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Original article

Bone health in a prospective cohort of postmenopausal women receiving aromatase inhibitors for early breast cancer

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ABSTRACT

Objective: Baseline bone health in postmenopausal women is poorly characterized in prospective series of early breast cancer (EBC) patients candidates to aromatase inhibitor (AI) therapy. Our objective is to comprehensively evaluate bone health in a prospective clinical cohort of patients recruited prior to adjuvant AI therapy, with the aim of establishing potential AI impact on bone loss and fractures.
Methods: From January 2006 to April 2010, we consecutively included 343 women with EBC who were about to start adjuvant AI therapy. Participants were assessed at baseline (before AI initiation) and at 3 months, with annual assessments thereafter. Bone mineral density (BMD), spine X-ray, bone metabolism (vitamin D [25(OH)D], bone turnover markers [BTM]), arthralgia and quality of life are measured.
Results: Mean age was 61.9 years; 197 (57.4%) had been previously treated with tamoxifen; 145 (42.3%) were taking exemestane, 187 (54.5%) letrozole, and 11 (3.2%) anastrozole.
Analysis of baseline data shows only 59 women (17.7%) had normal BMD; 200 (60.1%) had osteopenia and 74 (22.2%) had osteoporosis; 39 women (11.4%) had a prevalent fracture, 293 (89.1%) had 25(OH)D insufficiency (<30 ng/ml), and 61 (18.5%) severe deficiency (<10 ng/ml). Low 25(OH)D concentrations were associated with lower BMD and 233 (67.9%) participants had some degree of arthralgia.
Conclusions: Low bone mass, prevalent fractures and vitamin D insufficiency were highly prevalent among candidates to adjuvant AI for EBC. Therefore, it is crucial to assess BMD, prevalent fractures and 25(OH)D concentrations before starting AI therapy and during follow-up.

Introduction

Breast cancer is the most prevalent type of neoplasm in women, and the second highest cancer-related cause of death in developed countries.[19] Fortunately, many patients achieve long-term survival due to therapeutic improvements in recent years. A major advance for postmenopausal women with receptor-positive breast cancer has been the incorporation of aromatase inhibitors (AI) into adjuvant therapy.[33] Improved survival has led us to review quality of life issues, particularly those related with adjuvant treatments.

Aromatase inhibitors (anastrozole, exemestane and letrozole) massively deplete circulating estrogens in postmenopausal women. Their use has been related to an increased risk of bone loss and fractures in women receiving these drugs for 2–5 years as adjuvant treatment.[3,6,26] Guidelines have been developed to help clinicians prevent and manage AI-associated bone loss[13,28]; but these guidelines are based on large AI clinical trials, a setting which might well differ from actual practice.

In the pivotal trials of AI in adjuvant settings, the baseline bone mineral density (BMD) status of patients was not reported.[26] Although osteoporotic fractures constitute the most important risk factor for the development of incident fractures[20]; their prevalence prior to AI therapy in these trials is also not known.

We are currently conducting a prospective, non-selected, cohort study to investigate bone health (BMD, fractures occurrence, bone turnover markers (BTM), and vitamin D concentrations) in postmenopausal women treated for EBC with adjuvant AI therapy. The

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main aim is to provide data from actual practice to establish the potential role of various assessments and interventions to correctly evaluate and reduce the impact of AI therapy on bone loss and fractures.

Methods

Study design

Prospective, non-selected, observational, clinical cohort study, conducted at the Breast Cancer Unit and Bone Metabolism Unit, Hospital del Mar, Barcelona, Spain.

Subjects

From January 2006 to April 2010, Caucasian postmenopausal women with early breast cancer (EBC), candidates to be treated with AI and attending the outpatient Breast Cancer Unit, were consecutively invited to participate in this trial and, after signing informed consent, were included in the study. (See Patients Flowchart, Fig. 1.) Some of the 343 participants had received tamoxifen for 2–3 years or 5 years (switch group), and others were prescribed AI as initial therapy (upfront group).

Postmenopausal status was defined as patients >55 years old with amenorrhoea during >12 months, or those ≤55 with levels of luteinizing hormone >30 mIU/ml or follicle-stimulating hormone values >40 mIU/ml.[4]

Patients were excluded if they had a history of any bone disease, rheumatoid arthritis, or metabolic or endocrine diseases potentially affecting BMD; prior diagnosis of Paget's bone disease or osteomalacia; or concurrent or previous treatment with bisphosphonates, oral corticosteroids or any other bone-active drugs.

Measurements

The following assessments have been recorded at baseline and, unless otherwise noted (BMD and X-rays), after 3 months of AI, calcium and vitamin D therapy. Measurements will be repeated annually throughout the AI treatment period.

Bone mineral density

At baseline and annually, BMD is measured at lumbar spine L2-L4 (LS), femoral neck (FN) and total hip (TH) using a dual-energy X-ray densitometer QDR 4500 SL® (Hologic, Waltham, Mass, USA), following the usual protocol in our Bone Metabolism Unit. In our department, the technique has an in vivo coefficient of variation (CV) of 1.0% for LS, 1.65% for FN and 1.60% for TH measurements.

Spine and non-vertebral fractures

Previous non-fragility fractures, height decrease, and back pain were recorded at baseline. Thoracic and lumbar spine X-rays, performed at baseline and annually, will identify or rule out silent spine fractures.[10] Fractures produced with low trauma or caused by a fall from a standing height or less are defined as non-vertebral osteoporotic fractures. Hip, pelvis, distal femur, proximal tibia, multiple rib, forearm, and proximal humerus fracture sites are considered.[5] Fractures of fingers and toes are excluded.

Serum levels of 25-hydroxy-vitamin D and PTH

Plasma concentrations of 25-hydroxy-vitamin D (25(OH)D) are determined by competitive immunoluminometric direct assay with directly coated magnetic microparticles (DiaSorin Iberia SA, Madrid, Spain). Our laboratory is part of the vitamin D external quality assessment programme of the College of American Pathologists (www.cap.org). The detection threshold of the tool is 4.0 ng/ml, intra-assay CV is 5.7%, and inter-assay CV is 9.9%. We have defined *normal* concentrations of 25(OH)D as ≥30 ng/ml,

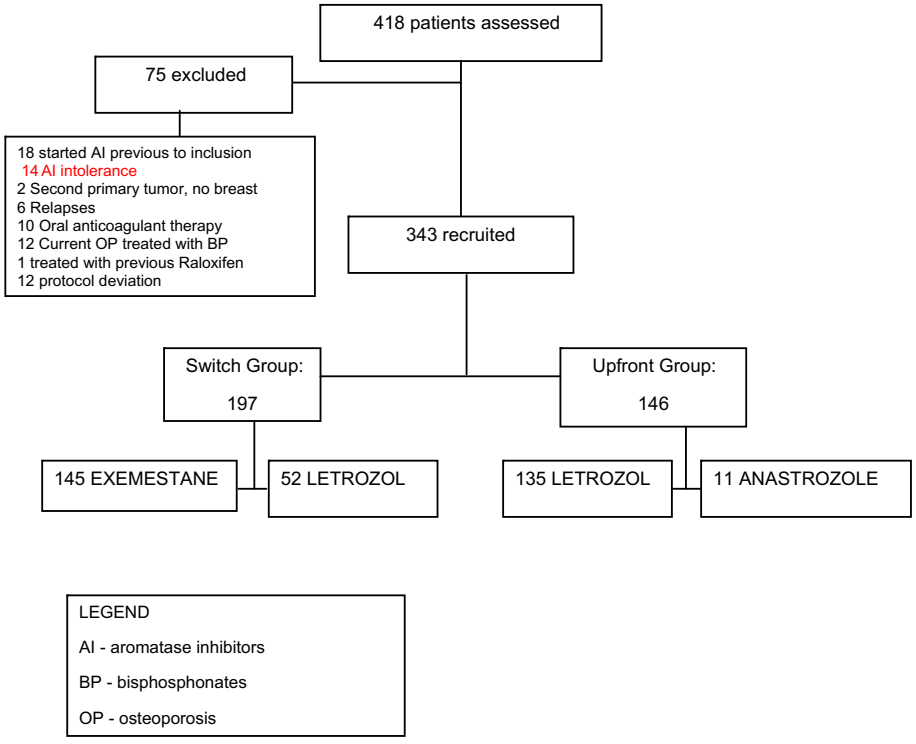

Fig. 1. Flowchart of patients' inclusion.