Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial


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Received 2 December 2008; revised 15 January 2009; accepted 19 January 2009

Introduction

Aromatase inhibitors (AIs) profoundly lower circulating estrogen levels in postmenopausal women [1, 2], predisposing them to increased bone loss and fracture risk, while tamoxifen has a protective effect on bone loss in postmenopausal women [3]. The increase of bone fractures for patients who receive AIs compared with tamoxifen is described in all recent adjuvant trials comparing AIs to tamoxifen in postmenopausal breast cancer patients, including the Breast International Group (BIG) 1-98 trial [4–10]. All these studies consistently show that AIs are associated with superior disease control compared with tamoxifen. In 2004, an expert panel of the American Society of Clinical Oncology, after review of the published data, recommended including an AI in the adjuvant setting either as initial treatment or after treatment with tamoxifen for adjuvant hormonal therapy for postmenopausal women with hormone receptor-positive breast cancer [11]. Apart from AIs being regarded as part of routine adjuvant therapy for postmenopausal breast cancer patients, they are being studied...
in combination with ovarian suppression in premenopausal breast cancer patients and even for prevention. It is therefore important to thoroughly evaluate these newer agents for side-effects. Postmenopausal women naturally experience increased bone loss and are at risk of fractures, which can severely impact their quality of life and impair their ability to cope with the activities of daily life. Any increase in this risk is of importance in evaluating the costs and benefits of AIs in adjuvant therapy.

Most of the large clinical trials involving AIs compared an AI to the standard agent tamoxifen, either as 5 years of initial therapy [4, 5, 10] or after 2–3 years of tamoxifen [6, 7, 12]. Bone loss and increased fracture rates for the patients who received an AI have been observed in all these trials, and any difference in bone loss might partially reflect the protective effect of tamoxifen [3]. In the MA.17 trial comparing letrozole to placebo in patients who had received 5 years of tamoxifen, there was no statistically significant difference in the clinical fracture incidence or in reported osteoporosis [13], but a bone substudy concluded that in this setting letrozole caused a modest increase in bone resorption and reduction in bone mineral density (BMD) in the spine and hip compared with placebo [14]. A recent update that accounted for patients from the control group who were offered to switch from placebo to letrozole after the results were known reported a statistically significant increase in bone fractures among those patients who switched to letrozole compared with those who remained on placebo [15]. A recent published review summarized the clinical and preclinical data regarding the effects of AIs on BMD, markers of bone turnover, and clinical fracture rates [16].

In this study, we investigate the incidence and timing of bone fractures for patients on letrozole compared with tamoxifen in the BIG 1-98 trial and develop a risk profile of patients more likely to have a bone fracture while on treatment.

methods

BIG study 1-98 is a phase 3, double-blind trial to evaluate the effect of letrozole compared with tamoxifen administered postoperatively to patients with operable breast cancer. From March 1998 to May 2003, 8010 postmenopausal women with hormone receptor-positive invasive breast cancer were randomized to one of the four following options: monotherapy with tamoxifen (20 mg daily) for 3 years, letrozole (2.5 mg daily) for 5 years, sequential therapy comprising tamoxifen for 2 years followed by letrozole for 3 years, or letrozole for 2 years followed by tamoxifen for 3 years. Patients were enrolled in the two-arm option of letrozole or tamoxifen from March 1998 to March 2000 and the four-arm option from April 1999 to May 2003. The current analysis focuses on the 4893 patients who were randomized to the two monotherapy arms (two- and four-arm options) in BIG 1-98 and received at least some study medication.

The study was coordinated by the International Breast Cancer Study Group (IBCSG) on behalf of the BIG. The ethics committees and required health authorities of each participating center approved the study protocol, and all patients gave written informed consent. Details of study conduct and results of the primary core analysis of the comparison of letrozole to tamoxifen using data from patients randomized to all four arms [4] and results from patients randomized to the two monotherapy arms [8] have been previously reported.

The trial case report forms collected specific information on bone fractures every 6 months during trial treatment, including grade, date, cause (osteoporosis, metastasis, trauma, other), and site. Bone fractures were graded as grade 2 (fracture not requiring surgery) or grade 3 (fracture requiring surgery). All bone fractures were centrally reviewed by the medical review team (MR and HH) at the IBCSG Coordinating Center and investigators were asked to provide details of the cause of the fracture. Particular attention was given to the adequacy of the traumas to the presence of osteoporosis, assessment tools used to measure the bone density, and concomitant medication or condition promoting bone loss. The trial protocol mentioned that the use of bisphosphonates was permitted and should be recorded, but it did not make any recommendation with regard to the identification of risk factors for osteoporosis, measurement of BMD, or the use of calcium or vitamin D supplements.

The end point in this study was any bone fracture. In addition, we evaluated causes of fracture as recorded in the case report form, including osteoporosis, trauma, and metastasis, but because of small numbers and lack of clear definitions, these are not presented. Only fractures occurring during study medication were included. The 425 patients (17%) randomized to receive 5 years of tamoxifen but who chose to crossover to letrozole (subsequent to the publication of initial efficacy results and according to addendum 5 of the protocol) are included in the analysis but only fractures up to the time patients went off tamoxifen treatment were considered.

The baseline characteristics listed in Table 1 were collected at study entry and were compared between treatments using two-sided Fisher’s exact tests [17] and two sample t-tests. Baseline risk factors examined for potential increased risk of bone fracture included treatment allocation, age, body mass index (BMI), smoking history, prior osteoporosis and prior bone fracture. Subpopulation treatment effect pattern plots (STEPPs) were used to investigate the pattern of differences in incidence of bone fractures between treatment arms according to patient age at study entry [18, 19]. In these plots, the y-axis shows the incidence (percentage) of bone fractures for each treatment group. The incidence rates per 1000 women-years were also provided for each treatment group, calculated either allowing only one fracture per patient or including all fractures in patients who had multiple fractures.

Table 1. Baseline patient characteristics and co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Letrozole (N = 2448)</th>
<th>Tamoxifen (N = 2447)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>61.9 (8.0)</td>
<td>61.7 (7.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m² (SD)</td>
<td>26.8 (5.0)</td>
<td>26.9 (5.2)</td>
</tr>
<tr>
<td>Known osteoporosis</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>No</td>
<td>95.7</td>
<td>95.6</td>
</tr>
<tr>
<td>Yes</td>
<td>4.3</td>
<td>4.4</td>
</tr>
<tr>
<td>History of bisphosphonates use</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>No</td>
<td>98.9</td>
<td>98.7</td>
</tr>
<tr>
<td>Yes</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>History of bone fracture</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>No</td>
<td>91.0</td>
<td>90.7</td>
</tr>
<tr>
<td>Yes</td>
<td>9.0</td>
<td>9.3</td>
</tr>
<tr>
<td>History of smoking</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>No</td>
<td>65.4</td>
<td>64.6</td>
</tr>
<tr>
<td>Yes</td>
<td>34.6</td>
<td>35.4</td>
</tr>
<tr>
<td>HRT before randomization</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>No</td>
<td>65.1</td>
<td>63.0</td>
</tr>
<tr>
<td>Within the last 3 months</td>
<td>16.6</td>
<td>18.8</td>
</tr>
<tr>
<td>&gt;3 months ago but &lt;5 years</td>
<td>12.9</td>
<td>13.0</td>
</tr>
<tr>
<td>5 years ago or more</td>
<td>5.5</td>
<td>5.3</td>
</tr>
</tbody>
</table>

SD, standard deviation; HRT, hormone replacement therapy
fractures during treatment. The 95% exact confidence intervals of the incidence rates per 1000 woman-years were calculated based on a Poisson distribution.

Time from randomization to the first report of the bone fracture was compared via a stratified log-rank test, with strata defined by randomization option (two arm or four arm) and chemotherapy (yes or no), based on the stratum at randomization and combining the two chemotherapy strata [4]). Cox proportional hazards models were used to compare time to first bone fracture of a given type between the treatment groups [20]. These models were also stratified by randomization option and chemotherapy. In the univariate Cox model, only treatment effect was included. To test the interactions of treatment by a specific risk factor, the Cox model including the treatment group, the specific risk factor, and their interaction term was used. A more extensive multivariate Cox model was also employed to examine the treatment effect. Besides the treatment group, the model was adjusted for potential risk factors such as age at randomization (≥55 versus <55 years), BMI (≥30 versus <30 kg/m²), smoking history, presence of osteoporosis at baseline, previous history of bone fracture at baseline, previous history of hormone replacement therapy (HRT) at baseline (no versus yes), and whether or not the patient had received bisphosphonates before the bone fracture (as a time-varying variable). The relatively young age cut-off was used to separate patients who may have some continuing ovarian function into the younger group. If >1.5% of patients had a missing value for a particular covariate, an indicator for whether or not the covariate was missing was included in the model.

Competing risk models with disease-free survival (DFS) events (disease recurrence, secondary malignancy, and death without recurrence) as competing events were also used to evaluate the treatment effects on time to first bone fracture [21].

results

patients

The median follow-up for this analysis is 60.3 months. Of the 4895 patients, 2448 received letrozole and 2447 received tamoxifen. Table 1 shows the baseline patient and disease characteristics observed according to treatment group. The groups were well balanced with no statistically significant differences between them for any of the baseline characteristics.

Table 2. Incidence of bone fractures

<table>
<thead>
<tr>
<th></th>
<th>Letrozole (N = 2448)</th>
<th>Tamoxifen (N = 2447)</th>
<th>Total (N = 4895)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>A: According to grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2220</td>
<td>90.7</td>
<td>2287</td>
</tr>
<tr>
<td>Grade 2*</td>
<td>147</td>
<td>6.0</td>
<td>118</td>
</tr>
<tr>
<td>Grade 3</td>
<td>81</td>
<td>3.3</td>
<td>42</td>
</tr>
<tr>
<td>Any fracture (grade 2 or 3)</td>
<td>228</td>
<td>9.3</td>
<td>160</td>
</tr>
<tr>
<td>Multiple fractures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2*</td>
<td>11</td>
<td>0.4</td>
<td>6</td>
</tr>
<tr>
<td>Grade 3</td>
<td>12</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>Any multiple fractures</td>
<td>23</td>
<td>0.9</td>
<td>10</td>
</tr>
<tr>
<td>B: Incidence rates per 1000 woman-years (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allowing one fracture per patient</td>
<td>25.21 (22.04–28.70)</td>
<td>18.10 (15.41–21.14)</td>
<td></td>
</tr>
<tr>
<td>Allowing multiple fractures per patient</td>
<td>27.08 (23.86–30.61)</td>
<td>18.72 (16.02–21.75)</td>
<td></td>
</tr>
</tbody>
</table>

*Grade 2: fracture not requiring surgery; grade 3: fracture requiring surgery. CI, confidence interval.

bone fracture incidence

Table 2A gives the incidences of bone fractures and multiple fractures by grade. The incidence of bone fractures overall was higher among patients treated with letrozole [L: 228 of 2448 women (9.3%) versus T: 160 of 2447 women (6.5%)]. Incidence according to grade was similar. The incidence of multiple bone fractures while on treatment was also higher among patients treated with letrozole [L: 23 of 2448 women (0.9%) versus T: 10 of 2447 women (0.4%)]. Table 2B shows the incidence of bone fractures, per 1000 woman-years.

Figure 1 shows the incidences of bone fractures during treatment according to age using the STEPP method. Patients who received letrozole had a higher incidence of bone fractures than patients who received tamoxifen. The pattern of differences in bone fracture incidence was generally consistent with regard to age at study entry, with relatively smaller differences for patients aged <55 and relatively larger differences for patients from 59 to 69 years old (Figure 1). The incidence of bone fractures was higher in older patients in both treatment arms.

sites of bone fractures

In the letrozole group, the most frequently observed sites of fractures were wrist (68 patients), femur (33 patients), thoracic spine (27 patients), humerus (25 patients), and ankle (21 patients). In the tamoxifen group, the most frequently observed sites of fractures were wrist (34 patients), thoracic spine (22 patients), rib (22 patients), and ankle (14 patients) (Table 3).

time to first bone fracture

A forest plot of hazard ratios for time to first bone fracture for all patients and various subgroups based on univariate Cox models is shown in Figure 2. Under letrozole, there were significantly more bone fractures (P = 0.002) than under tamoxifen. This difference remained consistent across most of the factors examined. Patients who received letrozole had more bone fractures regardless of whether their BMI ≥ 230 kg/m² (interaction P = 0.61), whether they had smoking history
Fractures while on treatment included age (interaction \( P = 0.001 \), Table 4) were consistent with those found in univariate models (\( P = 0.002 \)). The statistically significant risk factors for bone fractures while on treatment included age >55 at randomization (\( P = 0.01 \)), smoking history (\( P = 0.05 \)), presence of osteoporosis at baseline (\( P = 0.01 \)), previous history of bone fracture at baseline (\( P < 0.0001 \)), and previous history of HRT at baseline (\( P = 0.04 \)). Whether or not the patient had received bisphosphonates before the bone fracture (157 patients randomized to letrozole and 128 to tamoxifen received bisphosphonates before bone fracture) was not significantly associated with the occurrence of bone fracture (\( P = 0.24 \)).

Figure 3 presents the cumulative incidence of bone fracture, making allowance for a DFS event as a competing risk event. Competing risk models confirmed the results of the Cox models, showing significantly more or earlier occurrence of bone fractures in patients receiving letrozole (\( P = 0.0004 \)).

### Discussion

In this study population, the overall incidence of bone fracture was higher during treatment with letrozole, which is consistent with previous reports from other trials analyzing adjuvant treatment with AIs in postmenopausal women. The most recent update of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial [22], which is most closely similar in design to the monotherapy comparisons from BIG 1-98 in the present report, confirms the relative increased fracture rate of 55% for women during treatment with anastrozole.

Studies involving switch to an AI after prior tamoxifen may be more difficult to compare with ATAC or BIG 1-98 since the initial tamoxifen may have served to strengthen bone [3]. In contrast to the recent report of the International Exemestane Study (IES) [6], which tested the AI exemestane after 2 or 3 years of tamoxifen given before randomization, we found the higher incidence of fracture in women treated with an AI to be independent of baseline conditions (osteoporosis, previous bone fracture). Furthermore, the reported incidence of bone fracture per 1000 women-years among patients assigned to letrozole in the present study (27.08 per 1000 woman-years) is higher than the 19.2 per 1000 woman-years described in patients assigned exemestane [6]. Another difference between the findings of IES and BIG 1-98 is the frequency of hip, wrist, and spine fractures. These were rare in the IES report, in which the large majority of fractures were at other sites [9]. In contrast, we found that typically bone loss driven fractures (hip, wrist, and spine) accounted for 53.5% of patients who had fractures (122 of 228) during treatment with letrozole, and in particular wrist fractures made up 29.8% of all patients assigned letrozole who had a bone fracture (68 of 228). In the MA.17 trial, in which letrozole or placebo followed previous treatment with tamoxifen, despite decreased BMD, the rate of bone fracture was not significantly higher with letrozole [23].

Adjuvant treatment with AIs has been shown to improve outcome in postmenopausal women with early breast cancer and their use is steadily increasing. For this reason, it is important to recognize and if possible prevent adverse events. As illustrated in Figure 3, the trade-off between increased DFS with letrozole and increased risk of bone fractures with letrozole needs to be considered. The benefits of superior disease control associated with letrozole and lower incidence of fracture with tamoxifen should be considered with the risk profile for each individual patient. Bone loss and subsequent bone fractures may be avoided by accurately selecting and counseling patients and if appropriate treating women at risk for fractures.
for bone loss. This systematic evaluation should include risk factors such as those identified in this study, especially age, smoking history, osteoporosis, history of bone fracture, and history of HRT use, though this latter association may be due to a confounding of HRT use with decline in BMD.

In this trial, patients were not encouraged to take vitamin D and calcium for bone health, and no standardized guidelines for bisphosphonates use were recommended. More recent guidelines suggest routine recommendation of calcium and vitamin D supplements, plus baseline BMD measurement, with follow-up if the initial result is in the osteopenic range [9]. Application of these guidelines would be likely to reduce the excess risk of bone fracture associated with AI use in future [24]. Meanwhile, the recognition of risk factors associated with increased fracture risk may assist in reaching a clinical balance.
between the superior antitumor efficacy of AIs over tamoxifen and the risks of bone fracture.

**funding**

Novartis to BIG 1-98; Swedish Cancer Society, The Cancer Council Australia, Australian New Zealand Breast Cancer Trials Group, Frontier Science and Technology Research Foundation, Swiss Group for Clinical Cancer Research (SACK), National Cancer Institute (CA-75362), Cancer Research Switzerland/ Oncosuisse and the Foundation for Clinical Cancer Research of Eastern Switzerland (OSKK) to IBCSG.

**acknowledgements**

The BIG 1-98 trial coordinated by IBCSG. clinicaltrials.gov ID=NCT00004205

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