Journal of Bone Oncology 7 (2017) 1–12

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Review Article

Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO, IMS, and SIOG

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ARTICLE INFO

Keywords:
Breast cancer
Osteoporosis
Endocrine treatment
Fracture

ABSTRACT

Background: Several guidelines have been reported for bone-directed treatment in women with early breast cancer (EBC) for averting fractures, particularly during aromatase inhibitor (AI) therapy. Recently, a number of studies on additional fracture related risk factors, new treatment options as well as real world studies demonstrating a much higher fracture rate than suggested by randomized clinical controlled trials (RCTs). Therefore, this updated algorithm was developed to better assess fracture risk and direct treatment as a position

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[2] CABS: Cancer and Bone Society.
[3] ECTS: European Calcified Tissue Society.
[4] IEG: International Expert Group for AIBL.
[5] ESCEO: European Society for Clinical and Economics Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases.
[6] IMS: International Menopause Society.
[7] SIOG: International Society for Geriattric Oncology.

http://dx.doi.org/10.1016/j.jbo.2017.03.001
Received 9 March 2017; Accepted 10 March 2017
Available online 23 March 2017

Bisphosphonate
Denosumab

statement of several interdisciplinary cancer and bone societies involved in the management of AI-associated bone loss (AIBL).

Patients and methods: A systematic literature review identified recent advances in the management of AIBL. Results with individual agents were assessed based on trial design, size, follow-up, and safety.

Results: Several fracture related risk factors in patients with EBC were identified. Although, the FRAX algorithm includes fracture risk factors (RF) in addition to BMD, it does not seem to adequately address the effects of AIBL. Several antiresorptive agents can prevent and treat AIBL. However, concerns regarding compliance and long-term safety remain. Overall, the evidence for fracture prevention is strongest for denosumab 60 mg s.c. every 6 months. Additionally, recent studies as well as an individual patient data meta-analysis of all available randomized trial data support additional anticancer benefits from adjuvant bisphosphonate treatment in postmenopausal women with a 34% relative risk reduction in bone metastasis and 17% relative risk decrease in breast cancer mortality that needs to be taken into account when advising on management of AIBL.

Conclusions: In all patients initiating AI treatment, fracture risk should be assessed and recommendation with regard to exercise and calcium/vitamin D supplementation given. Bone-directed therapy should be given to all patients with a T-score < -2.0 or with a T-score of < -1.5 SD with one additional RF, or with ≥ 2 risk factors (without BMD) for the duration of AI treatment. Patients with T-score > -1.5 SD and no risk factors should be managed based on BMD loss during the first year and the local guidelines for postmenopausal osteoporosis. Compliance should be regularly assessed as well as BMD on treatment after 12 - 24 months. Furthermore, because of the decreased incidence of bone recurrence and breast cancer specific mortality, adjuvant bisphosphonates are recommended for all postmenopausal women at significant risk of disease recurrence.

1. Introduction

Breast cancer is the most frequent cancer in women leading to a significant morbidity and mortality [1]. Early diagnosis and improved treatment regimens have significantly increased survival leading to a greater potential for experiencing long term side effects from cancer treatments including bone loss and fractures. Skeletal homeostasis is achieved through coupled and balanced bone resorption and bone formation. Several local and systemic factors regulate these processes, including estrogen, a key regulator of bone resorption. Physiologic decreases in estrogen levels after menopause lead to an increased risk for osteoporosis (low bone mineral density [BMD]) and fractures, and this risk can be exacerbated by breast cancer and its therapies [2]. Systemic therapies for breast cancer can additionally interfere with bone turnover, either through their effects on gonadal steroid hormone production or by inhibiting peripheral aromatization into estrogen [2–4]. In addition, some therapies for breast cancer might directly affect bone formation [5]. Regardless of the underlying mechanism, patients with breast cancer are at risk for cancer treatment-induced bone loss (CTIBL).

The majority of breast malignancies are hormone responsive, and adjuvant endocrine therapy is used routinely to prevent breast cancer recurrence and death [6,7]. Tamoxifen was the past treatment of choice for endocrine-responsive postmenopausal breast cancer and was found to preserve BMD in postmenopausal (but not premenopausal) women [8], and fracture risks remained similar in postmenopausal tamoxifen users and non-users [9]. However, aromatase inhibitors (AI) have now replaced tamoxifen as the treatment of choice for hormone-responsive breast cancer in most postmenopausal women because of both better efficacy and fewer serious side effects such as induction of uterine cancers and thromboembolic events.[6,7,10,11] However, because AIs prevent peripheral estrogen production, they suppress estrogen levels beyond that attained from a natural menopause, thereby leading to accelerated bone loss and an increased fracture risk [12–15].

Besides a reduction in quality of life, increased morbidity and treatment induced fractures lead to an increase in the health economic burden. A recent study reported that compared to the general population, breast cancer patients had fracture incidence rate ratios of 1.25 (95% CI: 1.23–1.28) and 1.18 (95% CI: 1.14–1.22) for hospitalization due to any bone fracture and hip fracture, respectively. These ratios remained significantly increased for 10 years. Women taking aromatase inhibitors were at an increased risk of fracture as compared with women taking tamoxifen (HR 1.48; 95% CI: 0.98–2.22). Additionally, breast cancer patients hospitalized for a bone fracture showed a higher risk of death (HR 1.83; 95% CI: 1.50–2.22) compared with those without bone fracture [16].

1.1. What is the size of the problem?

AI-associated bone loss (AIBL) leads to a marked increase of bone resorption, with a 2–4 fold increased bone loss compared to physiologic postmenopausal BMD loss.[12,15,17–24] As a result, women receiving adjuvant AI therapy for breast cancer are at increased risk for fractures [25–28], which leads to increased morbidity and mortality [29]. Randomized controlled trials (RCTs) including an AI for 5 years suggested an increased absolute fracture risk of around 10% indicating that one out of ten women will eventually fracture [25–28]. However, these studies had stringent inclusion and exclusion criteria that may not reflect fracture risk in the unselected population seen in routine clinical practice. The real-world fracture risk has been investigated in a number of case-control studies, prescription based analysis as well as single center studies and even in a recent RCT. In the latter, the fracture incidence in women with BC on an AI was reported to be around 18–20% after 5 years follow-up indicating that in clinical practice, about one in five women will sustain an AI related fracture [30–38]. After termination of AI treatment, bone turnover normalizes, BMD and fracture risk can partially recover [25–28]. Recently, conflicting evidence on the increased duration of AI treatment for up to 10 years has been reported [39–42]. For those advocating an increased duration of AI treatment for up to 10 years, a further increased fracture risk, adding to the 2–3% per annum has to be taken into account.

1.2. How to assess osteoporosis related fracture risk

In 1993, the first operational definition of osteoporosis was based on a decreased in BMD eg. a T-score at the femur neck of < -2.5 [43,44]. In the past years, we have accumulated an expanded understanding of fracture risk factors other than BMD [5,45], resulting in several national and international bone health guidelines being updated to provide more comprehensive insights into fracture risk assessment and clinical decision making regarding antiresorptive therapy (Table 1) [5,6,11,46–53] A key advance in this field has been the development of the FRAX algorithm developed by the former WHO Collaborating Center at Sheffield, UK (http://www.sheffield.ac.uk/FRAX/), an easy-to-use online tool for assessing fracture risk in postmenopausal women with or without BMD data. The FRAX algorithm is based on data from large-scale, population-based cohorts from different parts of the world, and uses factors such as age, body mass index (BMI), smoking history,