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Guidelines

Guidelines for diagnostics and treatment of aromatase inhibitor-induced bone loss in women with breast cancer A consensus of Lithuanian medical oncologists, radiation oncologists, endocrinologists, and family medicine physicians

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ABSTRACT

The aim of this article is to inform about cancer treatment-induced bone loss, to identify patients at risk and those that can benefit from bone targeted treatment as well as highlight the importance of the multidisciplinary approach in the bone health in cancer care. Patients with breast cancer treated or intended to be treated with aromatase inhibitors belong to a high-risk group because their fracture risk increases up to 30% due to a significant decrease in bone mineral density within 6–12 months after the start of hormonal treatment. To evaluate bone status and predict risk for fractures, lateral thoracic and lumbar spine X-ray imaging, bone mineral density measurement by dual energy X-ray absorptiometry at the lumbar spine L1–L4 vertebrae and/or hip and fracture risk factors assessment are mandatory tests prior to hormonal treatment. Morbidity and mortality associated with bone loss can be prevented with appropriate screening, lifestyle interventions, and therapy. Algorithm for the management of bone health in breast cancer patients was established in Lithuania to screen patients with increased risk for bone loss and to provide adequate specific osteoporosis treatment.

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1. Introduction

Breast cancer is the most frequent cancer among women with an estimated up to 1500 new cases diagnosed annually in Lithuania [1]. Breast cancer mortality is decreasing thanks to early detection and improved treatment, but there are still wide differences in treatment offered to patients in terms of cancer treatment induced clinical situations. Both cancer itself and different therapies can have profound effects on bone metabolism. Breast cancer patients are at risk for glucocorticoid, estrogen (ER) deprivation, chemotherapy-induced bone loss which may result in pathological fractures, hypercalcemia, bone pain and decline in performance status [2–5].

Hormonal therapy plays an important role in the treatment of women with ER or progesterone (PR) receptor-positive breast cancer. Therapy with the selective estrogen receptor modulator tamoxifen or aromatase inhibitors (AI) reduces breast cancer recurrence and improves overall survival. Tamoxifen competitively inhibits estrogen binding to estrogen receptor and has a different effect to bone in pre- and postmenopausal women. Tamoxifen has a favorable impact on bone mineral density (BMD) in postmenopausal breast cancer patients, but increases bone loss in premenopausal women. AI therapy is associated with increased bone turnover that leads to loss of BMD and an increased fracture rate. The effect of AI therapy is the reduction of estrogen levels leading to upregulation of RANK (receptor activator of nuclear factor, κB) ligand signaling in bone. The skeletal effects observed are inversely correlated with baseline BMD and serum estradiol concentrations [4,5].

Bone loss is very much expressed in young women with treatment-induced ovarian suppression. Medications known to cause early menopause trigger rapid bone loss and increase risk of bone fracture. The highest rates for bone loss are observed in premenopausal women who experience chemotherapy or endocrine treatment – induced acute ovarian ablation. The skeletal status of these patients should be assessed and they must be followed up and get specific osteoporotic treatment. Besides of the reduction of estrogen levels and early menopause, a few pathogenetic pathways of bone loss are known. First, breast cancer itself, in the absence of bone metastases, directly affects bone metabolism by stimulating release of transforming growth factors and so increasing osteoclastic activity. Secondly, bone mass decreases by 6%–10% within the first two years as a consequence of ovarian function suppression due to chemotherapy or treatment with gonadotropin-releasing hormone agonists (GnRHa) in premenopausal women or as a result of reducing estrogen levels in postmenopause [3,6,7]. Bone loss is further accelerated by the AI, as BMD decreases up to 17.3% over 3 years. Bilateral oophorectomy causes even more significant reduction of total bone mass of up to 20% within 18 months and BMD appears to continue decreasing thereafter [3]. In comparison, BMD loss in healthy postmenopausal women is up to ~3% annually [3]. Therefore, women treated with AI present a more than 30% higher risk of fractures compared to age-matched healthy postmenopausal women [2]. Hence, patients who are intended to or are being treated with AI, regardless their age, should be examined, observed and treated because of a possible BMD decrease and increased risk of fractures. It should be noted that factors such as baseline BMD, age, time since menopause and adequate calcium and vitamin D intake as well as other risk factors can influence the bone health.

In order to provide breast cancer healthcare quality assurance the national guidelines, based on a review of the evidence based data, were created. These guidelines and algorithm are dedicated to physicians of all specialties to support clinical relevance of bone loss due to breast cancer treatment and to give guidance on how to reduce the risk of bone fractures. These guidelines were prepared taking into account experience of other countries as well as breast cancer epidemiology and treatment characteristics in Lithuania [1–7]. Existing Lithuanian guidelines for diagnostics and treatment of osteoporosis and reimbursement conditions by the Lithuanian health insurance fund were also considered [8–10].

2. Methodology used to prepare guidelines

The guidelines were developed by the group of Lithuanian physicians, representing clinicians who manage breast cancer and bone specialists who are interested in identification and management of postmenopausal and secondary osteoporosis. The group decided to conduct a project ''Management of bone loss associated with cancer treatments.'' The group agreed on the main objective of the guidelines: to provide guidance on appropriate management of bone loss associated with cancer treatments, and that the guidelines is needed for all physicians who treat, consult or follow up patients with breast cancer.

The group decided that a systemic literature search should be conducted followed by assimilation of the evidence. The MEDLINE/PubMed and databases were searched from 2008 to 2013. Randomized controlled trials, meta-analyses, and existing guidelines were assessed by individual members of the project working group.

Few literature sources selected by the group were considered as the most appropriate to serve as a basis for the local algorithm for diagnostics and treatment of AI-induced bone loss in women with breast cancer. The initial algorithm was created and discussed at the group meeting. The final version was published in Lithuanian medical journals in 2013 and presented in national conferences of endocrinologists and oncologists.

3. Diagnostics and treatment of aromatase inhibitor-induced bone loss

The choice of endocrine therapy should be based on the characteristics and prognosis of the underlying breast cancer, rather than pre-existing status of bone health provided that appropriate monitoring and treatment of bone loss is ensured.

3.1. *Examination of breast cancer patients without bone metastases with predicted bone loss due to ongoing or intended treatment with AI*

3.1.1 Medical oncologist or radiation oncologist (later oncologist) assigns treatment for women with breast cancer. Bone status must be assessed in all women with breast

cancer who are treated or intend to be treated with AI. These guidelines for diagnosis and treatment are not applied when bone metastases are evident. There are two parts in this algorithm depending to whom it is applied (Fig. 2):

- Women who experience premature menopause due to chemotherapy or ovarian suppression, ablation or removal;
- Postmenopausal women receiving treatment with AI.

There are no specific monitoring or treatment requirements for:

- Women who continue to menstruate after treatment for early breast cancer;
- Postmenopausal women aged more than 45 years who do not require endocrine treatment or who are receiving tamoxifen therapy.

According to these guidelines, oncologist is the first physician to investigate women with breast cancer without bone metastases, who are treated or intend to be treated with AI. After initial tests (see 3.1.3 in Section 3.1) and bone status assessment for osteoporotic fractures as well as BMD, oncologist may refer patient for a consultation and administration of treatment to rheumatologist, endocrinologist or another specialist, whose medical license includes diagnostics and treatment of osteoporosis, or refer to a family physician for detailed assessment of bone loss, administration of treatment and observation.

3.1.2 Bone status is evaluated in patients who are treated or intend to be treated with AI, including women with ovarian function suppression (bilateral oophorectomy, treatment with GnRHa, chemotherapy) in premature menopause [1], and postmenopausal women at risk for BMD decrease as early as 6 months after the start of AI therapy.

3.1.3 Initial tests to evaluate bone status for possible osteoporotic fractures and BMD:

3.1.3.1 Finding out if during a previous year patient experienced osteoporotic fracture spontaneously or from low-energy trauma. Radiological confirmation of fracture is mandatory. Osteoporotic fracture – spontaneous or low energy trauma associated fracture unrelated to malignant or otherwise pathological process in the bone. Term osteoporotic fracture does not include facial, tarsal, metatarsal and metacarpal fractures. Low energy trauma is defined as a fall from a standing height or trauma that would not result in a fracture in a healthy individual. The future risk of fracture is considerably enhanced by previous fracture, which at least doubles a risk of subsequent fracture independently of BMD, in particular for vertebral fractures.

3.1.3.2 Lateral thoracic and lumbar spine X-ray imaging. Radiographs should be evaluated with particular attention to small degree vertebral compression fractures. Diagnostics of osteoporosis related vertebral fracture is the most difficult as diagnosis sometimes is made on the minimal changes in the shape of vertebral body only. Furthermore, some vertebral fractures are asymptomatic, thus remain undiagnosed in as many as 60%–75% of patients. These asymptomatic fractures are associated with an increased risk of future fractures. That is why even in asymptomatic patients we must to perform lateral thoracic and lumbar spine X-ray. This investigation helps us not only to calculate fracture risk but also differentiate osteoporotic fracture from other degenerative vertebral diseases.

3.1.3.3 BMD measurement by DXA (lumbar spine L1–L4 vertebrae and/or at hip site) prior to or during breast cancer treatment with AI and repeated as specified by the order of Lithuanian Ministry of Health (MoH) [10]. Osteoporosis, a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture, has been operationally defined on the basis of BMD assessment. According to WHO criteria osteoporosis is defined as a BMD that is 2.5 standard deviations or more below the average value for young healthy women (*T*-score of ≤−2.5 SD). This criterion has been widely accepted in many countries, including Lithuania, provides both a diagnostic and intervention threshold. BMD testing using dual energy X-ray absorptiometry (DXA) is a gold standard to diagnose osteoporosis, assess fracture risk and evaluate treatment effectiveness. BMD test has a high specificity but low sensitivity which means that BMD alone is not an optimal for the detection of individuals at high risk of fracture because bone strength reflects the integration of both – bone density and bone quality [10].

3.1.4 Assessment and calculation of risk factors for bone fracture and fall risk factors.

In the past decade a lot of risk factors other than BMD were identified. They are partially or fully independent of BMD. Evaluation of the risk factors helps to find patients with high risk for fractures. WHO working group has identified the following key risk factors for fractures: increasing age, female gender, premature menopause, personal history of fracture, parental history of hip fracture, low body mass index, current smoking, excess alcohol consumption, diseases and medications known to increase fracture risk such as, rheumatoid arthritis, ankylosing spondylitis, immobility, Crohn's disease, glucocorticoid use, etc. [11].

If there is no fracture but *T*-score ≤ −1.5 SD, fall risk factors should be evaluated as they play an important role in the occurrence of fractures. Fall risk factors are as follows: age (>80 years), falls during the previous year, history of musculoskeletal and neuromuscular diseases and conditions resulting in impaired balance and coordination, reduced vision, hearing loss, use of psychotropic drugs or more than four medications [12].

3.1.4.1 Detailed evaluation of bone fracture risk factors should be performed if initial tests (listed in 3.1.3 in Section 3.1) for osteoporotic fracture are negative, BMD measurement by DXA demonstrates *T*-score > -2.5 but ≤ -1.5 and a patient has at least one fall risk factor. Bone fracture risk factors can be assessed either by oncologist or by family doctor, rheumatologist, endocrinologist or other specialist.

3.1.4.2 Bone fracture risk factors for women with breast cancer differ from those observed in postmenopausal osteoporosis as specific, cancer treatment-related risk factors, appear: e.g., treatment with AI >6 months, chemotherapy-induced menopause, radiotherapy, tamoxifen use in premenopausal period. Above listed therapies, particularly those that induce a premature menopause or decrease postmenopausal estrogen concentration result in an increased skeletal morbidity. The degree and speed of decreasing of estrogen concentration depends from given therapies and individual skeletal health condition. AI are highly potent inhibitors of estrogen production that suppress circulating estrogen to almost undetectable levels. That is why AI therapy has a significant and rapid effect on bone physiology. Tamoxifen is probably the most widely used endocrine treatment for breast cancer worldwide. Tamoxifen protects against bone loss in postmenopausal women, but increases bone loss in premenopausal women. Equally important are other fracture risk factors: age (>65 years), low body mass index (<20 kg/m^2), hip fracture among first degree relatives, spontaneous or low-energy trauma associated fracture, glucocorticoid use, etc. (listed in Fig. 1).

3.2. *Diagnostics and treatment of bone loss induced by breast cancer treatment with AI*

3.2.1 If initial tests and bone status assessment reveal at least one of the conditions below: radiographically confirmed osteoporotic bone fracture in a previous year due to spontaneous or low energy trauma, compression fracture of at least one vertebrae in spinal X-ray, *T*-score ≤ -2.5 at BMD measurement by DXA in combination with at least one fall risk factor, the patient must be informed that specific treatment and care are needed for bone loss in accordance to the order established by MoH [10]. Specific treatment and observation are provided by family physician or other specialist, whose medical license allows diagnosing and treating osteoporosis.

3.2.2 If a patient has none of the above conditions, but BMD measurement by DXA shows *T*-score > -2.5 but ≤ -1.5 in combination with at least one fall risk factor, fracture risk factors must be assessed (listed in 3.1.4.2 in Section 3.1). If ≥2 risk factors and in combination with at least one fall risk factor are identified: the patient must be informed that specific treatment and care are needed for bone loss in accordance to the order established by MoH [10].

If <2 risk factors are identified: repeated testing according to this algorithm should be performed in 1–2 years after the AI treatment start or earlier in case of spontaneous or low-energy trauma associated osteoporotic fracture.

3.2.3 If *T*-score > -1.5 is found at BMD measurement by DXA, repeated testing is recommended in 1–2 years after the AI treatment start or earlier in case of spontaneous or low-energy trauma associated osteoporotic fracture.

3.2.4 For all patients regardless their age and test results general measures should be applied: physical activity, adequate calcium (at least 1000 mg daily) and vitamin D (800–1000 IU daily) supplementation, lifestyle interventions. Measuring of vitamin D serum concentration in women who start treatment with AI is recommended in some guidelines. We do not recommend this test in our guidelines because vitamin D deficiency is very common among the general population in Lithuania including patients with breast cancer. A daily dose of vitamin D 800–1000 IU or weekly dose of up to 10,000 IU are recommended in the most recent international guidelines and these doses are safe. Beyond bone health vitamin D has been reported to have preventive effects on breast cancer but results remain controversial [6].

The main objectives of treatment are to reduce fracture risk and avoid fractures, to stabilize and increase bone mass, to treat fracture related symptoms, and to improve patient's performance status. The most commonly used medications to correct decreased BMD due to postmenopausal osteoporosis are oral bisphosphonates, but these agents do not have indications for the treatment of cancer treatment-induced bone loss. Therefore, denosumab 60 mg subcutaneous injections every 6 months or zoledronic acid 4 mg infusions every 6 months are recommended for these patient [6,13]. In Lithuania zoledronic acid infusion 4 mg every 6 months is not reimbursed by the Health insurance fund, also 5 mg infusion annually does not have approved indication for treatment of cancer treatment-induced bone loss. In Lithuania treatment with denosumab is reimbursed for the treatment of postmenopausal osteoporosis with pathological (osteoporotic) fracture, postoophorectomy osteoporosis with pathological (osteoporotic) fracture,

- AI therapy > 6 months
- Age (> 65 years)
- Early menopause
- Chemotherapy-induced menopause
- Radiotherapy*
- Tamoxifen use in premenopausal period
- Low body mass index (<20 kg/m^2)
- Hip fracture among first-degree relatives
- Spontaneous or low-energy trauma-associated fracture
- Oral glucocorticoids use ≥ 7.5 mg per day over 3 months
- Alcohol abuse (>3 standard alcohol units per day)**
- Smoking

*Except radiotherapy for bone metastases.
**Standard alcohol unit amount is calculated using formula: Strength (Alcohol by Volume) x Volume (ml) ÷ 1000 = Number of units.

Fig. 1 – Fracture risk factors in women with breast cancer (7).

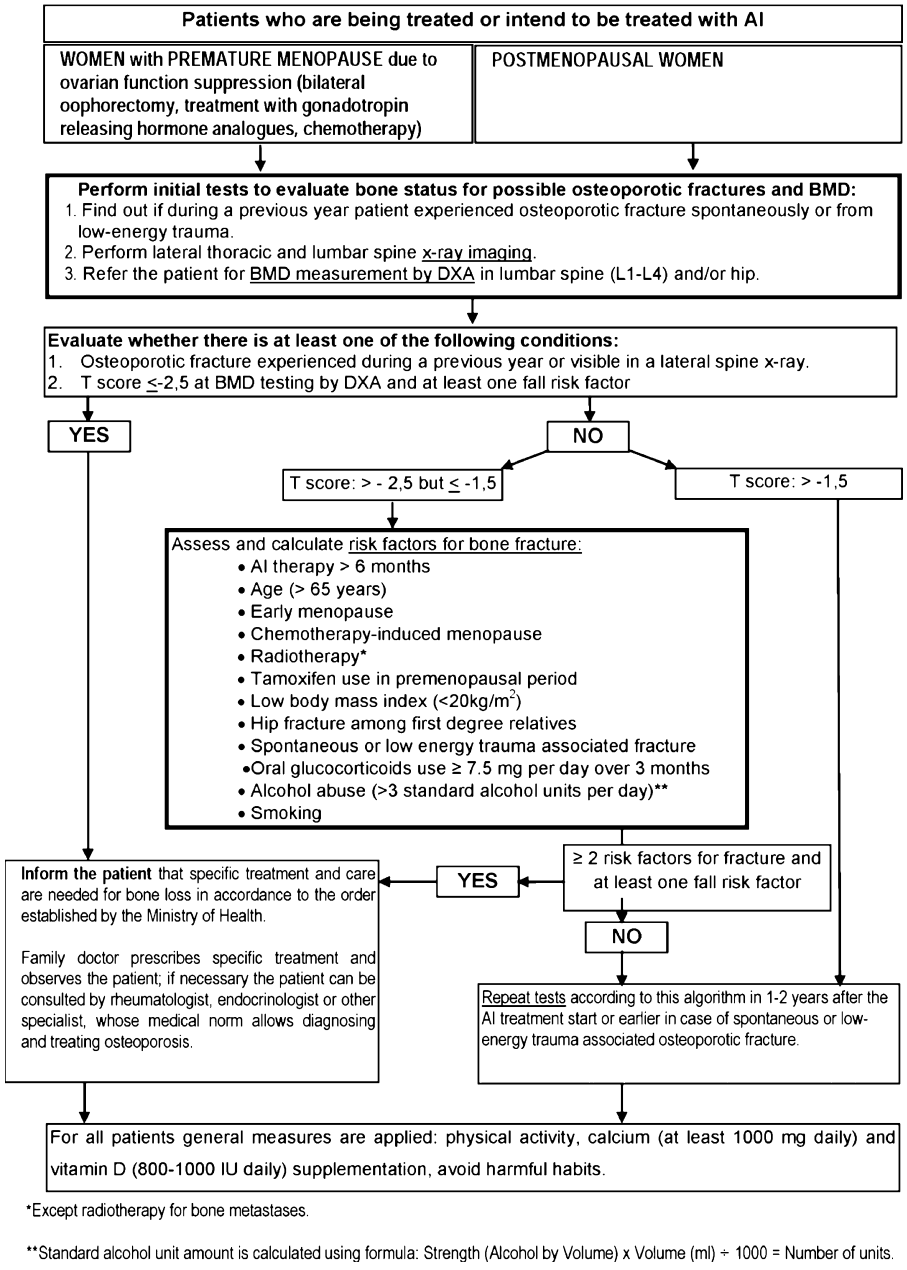

Fig. 2 – Algorithm for diagnostics and treatment of aromatase inhibitor-induced bone loss in women with breast cancer. *Note*: this algorithm is applied to women with breast cancer without bone metastases.

drug-induced osteoporosis with pathological (osteoporotic) fracture, postmenopausal osteoporosis without pathologic (osteoporotic) fracture, postoophorectomy osteoporosis without pathologic (osteoporotic) fracture, drug-induced osteoporosis without pathologic (osteoporotic) fracture.

3.3. *Duration of treatment*

Breast cancer patients receiving AI should be regularly observed for increased bone fracture risk, efficacy and safety of the specific treatment, potential drug interaction. The specific osteoporosis treatment should be applied in accordance to the order established by MoH or throughout the AI treatment period [10].

4. Discussion

Bone health is important component of comprehensive cancer care. 50%–70% of premenopausal women with breast cancer may experience early menopause [14]. The effects of chemotherapy on ovarian function depend on patient's age at treatment, type of regime, cumulative doses. Ovarian failure

occur in 60%–80% of the women receiving cyclophosphamide, methotrexate, 5-fluorouracil (CMF); in 50%, receiving Doxorubicin, cyclophosphamide, 5-fluorouracil (FAC) regimens with age-specific rates of 33% in women aged 30–39 years; 96%, between 40 and 49 years; and 100%, above age 50 [15]. Chemotherapy-induced ovarian failure is a high-risk factor for bone loss, which occurs by 6 months and increases at 12 months [16]. In premenopausal women, tamoxifen treatment is associated with bone loss, through its antiestrogen effects and it is rather bone protective after the menopause being a partial estrogen agonist [17]. Aromatase inhibitors play an important role in the treatment of postmenopausal women with hormone receptor positive breast cancer, both in the adjuvant and metastatic settings, but AI-induced bone loss is more severe than bone loss in healthy postmenopausal women [18]. It is very important, that AI cause a rapid decline of circulating estrogen levels and AI use is considered a high-risk factor for osteoporosis. Risk factors for bone fracture in breast cancer patients are AI therapy, T-score < -1.5, age > 65 years, low body mass index (BMI $< 20\ kg/m^2$), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use > 6 months, smoking (current and history of) [19]. Recent data indicate that loss of bone mass may play an important role in the implantation of tumor cells aggregates in bone (metastatic niche) from which bone or visceral metastases may be generated [20]. That is why bone health is an emerging concern in the breast cancer not only in advance stage but also in adjuvant setting with the possible elimination of micrometastases formation. Initial strategies for preventing bone loss and osteoporosis include nonpharmacologic recommendations for lifestyle and nutritional modifications, e.g., performing weight-bearing exercises and physical activity, avoiding tobacco use, limiting alcohol intake, having adequate intake of calcium (at least 1000 mg daily) and vitamin D (800–1000 IU daily). Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption. Oral bisphosphonates are commonly used medications to correct decreased BMD due to postmenopausal osteoporosis, but these agents do not have indications for the treatment of cancer treatment-induced bone loss. In Lithuania zoledronic acid infusion 4 mg every 6 months is not reimbursed by the Health insurance fund but zoledronic acid 5 mg infusion does not have approved indication for treatment of cancer treatment-induced bone loss. Receptor activator of nuclear factor kB ligand (RANKL) inhibitor (denosumab) is a human monoclonal antibody to RANKL that blocks osteoclast differentiation, proliferation, and function [21]. RANKL is an essential cytokine that is expressed on the surface of osteoblastic cells and osteocytes. Denosumab 60 mg subcutaneous injections every 6 months are recommended for AI treatment-induced bone loss [22,23].

5. Conclusions

Guidelines for diagnostics and treatment of aromatase inhibitor-induced bone loss in breast cancer patients prepared by representatives of Lithuanian oncology institutions in collaboration with multidisciplinary team provide guidance for the identification of patients who are at the highest risk of BMD loss and their evidence based management.

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