



Research Paper

Ibandronate: The loading dose concept in the treatment of metastatic bone pain



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ABSTRACT

Background/Aim: Severe bone pain is experienced by 60–80% of patients with metastatic bone disease, and has a profound impact on quality of life. Therefore, effective pain relief is an important goal in managing metastatic bone disease. Orthopedic surgeons are often challenged with patients presenting with newly diagnosed bone metastases and severe and disabling bone pain. It is important to provide fast and sufficient analgesia. Clinical trials have demonstrated that bisphosphonates reduce effectively and sustained bone pain by approved standard dosage over time. Open label prospective trials have shown that short time high dose i.v. Ibandronate is effective in rapid pain relief in different primary tumors.

Patients and methods: In 33 patients with metastatic bone pain from newly diagnosed skeletal metastases we utilized the loading-dose concept for intravenous ibandronate (6 mg infused over 1 h on 3 consecutive days).

Results: In 33 patients loading-dose ibandronate therapy significantly reduced bone pain within the first 5–7 days (VAS day 0: 6–8 vs. day 7: 3–4). Only 3 patients showed no response concerning a distinct pain reduction within the first days of therapy. There was no increase in pain medication.

Conclusion: This clinical observational study in selected patients with severe metastatic bone pain undergoing an intensive high dosed ibandronate-therapy for a short period demonstrated that loading-dose ibandronate (6 mg i.v., 3 consecutive days) resulted in a reduction of pain within days.

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1. Introduction

Tumor metastases of the skeleton occur in up to 80% of patients in progressed stages of cancer, most commonly in cases of breast, lung, prostate, kidney and thyroid tumors [1,2]. Bone metastases are often associated with pathologic fractures, hypercalcemia and spinal cord compression, as well as severe bone pain [3]. Orthopedic surgeons are challenged with patients presenting with newly diagnosed bone metastases and severe and disabling pain. Skeletal pain is commonly divided in 3 groups: ongoing pain, incident breakthrough pain and movement-evoked breakthrough pain [4,5]. Initially bone cancer patients most frequently suffer from ongoing pain, hurting as a dull, constant throbbing pain that intensifies with time [6]. In advanced stages of bone cancer extreme pain can occur spontaneously, or after weight-bearing or movement of the affected extremity [7]. Breakthrough pain is

difficult to control, often high doses of opioids and non-steroidal drugs are required, accompanied by adverse effects like somnolence, cognitive impairment and constipation [4,6]. Metastatic bone disease is a consequence of a tumor-induced imbalance of the activities of osteoclasts and osteoblasts. Bisphosphonates have been shown to be a real alternative by reducing bone pain from metastases, probably by inhibiting the underlying processes of osteoclast-mediated bone resorption [1]. First- and second-generation bisphosphonates like clodronate or pamidronate, showed significant analgesic effects in patients with metastatic bone pain [8,9]. In the need for rapid relief of severe metastatic bone pain, especially for breakthrough and opioid-resistant pain, without the negative side effects of opioids, the third generation bisphosphonate Ibandronate has been examined as a possible treatment option for patients suffering from metastatic breast cancer [2,10–12]. A large multicenter study of patients with metastatic breast cancer evaluated the impact of intravenous Ibandronate on skeletal-related events and bone pain. Patients treated with 6 mg Ibandronate intravenously every 4 weeks for 2 years experienced significant reduction in bone pain compared to a control group [13]. Mancini et al. showed in 18 patients with metastatic bone

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disease, receiving a nonstandard treatment with 4 mg Ibandronate intravenously for 4 consecutive days significantly reduced bone pain scores within 7 days [2]. Patients attending orthopedic departments with newly diagnosed bone metastatic disease are in need of rapid pain relief before being transferred to further treatment modalities. Therefore, the purpose of this current study was to evaluate the short-term efficacy and safety of loading dose Ibandronate (6 mg intravenously administered for 3 consecutive days by a 1 h infusion) in patients with newly diagnosed metastatic bone disease of different primary tumors, suffering from severe bone pain.

2. Patients and methods

Thirty-three patients with symptomatic skeletal metastases from different tumor origins were treated with intravenous Ibandronate in an open, prospective, non-randomized study. The median age of patients was 59 years (33–78 yrs) (Table 1). All patients had radiologically confirmed bone metastases and were experiencing opioid resistant pain in site of the skeletal metastases. 23 patients described vertebral bone pain due to vertebral metastases, 3 patients complained about hip pain, 7 patients described all body pain. All of the patients were admitted due to the bone pain, for none of the patients an orthopedic operation was scheduled. None of the patients had received bone radiotherapy or bisphosphonate therapy previously. Furthermore, patients were excluded if they had moderate or severe hypercalcaemia (serum calcium > 12 mg/dL), impaired renal function (serum creatinine > 1.5 mg/dL), a change to their hormonal treatment or chemotherapy during 2 months before study entry.

During the study the patients received only Ibandronate plus

opioids and non-steroidal antiphlogistic drugs. Patients were withdrawn from the study if they received other interventions that could have affected their level of pain. Ibandronate 6 mg was infused intravenously for 1 h on days 1, 2, 3 of the study. All patients were followed up until day 7 of the study. Physical examinations and assessments of vital signs were conducted on day 1 and every 2nd day thereafter. Efficacy variables included pain, and the use of analgesic. Bone pain was assessed using a visual analog scale from 0 (no pain) to 10 (worst pain imaginable) [14]. Changes in pain severity during treatment were rated as improvement when the sum of decreases in pain scored between visits outweighed the sum of increases [10]. Indirect measurement of pain was received by using the Morphine Equivalent Daily Dose (MEDD) index of opioid consumption. The MEDD is calculated as the daily morphine dose (in milligrams) multiplied by an MEDD factor of three for intravenous treatment, two for subcutaneous therapy or one for oral treatment [14]. Adverse events were monitored throughout the study (total of 7 days) and for 4 weeks after. Laboratory parameters reflecting renal function and serum calcium levels (Normal values, 8.5 to 10.3 mg/dl) were evaluated every day throughout study time.

Data for each assessment point are expressed as the mean value plus standard deviation. One tailed paired *t*-tests were performed to analyze the effects of ibandronate treatment. Significance level was set at $p < 0.05$.

The trial had been approved by the institutional ethics committee.

3. Results

The study included 33 patients with a variety of different primary tumors (Table 1). The median age of patients was 59 years (33–78 yrs). The median duration of inpatient hospitalization before starting therapy was 1 day (0–2 days). All patients remained hospitalized until they were transferred to further treatment modalities (e.g. surgery, chemotherapy, radiation) with a median stay of 9 days (range 7–10 days). At day 0, all patients enrolled in the study were experiencing severe bone pain (mean visual analog pain score 6.8 (6–8)) while receiving an equivalent of 400 mg/d oral morphine. Pain intensity significantly decreased on day 3–5 (mean VAS 4.9 (3–7)) ($p < 0.01$) and day 5–7 (mean VAS 3.7 (2–7)) ($p < 0.01$) compared to day 0 (mean VAS 6.8 (6–8)) (Fig. 1). Significant reductions from baseline in visual analog pain scores while receiving ibandronate were not based on an increased use of other analgetics. None of the patients showed an increase in MEDD index throughout the study period (Fig. 2). Only one patient not responding to Ibandronate needed additional analgesic measures with regularly used fentanyl patches. Side effects consisted mainly of fever on the day following the first intravenous

Table 1
Patient characteristics.

Primary tumor	Age in yrs	Mean baseline VAS pain score	Mean VAS pain score at day 5–7
Breast	78	7	4
Breast	52	6	2
Breast	72	7	4
Breast	51	6	2
Breast	71	7	2
Breast	34	6	3
Breast	71	7	4
Breast	42	9	3
Breast	47	7	3
Breast	71	6	4
Breast	69	5	3
Breast	75	8	4
Breast	44	6	3
Breast	57	7	4
Breast	68	6	3
Breast	76	8	5
Breast	50	8	3
Breast	61	6	2
Breast	42	8	3
Breast	66	7	4
Renal Cell Carcinoma	69	7	5
Renal Cell Carcinoma	61	6	4
Renal Cell Carcinoma	51	7	3
Renal Cell Carcinoma	56	7	3
Renal Cell Carcinoma	62	8	5
Urothelium Carcinoma	74	7	7
Urothelium Carcinoma	69	7	3
Urothelium Carcinoma	64	8	5
Bronchial Carcinoma	63	8	7
Bronchial Carcinoma	52	8	2
Malignant Melanoma	57	7	3
Malignant Melanoma	67	6	3
Neuroendocrine tumor	33	7	3

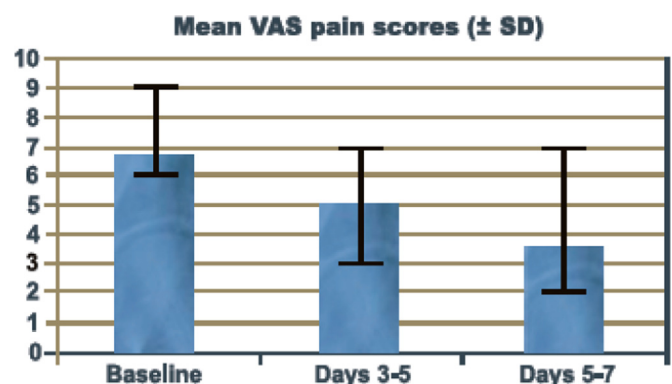


Fig. 1. : Mean VAS pain scores.

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