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PERSPECTIVE

Management manual for cancer treatment-induced bone loss (CTIBL): position statement of the JSBMR

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Abstract

Androgen deprivation therapy and aromatase inhibitors are known to cause a decrease in bone mineral density and an increase in fractures. Patients receiving these treatments have been shown to have a fracture risk equal to or greater than that of patients with osteoporosis with prevalent fractures. This manual was created to prevent fractures in patients with cancer treatment-induced bone loss with high fracture risks who cannot be treated under the current Japanese guideline for the prevention and treatment of osteoporosis. This manual recommends drug treatment for patients with BMD $-2.0 \leq T$ score < -1.5 with the family history of hip fracture or 15% or more 10-year probability of major osteoporotic fractures by FRAX®; or in patients with BMD T score < -2.0. It is important to verify whether the use of this manual can reduce fractures and improve the quality of life of patients with cancer treatment-induced bone loss by prospective studies.

Keywords Aromatase inhibitor · Androgen deprivation therapy · Fracture · Bone mineral density

Background and objective

Aromatase inhibitors (AIs) and androgen deprivation therapy (ADT) have greatly improved the clinical outcome of patients with hormone-sensitive breast and prostate cancers, respectively. On the other hand, these treatments are known to cause a decrease in bone mineral density (BMD) and an increase in fractures [1]. It has been reported that the occurrence of fractures not only significantly impairs the patients' quality of life, but also almost doubles the frequency of subsequent fractures and worsens the prognosis of life [2]

ADT has been shown to increase the risk of fractures by 2–3 times depending on the bone sites [3]. AIs have also been reported to cause approximately two times increase in fracture risk compared to tamoxifen treatment [4]. These results indicate that patients receiving ADT or taking AIs have a fracture risk equal to or greater than that of patients with osteoporosis with prevalent fractures.

According to the current Japanese guideline for prevention and treatment of osteoporosis, drug treatment is recommended for (a) patients with existing fractures in the spine or hip; (b) patients with BMD greater than 70% and less than 80% of young adult mean (YAM) and with fragility fractures other than spine or hip; (c) patients with BMD

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greater than 70% and less than 80% of YAM, and either 15% or more 10-year probability of major osteoporotic fractures by FRAX® or family history of hip fractures; or (d) patients with BMD at or below 70% of YAM or *T* score −2.5 [4]. However, in CTIBL patients, there is a possibility that fractures cannot be prevented under the current guideline for the treatment of osteoporosis, because cancer treatment itself increases fracture risk to a level similar to that in patients with osteoporosis having fragility fractures.

The objective of this manual is to prevent fractures in CTIBL patients with high fracture risks who cannot be treated under the current guideline for the prevention and treatment of osteoporosis.

Basis for the proposal

So far, there is not enough evidence in Japan showing the relationship between BMD and fracture risk, or the effects of treatment drugs for osteoporosis on BMD and fractures in CTIBL patients. Therefore, this manual is produced based upon the following observations and proposals made from the evidence created mostly outside Japan:

(a) It is estimated that patients undergoing ADT and AI treatment suffer from CTIBL and have similar fracture risk as those in patients with osteoporosis with prevalent fractures [3, 5].
(b) According to the report of the National Comprehensive Cancer Network (NCCN) Task Force in the United States, if *T* score ≥ −1.0, follow-up observation is recommended; if −1.5 ≤ *T* score < −1.0, measurement of serum 25-hydroxyvitamin D [25(OH)D] and follow-up observation are recommended; if −2.0 ≤ *T* score < −1.5, measurement of 25(OH)D and consideration of medication are recommended; if *T* score < −2.0, measurement of 25(OH)D and strong consideration of medication are recommended. In all cases, it is recommended that follow-up observations should be made by measuring BMD every two years with dual energy X-ray absorptiometry (DXA) [6].
(c) In joint position statements by societies including International Osteoporosis Foundation (IOF), Cancer and Bone Society (CABS), European Calcified Tissue Society (ECTS), and International Menopause Society (IMS), in patients with *T* score > −2.0 and without other fracture risk factors, encouragement of Ca/vitamin D intake and measurement of BMD every 1–2 years are recommended. In patients with *T* score < −2.0, encouragement of Ca/vitamin D intake and treatment with denosumab or bisphosphonate, BMD monitoring every 2 years and compliance check with oral therapy are recommended. In cases with two fracture risk factors, Ca/vitamin D intake and treatment with denosumab or bisphosphonate, BMD measurement every 2 years and compliance check with oral therapy are recommended as in the case of *T* score < −2.0. Risk factors listed here were older than 65 years, *T* score < −1.5, smoking (current and past), BMI < 24, family history of hip fractures, fragility fractures after age 50, and oral glucocorticoids for more than 6 months [7].

Recommendations

All patients starting ADT or AIs are advised to evaluate their serum 25(OH)D level and other risk factors for fractures, and are encouraged to exercise moderately. They are then evaluated for osteoporosis, and if they are diagnosed to already have osteoporosis, they are treated accordingly. In patients with lumbar spine or proximal femoral BMD *T* score ≥ −1.5, BMD measurement should be repeated every 1–2 years. In patients with BMD −2.0 ≤ *T* score < −1.5 with the family history of hip fracture or 15% or more 10-year probability of major osteoporotic fractures by FRAX®; or in patients with BMD *T* score < −2.0, drugs for the treatment of osteoporosis should be administered (Fig. 1). In addition, we recommend more frequent BMD measurements for patients who are at risk of rapid progression of CTIBL due to powerful ADT such as blockage of androgen receptor signaling by apalutamide and systemic inhibition of androgen production by abiraterone with prednisolone replacement.

Treatment

Patients are indicated for drug treatment following the proposed algorithm in Fig. 1. Many reports have been published regarding the effect of treatment drugs on BMD and fracture incidence in CTIBL patients. Those studies demonstrate that both denosumab and bisphosphonates are effective in preventing and/or treating CTIBL. The primary endpoint in most of those studies was their effect on increasing BMD. However, based upon the observation that an increase in BMD especially at the total hip is associated with a reduction in fracture incidence in osteoporosis, BMD increase can be regarded as a surrogate for the effect of drugs on fracture prevention in CTIBL as well [8].

Effects of bisphosphonates and denosumab have been extensively studied for patients with CTIBL, and encouraging results have been reported particularly with zoledronic acid and denosumab [9–12]. In Japan, the results of treatment with zoledronic acid [13, 14], and denosumab [15–17] have also been reported with similar results. Although first-line drugs are not specified in this manual, zoledronic acid and denosumab can be drugs of choice for the treatment of

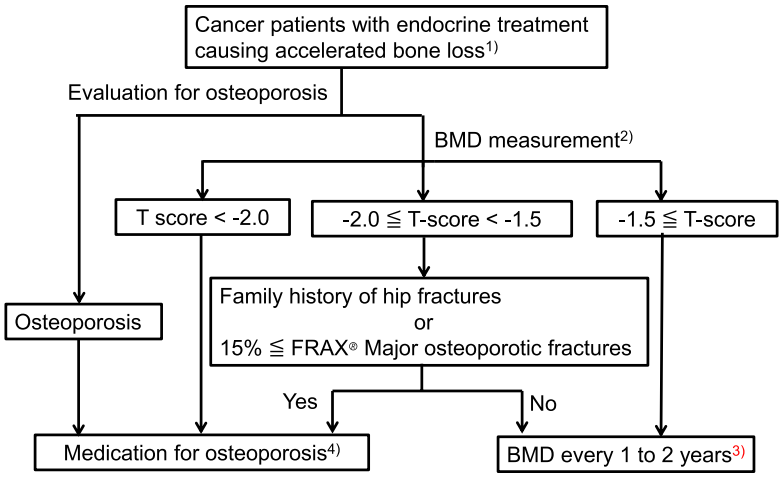

Fig. 1 Algorism for the management of CTIBL patients. If patients are diagnosed to already have osteoporosis, they should be treated accordingly. If their lumbar spine or proximal femoral BMD *T* score ≥ -1.5, repeat BMD measurement every 1–2 years. If their BMD $-2.0 \leq T$ score < -1.5 with the family history of hip fracture or 15% or more 10-year probability of major osteoporotic fractures by FRAX®; or if BMD *T* score < -2.0, drugs for the treatment of osteoporosis should be administered

Notes
1) Provide general measures such as evaluation of serum 25(OH)D concentration and other risk factors for fractures, and encourage modest exercise.
2) Use lumbar vertebrae without fractures. Use femoral BMD if more than 2 lumbar vertebrae (L1-L4) without fractures are not available.
3) More frequent measurements are recommended for patients who are at risk of rapid progression of CTIBL due to powerful ADT such as apalutamide and abiraterone with prednisolone.
4) Encouraging results have been reported with bisphosphonates, especially zoledronic acid, and denosumab. Avoid the use of teriparatide that may aggravate primary or metastatic malignant bone lesions.

CTIBL. We also recommend not to use teriparatide for the treatment of CTIBL, because it may aggravate primary or metastatic malignant bone lesions.

Future directions

CTIBL patients without the diagnosis of osteoporosis may suffer from fracture, because CTIBL itself increases fracture risk by 2–3 times. Because these patients cannot be treated for the prevention of fracture under the Japanese guideline for the prevention and treatment of osteoporosis, this manual was created to reduce fracture risk in CTIBL patients. As mentioned before, there is not enough evidence concerning the incidence of fractures, the effect of treatment and the outcome of CTIBL patients in Japan. Therefore, it is important to verify whether the use of this manual can reduce fractures and improve QOL of CTIBL patients by prospective studies.

Compliance with ethical standards

Conflict of interest S.F. has received research grants from Astellas Pharma and Teijin Pharma. S.S. has received consulting fees, speaking fees, and/or honoraria from Asahi Kasei Pharma, Astellas Pharma, Chugai Pharmaceutical, Daiichi-Sankyo, Eisai, Eli Lilly Japan, MSD, Ono Pharmaceutical, Pfizer, Takeda Pharmaceutical and Teijin Pharma. T.T. received research donation and lecture fee from Daiichi Sankyo. S.H. has received research grants and honoraria from Astellas pharma, Takeda Pharmaceutical, Astrazeneka and Sanofi. T.S. has received research grants from Astellas Pharma, Eisai, Daiichi-Sankyo, Chugai Pharmaceutical and Eli Lilly Japan, as well as lecture and/or consulting fees from Asahi Kasei Pharma and Daiichi-Sankyo. T.M. has received consulting fees from Chugai Pharmaceutical, Amgen Astellas Biopharma, Teijin Pharma and Daiichi-Sankyo.

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