A Case of Bone, Lung, Pleural and Liver Metastases from Renal Cell Carcinoma Which Responded Remarkably Well to Zoledronic Acid Monotherapy

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Herein, we report a rare case in which bisphosphonate zoledronic acid (ZA) effectively treated not only multiple bone metastases but also lung, pleural and liver metastases from renal cell carcinoma (RCC). Recently, ZA is used to treat skeletal-related events (SREs) such as bone pain caused by bone metastasis from many kinds of cancer. The patient in the present report had multiple bone metastases from RCC. Remarkable improvement of the bone metastasis was observed following treatment with ZA at a dosage of 4 mg administered once every 4 weeks. Moreover, lung, pleural and liver metastases also diminished markedly in size in response to the treatment. The metastases have shown no progression for 20 months since starting the ZA treatment. We believe that the present report is the first of its kind announcing that ZA monotherapy has been effective for lung, pleural and liver metastases from RCC.

Key words: renal cell carcinoma – lung metastasis – pleural metastasis – bone metastasis – zoledronic acid

INTRODUCTION

Bone, lung, pleural and liver metastases from renal cell carcinoma (RCC) commonly occur (1). Sometimes surgical resection is recommended for cases in which the metastasis is resectable and the patient’s performance status is good (2). However, most patients are treated with immunotherapy and/or molecular target drugs (sorafenib, sunitinib and temsirolimus). Recently, bisphosphonate zoledronic acid (ZA) is widely accepted as a standard treatment for bone metastasis from RCC. Herein, we report a rare, clinical case in which ZA rendered good results for lung, pleural and liver metastases as well as bone metastases.

CASE REPORT

The patient was a 37-year-old woman diagnosed as having right RCC (cT2, N0, M0). She was surgically treated, having undergone radical right nephrectomy in November 2005. The resected tumor was pathologically diagnosed as RCC expansive type clear cell carcinoma G2>1 INFα, v (-) 9.5 cm pT2. Post-operative immunotherapy was recommended, but it was not administered because the patient did not desire it. Two months after the surgery, nodes suggestive of metastases were detected bilaterally on chest CT. Interferon-α (IFN-α) therapy (Sumiferon® 6 million units) was started three times a week following 2 weeks of continuous administration in March 2006. However, the lung metastases grew in size. IFN-α therapy was then switched to TS-1® therapy, but this was also not effective. On the basis of the results of these drugs, the patient’s condition was classified as a progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST).

One year after the detection of lung metastases, the patient underwent a bilateral upper lobectomy. Pathological examination of the resected tissue confirmed the diagnosis of lung metastasis from RCC. CT after 2 months of lobectomy showed no metastasis of RCC (Fig. 1A and B). However, 5 months after this operation, a new, thickened, pleural...
lesion appeared in the left pleura (Fig. 1C and D). We diagnosed this lesion as a new metastasis, for the following reasons:

(i) the resected pulmonary nodes were pathologically identified as RCC metastases;
(ii) the lesion developed too late to have been attributed to an inflammatory change following the surgical procedure; and
(iii) it was localized on only the left side.

Therapy with interleukin-2 (IL-2) (Imunace® 700 thousand units) was started three times a week in June 2007. However, left pleural effusion developed and a new, solid liver metastasis (12 mm) was discovered (Fig. 2A). On the basis of the effects of the IL-2, the patient’s condition was classified as PD. The patient complained of severe dyspnea, so we stopped the IL-2 treatment and performed pleurocentesis three times, and performed a pleurodesis by picibanil once. The pleural effusion appeared bloody without infection. Although the cytology reports for the pleural effusion were negative every time, the possibility of false negatives could not be ruled out, so pleuritis carcinomatosa was considered to be the most likely clinical possibility as opposed to other choices such as inflammation. The pleural effusion decreased and the dyspnea was slightly improved after pleurodesis. However, chest CT revealed an appearance of bilateral multiple lung metastases <1 cm in at least 18 places as well as aggravation of the pleural metastases (Fig. 3A and B). The patient was informed of various possible treatments and their anticipated prognoses including anticipated life expectancies. She refused any further active treatments and requested only conservative therapy. In December 2007, the patient began to complain of pain in her left ankle. Bone scintigraphy revealed multiple bone metastases affecting the left ankle, the right scapula, the right iliac bone and the right 9th rib, and a foot CT revealed osteolytic change in the left ankle bone (Fig. 4A and B). ZA (Zometa® 4 mg) therapy was started (administered once every 4 weeks) for pain relief. Other treatments were not administered during the ZA therapy. The pain improved gradually after the start of this therapy. Three months later, bone scintigraphy indicated lower-uptake, and a foot CT revealed osteoblastic change in the left ankle bone metastasis (Fig. 3C and D). The effect of ZA on the bone metastases was classified as a partial response (PR) according to the RECIST. Furthermore, she was aware of disappearance of her dyspnea. Surprisingly, a chest CT also revealed almost complete response according to the RECIST criteria 6 months after ZA therapy (Fig. 3C and D). Furthermore, serum levels of C-reactive protein (CRP) that is known as a prognosis marker of RCC (3) and bone-related marker [alkaliphosphatase, bone-derived alkaliphosphatase and carboxyterminal telopeptide of type-I collagen (I-CTP)] were declined by ZA treatment. Especially, elevated CRP and I-CTP decreased to normal range 1 year later of ZA treatment (Table 1). Moreover, liver metastasis showed a PR according to the RECIST criteria 14 months after ZA therapy (Fig. 2B). Until now, 20 months after the start of ZA therapy, no sign of recurrence has been noted.

Figure 1. Lung CT. (A and B) Two months after bilateral lobectomy. There is no pleural metastasis. (C and D) Five months after bilateral upper lobectomy. C and D show the same slices of CT as A and B, respectively. Arrows show newly formed pleural metastasis. CT, computed tomography.
DISCUSSION

Metastases from RCC respond poorly to anticancer chemotherapy/radiotherapy, and surgical treatment is considered to be the most effective modality for the treatment of metastatic RCC (2). Over the past two decades, immunotherapy with IFN-α, IL-2 etc. has been used as the standard therapy in dealing with inoperable cases of recurrent RCC (e.g. multiple metastases, poor performance state). Treatments such as TAE, gamma-knife and radiation are sometimes chosen for palliative therapy in cases of brain and bone metastases. In recent years, molecule-targeted drugs, such as sorafenib, sunitinib and temsirolimus, have begun to be used clinically, and their effectiveness against immunotherapy-resistant RCC has been reported. However, it remains unknown whether or not treatment with these drugs can suppress the growth of cancer for long periods of time.

Concerning sites of metastases, lung, pleural and lymph node metastases are likely to respond relatively well to immunotherapy with IFN-α, IL-2 etc., and the prognosis of these cases is said to be relatively favorable when compared with that of cases with metastasis to other organs like bone and intraperitoneal solid organs (e.g. the liver and the pancreas among others). However, the response rate of lung metastasis to immunotherapy is reported to be only ~20–30%, and the 5-year survival rate is reported to be ~15%.

Patients with RCC bone metastasis often present with skeletal-related event (SREs) such as bone pain. Bone metastasis is visible on X-rays as an osteolytic change. Immunotherapy is primarily used to deal with bone metastasis but response has not been good. Radiotherapy and/or surgical resection is also adopted in cases with pain or reduction of the ADL. Generally, the prognosis in cases of bone metastases tends to be poor. Recently, bisphosphonate has begun to attract close attention as a new agent for the treatment of bone metastasis. This drug has been shown to improve the SRE of bone metastasis from the genitourinary cancers, suppressing their growth (4).

The present case had shown relatively rapid progression of RCC. Lung metastases were resistant to immunotherapy and anticancer drug TS-1 therapy, but ZA was found to improve markedly the bone metastases and to also be effective against lung, pleural and liver metastases. We also previously encountered a clinical case of prostate cancer with bone metastasis in which bisphosphonate treatment reduced the serum level of PSA (5). One possible major mechanism underlying the actions of bisphosphonate against bone metastasis is induction of apoptosis of the osteoclasts distributed in the bone, leading to suppression of the proliferation of cancer cells or suppression of the formation of tumor growth factors by the bone (6). For this reason, bisphosphonate is considered to be particularly effective in cancers such as renal cancer etc., which are likely to be associated with osteolytic bone metastasis. In vitro and in vivo studies have demonstrated the direct antitumor activity of bisphosphonate against various cancer cell lines, including a renal cancer cell line. Indirect effects have also been noted (7). We also have reported evidence of the direct antitumor activity of bisphosphonate against a prostate cancer cell line (8).

Recently, the ABCSG-12 bone-mineral density study showed significant prolongation of the disease-free period following adjuvant bisphosphonate therapy after surgical resection.
resection of breast cancer (9). This report indicates that ZA is effective not only for bone metastasis but also for soft tissue organs metastasis. Possible mechanisms underlying the antitumor activity of bisphosphonate include induction of cancer cell apoptosis, suppression of cancer cell proliferation, inhibition of tumor angiogenesis, activation of gamma-delta T lymphocytes and suppression of tumor invasion (7,8,10–12). However, because of the pharmacokinetic parameters of bisphosphonate (distribution of 50% of the administered bisphosphonate in the bone and rapid excretion of the remaining 50% in the urine), direct antitumor activity of bisphosphonate on soft tissue organs other than the bone has not been expected.

In the present case, we do not know the exact mechanism promoting the response of the lung, pleural and liver metastases to bisphosphonate. In view of the pharmacokinetic features of bisphosphonate, direct effects of this drug against lung, pleural and liver metastases should be unlikely. If the features of RCC are also taken into account, it seems more probable that this drug affected tumor angiogenesis or the immune system of this patient, such as activation of gamma-delta T-lymphocytes, which, similar to immunotherapy, would result in indirect antitumor effects. Although we cannot conclude that bisphosphonate would be effective against all cases of RCC metastasis, we can say that bisphosphonate may serve well as one more option available in a

Figure 3. Lung CT before and after ZA therapy. (A and B) Circles and arrows show bilateral multiple lung metastases (<10 mm) and pleural metastasis, respectively. (C and D) Circles and arrows show almost complete response, the pleural metastasis having disappeared 6 months after ZA treatment.
multidisciplinary therapeutic approach to combating metastasis from RCC, especially if more such cases showing response to this therapy can be accumulated.

CONCLUSIONS

We recently encountered a case of bone, lung, pleural and liver metastases from RCC resistant to immunotherapy, in which treatment with ZA improved not only bone metastases, but also lung, pleural and liver metastases. It remains unknown why the ZA was effective against the lung, pleural and liver metastases in this case. If this question can be resolved, ZA may come to be regarded as one more valid option in a multidisciplinary treatment approach for metastasis from RCC.

Conflict of interest statement

None declared.

References


Table 1. Change of several serum marker by ZA treatment

<table>
<thead>
<tr>
<th></th>
<th>CRP (mg/dl)</th>
<th>ALP (IU/l)</th>
<th>BAP (U/l)</th>
<th>I-CTP (ng/ml)</th>
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<tr>
<td>Normal range</td>
<td>&lt;0.3</td>
<td>115–359</td>
<td>9.6–35.4</td>
<td>&lt;4.5</td>
</tr>
<tr>
<td>Before ZA</td>
<td>2.7</td>
<td>305</td>
<td>30.8</td>
<td>6.4</td>
</tr>
<tr>
<td>After ZA</td>
<td>0.2</td>
<td>167</td>
<td>14.6</td>
<td>4.4</td>
</tr>
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ZA, zoledronic acid; CRP, C-reactive protein; ALP, alkaliphosphatase; BAP, bone-derived alkaliphosphatase; I-CTP, carboxyterminal telopeptide of type-I collagen.

Fig 4. Bone scintigraphy and CT before and after ZA therapy. (A) Bone scintigraphy showing multiple bone metastases (arrows) when the patient complained of left ankle pain. (B) CT showing osteolytic change of ankle bone (arrow). (C) Bone scintigraphy showing lower accumulation (arrows) 4 months after ZA treatment. (D) CT showing improved osteolytic change of ankle bone after ZA treatment (arrow).