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Original Research

Osteoporosis treatment and 10 years' oestrogen receptor+ breast cancer outcome in postmenopausal women treated with aromatase inhibitors

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Abstract ***Background:*** Risk factors for breast cancer relapse are well-known, such as large tumour size or lymph node involvement. The aim of our study was to analyse the influence of bone mineral density, fractures and bisphosphonate or vitamin D prescription on 10 years' breast cancer outcome.

Patients and methods: This is a longitudinal and prospective cohort of 450 postmenopausal women with local oestrogen receptor (ER)+ breast cancer. For every patient, we analysed tumour characteristics, bone status at the beginning of aromatase inhibitor treatment and 10 years' cancer outcome with Cox model.

Results: Mean follow-up was 10.3 ± 3.0 years. Seventy nine women died, and 75 had a relapse; 30.7% had a history of fracture, 16.9% had a T-score ≤ −2.5 and 11.3% had vitamin D deficiency. Bisphosphonates were prescribed to 35.3% women for osteoporosis for a mean duration of 5 ± 1.7 years. Tumour size (hazard ratio [HR] = 1.32, $P \leq 0.01$) and the number of lymph nodes involved (HR = 1.07, $P = 0.03$) were significantly associated with relapse. Bisphosphonate treatment was significantly associated with a decreased risk of relapse (HR = 0.51, $P = 0.03$). Age at cancer diagnosis (HR = 1.07, $P \leq 0.01$) and vitamin D deficiency (HR = 1.85, P = 0.04) were significantly associated with an increased risk of death,

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whereas bisphosphonate treatment was associated with a decreased risk of death (HR = 0.46, $P = 0.01$).
Conclusion: Osteoporosis treatment, including vitamin D and bisphosphonates, is associated with a 50% reduction of relapse and death in women treated with aromatase inhibitors for ER+ breast cancer.

1. Introduction

For 15 years, a multidisciplinary approach combining surgery, radiotherapy, chemotherapy and hormonal therapy has significantly improved the prognosis of breast cancer, resulting in fewer recurrences or death. Thus, the survival rate at 5 years in North America and Europe is currently close to 90% [1], depending on well-known risk factors for relapse such as large tumour size, lymph node involvement, high-grade tumour, an absence of progesterone and oestrogen receptors and expression of human epidermal growth factor receptor (HER) protein [2]. Despite substantial progress in breast cancer biology knowledge, the prognosis for an individual patient remains to be fully understood. It has been shown that host factors such as younger age (<35 years), obesity and low activity level also represent risk factors for breast cancer relapse. Several data suggest that bone health could be an important parameter for breast cancer outcome. First, bone tissue is the main site for metastasis, particularly in oestrogen receptor (ER)+ breast cancers [3] with well-known mechanisms of tumour-stromal interactions in the development of bone metastasis [4]. Second, animal studies have shown that ovariectomy-induced osteoporosis can increase tumour growth in some cancers [5,6]. Third, vitamin D deficiency, which induced excessive bone remodelling and fractures, has been associated with a worse outcome of breast cancer [7]. Finally, high doses of bisphosphonates that decrease bone turnover are associated with better prognosis in early or advanced breast cancer [8].

On the other hand, chemotherapy and hormonotherapy can induce excess bone remodelling and bone resorption, decrease bone mineral density (BMD) and bone quality and finally increase the risk of vertebral, humeral and hip fractures [9]. Thus, it is now recommended to assess the risk of osteoporosis in women with breast cancer and to treat them using lifestyle recommendations, vitamin D supplementation and specific treatment such as bisphosphonates in the case of a history of osteoporotic fracture or low bone density [10].

The aim of this longitudinal study was to analyse, alongside classic risk factors for breast cancer relapse, the effects of BMD, fractures, vitamin D and PTH concentrations, vitamin D supplementation and bisphosphonate treatment on 10 years' breast cancer outcome.

2. Patients and methods

2.1. Patients

This prospective, observational and longitudinal study was conducted by both the Department of Rheumatology of the University Hospital of Angers and the Department of Medical Oncology of the Integrated Centre of Oncology of Angers. Inclusion period was from January 2004 to January 2006. During this period, 497 consecutive postmenopausal women with breast cancer were referred to our Department of Rheumatology to assess osteoporosis. Thirty-one were excluded because of metastasis history or discovering at the time of bone assessment. Sixteen patients were excluded because of incomplete oncologic data. Finally, inclusion in the cohort and follow-up were performed on 450 postmenopausal women with ER+ breast cancer (flow chart in Fig. 1).

2.2. Methods

2.2.1. Bone and general health

Methods have been already published [11]. All included women had a general and bone assessment within the first three months of aromatase inhibitor (AI) therapy. We performed an extensive medical history and a physical examination including age, age at onset of menopause, body mass index (BMI), family history of osteoporosis, personal history of fractures, medications, alcohol and tobacco use, physical activity, vitamin D supplementation and calcium food intake. A fasting serum sample including calcium (normal values: 2.25–2.60 mmol/l), phosphate (normal values: 0.82–1.45 mmol/l), albumin (normal values: 35–52 g/l), creatinine (normal values: 40–66 μmol/l), 25(OH) vitamin D (Nichols Institute Diagnostics, San Clemente, CA) (normal values: 75–250 nmol/l), parathyroid hormone (PTH) (Beckman Coulter, Brea, CA) (normal values: 15–65 pg/ml) and C-terminal telopeptide of type I collagen (CTX) (normal values for postmenopausal women: 0.33–0.78 μg/l) was collected. Measurements were performed immediately without freezing. BMD measurement was realised on the lumbar spine, femoral neck and total hip using dual energy X-ray absorptiometry operating in fan-beam mode (Hologic QDR 4500A densitometer; Hologic Inc., Waltham, MA). As