Effects of Alendronate on Bone Metastases and Hypercalcemia After Surgery for Hepatocellular Carcinoma

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Received April 14, 2000; accepted July 5, 2000

Alendronate, a bisphosphonate compound, lowers serum calcium in patients with cancer-associated hypercalcemia through its inhibitory effect on bone resorption and as a result symptoms associated with hypercalcemia improve. This study was carried out to investigate the effects of alendronate in patients with hypercalcemia due to bone metastasis of hepatocellular carcinoma (HCC). Two patients were evaluated. Their corrected serum calcium and α-fetoprotein (AFP) levels and their computed tomography (CT), bone scintigraphy and magnetic resonance imaging (MRI) findings were evaluated before and during alendronate treatment. After treatment, not only the corrected serum calcium levels but also AFP levels and bone pain decreased; in addition, the regression of the metastatic focus was noted in the MRI analysis. These tumor inhibitory effects of alendronate have not been reported in HCC before; and alendronate might serve to prevent bone metastases in patients with HCC. In conclusion, two patients who developed hypercalcemia associated with bone metastases after surgery for HCC were treated with alendronate and they experienced alleviation of the pain due to bone metastasis, improvement of their quality of life and a marked decrease in AFP levels with tumor regression.

Key words: alendronate – bisphosphonate – hepatocellular carcinoma – bone metastasis – hypercalcemia

INTRODUCTION

Hypercalcemia as a paraneoplastic syndrome appears in two forms: humoral hypercalcemia of malignancy (HHM) and local osteolytic hypercalcemia (LOH). In HHM, humoral factors, such as parathyroid hormone-related protein (PTHrP), produced by tumors induce and accelerate bone resorption by osteoclasts as well as calcium reabsorption by renal tubules (1). In LOH, a local factor produced by the tumor or host cells triggers the formation and activation of osteoclasts and accelerates bone resorption. Malignancy-associated hypercalcemia (MAH) is often associated with advanced cancer. When the serum calcium level exceeds 12 mg/dl, disruption of consciousness may occur and, depending on the rate of increase, various symptoms become evident; they may aggra-

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Abbreviations: AFP, α-fetoprotein; PTHrP, parathyroid hormone-related protein; LOH, local osteolytic hypercalcemia; MAH, malignancy-associated hypercalcemia; HHM, humoral hypercalcemia of malignancy

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CASE REPORT

The serum calcium level was corrected using an equation reported by Payne et al. (10). The serum calcium and AFP
levels of patients 1 and 2 changed during treatment with alendronate.

**PATIENT 1**

The patient, a 67-year-old woman with HCC complicated by chronic hepatitis B, underwent subsegmental resection of S5 and partial resection of S6 in July 1997. About 6 months later, intrahepatic recurrence of HCC was noted and on December 26, the AFP level increased to 4199 ng/ml (normal range <15 ng/ml). On January 6, 1998, the patient was hospitalized again and on January 16, transcatheter arterial embolization (TAE) was conducted. On February 4, the AFP level increased further to 20 796 ng/ml and aggravation of hepatic functions was observed as well as infection and an abscess at the site of insertion of the catheter for intravenous hyperalimentation. At that time, the patient complained of left hip joint pain and gait disturbance. Diclofenac sodium in suppositories was used for pain relief. On March 30, the AFP level increased to 143890 ng/ml. On April 1, an intrapelvic CT scan revealed a metastasis in the left iliac bone. On April 13, the corrected serum calcium level was as high as 12.1 mg/dl (normal range 8.5–10.3 mg/dl); calcitonin was given and the corrected serum calcium values became normal transiently. On April 20, bone scintigraphy revealed metastases in the cranial bones, thoracic vertebrae, right clavicle and bilateral ribs (Fig. 1). On May 19, the corrected serum calcium level increased again to 11.6 mg/dl (Fig. 2a). The AFP level increased further to reach 557 300 ng/ml. Serum alkaline phosphatase (ALP) activity was 1080 IU/l (normal range 81–231 IU/l) and skeletal ALP activity was 302.4 IU/l (normal range 27–154 IU/l). Symptoms of hypercalcemia including anorexia, nausea, vomiting, disturbance of memory and disruptions of consciousness (somnolence) were observed; thus, alendronate (10 mg) was administered from this day on. Two weeks after the start of treatment with alendronate, anorexia, nausea and vomiting disappeared and the level of consciousness was improved. Serum calcium values were controlled and symptoms associated with hypercalcemia improved. Furthermore, on June 16, the AFP level decreased to 341 470 ng/ml (Fig. 2a), ALP activity was 500 IU/l and skeletal ALP activity was 115 IU/l. ALP activity and skeletal ALP activity gradually decreased after 1 month on alendronate (Fig. 2b). The patient could not walk owing to osteolysis, but the pain in her left hip joint was alleviated. In this patient, only diclofenac sodium suppository was used to relieve pain. It was possible to relieve and control pain without using narcotics. Subsequently, intrahepatic recurrence increased and on July 29, the AFP level increased again to 70 914 ng/ml. ALP activity was 434 IU/l and skeletal ALP activity was 109 IU/l. On August 15, the patient died of hepatic failure with hyperbilirubinemia and hypertransaminasemia.
PATIENT 2

The patient, a 72-year-old man with HCC complicated by chronic hepatitis C, underwent subsegmental resection of S7 in March 1992. Because of recurrence of HCC, S5 was partially resected in May 1995. After the re-operation, multicentric recurrence was observed and percutaneous ethanol injection and TAE were repeated. Subsequently, the patient was carefully observed. The AFP level increased to 1285 ng/ml and the patient complained of swelling (12 × 10 cm) and pain in the left scapula, so on April 28, 1998, he was admitted. The AFP level further increased, reaching a maximum level of 1985 ng/ml. Cytological examination of the left scapula showed Class V tumor. On May 25, MRI revealed an osteolytic image in the left scapula, the tumor was 10.7 × 6.7 cm (Fig. 3a) and the diagnosis of bone metastasis of HCC was made. For the treatment of bone pain, pentazocine was administered, but relief of the pain was insufficient. The corrected serum calcium level showed a mild increase to 10.5 mg/dl and the patient complained of swelling (12 × 10 cm) and pain in the left scapula, so on April 28, 1998, he was admitted. The AFP level further increased, reaching a maximum level of 1985 ng/ml. Cytological examination of the left scapula showed Class V tumor. On May 25, MRI revealed an osteolytic image in the left scapula, the tumor was 10.7 × 6.7 cm (Fig. 3a) and the diagnosis of bone metastasis of HCC was made. For the treatment of bone pain, pentazocine was administered, but relief of the pain was insufficient. The corrected serum calcium level showed a mild increase to 10.5 mg/dl and the patient complained of swelling (12 × 10 cm) and pain in the left scapula, so on April 28, 1998, he was admitted. The AFP level further increased, reaching a maximum level of 1985 ng/ml (Fig. 4a) and the patient was started on alendronate (10 mg) on June 3. The swelling of the left scapula tended to regress and pain relief became possible by treatment with pentazocine at half the previous dose, 2 weeks after the start of the administration of alendronate. On June 9, ALP activity was 1053 IU/l and skeletal ALP activity was 273 IU/l. On June 27, the patient could be discharged from the hospital. On July 24, ALP and skeletal ALP activity had decreased to 702 and 232 IU/l, respectively (Fig. 4b). MRI also revealed regression of the metastatic focus in the left scapula, and the tumor was 4.3 × 3.8 cm after 3 months of treatment (Fig. 3b). Subsequently, the patient received alendronate every 2 weeks and the pain was controlled without pentazocine treatment. On August 21, the AFP level decreased to 646 ng/ml and the corrected serum calcium level fluctuated around 9.5 ng/ml. The swelling of the left scapula tended to regress and pain relief became possible by pentazocine treatment at half the previous dose. No carcino- static compound had been administered as yet. The patient died of hepatic failure and rupture of varix in October 1999.

DISCUSSION

Paraneoplastic syndrome refers, in general, to symptoms in cancer-bearing patients that cannot be readily explained, either by enlargement, infiltration or metastasis of tumors or by elaboration of hormones, indigenous to the tissue from which the tumor arose. HCC is a cancer associated with many paraneoplastic syndromes. One of them, MAH, often may be mistaken for the terminal stage in cancer patients. Patients suddenly experience consciousness disruptions or fall into comatose state.
states and communication is no longer possible; this condition can lead to their death. In our patients with HCC bone metastasis-associated hypercalcemia, treatment with alendronate to improve MAH was associated with a significant improvement of their QOL.

Throughout the clinical course of our two patients, plasma PTHrP was not elevated [19.4and 36.6 pmol/l in patients 1 and 2, respectively (normal range 13.8–55.3 pmol/l)], although PTHrP was increased in more than 90% of patients with HHM (11) and hypercalcemia was diagnosed as LOH.

Although we could not measure bone resorption markers, serum levels of skeletal ALP were very high before administration of alendronate in both patients, suggesting the presence of high bone turnover due to bone metastases. After administration of alendronate, skeletal ALP activity decreased by 66.0% in patient 1 and by 15.1% in patient 2 (Figs. 2b and 4b), as reported previously (12,13). Skeletal ALP started to decrease within a few days after the initiation of alendronate therapy in patient 1, suggesting a reduction of bone resorption by alendronate.

Daily urinary Ca levels were decreased after administration of alendronate in both patients in comparison with before. The decreases in AFP during alendronate treatment were particularly marked. There have been some reports of decreases in tumor markers in breast cancer and prostatic cancer (14). However, to our knowledge, decreases in AFP, by bisphosphonate treatment in HCC patients, have not been reported. In our cases, AFP levels decreased, particularly in patient 2, and regression of the metastatic focus with necrosis in the scapula was confirmed on MRI with a reduction in the size of metastatic focus by 24.4%. These findings and the reduction in AFP in the two patients with HCC, warrant further investigation into the adjuvant effect of alendronate in HCC patients.

References