European Geriatric Medicine xxx (2017) xxx–xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Research paper

Evidence for the prevention of bone loss in elderly and old early non-metastatic breast cancer patients treated with aromatase inhibitors

V. Gunmalm [a,b], N.R. Jørgensen [c,d], B. Abrahamsen [d,f], P. Schwarz [a,e,*]

[a] Research centre of ageing and osteoporosis, department of endocrinology, Rigshospitalet, 9, Blegdamsvej, 2100 København Ø, Denmark
[b] Department of geriatric medicine, Rigshospitalet Glostrup, 69, Nordre Ringvej, 2600 Glostrup, Denmark
[c] Department of clinical biochemistry, Rigshospitalet, 9, Blegdamsvej, 2100 København Ø, Denmark
[d] OPEN, institute of clinical research, university of Southern Denmark, 19, Winsløwparken, 5000 Odense C, Denmark
[e] Faculty of health sciences, Copenhagen university, 3, Blegdamsvej, 2200 København N, Denmark
[f] Holbæk hospital, department of medicine, 4300 Holbæk, Denmark

ARTICLE INFO

Article history:
Received 29 March 2017
Accepted 26 June 2017
Available online xxx

Keywords:
Breast cancer
Aromatase inhibitors
Bone
BMD
Bone loss
Elderly
Old

ABSTRACT

Breast cancer (BC) is the most common cancer amongst women worldwide. Bone health is emerging as an important issue for BC survivors. In this literature study, we focus on agents for preventing bone loss in early non-metastatic estrogen receptor positive BC in treatment with aromatase inhibitors (AI) and to assess the evidence for antiresorptive treatment of bone loss in early non-metastatic breast cancer. We included randomized controlled trials (RCT's) comparing: (a) bisphosphonates and control; (b) different bisphosphonates; (c) denosumab and control and (d) bisphosphonates vs. denosumab in early non-metastatic BC women in AI treatment. Among antiresorptives, zoledronic acid currently has the highest evidence for prevention of AI associated bone loss in early non-metastatic BC. Data on fracture prevention among all patients, elderly and old is sparse. More randomized controlled studies are needed with the focus of bone loss and fracture prevention especially among the elderly and old early non-metastatic BC women.

1. Background

Breast cancer (BC) is the most common cancer amongst women worldwide with the elderly and old women being the most affected [1]. Although the incidence of BC is increasing at all ages, the overall breast cancer death rate has dropped steadily since the beginning of 1990s through early detection and advances in systemic therapy [2]. As more women at all ages are now surviving BC, more focus is placed on survivorship issues. Bone health is emerging as an important issue for BC survivors. Treatment for BC is often associated with bone loss due to the cancer treatment which increases the risk of skeletal morbidity [3]. Among elderly and old women this bone loss might be of highest relevance due to the higher risk of osteporotic fracture [1]. Estrogen is an essential hormone in maintaining bone health. In hormone responsive BC, ovarian suppression is an effective endocrine therapy for reducing the risk of recurrent BC and improving overall survival [4,5]. However, this treatment induces a premature menopause and in the postmenopausal women, the low natural estrogen level is blocked to below biochemical detection level which accelerates the risk of bone loss and osteoporosis in young, elderly and old BC survivors. Aromatase inhibitors (AIs) are emerging as the standard endocrine therapy in hormone responsive breast cancer in post-menopausal women. AIs work by reducing tissue and plasma estrogen levels through the inhibition of peripheral conversion of androgens to estrogens. The rate of bone loss is as high as 13% within the first 12 months of treatment [6] and decreases slowly with the duration of AI treatment. However, AI alone do not explain the increased bone loss in BC survivors. The increased fracture risk compared with age-matched women without BC is not only caused by AI but is also caused by other risk factors (Table 1). Despite the

* Corresponding author. Research centre of ageing and osteoporosis, department of endocrinology, Rigshospitalet, 9, Blegdamsvej, 2100 København Ø, Denmark.
E-mail address: Peter.schwarz@regionh.dk (P. Schwarz).

http://dx.doi.org/10.1016/j.eurger.2017.06.004
1878-7649/

Table 1
Risk factor of bone loss in post-menopausal women suffering breast cancer.

Advancing age > 65 years
AI therapy
Chemotherapy induced menopause
Low body-mass index
Family history of hip fracture
Personal history of fragility fracture after age 50 years
Corticosteroid use
Excessive alcohol consumption and smoking

importance of especially age as a risk factor for fractures, older women starting treatment with AIs for treatment of BC are less likely to undergo recommended bone density assessment [1].

There is evidence for a higher risk of osteoporotic fracture for women with BC compared with age-matched women without BC [1]. It has been shown in women with advanced breast cancer, that bisphosphonates (oral and i.v.) and denosumab (s.c.) reduced the risk of developing skeletal related events (SRE's), as well as delaying the time to SREs [7]. Wong et al furthermore showed in their systematic review that some bisphosphonates may also reduce bone pain and may improve quality of life [7]. However, it remains uncertain what timing or duration of treatment should be recommended for these patients with advanced breast cancer.

The reason for the increased risk is somewhat yet unexplained. Established risk factors such as low BMD, age above 65 years, low body mass, early onset of menopause, family history of fragility fracture, use of significant corticosteroid, alcohol and smoking might explain some of the risk. However, AI's and chemotherapy might also be significantly involved [8–13].

In combination these factors, age, genetic, environmental and cancer treatment related factors in an unknown fashion leads to the increased bone loss and loss of bone strength and thereby to the increased risk of fractures among women receiving AI treatment. The effects of chemotherapy are toxic effects of the drugs on the bone cells, lack of vitamin D, calcium and other nutrients following nausea and vomiting, whereas AIs suppress plasma estrogen levels by inhibiting or inactivating aromatase, which is an enzyme that is responsible for the synthesis of estrogen from androstenedione and testosterone [8].

The treatment options are calcium and vitamin D in combination with anti-resorptive medications. Anabolic agents i.e. Forteo/Forsteo should be avoided and viewed as contra-indicated due to the cancer disease and is generally not recommended for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase or prior external radiation such as in BC or implant radiation therapy involving the skeleton [14]. However, the optimal drug of choice for the prevention of accelerated bone loss due to cancer treatment and prevention, i.e. chemotherapy and AI in postmenopausal women is currently unknown, and especially in the elderly and old the data seem sparse. In the following, our focus is on the prevention of osteoporotic fractures in the elderly and old patients and not on any potential antitumor effects of antiresorptive drugs; readers are referred to reviews by Zhao and Hu [15] and Gül et al. [16].

Accordingly, we shall focus on agents for preventing bone loss in postmenopausal women with early non-metastatic estrogen receptor positive BC in treatment with AIs and to assess the evidence of antiresorptive treatment of bone loss in especially elderly and old women.

2. Methods

We searched the Specialized Register of trials maintained by the Cochrane Breast Cancer Group (CBCGSR), *PubMed* and *EMBASE* on March 16, 2017.

2.1. Search strategy

BC and age (44,475), BC and bone (18.041), BC and bone and treatment (12.903).

BC and bone and treatment and RCT showed 14 studies and BC and treatment and RCT showed 274 studies which was screened. BC and treatment and bisphosphonates gave 2257 studies and we changed treatment to zoledronic acid (835 studies) and denosumab (251 studies). Based on those in total 1374, we screened the abstracts (PS) based on the following inclusion criteria: randomized controlled trials (RCT's) comparing:

- bisphosphonates and control;
- different bisphosphonates;
- denosumab and control;
- bisphosphonates vs. denosumab in women with early non-metastatic BC in AI treatment.

2.2. Exclusion criteria

RCT-studies studies of the above treatment options vs. controls in advanced breast cancer, studies of mixed diseases.

3. Results

In total, evaluation of zoledronic acid (ZA) treatment showed 18 RCT studies on BMD or fracture. However, in several cases, the cohorts were reported on more than once. We found in total 7 distinct cohorts evaluated after 12 to 61 months (Table 2) [17–23]. In all cohorts, the treatment was ZA 8 mg/year vs placebo (n = 1,551 vs. 1,550). The absolute difference in mean lumbar spine and total hip BMD's between patients in treatment or placebo was 8.9% and 5.9%, respectively. The study designs are different. There is limited data available regarding fracture risk reduction (four studies with a total of 78 fractures) [17,20,21,23]. A meta-analysis of the four fracture studies showed a non-significant reduction in fracture risk with an RR of 0.72 [95% CI: 0.40, 1.30]. There was visible variation in the effect size between studies though there was nominally no significant statistical heterogeneity (I^2 = 9%, P = 0.33).

The studies reported on almost identical age groups (Table 3). The evaluation of Risedronate (Ris) treatment showed 9 RCT studies on BMD or fracture [24–32]. However, 1 study reported only on bone markers [30] and BMD was based on one of the other studies [24]. Of the remaining 7 studies, 1 study is reported alone (see below) as it was a mix of Aln and Ris and 1 was excluded due to a study length of 6 months and 2.5 mg Ris per day [32]. The remaining 6 studies reported were 24-month RCT's [24,25,27–29,31]. In all 6 studies, the treatment was Ris 35 mg/week vs. placebo (n = 477 vs. 338). The absolute difference in mean lumbar spine and total hip BMD between patients in the treatment or placebo groups was 4.4% and 3.2%, respectively [24,25,27–29,31]. The study of Sergi et al. [28] investigated elderly women with early breast cancer mean age about 12 years older compared to the other studies, i.e. mean age group A 77.1 ± 4.2 years and group B 76.0 ± 5.0 years. In group A (controls), none of 28 enrolled patients had osteoporosis based on BMD or prevalent fractures whereas 71% of the 30 patients in group B were osteoporotic and 76% had prevalent vertebral fractures. After 24 months, 1 vertebral fracture was observed in the control group A whereas no fractures were observed in the Ris treatment group.

Two RCT's are published on alendronate (Aln) [33,34]. Of these two studies, only one study had a long-term follow-up (36 months) [33]. None of the studies on bisphosphonate reported severe side-

Please cite this article in press as: Gunmalm V, et al. Evidence for the prevention of bone loss in elderly and old early non-metastatic breast cancer patients treated with aromatase inhibitorsEarly non-metastatic estrogen positive breast cancer and bone–>. Eur Geriatr Med (2017), http://dx.doi.org/10.1016/j.eurger.2017.06.004