Bone 58 (2014) 11–16

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Rapid Communication

Bisphosphonate therapy for unresectable symptomatic benign bone tumors: A long-term prospective study of tolerance and efficacy☆

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ARTICLE INFO

Article history:
Received 9 June 2013
Revised 30 September 2013
Accepted 3 October 2013
Available online 11 October 2013

Edited by: Harry Genant

Keywords:
Bone tumor
Bisphosphonate
Tolerance

ABSTRACT

Objectives: To evaluate the long-term tolerance of bisphosphonates proposed as an alternative therapeutic option for symptomatic unresectable benign bone tumors and to evaluate the long-term efficacy of this treatment.
Methods: From March 2007 to March 2011, patients with unresectable symptomatic benign bone tumors were consecutively included in this institutional review board-approved study and treated with bisphosphonates. Prospectively long-term follow-up is reported. The study endpoints were to describe the long-term tolerance, the clinical evolution of pain for each patient and the radiological success defined as a complete disappearance of inflammation and ossification of the bone lesion. All complications and side effects were recorded.
Results: Eight patients (mean age 16 years; range 7–42) with various tumor subtypes were included: aneurysmal bone cysts (N = 5), Langerhans cell histiocytosis (N = 1), osteoblastoma (N = 1), and a giant cell tumor (N = 1). Tumors were located in cervical (N = 4) or thoracic (N = 1) vertebrae, femoral shaft (N = 1), acetabulum (N = 1) and sacrum (N = 1). Mean number of bisphosphonate cycles was 3 (range: 1–6) over a median period of 10 months. The median clinical and imaging follow-up period was 21 months (6 to 63 months). No severe complications due to treatment or lesion recurrence were reported. Pain disappeared within 6 weeks of the first cycle for all but one patient. Ossification of the bone lesion was observed for all patients but one, complete for two and partial for the five others.
Conclusions: Bisphosphonates appear to be an effective option without adverse effects for the non-operative management of symptomatic benign bone tumors.

Introduction

Symptomatic benign bone tumors can be a therapeutic challenge because of their intra-articular location or their close relationship with vascular structures or nerve roots. When these lesions are extensive into and/or outside the bone, minimally-invasive percutaneous procedures such as thermotherapies are challenging and treatment may be incomplete. Whereas in these situations, open surgery may be an ultimate option, bisphosphonates (BP) could be another alternative. These drugs are well-tolerated and have long been used for the management of various bone disorders such as osteoporosis, prevention of bone metastasis complications, or Langerhans cell histiocytosis (LCH) disease [1–4], with known effects on skeletal-related events and pain. They are stable analogs of endogenous pyrophosphate, a regulator of bone metabolism. Their ability to inhibit osteoclastic-mediated bone resorption is well known, but more recent studies have demonstrated potential anti-tumoral properties such as reducing proliferation and inducing apoptosis of tumor cell lines [5]. This has been observed particularly in third-generation nitrogen-containing compounds, also known as "aminobisphosphonates" such as pamidronate or zoledronic acid [5]. While all mechanisms are not yet completely understood, bisphosphonates inhibit tumor cell adhesion and invasion of the extracellular bone matrix [6] by interfering with osteoclastic activity or limiting the production of growth factors from the bone, thus breaking the self-stimulatory cycle of tumor progression. Moreover, preliminary findings indicate that some bisphosphonates may be angiostatic and can modulate immune responses [7].

Based on these data, we hypothesized that bisphosphonates could be a potential therapeutic option in the management of symptomatic benign bone tumors whatever their origins or locations. As long-term outcomes after BP therapy have not been previously reported, the purpose of this prospective study was twofold: first, to evaluate the long-

Abbreviations: ABC, aneurysmal bone cyst; BP, bisphosphonate; GCT, giant cell tumor; LCH, Langerhans cell histiocytosis; MDT, multidisciplinary meeting.

☆ No funding was received for this publication.

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8756-3282/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bone.2013.10.004

term tolerance of bisphosphonates proposed as an alternative therapeutic option for symptomatic unresectable benign bone tumors and second, to evaluate the long-term efficacy of this treatment.

Materials and methods

This single institution study was approved by the institutional review board and performed in compliance with the Helsinki Declaration. Written informed consent was obtained from all patients, or from parents of patients under 18 years old.

Patient selection

Patients meeting the following criteria were included in the study: presentation of symptoms (pain or discomfort) between March 2007 and March 2011; presence of a symptomatic histologically-proven benign bone tumor; percutaneous thermal ablation not possible (due to location or size of lesions, ineffective or refused by the patient); en-bloc resection or extended intralesional curettage not possible (due to location or size of the lesion) or refused by the patient; and treatment option approved in a multidisciplinary team (MDT) meeting.

Bisphosphonate therapy

We used pharmacological doses typically proposed in the treatment of osteoporosis: adult (≥18 years old) patients were treated with 1 cycle of 4 mg of zoledronic acid (Zometa®, Novartis, Rueil-Malmaison, France), whereas patients <18 years old were treated with 1 mg/kg of pamidronate (Aredia®, Novartis, Rueil-Malmaison, France) to limit the risk of toxicities [8]. For both groups, the same follow-up protocol was proposed. A clinical evaluation of pain and/or discomfort was performed at one month. If patients reported a total improvement of pain, treatment was stopped. If patients reported an incomplete improvement of symptoms, two further cycles of bisphosphonates were planned. If necessary, additional cycles could be proposed until complete resolution of symptoms. If no improvement was observed after the first administration, treatment was stopped and the patient's case was referred for discussion in an MDT meeting to identify a suitable alternative therapeutic option.

Follow-up

Long-term clinical and imaging follow-up was carried out after the last injection of bisphosphonates. Clinical evaluation of pain (Visual Analog Scale) was recorded one month after the last bisphosphonate cycle and subsequently every three months over the first year, every six months for the following two years, and once a year thereafter. In addition, imaging follow-up was performed with a contrast-enhanced MRI and CT-scan at three and six months, and then once a year.

Statistical analysis

All data relating to the treated patients were prospectively compiled on the basis of all medical, biological, imaging and biopsy reports by one of the authors (F.C.). Data were prospectively entered into a worksheet for storage (Excel; Microsoft, Redmond, WA, USA). The primary study endpoint was to evaluate the tolerance of BP therapy. Therefore, all complications and side effects were recorded and classified on the basis of criteria proposed by the National Cancer Institute Common Terminology Criteria Adverse Events (CTCAE, version 4.0). The second was the clinical evolution of pain for each patient. The third was the radiological success defined as a complete disappearance of inflammation on MR imaging and ossification of the bone lesion (with no increase in size) on CT-scan. Lesion density in Hounsfield units (HU) was measured for each lesion on a CT-scan on a similar region of interest (ROI) of 40 mm^2 before and 6 months after the last injection of BP. The relative

Table 1
Patient and tumor characteristics for patients with benign unresectable bone tumors treated with bisphosphonates.

Patient	Age (years)	Gender	Previous treatments	Location	Size (mm)	Histology	Initial pain (VAS[a])	Number of cycles	Duration of BP therapy (months)	Bisphosphonate	Outcomes (VAS)	Follow-up (months)	Radiological feature of response
1	15	F	–	Femur	60	ABC[b]	6/10	3	16	Pamidronate	No residual pain (0/10)	21	Ossification
2	20	F	–	T4	36	LCH[c]	6/10	1	–	Zoledronic acid	No residual pain (0/10)	45	Complete ossification
3	12	F	–	C4	35	Osteoblastoma	8/10	2	12	Pamidronate	Slight positional discomfort (1/10)	42	Complete ossification
4	13	M	Laser	Acetabulum	22	ABC	7/10	3	8	Pamidronate	No residual pain (0/10)	8	Partial ossification
5	7	F	–	C6	34	ABC	8/10	4	12	Pamidronate	No residual pain (0/10)	14	Partial ossification
6	19	M	–	C2	87	ABC	8/10	1	–	Zoledronic acid	Failure (8/10)	6	Failure
7	17	M	Percutaneous sclerosis	Sacrum	67	ABC	7/10	3	8	Zoledronic acid	No residual pain (0/10)	22	Partial ossification
8	42	M	–	C5	42	GCT[d]	6/10	6	6	Zoledronic acid	No residual pain (0/10)	63	Partial ossification
Mean (range)	16 (7–42)				48 (22–87)			3 (1–6)	10 (6–16)			20 (6–63)	

[a] VAS: Visual Analog Scale.
[b] ABC: aneurysmal bone cyst.
[c] LCH: Langerhans cell histiocytosis.
[d] GCT: giant cell tumor.