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► To cite this version:

Liliana Montella, Raffaele Addeo, Giovannella Palmieri, Michele Caraglia, Gregorio Cennamo, et al.. Zoledronic acid in the treatment of bone metastases by hepatocellular carcinoma: a case series. Cancer Chemotherapy and Pharmacology, 2009, 65 (6), pp.1137-1143. 10.1007/s00280-009-1122-6 . hal-00568265

HAL Id: hal-00568265

<https://hal.science/hal-00568265>

Submitted on 23 Feb 2011

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ZOLEDRONIC ACID IN TREATMENT OF BONE METASTASES BY HEPATOCELLULAR CARCINOMA: A CASE SERIES.

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ABSTRACT

Purpose: The survival of patients with hepatocellular carcinoma (HCC) is improved with advancements in various diagnostic tools and treatment modalities. Consequently, bone metastases from HCC are diagnosed more frequently. 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 as concerns pain reduction, analgesic drug consumptions 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:**

Fifteen 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 3 administration (15/17 patients) of zoledronic acid was 7,1 (± 0.24), and after three months 5,3 (± 0.20). This improvement was independent from the sex, the presence of number 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.

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 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, less than one year of mean survival if left untreated. Treatment options and outcome of HCC patients ultimately depend on tumor extension and the severity of underlying liver cirrhosis. Multimodality treatment of liver lesions prolonged survival [2] and recent introduction of biologic treatments gave a real chance of prolonged disease control [3]. Moreover, the available diagnostic tools increased both the rate of small HCC detected and extrahepatic metastatic sites. In this new scenario, metastatic disease is increasingly disclosed. 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 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 were not significantly influential in the outcome of patients. In fact 90% of patients with bone metastases only as extrahepatic disease died from hepatic causes and none patients 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, making sometimes difficult radiotherapy administration. In fact, bone involvement by tumor may contribute to multifactorial pathogenesis of pancytopenia in HCC patients. When spine is involved, clinical presentation may be critical and require prompt intervention [6]. Moreover, bone metastases may cause pain, discomfort and functional inability.

Representing both a manifestation of systemic disease as well as causing localized symptoms, bone metastases require a multidisciplinary therapeutic approach.

Treatment of bone metastases is based on radiotherapy on bone lesions especially if painful and/or critical for 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 proven 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.

Following we describe the pattern of presentation and treatment of bone metastases in 17 advanced HCC patients which were evaluated among more than 50 patients come at 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). Patients were required to have HCC confirmed by biopsy or diagnosed by clinical criteria (hypervascular liver masses more than 2 cm and alfafetoprotein 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 $\leq 1.5 \times$ ULN was required together with a serum calcium level revised by albumin levels >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 Local Ethical Committee and every patient gave written informed consent prior to study entry. No funding source was provided.

Bone metastases were monitored by CT and/or MRI every six months. Exclusion criteria included previous radiotherapy on bone metastasis until four 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, history of active bleeding. Zoledronic acid was started at the diagnosis of bone metastases and administered monthly according to Cr Cl. The administered dosages were the following: 4 mg if basal Cr Cl was upper 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 minutes. 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 censored. OS was both determined by Kaplan-Meier product-limit method [14].

RESULTS

Five females and twelve 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 was considered responsible for chronic liver damage, in two cases double infection by HCV and HBV was detected. Ten patients were Child-Pugh class A, four were Child-Pugh class B, 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 pts), percutaneous ethanol injection (PEI) and/or radiofrequency ablation (7 pts), intra-arterial chemotherapy (5 pts), systemic treatments (14 patients). 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 (pts 1,8) were treated with sorafenib plus octreotide (DeI Prete S, Montella L, Caraglia M, Maiorino L, Montesarchio V, Cennamo G, Leo L, Palmieri G, Bianco M, Addeo R. 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. 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%), ribs (8/17, 47%). Two

patients had single bone metastases (pts 9,15). Ten patients presented 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 n.5 disease progression was announced by the appearance of a tumor corresponding to rib cage (fig.2a) which was confirmed by CT (fig.2b). Two patients (pts 1 and 8) were hospitalized with low backache. All patients referred relentless pain despite various analgesic treatments. Zoledronic acid was administered in all patients (total number of administrations: 93, mean number of administrations: 5.47). Fifteen patients received at least 3 administrations. Four patients received concomitant radiotherapy. One patient (pt1) 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 (pts 1, 3, 7) showed serum calcium revised by albumin levels below 8,4 mg/dL despite oral and intravenous calcium administration and stopped therapy after a maximum of three administrations. One of this patient (pt3) showed bone disease progression. Zoledronic acid was well tolerated and only in one case we registered an acute phase reaction (low-grade fever) 24 hours 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 maintained within the start-up range during the follow-up. In fig.2c bone remodelling 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 3 patients progressed. During follow-up eleven 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 3 administration (15/17 patients) of zoledronic acid was 7,1 (± 0.24), and after three 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 produce increasing pain control with reduced need of analgesic drugs. A decrease in narcotic score was also observed, but this change was not statistically significant when using analysis of variance. In particular the patient n.7 with advanced tumor disease gained fast and significant clinical benefit from the only administration of zoledronic acid performed. In fact, he spontaneously stopped to use morphine for breakthrough pain. However, all patients did not completely stop analgesic drugs. The patient n.3 which stopped zoledronic acid for persistent hypocalcemia showed bone progression seven months after the last zoledronic acid administration, while the other patients did not experience bone progression and skeletal complications. All patients recovered as concerns functional abilities previously compromised. 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 showed among extrahepatic sites of disease in HCC patients. Bone scintigraphy is not mandatory among staging examination in this tumor if there is not clinical suspicion of bone metastases. However, the increasing survival due to improvement in local therapies and the available targeted therapies are changing the clinical features of this tumor. In 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, search for bone metastases was advocated in patients with long-standing 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 is 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 tumour cells. The nitrogen containing bisphosphonates are much more potent than first generation compounds. Specifically, they acquire the ability to inhibit the farnesyl pyrophosphate 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 tumour 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 of radiotherapy, spinal cord compression, 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 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 as concern 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 two-fold and four- to five-fold increased risk for fracture, respectively [24]. Therefore, bone is already fragile in cirrhotic patients independently from metastases. The management of advanced HCC patients becomes even more complicated in 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 was reported until now [5]. The present is the first 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 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 [26,27,28], that ZA may help in the management of pain.

This can be particularly important because of impaired liver metabolism of drug and increased risk for encephalopathy in these patients. The referred need to continue analgesic drugs was mostly related not only to bone pain, but also to abdominal pain which is frequent in multinodular HCC. HCC patients are difficult to be evaluated as concern analgesic assumption and eventual reduction over time. In fact, opioid drug may be preferred to minor analgesic drugs, i.e. nonsteroidal anti-inflammatory drug because of reduced risk of bleeding. An increased use of drugs considered on the upper level of 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 use was used in patients with Cr Cl below 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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Figure Legends

Fig.1 Coronal 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.

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

Table 1
Comprehensive patients' profile

Pt	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	4472	Dead (10 months)
4	M/66	HCV	A	Liver, lung, ribs, right humerus, left femur	Liver surgery, CT, bone RT, sorafenib+OCT	11	545	Alive (14 mo.)
5	M/63	NAS	A	Liver, lung, abd lymph nodes, ribs, pelvis, dorsal vertebrae	bone RT, sorafenib+OCT	5	30000	Dead (6 mo.)
6	M/79	HCV	A	Liver, dorsal vertebra, pelvis	RFA, PEI, bone RT, sorafenib+OCT	9	13900	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	1430	Dead (6 months)
8	M/64	HCV	B	Rib, pelvis, lumbar vertebra	RFA, PEI, TACE, liver surgery	1	11850	Dead (1 month)
9	F/80	HCV	A	Liver, right femur	bone RT,	7	3,2	Alive (9 months)

					sorafenib+OCT			
10	M/66	HCV	B	Liver, thoracic and abd lymphnodes, rib, skull, sternum, lumbar vertebrae, sacrum	Naïve, bone RT	3	5,4	Dead (5 months)
11	M/67	HCV-HBV	A	Liver, abd lymphnodes, pelvis, thoracic and lumbar vertebrae	Sorafenib	4	225,3	Alive (6 months)
12	F/71	HCV	B	Liver, abd lymphnodes, pelvis, ribs, left clavicle, left humerus, right femur	TACE	9	192	Dead (7 months)
13	M/60	HCV	A	Liver, abd lymphnodes, pelvis, ribs, left clavicle, ribs, sternum	RFA, sorafenib	10	609,9	Alive (12 months)
14	F/68	HCV-HBV	C	Liver, abd lymphnodes, 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 lymphnodes, pelvis	CT	8	350	Dead (15 months)

Legend: 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.







