approval and written informed consent from the patient, ZA was started at 4 mg intravenously every 3 weeks from 22 months instead of incadronate. After 2 months of treatment, both the biochemical markers of bone formation (bone specific alkaline phosphatase and osteocalcin), as well as bone resorption, urinary deoxypyridinoline, serum pyridinoline cross-linked C-telopeptides of Type I collagen (1CTP), and urinary pyridinoline cross-linked N-telopeptides of Type I collagen (NTx) had a tendency toward decline compared with the pretreatment levels, although there were no alterations on these markers before and after treatment with incadronate (Table 1).

The patient’s lumbago symptoms dramatically improved, from grade 3 to grade 1. We estimated this level of change according to the National Cancer Institute’s Common Toxicity Criteria (Version 2.0). Furthermore, the dose of fentanyl, which was used as an analgesic, was reduced from 7.5 mg/3 days to 2.5 mg/3 days with a decline in the PSA levels from 571.5 ng/mL to 113.8 ng/mL (Fig. 1).

A bone scintigraphy showed slightly decreased accumulations on multiple ribs, vertebrae, and the left ischia bone. We should note, however, that it is generally difficult to estimate accurately the therapeutic effect on bone metastatic lesions using bone scintigraphy (Fig. 2). Furthermore, we radiographically confirmed a ≥50% reduction in bone pain at 21 months.

Table 1 Modifications of biochemical markers before and 2 months after zoledronic acid treatment

<table>
<thead>
<tr>
<th>Biochemical marker</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BALP (U/L)</td>
<td>708</td>
<td>544</td>
</tr>
<tr>
<td>Osteocalcin (ng/mL)</td>
<td>7.0</td>
<td>6.6</td>
</tr>
<tr>
<td>D-Pyd (mmol/mmol Cr)</td>
<td>10.4</td>
<td>5.3</td>
</tr>
<tr>
<td>1CTP (ng/mL)</td>
<td>17.6</td>
<td>16.9</td>
</tr>
<tr>
<td>NTx (pmol BCE/μmol Cr)</td>
<td>182.4</td>
<td>93.5</td>
</tr>
</tbody>
</table>

BALP, bone-specific alkaline phosphatase; BCE, bone collagen equivalents; Cr, creatinine; 1CTP, serum pyridinoline cross-linked C-telopeptides of Type I collagen; D-Pyd, urinary deoxypyridinoline; NTx, urinary pyridinoline cross-linked N-telopeptides of Type I collagen.

Correspondence: Nobuyuki Kikuno MD PhD, Department of Urology, Shimane University School of Medicine, 89-1 Enya-cho, Izumo 693-8501, Japan. Email: k481219@med.shimane-u.ac.jp

Received 11 November 2005; accepted 15 March 2006.
response rate in the two measurable diseases: para-aortic and right external iliac lymph node metastasis.

The therapeutic effects in the primary lesion were pathologically estimated using needle biopsy specimens and radiographically using computed tomography (CT) taken before and two cycles after ZA treatment commenced. Our estimations are based on the General Rule for Clinical and Pathological Studies on Prostate Cancer (Version 3.0). They show that the primary lesion improved from grade 0b to grade 1, and that the reduction rate of the size at the primary lesion was 41.2%. The therapeutic effects of this treatment continued after five cycles with a decline in the serum PSA level, and the progression-free survival time is currently about 4 months.

Discussion

Recently, taxane-based chemotherapy has been clinically proven to have a significant therapeutic effect in HRPC patients. However, its effect on metastatic bone lesion remains limited. Bisphosphonate selectively accumulates in the bone matrix, and it is taken into osteoclasts during bone absorption, causing apoptosis of the osteoclasts. However, cancer cells secrete a number of substances that stimulate osteoclast functions and result in osteolysis. Consequently, various growth factors are released from the destroyed bone matrix, leading to tumor adhesion and bone growth. Thus, we can aid the management of cancer induced bone disease by inhibiting osteoclastic activity with bisphosphonate. Histomorphometric studies of metastatic bone lesions in those with prostate cancer have shown that some sclerotic lesions are actually mixed in nature, with increased activities of both osteoblasts and osteoclasts.

Although antitumor effects have been reported for many bisphosphonates, ZA has demonstrated the most potent effects in the broadest range of tumor models. ZA has shown to have significant antitumor

---

**Fig. 1** Clinical course of the patient, showing serum prostate-specific antigen (PSA) level decreased after zoledronic acid (ZA) treatment.

**Fig. 2** Bone scintigraphy and computed tomography (CT) before and after zoledronic acid (ZA) treatment are shown. Each arrow on bone scintigraphy and CT indicates bone metastatic lesions on multiple ribs, vertebrae, and left ischia bone and the measurable disease right external iliac lymph node metastasis.
effects on prostate cancer cells \textit{in vitro} and \textit{in vivo} to inhibit bone metastasis, reduce the size of established bone lesions, and significantly reduce tumor-induced osteolysis.\textsuperscript{4,5} According to these previous investigations, the decline in both bone formation and resorption markers in this case indicates ZA’s efficacy on bone metastatic lesions. This is the first report to demonstrate that ZA is effective for the treatment of measurable diseases, adding a decline in PSA even if a patient with metastatic HRPC has received taxane-based chemotherapy combined with dexamethasone as a prior therapy. Although the molecular mechanism for these responses and survival benefit of ZA for metastatic HRPC is unclear, this case supports the hypothesis that ZA may not only improve the patient’s quality of life but that it also has a direct antitumorigenic effect in patients with metastatic HRPC. This suggests ZA’s future role will continue to expand.

\textbf{References}


