Journal of Bone Oncology 1 (2012) 24–29

Contents lists available at ScienceDirect

Journal of Bone Oncology

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

Research Article

Differential effect of zoledronic acid on normal trabecular and cortical bone density in oncologic patients with bone metastases

Carlo C. Quattrocchi [a,*], Paola Dell'Aia [a], Yuri Errante [a], Filomena Occhicone [a], Daniela Longo [b], Vladimir Virzì [c], Giuseppe Tonini [c], Nicola Napoli [d], Daniele Santini [c], Bruno Beomonte Zobel [a]

[a] Radiology at University Campus Bio-Medico of Rome, via Alvaro del Portillo, 21, Rome 00128, Italy
[b] IRCCS Ospedale Pediatrico Bambino Gesù, Radiology, Piazza Sant'Onofrio, 4, Rome 00100, Italy
[c] Oncology at University Campus Bio-Medico of Rome, via Alvaro del Portillo, 21, Rome 00128, Italy
[d] Endocrinology at University Campus Bio-Medico of Rome, via Alvaro del Portillo, 21, Rome 00128, Italy

ARTICLE INFO

Article history:
Received 12 January 2012
Received in revised form
23 February 2012
Accepted 23 February 2012
Available online 24 March 2012

Keywords:
Bone metastasis
Cortical bone
Trabecular bone
CT Density
Zoledronic acid
Osteolytic

ABSTRACT

Purpose: To evaluate bone density changes at the level of normal bone and bone metastases after zoledronic acid (ZA) treatment in oncologic patients.

Materials and methods: We retrospectively evaluated 72 consecutive adult patients with histologically confirmed solid tumors with at least 1 newly diagnosed bone metastatic lesion. Bone metastases were diagnosed by bone scans and confirmed with computed tomography (CT). Patients received intravenous ZA, 4 mg, by 15-min infusion every 28 day through a peripheral or a central venous access and were monitored for at least 3 months and a maximum of 24 months. Bone density was determined at the level of bone metastases and at the level of normal trabecular and cortical bone using a ROI-based approach.

Results: A significant increase was demonstrated at the level of normal trabecular bone of the calvarium and the femoral neck. No significant increase of density was observed at the level of the normal cortical bone. Bone metastases showed a significant increase in CT density as compared to baseline up to 24 months after zoledronic acid.

Conclusion: We have found that long term treatment with ZA increases trabecular bone density in oncologic patients whereas normal cortical bone changes are not detectable.

1. Introduction

Patients with advanced breast, prostate, lung and colo-rectal cancer frequently develop bone metastases (BMs). These lesions may be asymptomatic or may cause pain, pathologic fractures, malignant hypercalcemia, epidural spinal cord compression and/or shorten survival [1]. The underlying pathophysiology of BMs involves reciprocal interactions between tumor cells and the bone micro-environment that lead to the disruption of the balanced physiological activity between osteoblasts and osteoclasts. Loss of this critical balance results in a spectrum of osteolytic to osteoblastic bone lesions [2].

Computed tomography (CT) provides accurate morphological images of bone, allowing visualization of cortical and trabecular bone, tumor margins and dimensions [2]. Anatomical extension of lesions is depicted on CT studies as well as the presence of sclerosis in the context of lytic lesions [3]. Whole-body CT scans are diffusely used to detect osteolytic, mixed or osteoblastic bone lesions in the staging, follow-up and re-staging studies of oncological patients. CT scans are also considered crucial in the assessment of the bone response to therapy [2,4,5]. In osteolytic bone metastases, indeed, an increase of density is considered an indicator of response to therapy [2].

As potent inhibitors of osteoclast function, biphosphonates are being incorporated into the management of metastatic bone disease [6], with beneficial effects on skeletal complications [7,9], bone pain [9], quality of life [7–9], particularly in advanced breast cancer [7,10], multiple myeloma [8,11], and more recently in lung, prostate and kidney cancer [12,13]. Zoledronic acid (ZA) is a potent third generation nitrogen-containing biphosphonate, which has been widely used in the treatment of Paget's disease of bone [14], hypercalcemia [15], multiple myeloma [16], breast cancer BMs [16], prostate cancer BMs [17], lung cancer BMs [18] and osteolytic BMs [19,20].

In patients with BMs, decrease of bone density is the consequence of several factors, not only of pathologic mechanisms at

* Corresponding author. Tel.: +39 333 4167636.
E-mail address: c.quattrocchi@unicampus.it (C.C. Quattrocchi).

2212-1374/$ - see front matter © 2012 Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
doi:10.1016/j.jbo.2012.02.001

bone metastatic sites, but also of the normal ageing process, of concurrent postmenopausal or drug-related osteoporosis, or of androgen-deprivation therapy in men with prostate cancer [21].

In multicenter randomized controlled trials, once yearly injection of 5 mg of ZA has been demonstrated to significantly reduce the risk of vertebral and hip fractures in postmenopausal women [22] and the risk of recurrence of clinical fractures in men and women with a recent hip fracture [23].

Sclerosis of bone metastases has been documented by CT imaging after ZA treatment in studies [24–26] conducted on patients at an advanced stage of cancer. However, the CT changes of the normal bone after ZA treatment in oncological patients has not yet been established.

The primary aim of this study was to determine CT density changes of the normal trabecular and cortical bone tissue in oncological patients undergoing routine whole body CT examinations; as reference, in the same group of patients, the rate of sclerosis of bone metastases up to 24 months after the initiation of ZA treatment was evaluated.

2. Materials and methods

2.1. Patients

We conducted a retrospective analysis of adult patients with histologically confirmed solid tumors with at least 1 newly diagnosed bone metastatic lesion. Bone metastases were diagnosed by bone scans and confirmed on CT images. The study was carried out according to the principles of the Declaration of Helsinki. Our institutional review board approved the study and all patients provided a written informed consent to receive ZA administration and to undergo CT examinations.

The patients underwent therapy with ZA (Zometa®, Novartis Pharma, USA) in the period between December 2004 and February 2010. We included patients with a total bilirubin level lower than 2 mg/dL, and serum creatinine level lower than 2 mg/dL, to avoid the effects of prolonged immobility and hepatic or renal osteodystrophy on bone metabolism. Patients with proven peptic ulcer, poor performance status unrelated to bone disease (WHO 3 ± 4), Paget's disease, primary hyperparathyroidism, administration of calcitonin and any prior treatment with bisphosphonates were excluded from the study.

Concurrent cytotoxic, hormonal or steroid therapy was permitted. Each patient was treated with chemotherapy and/or radiotherapy, using an individualized therapeutic approach according to the current international recommendations and the institutions' practice. Patients with metastatic breast cancer were allowed to receive hormonal therapy with tamoxifen or aromatase inhibitors in case of estrogen and/or progesterone receptor positive disease. Patients with castration-sensitive metastatic prostate cancer as well as patients with castration refractory disease were allowed to continue androgen deprivation therapy with luteinizing hormone-releasing hormone (LHRH) analogs and/or anti-androgens. Patients received intravenous ZA, 4 mg, by 15-min infusion every 28 day through a peripheral or a central venous access and were monitored for at least 3 months and a maximum of 24 months. According to standard procedures, supplementation with vitamin D (400 Units/die) and calcium (500 mg/die) was added.

All patients were monitored for skeletal related events (SREs) by physical examination and by diagnostic imaging techniques (X-rays, CT scan, or magnetic resonance imaging scan) at any symptom or sign indicating skeletal disease progression. The definition of SRE included pathologic fractures, surgery or radiotherapy to bone to treat or prevent an impending fracture, palliative radiotherapy to bone, spinal cord compression, malignant hypercalcemia, and changes in antineoplastic therapy because of worsening bone pain.

2.2. CT scans

CT images were obtained using a 16 and a 64 slice CT scanner (Somatom Sensation, Siemens, Erlangen, Germany). Whole body CT scans were acquired at baseline (prior to treatment) and every 3 and/or 6 and/or 12 months, according to the staging and restaging needs of each patient, to the current international recommendations and to the institutions' practice. WBCT used for the analysis were performed up to 24 months after the initiation of treatment with ZA. Images were obtained using the whole body protocol (KV 120, 140 mAs, B30 kernel) and were reformatted at 5 mm section thickness, before and after bolus administration of non-ionic iodinated contrast agent, at the concentration of 350 mg/mL (Iobitridol, Xenetix®, Guerbet, France), injected intravenously with a power injector (EnVision; Medrad Italia, PV, Italy) (total volume = 120 mL, flow = 3 mL/min).

Image evaluation was conducted on a separate workstation applying bone-specific Hounsfield Units (HU) windows (width: 2500 HU; window level: 480 HU). By using a two-reader consensus, C.C.Q. and P.D. drew regions of interest (ROIs) on images obtained in the contrast-enhanced scan (60–70 s after contrast injection). After opening the CT scans on the eFilm workstation (MERGE-Healthcare, NL), images were anonymized with no access to the date of the examination. ROIs were chosen at the level of the bone metastases on the basis of concordant CT and bone scans at baseline. Bone lesions previously treated by radiotherapy were not considered for analysis.

ROIs were drawn at the level of normal trabecular and cortical bone in the occipital calvarial bone chosen as a non-weight-bearing, and in the left femoral neck chosen as a weight-bearing skeletal segment. At the level of the normal trabecular bone of the left femoral neck, negative values related to the high content of fatty bone marrow were not considered for analysis and alternative ROIs were drawn.

At each site, three circle-sized ROIs (0.1 cm^2 for bone metastases and normal trabecular bone and 0.05 cm^2 for normal cortical bone) were drawn on an eFilm workstation (MERGE-Healthcare, NL) and the average value was used for analysis (Fig. 1). Since mixed bone metastases are frequent in patients with advanced cancer, two groups of predominantly lytic or predominantly sclerotic metastases were classified according to an attenuation threshold value of 300 HU, as previously reported [27]. Measurements were obtained at baseline CT and at the CT scans performed 12 and 24 months after the initiation of ZA treatment.

2.3. Statistical analysis

Patient demographic data, clinical data, primary tumor characteristics and CT density measurements were loaded on a database.

The absolute data were plotted and the relative increments to baseline were calculated.

Descriptive statistics (median, quartiles, ranges, average and standard deviation) was performed. The difference between groups was determined using the non-parametric Wilcoxon signed ranks test on the SPSS platform (SPSS, 14.0). The $p = 0.05$ was considered as the threshold for a significant difference among groups.

3. Results

3.1. Patients

We included 72 consecutive patients (35 males and 37 females). The mean age at the diagnosis of bone metastases was 67 ± 12 ($\pm$ standard deviation) years. Demographic details are