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Original article

Fracture incidence in pre- and postmenopausal women after completion of adjuvant hormonal therapy for breast cancer

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ABSTRACT

Introduction: Although the effect of hormonal therapy (HT) on fracture risk during treatment of breast cancer is established, information about fracture incidence after completion of HT is scarce. In this hospital based observational study we evaluated fracture rates after completion of HT in pre- and postmenopausal women with breast cancer.
Methods: All women diagnosed with breast cancer in the VieCuri Medical Center between 1998 and 2005 who started adjuvant HT with aromatase inhibitors or tamoxifen were included (n = 289). Data on fracture rate, fracture type and risk factors for fracture after completion of HT were collected.
Results: The overall fracture rate was 12% in pre- and 15% in postmenopausal women respectively during an average follow-up of 3.1 ± 2.9 years. The number of patients with at least one fracture was 41 (14%). There was no difference in fracture rates between different types of HT ($P = 0.15$). The most common types of fractures were toe/finger fractures in premenopausal- and hip and major fractures in postmenopausal women. Median time to first fracture was shorter in premenopausal women (1.4 years, IQR 0.2–3.5) than in postmenopausal women (2.4 years, IQR 0.7–5.1, $P = 0.01$). A history of previous fracture was a significant risk factor for fracture in postmenopausal women (HR 3.9, 95% CI 1.3–11.7).
Conclusion: Fracture rates in the first years after cessation of HT for breast cancer were 12% and 15% for pre- and postmenopausal women respectively. The most common fractures in postmenopausal women were hip and major fractures.

Introduction

Breast cancer is the most common type of cancer among women [1]. Incidence rates as well as survival rates for breast cancer have increased with about 5% between 1990 and 2002 [2]. In January 2003, 1 in 73 European women was living with a previous diagnosis of breast cancer [3].

One of the reasons for the improving survival of patients with hormone receptor positive breast cancer is the introduction of hormonal therapy (HT) as standard adjuvant therapy (tamoxifen and aromatase inhibitors (AIs)) [4]. Both AIs and tamoxifen inhibit the stimulating effect of estrogen on breast tissue [5,6]. The use of AIs as adjuvant treatment for breast cancer has increased rapidly due to the fact that AIs (either alone or in combination with tamoxifen) have shown a significant survival benefit over other endocrine therapies [7–10]. In patients receiving HT, bone health is a major point of interest. A decrease in estrogen causes loss of bone mineral density (BMD) [11] which increases the risk of a clinical fracture [12]. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial in postmenopausal women reported significantly more fractures during treatment with anastrozole compared to tamoxifen (OR 1.33, 95% CI 1.15–1.55), but no differences in fracture rates were found after completion of therapy (OR 0.98, 95% CI 0.74–1.30)

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[13]. The Austrian Breast & Colorectal Cancer Study Group 12 (ABCSG-12) trial in premenopausal women found no differences in fracture incidence between tamoxifen and anastrozole during or after treatment [14,15].

The European osteoporosis guideline does not mention adjuvant HT as secondary cause for osteoporosis [16] while Dutch national guidelines do [17]. Neither of them mentions how to approach bone health after completion of adjuvant HT. Therefore, information on the fracture rate in breast cancer survivors after completing HT is needed.

The aim of this study was to evaluate fracture rates after completing HT in pre- and postmenopausal breast cancer patients. Time to first fracture, type of fracture and specific risk factors were evaluated.

Materials and methods

Patients

This observational chart review study included data of all patients diagnosed with breast cancer in the VieCuri Medical Center between 1998 and 2005 who started adjuvant therapy with AIs or tamoxifen (N = 427). VieCuri Medical Center is a large non-academic teaching hospital in the southeastern part of the Netherlands. Diagnosis of breast cancer was based on pathology reports and clinical diagnosis at admission.

Women with known osteoporosis at diagnosis were excluded (N = 7), as were stage IV breast cancer patients (N = 10), patients who initially accepted but later refused HT (N = 7), patients with missing files (N = 2), patients with a pathological fracture (N = 1) and patients who died within 5 years after diagnosis (N = 111). After exclusion, data of 289 patients were included in this study. The Ethics Committee of the institution approved the study.

Definitions and procedure

Patient-, tumor-, treatment- and fracture characteristics were retrieved from medical records. Date of breast cancer diagnosis was defined as date of pathological diagnosis. Menstrual status at diagnosis was defined as pre- or postmenopausal. When no information was available about menstrual status, women >55 years were labeled postmenopausal. Type of hormonal therapy (HT) was defined as tamoxifen, aromatase inhibitor or both (the latter meaning patients who switched therapies at any point during treatment). If no information was available on whether or not women had switched therapy, patients were defined as “not switched”. Date of cessation of HT was defined as last day of HT or the date 5 years after date of diagnosis when no information was available. Duration of HT was defined as date of diagnosis to date of cessation of HT. The duration of HT was corrected for chemotherapy. This was done because HT was not initiated until chemotherapy treatment was completed. Therefore we corrected the duration of HT for the average duration of the different chemotherapy regimens using 24 weeks for Cyclophosphamide, Methotrexate and Fluorouracil (CMF), 15 weeks for 5-Fluorouracil, Epirubicine and Cyclophosphamide (FEC) and 16 weeks for other types of chemotherapy. The mean duration of HT was 5.8 ± 2.0 years. Duration of follow-up was defined as date of cessation of HT to death or end of study (1st of September 2012).

All fractures were checked by evaluation of X-rays and were recorded by date, type and location. Fractures were classified according to Center et al. [18] into hip fractures, major fractures (vertebra, pelvis, distal femur, proximal tibia, multiple rib, and humerus), minor fractures (all remaining osteoporotic fractures, except fingers and toes), and finger and toe fractures. Fracture rates were given as percentage and were defined as at least one fracture, excluding multiple fractures within one patient. The only exception was type of fracture for which all fractures were used, including fractures that occurred within the same person. Time to first fracture was defined as time from cessation of HT to first fracture.

Other characteristics that were collected were: height, body weight and body mass index (BMI) at cessation of hormonal therapy; smoking status at cessation of HT; pathological tumor stage; administration and type of chemotherapy before start of HT; history of fracture before cancer diagnosis (defined as >1 fracture, not caused by a high-energetic trauma); co-morbidity at diagnosis (chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis (RA)); medication use at any point during follow-up (bisphosphonates, calcium, vitamin D, corticosteroids); and presence of at least one risk factor for falls (lower extremity osteoarthritis; ≥1 falls per year; impaired vision (including cataract); urine-incontinence; and the use of a walking-aid).

Statistical analysis

Continuous variables were presented as mean with standard deviation and categorical variables were presented as number with percentage. Baseline characteristics were stratified for menopausal status. Differences between categorical variables were calculated using the Chi square test, and between not normally distributed variables using an independent-samples median test.

Kaplan–Meier curves were used to show cumulative time to first fracture. Patients who died before occurrence of a fracture or who did not develop a fracture before the end of the study were censored at date of death or end of study, respectively. Differences in cumulative time to first fracture between treatment groups were tested with the log-rank test. Time to first fracture was presented as median with interquartile range (IQR). Cox proportional hazard models were used to calculate independent hazard ratios for developing ≥1 fracture, with and without adjustment for age. For all statistical analyses IBM SPSS Inc., version 20 (Chicago, IL, USA) was used.

Results

Population description

Patient characteristics according to menopausal status are presented in Table 1. Of all patients 29% (N = 83) was premenopausal at diagnosis; 32% used tamoxifen (N = 92), 14% used AI (N = 39) and 55% used both (N = 158). The mean duration of HT was 5.8 ± 2.0 years. Mean age at moment of cessation of HT was 51.6 ± 7.1 years in premenopausal patients and 71.4 ± 10.1 years in postmenopausal patients. The mean follow-up period from cessation of HT was 3.1 ± 2.9 years. During follow-up 23% of the patients died (N = 67).

Fracture rates (Table 2)

In total 41 patients sustained one or more fractures during follow up (14%). Fracture rates were 12% (N = 10) in premenopausal women and 15% (N = 31) in postmenopausal women. Fracture rate per treatment group was 20% for tamoxifen (N = 18), 8% for AI (N = 3) and 13% for both (N = 20). These fracture rates were not significantly different between groups ($P = 0.15$). The total number of fractures was 54; 10 in premenopausal women and 44 in postmenopausal women. Nine postmenopausal women sustained more than one fracture. The most common fractures were toe/finger fractures (60%, N = 6) in premenopausal patients and major (55%, N = 24) and hip fractures (16%, N = 7) in postmenopausal patients.