Case report

Long-term effect of intermittent cyclical etidronate on microarchitecture and quality of trabecular bone in an elderly woman with severe osteoporosis

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Introduction

Osteoporosis is internationally defined as a systemic skeletal disease, characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility of the skeleton and susceptibility to fracture [1]. For this reason, pharmaceutical interventions should be aimed at preventing fragility fracture related to osteoporosis. Bisphosphonates (BPs) are the first line of agents developed for preventing vertebral fracture [2]. Because of properties of inhibiting activities of osteoclasts, BPs are clinically useful in increasing bone mass and reducing incidences of fragility fracture in osteoporosis. Etidronate is a first-generation BP that is approved in several countries, including Japan [3], for clinical use in the treatment of osteoporosis as well as Paget’s disease of bone and hypercalcemia associated with malignancy.

This chemical compound is known to have a relatively narrow therapeutic window between doses adequate for inhibitory effect on bone resorption [4] and that inducing the risk of calcification defects of the bone matrix [5,6]. Therefore, etidronate is commonly administered to osteoporotic patients intermittently at a dose of 200 or 400mg for 2 weeks followed by about 10 weeks free from drug administration, and this cycle is repeated (intermittent cyclical etidronate, ICE). Although previous clinical trials with ICE have shown antvertebral fracture efficacy in postmenopausal women with osteoporosis [7–13], little is known of the long-term effects of ICE on microarchitectural change and its safety profile in bone tissue.

We evaluated the histomorphometry and microarchitecture of trabecular bone at tissue levels in addition to bone mass in an elderly woman with established osteoporosis and at a high risk of subsequent fragility fracture, who underwent iliac crest bone biopsy more than 3 years following the initiation of ICE.

Case report

The patient was an 80-year-old Japanese woman. She was diagnosed as having osteoporosis when aged 70 years because she developed lower back pain and sustained multiple vertebral fractures (Fig. 1). At 75 years of age, she was admitted at Osaka City University Hospital. Lumbar spine bone mineral density (BMD) determined by dual X-ray absorptiometry (QDR2000; Hologic, Waltham, MA, USA) was 0.509g/cm², equivalent to 50.3% of the mean value of that of the Japanese young female population. Other generalized metabolic bone disorders such as osteomalacia were excluded by the findings of histology from an iliac crest bone biopsy after tetracycline (TC) double labeling. Thereafter, she received 100U/week of human parathyroid hormone PTH(1-34) subcutaneously for 12 months, resulting in a progressive increase in lumbar spine BMD [14]. Following the treatment with human PTH(1-34) she was administered 20 U/week of salmon calcitonin intramuscularly for 27 months. Although the BMD decreased to the basal level of the first visit during the salmon calcitonin treatment, newly developed vertebral fractures were not found on radiographs in this clinical course, and her lower back pain was gradually alleviated, leading to quality of life (QOL) improvement.

When she was 78 years old, these pharmaceutical interventions were followed by treatment with ICE (200mg/day of etidronate, Didronel; Sumitomo Phar-
pharmaceutical, Osaka, Japan) before bedtime for 2 weeks followed by 10 weeks free from the administration of etidronate and supplementation of 600 mg/day of calcium (Ca) l-aspartate (79 mg elemental Ca) given after meals (Fig. 2). A significant increase in spinal BMD was observed, and there was no incidence of vertebral fractures. She did not complain further of backache or loss of body height, eventually leading to improvement of her QOL. Forty-two months following the initiation of ICE, a second iliac crest bone biopsy was performed by vertical approach after double labeling with tetracycline hydrochloride to exclude abnormality of bone quality and confirm the safety of bone at bone remodeling unit (BRU) and tissue levels. Informed consent was obtained from her to participate in the present investigation for the evaluation of the long-term effects of ICE on histomorphometry and microarchitecture of trabecular bone tissue. Bone specimens were embedded with methylmetacrylate (MMA), and undecalcified and Goldner-stained thin sections were prepared for bone histomorphometry using semiquantitative software (Osteomeasure; Osteometrics, Atlanta, GA, USA). Although microscopic observation under ultraviolet light revealed relatively reduced surfaces of TC labeling, we could not find any evidence of mineralization defect of bone matrix (e.g., unclear double TC labeling and increased osteoid width) or adynamic bone characterized by a marked reduction in the number of osteoblasts and osteoclasts (Fig. 3). No abnormalities of bone quality were noted by microscopic observation under polarized light (Fig. 3). Bone histomorphometry using paired biopsy revealed both increase in bone volume and decrease in osteoid volume/surface. Osteoid thickness increased by a small extent, staying within a normal range. Bone eroded/osteoclast surface of the trabecular bone was decreased. However, all the values of these parameters were within reference ranges of postmenopausal women previously reported [15]. Similar to static parameters, dynamic parameters related to bone formation were also decreased, except mineral apposition rate, which reflected mineralization at BRU levels (Table 1).

The MMA-embedded block together with one from the previous biopsy were employed to be scanned with a µ focus X-ray CT device (Nittetsu Elex, Tokyo, Japan) and then the images of two- and three-dimensional (2D, 3D) microarchitecture of trabecular bone were reconstructed and were subjected to measurements of microarchitectural parameters and node-strut analysis [16]. Values of the parameters of microarchitecture of the trabecular bone (e.g., bone volume, trabecular

Fig. 1. Lateral views of spinal radiographs at first admission denoting multiple vertebral fractures

Fig. 2. Pharmaceutical interventions and change in lumbar spine bone mineral density

Fig. 3. Unstained sections obtained by second iliac crest biopsy. Surfaces of tetracycline (TC) labeling were relatively reduced without any appearance of unclear double TC labeling under UV (left panel, ×200). Observation of bone matrix under polarized light denoted normal lamellar pattern (right panel, ×200)