Cancer Chemother Pharmacol (2010) 65:1137–1143
DOI 10.1007/s00280-009-1122-6

ORIGINAL ARTICLE

# Zoledronic acid in the treatment of bone metastases by hepatocellular carcinoma: a case series

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Received: 16 April 2009 / Accepted: 2 September 2009 / Published online: 16 September 2009


**Abstract**
*Purpose* The survival of patients with hepatocellular carcinoma (HCC) has improved with advancements in various diagnostic tools and treatment modalities. Consequently, bone metastases from HCC are diagnosed more frequently. The aims of the present study was to describe the clinical features and treatment of HCC patients presenting with bone metastases. In particular, we evaluated the role of zoledronic acid in these patients especially with regard to pain reduction, analgesic drug consumption and safety.
*Methods* Between December 2006 and July 2008, we recruited 17 (male:female, 12:5, median age, 68 years; age range, 62–85 years) consecutive patients. Spinal metastases were present in 11 patients (64.7%). Zoledronic acid was administered in all patients (total number of administrations, 107; mean number of administrations, 6.29).
*Results* A total of 15 patients received at least three administrations of zoledronic acid and reported clinical benefit with pain reduction and tapering of analgesic drugs. Before starting treatment, the mean VAS for patients who received at least three administrations (15/17 patients) of zoledronic acid was 7.1 (±0.24), and after 3 months 5.3 (±0.20). This improvement was independent of the sex, the extent of metastasis and the concomitant anticancer treatment. No significant side effects were registered in this series of patients. Median survival was 10 months (CI 6,353–13,647).
*Conclusions* Zoledronic acid may be helpful in treating bone metastases in HCC patients. Patients regularly receiving zoledronic acid showed significant pain relief.

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**Keywords** Zoledronic acid · Bone metastases · Liver · Hepatocellular carcinoma · Bisphosphonate

## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide in terms of incidence [1]. Only 30% of HCC are diagnosed in the early stage and can be treated with potentially curative treatments, while the majority of tumors are diagnosed when advanced, has limited chances of cure and a dismal prognosis, and less than 1 year of mean survival if left untreated. Treatment options and the outcome of HCC patients ultimately depend on tumor extension and the severity of underlying liver cirrhosis. Multimodality treatment of liver lesions prolong survival [2] and the recent introduction of biologic treatments provide an opportunity for prolonged disease control [3]. Moreover, the available diagnostic tools increase both the rate of small HCC detected and extrahepatic metastatic sites. In this new scenario, metastatic disease has been increasingly diagnosed. The most common sites are the lung, abdominal lymph nodes and bones [4]. Autopsy series have shown that bone metastases followed lung and adrenal secondary lesions [5]. Bone metastases are reported less frequently than lung and lymph node metastases, i.e., 2–20% as compared to 37–70% and 23–45%, respectively [6]. The most frequent sites of bone metastases are the spine, pelvis, ribs and skull in that order [7].

Approximately half of patients with solid tumors metastasizing to bone experience one or more skeletal events (including pathologic fractures, spinal cord compression, radiotherapy or surgery to bone and hypercalcemia) during the course of their disease [8]. In a study evaluating the prognosis of HCC patients with metastatic disease, bone metastases did not significantly influence the outcome of patients. In fact, 90% of patients with bone metastases only as extrahepatic disease died from hepatic causes and none died from extrahepatic disease [9]. Single bone lesion was associated with a favorable outcome, while multiple bone lesions may be associated with severe pain and increasing rate of leukopenia, anemia and thrombocytopenia, sometimes making radiotherapy administration difficult. In fact, bone involvement by tumor may contribute to multifactorial pathogenesis of pancytopenia in HCC patients. When the spine is involved, the clinical presentation may be critical and require prompt intervention [6]. Moreover, bone metastases may cause pain, discomfort and functional inability. Bone metastases represent a manifestation of systemic disease, as well as cause localized symptoms, which require a multidisciplinary therapeutic approach.

Treatment of bone metastases is based on radiotherapy on bone lesions especially if painful and/or critical due to impending fractures. Radiation therapy provides both localized and systemic treatment options in addition to chemohormonal therapies and surgery [10]. Bisphosphonates delay cancer-related skeletal complications in patients with bone metastases [11]. Radionuclide therapy is shown to be useful and cost-effective in relieving bone pain in metastatic disease and may be more effective when combined with chemotherapy, bisphosphonates and radiation therapy [12].

Zoledronic acid is a highly potent new-generation bisphosphonate. It has been proven to be effective in the treatment of bone metastases secondary to all solid tumor types and bone lesions from multiple myeloma, based on the results of three large, randomized, phase III clinical trials enrolling more than 3,000 patients [8]. Differently from breast cancer and myeloma, no guidelines have been developed for patients with bone metastases by solid tumors other than breast cancer. Therefore, treatment with zoledronic acid at the first diagnosis of metastatic bone disease is a reasonable approach [8]. Administration of zoledronic acid is generally safe when the patients are monitored for the risk of renal toxicity and osteonecrosis of the jaw.

We describe the pattern of presentation and treatment of bone metastases in 17 advanced HCC patients, evaluated from among more than 50 patients, who came to our observation. In particular, the use of zoledronic acid in these patients is presented.

## Methods

Between December 2006 and July 2008, we recruited 17 (male:female, 12:5) consecutive HCC patients presenting with bone metastases (Table 1). The patients were required to have HCC confirmed by biopsy or diagnosed by clinical criteria (hypervascular liver masses of more than 2 cm and alpha fetoprotein of more than 400 ng/dL) and bone metastases confirmed by bone biopsy or demonstrated by at least two radiographic methods (bone scintigraphy and computed tomography (CT) or magnetic resonance imaging (MRI)). Adequate renal function defined as a serum creatinine level of $\leq$1.5× ULN was required together with a serum calcium level revised by albumin levels of >8.0 mg/dL. In particular, creatinine clearance (Cr Cl) was calculated for each patient. Moreover, all patients were screened for potential risk factors of osteonecrosis of the jaw. The patients were clinically evaluated and monitored by biochemistry every month. The study protocol was approved by the local ethical committee and every patient

**Table 1** Comprehensive patients' profile

| Patient | S/A | Etiology | Child | Sites of disease | Treatment | ZA | Basal alpha-FP (UI/mL) | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | F/69 | HCV | B | Liver, lumbar vertebrae | PEI, RFA, bone RT (stopped), OCT | 3 | 7.83 | Dead (10 months) |
| 2 | M/62 | HCV | A | Liver, Lumbar vertebrae | CT, bone RT, sorafenib + OCT | 7 | 273 | Dead (7 months) |
| 3 | M/68 | HCV | A | Liver, abd lymph node, ribs, dorsal and lumbar vertebrae, pelvis | RFA, TACE, bone RT, sorafenib + OCT | 3 | 4,472 | Dead (10 months) |
| 4 | M/66 | HCV | A | Liver, lung, ribs, right homerus, left femur | Liver surgery, CT, bone RT, sorafenib + OCT | 11 | 545 | Alive (14 months) |
| 5 | M/63 | NAS | A | Liver, lung, abd lymph nodes, ribs, pelvis, dorsal vertebrae | Bone RT, sorafenib + OCT | 5 | 30,000 | Dead (6 months) |
| 6 | M/79 | HCV | A | Liver, dorsal vertebra, pelvis | RFA, PEI, bone RT, sorafenib + OCT | 9 | 13,900 | Alive (10 months) |
| 7 | M/69 | HCV | A | Liver, left femur, dorsal and lumbar vertebrae, ribs, pelvis | LT, bone RT, RFA and TACE, sorafenib + OCT | 2 | 1,430 | Dead (6 months) |
| 8 | M/64 | HCV | B | Rib, pelvis, lumbar vertebra | RFA, PEI, TACE, liver surgery | 1 | 11,850 | Dead (1 month) |
| 9 | F/80 | HCV | A | Liver, right femur | Bone RT, sorafenib + OCT | 7 | 3.2 | Alive (9 months) |
| 10 | M/66 | HCV | B | Liver, thoracic and abd lymph nodes, rib, skull, sternum, lumbar vertebrae, sacrum | Naïve, bone RT | 3 | 5.4 | Dead (5 months) |
| 11 | M/67 | HCV-HBV | A | Liver, abd lymph nodes, pelvis, thoracic and lumbar vertebrae | Sorafenib | 4 | 225.3 | Alive (6 months) |
| 12 | F/71 | HCV | B | Liver, abd lymph nodes, pelvis, ribs, left clavicle, left homerus, right femur | TACE | 9 | 192 | Dead (7 months) |
| 13 | M/60 | HCV | A | Liver, abd lymph nodes, pelvis, ribs, left clavicle, ribs, sternum | RFA, sorafenib | 10 | 609.9 | Alive (12 months) |
| 14 | F/68 | HCV-HBV | C | Liver, abd lymph nodes, pelvis, right femur, lumbar and sacral vertebrae | RFA, CT, bone RT | 5 | 109 | Dead (13 months) |
| 15 | F/70 | HCV | A | Liver, left femur | TACE, CT | 11 | 5 | Alive (8 months) |
| 16 | M/66 | Alcohol | C | Liver, abd lymph nodes, dursal vertebrae | CT | 9 | 570 | Dead (6 months) |
| 17 | M/85 | HCV | C | Liver, abd lymph nodes, pelvis | CT | 8 | 350 | Dead (15 months) |

*Pt* patient, *S/A* sex/age, *abd* abdominal, *ZA* zoledronic acid, *PEI* percutaneous ethanol injection, *TACE* transarterial chemoembolization, *CT* chemotherapy, *RFA* radiofrequency ablation, *LT* liver transplantation, *RT* radiotherapy

gave written informed consent prior to study entry. No funding source was provided.

Bone metastases were monitored by CT and/or MRI every 6 months. Exclusion criteria included previous radiotherapy on bone metastasis until 4 weeks before starting zoledronic acid, an advanced second primary malignancy, significant medical comorbidities, clinically significant cardiovascular disease including uncontrolled hypertension, myocardial infarction and unstable angina, NYHA grade II or greater congestive heart failure or history of active bleeding. Zoledronic acid was started on diagnosis of bone metastases and administered monthly according to Cr Cl. The administered dosages were the following: 4 mg if basal Cr Cl was greater than 60 mL/min; 3.5 mg if Cr Cl was 50–60 mL/min; 3.3 mg for Cr Cl of 40–49 mL/min; 3 mg for Cr Cl of 30–39 mL/min. Zoledronic acid was diluted in 100 mL of physiologic solution and administered in 15 min. All patients received 500 mg calcium supplemented with 400 IU of vitamin D daily and eventual intravenous calcium gluconate administration if needed.

Pain assessments were conducted at baseline and after three infusions using a 100-mm visual analog scale (VAS) and analgesic consumption recorded at each examination.

A descriptive analysis was performed using the mean values of each variable and the corresponding inferior and superior standard deviation (SD). Kruskal–Wallis one-way

analysis of variance by ranks was used to compare medians among groups of variables with non-parametric and independent distribution (such as the narcotic score between groups) [13].

The overall survival (OS) time was calculated as the period from the date of starting treatment until death from any cause or until the date of the last follow-up, at which point data were collected. OS was determined by Kaplan–Meier product-limit method [14].

## Results

Five females and 12 males presenting with bone metastases were treated with zoledronic acid. Median age of the patients was 68 years (age range 62–85 years). ECOG performance status was 0–2. Underlying HCV infection was detected in all patients but four. In one patient no causative agent was identified, one patient had ethanol abuse that was considered to be responsible for chronic liver damage, and in two cases double infection by HCV and HBV was detected. Ten patients were Child-Pugh class A, four were Child-Pugh class B and three were Child-Pugh C. All patients had multinodular HCC. Only three patients were naïve from local and systemic therapies. The patients were previously treated with different options: liver surgery [2 patients (pt)], percutaneous ethanol injection (PEI) and/or radiofrequency ablation (7 pt), intra-arterial chemotherapy (5 pt) and systemic treatments (14 pt). Most of the patients (10 out of 17, 58.8%) had received local and systemic therapies. One patient (pt 7 in Table 1) presented recurrence on transplanted liver and concomitant bone metastases. He received radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) on transplanted liver. At presentation of bone metastases, 11 out of 17 patients showed alpha-fetoprotein levels higher than 200 ng/mL. All patients but two (pt 1 and 8) were treated with sorafenib plus octreotide (Del Prete S, Montella L, Caraglia M, Maiorino L, Montesarchio V, Cennamo G, Leo L, Palmieri G, Bianco M and Addeo R, on behalf of SOLAR study group. Sorafenib plus long-acting octreotide in advanced hepatocellular carcinoma. Preliminary results of a multicenter ongoing study, American Society of Clinical Oncology 2008 Chicago (USA) Annual Proceedings). One patient (pt 1) received octreotide alone. The most frequent sites of bone metastases in the present series were spine (11/17, 64.7%), pelvis (10/17, 58.8), long bones (6/17, 35%) and ribs (8/17, 47%). Two patients had single bone metastases (pt 9 and 15). Ten patients presented with extrahepatic disease other than bone (lungs and/or abdominal lymph node). In Fig. 1, wedge compression fracture of the first lumbar vertebra together with a liver lesion and right adrenal gland involvement by tumor were shown. In patient

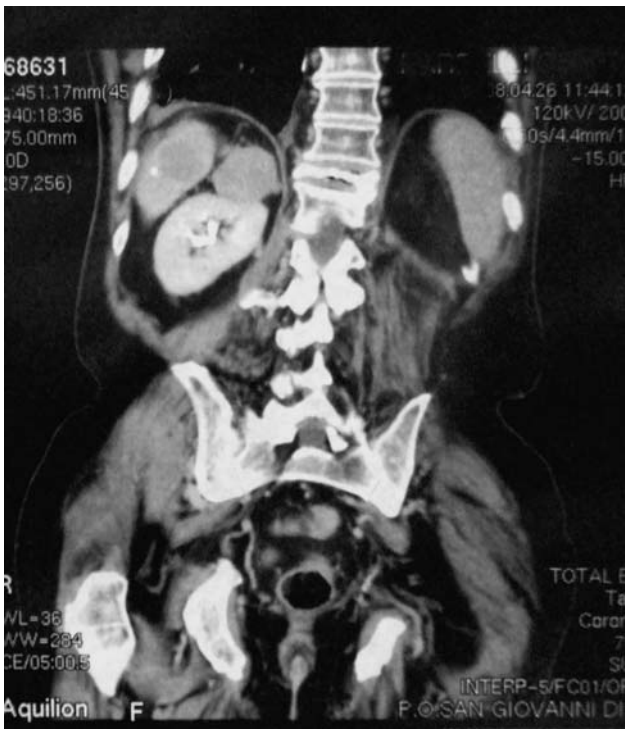


**Fig. 1** Choronal section of CT scan showing wedge compression fracture of the first lumbar vertebra together with a liver lesion and right adrenal gland involvement by tumor

no. 5, disease progression was announced by the appearance of a tumor corresponding to the rib cage (Fig. 2a), which was confirmed by CT (Fig. 2b). Two patients (pt 1 and 8) were hospitalized with low backache.

All patients referred to relentless pain despite various analgesic treatments. Zoledronic acid was administered in all patients (total number of administrations, 93; mean number of administrations, 5.47). As much as 15 patients received at least three administrations.

Four patients received concomitant radiotherapy. One patient (pt 1) stopped radiotherapy on bone lesions because of thrombocytopenia. One patient received only one administration of zoledronic acid because of death due to variceal bleeding. Three patients (pt 1, 3 and 7) showed serum calcium revised by albumin levels less than 8.4 mg/dL despite oral and intravenous calcium administration and stopped therapy after a maximum of three administrations. One of these patients (pt 3) showed bone disease progression. Zoledronic acid was well tolerated and only in one case we registered an acute phase reaction (low-grade fever) 24 h after the first administration. Basal Cr Cl ranged from 40 to 95 mL/min. Four patients had Cr Cl below 49 mL/min. However, this value was maintained within the start-up range during the follow-up. In Fig. 2c, bone remodeling after two administrations of zoledronic acid in the same patient, shown in Fig. 2a and b, was imaged. Six patients (66.6%) remained stable, while three patients progressed.

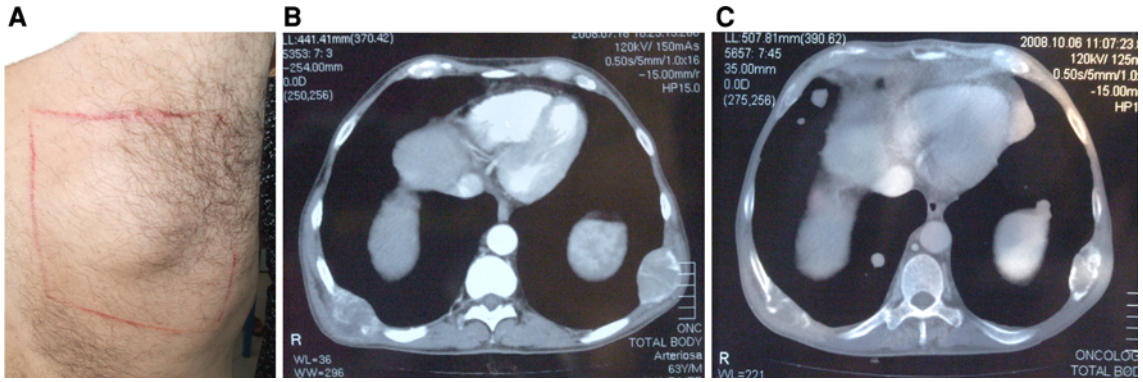


**Fig. 2** Clinical (**a**) and CT (**b**) images of rib involvement by tumor. In **b** CT shows metastases located at VI rib at the *left* and VII at the *right*. **c** shows the same lesions after zoledronic acid treatment

During follow-up 11 patients died because of progressing cirrhosis and/or tumor. Mean survival was 10.25 months (CI 95%, 8.245–12.255 months). All treated patients appeared to benefit from zoledronic acid in terms of pain reduction and tapering of analgesic drugs. Before starting treatment, the mean VAS for patients who received at least three administration (15/17 patients) of zoledronic acid was 7.1 (±0.24), and after 3 months 5.3 (±0.20). Radiotherapy was administered before zoledronic acid and, despite an initial benefit, we were unable to reduce or stop treatment with analgesic drugs in our patients. However, zoledronic acid administration produced increasing pain control with reduced need of analgesic drugs. A decrease in narcotic score was also observed, but this change was not statistically significant on analysis of variance. In particular, patient no. 7 with advanced tumor disease gained fast and significant clinical benefit from the administration only of zoledronic acid. In fact, he spontaneously stopped using morphine for breakthrough pain. However, all patients did not completely stop analgesic drugs. Patient no. 3, who stopped zoledronic acid due to persistent hypocalcemia showed bone progression 7 months after the last zoledronic acid administration, while the other patients did not experience bone progression and skeletal complications. All patients recovered with regard to functional abilities previously compromised. The median survival was 10 months (CI 6,353–13,647).

## Discussion

Bone metastases are the most common cause of cancer-related pain and often require palliative radiotherapy. Skeletal complications such as painful and debilitating pathologic fractures and spinal cord compression can seriously compromise life of patients and may require surgical interventions. Moreover, bone metastases contribute to the deterioration in quality of life and independence of many cancer patients.

Bone metastases are rarely seen among extrahepatic sites of disease in HCC patients. Bone scintigraphy is not mandatory in the staging examination of this tumor, if there is no clinical suspicion of bone metastasis. However, improvement in local therapies and available targeted therapies are changing the clinical features of this tumor and increasing the chance of survival. In the presence of incidental bone pain, bone lesions can be detected. They are generally demonstrated by radiography, CT and nuclear scintigraphy. The plain film appearance of skeletal metastases from HCC was osteolytic in most cases. CT scans demonstrated the destructive nature of these lesions, which were associated with bulky soft tissue masses [15]. Since 1986, investigations for bone metastases were advocated in patients with longstanding cirrhosis or known hepatocellular carcinoma that also have skeletal symptoms [16]. Often, bone metastases from hepatocellular carcinoma are not detected by bone scintigraphy because of low uptake or a photopenic area in the tumor [17]. Last generation CT scans are significantly powered to detect bone lesions [18].

Bisphosphonates are taken up by the bone at sites of active bone metabolism and inhibit osteoclast activity and survival [19]. Novel bisphosphonates include pamidronate, ibandronate and zoledronic acid. They are characterized by the presence of nitrogen in their molecule and inhibit the mevalonate pathway in osteoclasts. Bisphosphonates also cause apoptosis in osteoclasts and may have apoptotic effects in tumor cells. The nitrogen-containing bisphosphonates are much more potent than first-generation compounds. Specifically, they acquire the ability to inhibit the farnesyl pirophosphate synthase enzyme that is essential for the isoprenoid synthesis and for the subsequent activation of signal transduction proteins, such as ras family proteins that are critically involved in the control of osteoclast and tumor cells proliferation and survival [20].

Several large clinical trials assessed the clinical activity of bisphosphonates, evaluating several primary end points of efficacy such as the time to first skeletal event, fractures,

the need for radiotherapy, spinal cord compression and hypercalcemia related to malignancy. Combined treatment with radiotherapy and zoledronic acid restores normal bone qualities with respect to bone density, microarchitecture and biomechanical strength [21].

Bisphosphonates seem to improve clinical results obtained with radiotherapy alone. Combined therapy such as RT + Z achieved a higher objective response rate measured as shrinkage and/or calcification of bone lesions and prolonged SRE-free survival than RT alone in patients with bone metastases from RCC [22].

Advanced HCC patients presenting with bone metastases are undoubtedly different from breast and prostate cancer patients with bone metastases, especially with regard to liver function impairment, prognosis and available effective treatments. Cirrhosis is an independent prognostic factor for osteoporosis [23]. Bone formation is reduced and bone turnover is low in liver cirrhosis. A reduction in bone mineral density leads to increased bone fragility, with osteopenia and osteoporosis leading to a twofold and four- to fivefold increased risk for fracture, respectively [24]. Therefore, the bone is already fragile in cirrhotic patients independent of metastases. The management of advanced HCC patients becomes even more complicated in the presence of bone metastases.

Limited experience has been reported in medical literature with bisphosphonates in bone metastases by HCC. Two patients who developed hypercalcemia associated with bone metastasis after surgery for HCC were treated with alendronate and experienced pain relief, improvement of their quality of life and a marked decrease in alpha-fetoprotein levels with tumor regression [25]. Only one case of bone metastases treated with zoledronic acid has been reported until now [5]. The present study is the first of a series describing the attempt to include zoledronic acid in the therapeutic strategy of advanced HCC with bone metastases. The exact value of zoledronic acid alone is difficult to be determined because of the limited number of evaluable patients and concomitant use of other treatments. However, patients regularly receiving zoledronic acid showed decreasing need for analgesic drugs and functional recovery, if the lesions were located in the spine and limbs, together with quality of life improvement.

In the present trial, pain scores in patients receiving ZA decreased from baseline at subsequent assessment, suggesting, as we previously demonstrated [26–28], that ZA may help in the management of pain. This can be particularly important because of impaired liver metabolism due to the drug and increased risk for encephalopathy in these patients. The need to continue analgesic drugs was mostly related not only to bone pain, but also to abdominal pain, which is frequent in multinodular HCC. The use of analgesics and their eventual reduction over time of HCC patients are difficult to evaluate. In fact, opioid drug may be preferred to minor analgesic drugs, i.e., nonsteroidal anti-inflammatory drugs, because of reduced risk of bleeding. An increased use of drugs considered on the upper level of the analgesic scale does not translate into worse conditions, thus making the impact of any drug on pain more difficult to be assessed. No patient who continued to receive zoledronic acid showed bone progression, while the only patient who stopped treatment because of persistent hypocalcemia showed new bone lesions. No skeletal complications were registered during zoledronic acid administration.

In this study, zoledronic acid was used in patients with Cr Cl less than 60 mL/min. No significant side effect was registered and, in particular, renal function did not worsen in this series of patients.

In conclusion, zoledronic acid was safe and effective in the treatment of bone metastases in the present series and may be considered as an important part of novel therapeutic strategies.

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