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Original article

Bone health and adherence to vitamin D and calcium therapy in early breast cancer patients on endocrine therapy with aromatase inhibitors

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ABSTRACT

Objectives: Randomized trials involving aromatase inhibitors (AIs) in the adjuvant treatment of breast cancer patients have reported increased osteoporosis risk. Bone loss can be reduced with appropriate life style, vitamin D and calcium supplements, and with bisphosphonate therapy. The aim of this analysis was to investigate adherence to vitamin D and calcium in postmenopausal breast cancer patients receiving adjuvant non-steroidal AIs, and oncologists' adherence to the bone health guidelines.
Material and methods: This prospective study included 438 newly diagnosed patients and those who have already been receiving non-steroidal AIs for up to 3.5 years. Median endocrine therapy duration before recruitment in the study was 10.5 months (interquartile 4.8–26.6).
Results: Densitometry was performed on 142 patients (32.4%) before initiation of endocrine therapy, and on additional 38 (8.6%) patients at second study visit. Densitometry was not performed on 258 (59%) patients. Vitamin D and calcium were prescribed to 329/438 (75.1%) patients at some point during the study. Patients who took more than 80% of the prescribed dose were considered adherent. Self-reported adherence was 88.4%. Osteoporosis was diagnosed in 24 patients (5.5%) of the total study population, bearing in mind that 258/438 (59%) patients did not have densitometry. Bisphosphonates were prescribed to 54/438 (12.3%) patients, whilst only 19 (35.2%) of those had osteoporosis.
Conclusion: In this analysis, lack of oncologists' adherence to the bone health guidelines was observed. In addition, a significant proportion of the patients did not adhere to the vitamin D and calcium.

1. Introduction

Osteoporosis resulting from accelerated loss of bone mineral density (BMD) is an important health issue for the patients with breast cancer [1]. Bone loss can greatly diminish the quality of life and increase risk of fracture. Aromatase inhibitors (AIs) play an important role in the treatment of postmenopausal patients with hormone-receptor positive breast cancer, both in the adjuvant and metastatic setting. Natural bone loss in postmenopausal women is accelerated by the further reduction in circulating estrogen caused by AIs [2–4]. Aromatase inhibitor-associated bone loss occurs at more than twice the rate of physiologic postmenopausal bone mineral density loss [5]. Major phase III trials involving AIs in the adjuvant setting have reported increased fracture risk [6–9], therefore AIs is considered to be a high-risk factor for osteoporosis. Morbidity and mortality associated with bone loss can be prevented with appropriate screening, lifestyle interventions, and therapy [10–13]. Consequently, the bone health guidelines for breast cancer patients have been issued [14–16]. Compliance to

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bone health guidelines within oncological community is questionable and, of course, of paramount importance. Herewith, we present the results of our study, where we investigated the adherence of patients and oncologists to the bone health guidelines in prospective manner.

2. Material and methods

This was a prospective, non-interventional, multicenter study of breast cancer patients in Croatia. A total of 23 oncologists from nine oncology units took part, representing majority of Croatian oncology institutions. The study was conducted between April 2011 and July 2014. The study protocol was reviewed and approved by Central Ethics Committee in Croatia. Both, newly diagnosed patients and those already receiving non-steroidal aromatase inhibitors for up to 3.5 years were enrolled. Inclusion criteria were early hormone dependent invasive breast cancer, postmenopausal status, ECOG (Eastern Cooperative Oncology Group) 0–1, and signed informed consent. Exclusion criteria were metastatic breast cancer, pregnancy or lactation, severe renal impairment, moderate to severe hepatic impairment, hypersensitivity to anastrozole, letrozole or any of excipients, concomitant treatment with drugs that contain estrogen, concomitant treatment with tamoxifen, previous treatment with tamoxifen and previous treatment with another aromatase inhibitor. According to the study protocol up to five follow-up visits were foreseen: 2, 6, 12, 18, and 24 months from baseline visit. Investigators were instructed to follow their standard follow-up clinical practice, as this was a non-interventional study.

The primary objective of the study was to evaluate the adherence of patients to treatment with non-steroidal aromatase inhibitors in every day clinical practice in Croatia [17]. Secondary objectives were patients' adherence to prevention or to treatment of osteoporosis, the analysis of the impact of socioeconomic factors on patients' adherence, and the assessment of effectiveness and safety of non-steroidal aromatase inhibitors.

Herewith, we reported data on patients' adherence to prevention or to treatment of osteoporosis and oncologists' adherence to bone health guidelines.

There were 470 patients screened in the study and data included in this analysis was obtained from 438 patients who did not violate inclusion criteria, who received at least one dose of aromatase inhibitor and had at least one examination after baseline visit (Fig. 1).

Standard clinical practice was analyzed by performance of densitometry before initation of AIs therapy, use of vitamin D and calcium, and bisphosphonate therapy where indicated. Patients were asked whether they were instructed by their oncologist to take vitamin D and calcium supplements, and if their answer was positive, they reported the number of doses omitted on monthly basis.

The use of vitamin D, calcium and bisphosphonates was additionally analyzed with regard to the adjuvant chemotherapy received, the type of non-steroidal aromatase inhibitor (anastrozole vs. letrozole) and T score from the last densitometry.

Patients' adherence was determined from Patient's Diary by calculating the number of omitted doses over the total duration of the therapy, defined by the first and the last dose taken during this study. Patients who took ≥80% of the prescribed dose of the vitamin D and calcium were considered adherent.

The investigator checked Patient's Diary at each visit. The worst adherence recorded in Patient's Diary between two visits, was recorded in patient's Case Report form. If the investigator determined that the patient was not taking the therapy regularly, he/she examined the reasons why.

Methods of descriptive statistics were used. Continuous variables were described by mean values, standard deviation, median, interquartile, and categorical variables were described by frequencies and percentages. Categorical variables were compared using chi-square test or exact test when appropriate. Quantitative variables were compared using Wilcoxon rank-sum test. Nul-hypothesis (no difference) was rejected if p-value was <0.05. All analysis were performed using SAS for Windows, version 9.3. SAS Institute Inc., Cary, NC USA.

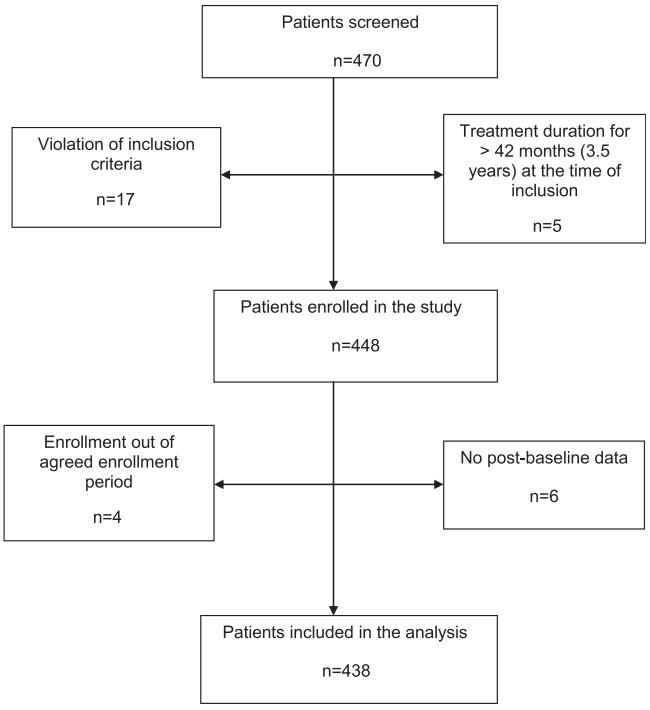

Fig. 1. Study profile.

3. Results

A total of 438 postmenopausal patients with early invasive hormone-dependent breast cancer, receiving upfront adjuvant endocrine treatment with non-steroidal aromatase inhibitors, were included in this analysis. Majority of patients had stage I/IIA disease and were treated with lumpectomy (54.6%) and radiotherapy (64.6%). Median adjuvant endocrine treatment duration before study recruitment was 10.5 months (interquartile 4.8–26.6). There were 387 patients (88.4%) treated with anastrozole and 51 patients (11.6%) treated with letrozole. Patients were followed up for an average of 23.5 ± 4.9 months. The median patient's age was 64.7 (interquartile 58.1–71.5). Detailed demographic data are presented in Table 1.

Densitometry was performed on 142 patients (32.4%) before initiation of endocrine therapy, and on additional 38 (8.6%) patients at the second visit. Overall, densitometry was performed on 180/438 (41.1%) patients.

Majority of patients who had densitometry (85/180) had T score between −2.5 and −1.

Details on densitometry data are presented in Table 2.

A total of 329/438 (75.1%) patients received vitamin D and/or calcium at some point during this study, and provided information on adherence. Self-reported non-adherence was observed in 38/329 (11.6%) patients.

The most common reasons for omitting doses of vitamin D and calcium were that patients forgot to take medication (201 out of 263 reports), patients felt that they didn't need the medication (17