Guidance for the prevention of bone loss and fractures in postmenopausal women treated with aromatase inhibitors for breast

Osteoporos Int (2012) 23:2567–2576
DOI 10.1007/s00198-011-1870-0

ORIGINAL ARTICLE

Guidance for the prevention of bone loss and fractures in postmenopausal women treated with aromatase inhibitors for breast cancer: an ESCEO position paper

R. Rizzoli · J. J. Body · A. De Censi · J. Y. Reginster · P. Piscitelli · M. L. Brandi · on behalf of the European Society for Clinical and Economical aspects of Osteoporosis and Osteoarthritis (ESCEO)

Received: 20 October 2011 / Accepted: 5 December 2011 / Published online: 20 January 2012

Abstract
Summary Aromatase inhibitors (AIs) are widely used in women with breast cancer, but they are known to increase bone loss and risk of fractures. Based on available evidence and recommendations, an ESCEO working group proposes specific guidance for the prevention of AIs-induced bone loss and fragility fractures.
Introduction Aromatase inhibitors (AIs) are now the standard treatment for hormone receptor-positive breast cancer. However, deleterious effects of AIs on bone health have been reported. An ESCEO working group proposes guidance for the prevention of bone loss and fragility fractures in postmenopausal women with breast cancer receiving AIs.
Methods A panel of experts addressed the issue of skeletal effects of AIs and effectiveness of antifracture therapies for the prevention of AI-induced bone loss and fractures. Recommendations by national and international organizations, and experts' opinions on this topic were evaluated.
Results All aromatase inhibitors are associated with negative effects on the skeleton, resulting in bone loss and increased risk of fragility fractures. Current guidelines suggest approaches that differ both in terms of drugs proposed for fracture prevention and duration of treatment.
Conclusion The ESCEO working group recommends that all AI-treated women should be evaluated for fracture risk. Besides general recommendations, zoledronic acid 4 mg i.v. every 6 months, denosumab s.c., or possibly oral bisphosphonates should be administered for the entire period of AI treatment to all osteoporotic women (T-score hip/spine ≤ -2.5 or ≥ 1 prevalent fragility fracture), to women aged ≥ 75 irrespective of BMD, and to patients with T-score $\leq -1.5 + \geq 1$ clinical risk factor or T-score $\leq -1.0 + \geq 2$ clinical risk factors. Alternatively, therapy could be considered in patients with a FRAX-determined 10-year hip fracture probability $\geq 3\%$.

Keywords Aromatase inhibitors · Bisphosphonates · Bone loss · Breast cancer · Fracture risk

R. Rizzoli
Division of Bone Diseases, Geneva University Hospitals and Faculty of Medicine,
Geneva, Switzerland

J. J. Body
Department of Medicine, CHU Brugmann, Université Libre de Bruxelles,
Brussels, Belgium

A. De Censi
Division of Medical Oncology, Galliera Hospital,
Genoa, Italy

A. De Censi
Division of Cancer Prevention and Genetics, European Institute of Oncology,
Milan, Italy

J. Y. Reginster
Department of Public Health Science, University of Liège,
Liège, Belgium

P. Piscitelli · M. L. Brandi (✉)
Department of Internal Medicine, University of Florence,
Largo Palagi 1,
50139 Florence, Italy
e-mail: m.brandi@dmi.unifi.it

Introduction

Breast cancer is the most frequent neoplasm in women—with its incidence still growing—and the first cause of

cancer mortality among women. Notably, a reduction in breast cancer mortality has been observed in recent years [1, 2]. Aromatase inhibitors (AIs) represent the gold standard adjuvant treatment for postmenopausal women with hormone receptor-positive breast cancer [3, 4] and for the management of metastatic disease [5]. AIs have shown significant advantages in terms of progression-free survival and especially distant recurrence compared to tamoxifen in large randomized controlled adjuvant therapy trials [6–8]. Furthermore, extended therapies with AIs (up to 10 years) are increasingly being introduced in women at higher risk of long-term recurrence, including patients with positive lymph node disease [9]. The aromatase enzyme, which is blocked by AIs, converts androgens into estrogens. This conversion is the main source of endogenous estrogens in postmenopause [10]. Bone loss represents a classic side effect of AI treatment [11–13]. This issue is of particular relevance since AI-treated women with breast cancer who develop a vertebral osteoporotic fracture are often suspected of metastatic disease, thus leading to additional investigations and avoidable costs for the health-care system due to unnecessary diagnostic procedures [14]. Therefore, it is very important (1) to identify the patients at increased risk of fractures, and (2) to introduce preventive antifracture treatments in women at increased risk of fracture who undergo adjuvant hormone therapy with AIs [14]. The American Society of Clinical Oncology (ASCO) has proposed specific recommendations regarding this issue, suggesting that all patients with T-score <−2.5 should start proper antifracture treatment with bisphosphonates [15]. However, many open questions still remain unanswered, including a general increase of fracture risk in women with breast cancer, their quality of life, the risk of falls, the duration of antifracture therapy, and vitamin D supplementation. Given the high incidence of breast cancer in postmenopausal women and the wide use of prolonged estrogen-suppressive therapies, the European Society for Clinical and Economical Aspects of Osteoporosis (ESCEO) working group strongly believes that it is necessary to manage the long-term effects of aromatase inhibitors on bone health. This position paper is aimed at providing physicians (oncologists and specialists in metabolic bone diseases) with updated guidance integrating the analysis of the most recent medical literature and recommendations from international societies or expert panels.

Methods

A panel of experts addressed the issue of skeletal effects of AIs and effectiveness of antifracture therapies for the prevention of AI-induced bone loss and fractures through a systematic search of published literature on PubMed. The results of available descriptive, cross-sectional, and prospective studies related to pathogenesis and severity of skeletal effects following aromatase inhibitors administration in women with breast cancer were analyzed, as well as recent trials investigating the effectiveness of existing antifracture therapies in the prevention of AI-induced bone loss and fractures. Recommendations of national and international organizations and societies or experts' opinions on this topic were also evaluated.

Assessment of skeletal effects of aromatase inhibitors

Aromatase inhibitors decrease bone mass and density, and increase fragility fractures incidence compared to tamoxifen [16, 17]. In healthy postmenopausal women, the rate of bone loss is about 1–2% per year [18]. The annual rate of bone loss in postmenopausal women receiving treatment with AIs because of breast cancer is elevated to around 2.5% [19]. Although AIs use is not standard in premenopausal women, a study of the combination of anastrozole with a GnRH agonist has shown an annual bone loss rate of 7.0% [20]. Induced menopause in young women following adjuvant chemotherapy is associated with accelerated bone loss which has been estimated up to 8% at 1 year [21]; bone loss is much higher in patients treated with AIs than in osteoporotic postmenopausal women [20, 22]. It is estimated that more than 30% of patients treated with anastrozole will have a diagnosis of osteoporosis in the subsequent years [23]. Some variations concerning the magnitude of skeletal side effects have been demonstrated between the different aromatase inhibitors. A significant bone loss in patients treated with anastrozole occurred both at spine (from −2% at 1 year up to −7% at 5 years) and hip (from −1% at 1 year up to −8% at 5 years), while a positive effect on BMD was observed for tamoxifen, a SERM [23]. A 2–4% BMD reduction at lumbar spine after 1 year on anastrozole was found in an indirect comparison of the ATAC, IES and MA-17 trials [24], while lower BMD reductions were reported in other trials for letrozole (3% at 7 years) [9] and exemestane (2% at 5 years) [24]. Cortical and trabecular bone at the radius and tibia in postmenopausal women treated with anastrozole for breast cancer was found to be lower using peripheral quantitative computed tomography [25]. A comparative study analyzing data from the same pivotal trials found significant BMD reductions in patients under anastrozole: −2.3%, −4.0%, 6.08% (at lumbar spine) and −1.5%, −3.9%, −7.2% (total hip) after 1, 2, and 5 years, respectively [26]. Also, treatment with letrozole resulted in significant bone loss: −3.3% and −5.3% (lumbar spine), and −1.4% and −3.6% (total hip) after the 1st and the 2nd year [26]. Decrease in BMD was apparently lower in patients treated with exemestane, possibly related to its steroidal structure: −1.7% and −1.0% (lumbar spine), and −1.4% and −0.8% (total hip) at 6 and 24 months, respectively [26]. These data

were confirmed in a recent meta-analysis showing significant BMD reductions both at lumbar spine and total hip: −6.1% and −7.2% for anastrozole at 5 years, −5.3% and −3.6% for letrozole after 2 years, and −4.0% and −2.0% for exemestane at 2 years [27]. Overall, there is a well-documented AI class effect in decreasing bone mineral density. This effect is of high magnitude and rapid. Estrogen inhibition influences bone remodeling and increases osteoclastic activity, which is documented by an increase in bone resorption markers, and finally results in bone loss [28]. On the other hand, tamoxifen administration in postmenopausal women with breast cancer has an opposite effect compared to its use before menopause (where the estrogen deprivation effect inducing bone loss is prevalent), thus resulting in a small but significant BMD increase [29]. While this effect has initially been deemed to be lower than with raloxifene [30, 31], the fracture incidence rates were found to be similar between the two SERMs in a large primary prevention trial (STAR) aimed at evaluating the preventive effect on breast cancer of raloxifene versus tamoxifen in postmenopausal women at risk for breast cancer [32]. A high incidence of vertebral fractures has been observed in women with breast cancer, mostly because of the premature menopause induced by cancer chemotherapy [33].

Women treated with AIs present a more than 30% higher risk of fractures compared to age-matched healthy postmenopausal women [22]. However, among women treated with AIs, the population at higher risk of fracture is younger than that normally observed in postmenopausal women [34] and presents a lower baseline risk of fracture [35]. This observation may explain why spontaneous fracture incidence in the ATAC study [6] was found to be lower than that observed in all major trials concerning osteoporotic fractures [36–39]. Anastrozole was associated with a higher risk of fracture at 5 years [40] and at 7 years compared with tamoxifen [41]. Also, letrozole was associated with a long-term (up to 5 years) higher risk of fracture if compared to tamoxifen in the initial report of the BIG 1-98 trial (6.5% vs. 9.3%, respectively) [12] as well as in more recent reports (5.7% vs. 4.0%) [42, 43]. The steroidal AI exemestane was also associated with a higher risk of fragility fractures in postmenopausal women with breast cancer after 1 year (7% vs. 5%) and 3 years (3.1% vs. 2.3%) when compared to tamoxifen [24, 44], with significant differences in BMD and bone remodeling biomarkers [24, 44]. However, the effect on the fracture risk was reversible when exemestane treatment was stopped [46]. The effects of AIs on the incidence of fragility fractures have been well documented as adverse events within pivotal trials, with bone loss being directly related to fracture risk increase [6, 16, 24, 27, 47, 48]. Table 1 summarizes the incidence of fragility fractures in main clinical studies using aromatase inhibitors as adjuvant therapy for breast cancer. Overall, the risk of fractures in patients treated with AIs seems to be higher in peripheral skeletal sites than spine or hip [43], a possible explanation for that being represented by the younger age of patients if compared to the studies carried out for the prevention of osteoporotic fractures [36–39]. Importantly, fractures occurring in all the trials on patients treated with AIs were reported as adverse events, thus not representing primary endpoints of the studies, and possibly producing an underestimation of spine and hip fracture incidence. On the other hand, because the fracture rates related to the use of AIs have almost always been reported in comparison to those of tamoxifen, this could overestimate the difference in the incidence of both groups because of the protective effect of tamoxifen on fracture risk. In addition, patients with breast cancer may have higher levels of estrogens at baseline that could explain differences in fracture incidence between patients treated with AIs and those who are osteoporotic [49].

Management of patients receiving anti-aromatase therapy

Calcium and vitamin D supplementation

In women starting adjuvant treatment because of breast cancer, serum concentrations of PTH, calcium, and 25-OH vitamin D should be tested before starting any AI treatment. Actually, vitamin D deficiency is very common among the general population, including postmenopausal women [50–52].

Table 1 Fractures in adjuvant studies with aromatase inhibitors in breast cancer

AI study	Number	Duration F/U, months	Fractures (%)		*P* value
			Aromatase inhibitor	Tamoxifen	
ATAC[6]	6,241[a]	68	11.0 (anastrozole)	7.7	<.0001
BIG 1-98[16]	8,010	35.5	5.8 (letrozole)	4.1	.0006
IES[24]	4,742	30.6	3.1 (exemestane)	2.3	.08
ARNO[48]	3,224	28	2.4 (anastrozole)	1.2	NR
				Placebo	
MA.17[9]	5,187	60	5 (letrozole)	5	.25

[a]Patients initially randomized: 9,366 (treatment arm, anastrazole+tamoxifen, including 3,125 pts, was suppressed)

NR not reported

Serum vitamin D levels at least above 75 nmol/l (30 ng/ml) may be considered as a target, but many patients present unrecognized vitamin D deficit at the time they are diagnosed with breast cancer [53]. This deficiency has been associated with a higher risk of cancer mortality in observational studies [54, 55]. Secondary hyperparathyroidism resulting from low serum concentrations of vitamin D might attenuate the antiresorptive action of bisphosphonates, thereby leading to a higher risk of fractures if compared to patients with normal levels of serum vitamin D [55, 56]. In conjunction with calcium, an antifracture effect has been demonstrated for vitamin D itself (at a dose of 700–800 IU/day), resulting in a 20% and 18% reduction of non-vertebral and hip fractures, respectively [57]. However, there are no conclusive data in breast cancer patients. Besides bone and muscle, other beneficial effects of vitamin D have been suggested, but they still remain controversial [53]. Beyond bone health, vitamin D has been reported to exert positive effects in the prevention of hypertension, cardiovascular diseases, falls, cancer incidence, and mortality [53, 55]. Some vitamin D direct preventive effects on breast cancer were reported by a recent metanalysis [58], but results remain controversial [59]. The doses currently used for vitamin D supplementation seem to be generally insufficient to restore adequate serum concentration [52]. While the association between vitamin D levels and breast cancer risk/prognosis is still controversial, the U-shaped relationship between 25-OH vitamin D levels and cancer or mortality risk observed in different studies suggests the need to avoid both deficient and too high levels [52, 60, 61]. A serum concentration of 25-OH vitamin D ≥40 ng/ml was associated with lower incidence of arthralgia in a specific prospective cohort study specifically designed to establish optimal levels of vitamin D for the prevention of AI-induced arthralgia [62], while the risk of arthralgia in patients with low concentration of 25-OH vitamin D (≤30 ng/ml) was confirmed in a separate study [63]. A weekly dose of up to 10,000 IU may thus be recommended in women with breast cancer based on recent international guidelines [64].

Efficacy of antiresorptive therapies in the prevention of AI-induced bone loss

Osteoporosis drugs used for the prevention of osteoporotic fractures in postmenopausal osteoporosis have also been proposed in women treated with AIs for breast cancer. An open-label, multicentric, randomized trial (Zometa-Femara Adjuvant Synergy Trial; Z-FAST/ZO-FAST) evaluated the effect of concurrent administration of zoledronic acid i.v. at a dose of 4 mg every 6 months (from the beginning of AI treatment or as delayed additional therapy on the basis of subsequent BMD values or in case of osteoporotic fracture) and letrozole 2.5 mg per day over a 5-year period [65–70]. After 1 year, mean lumbar spine BMD increased by 1.9% when compared with the baseline in patients who started treatments with both zoledronic acid and letrozole from the beginning (upfront arm), while a −2.4% reduction was observed in patients assigned to the delayed treatment arm of the study [65–68]. The Z-FAST trial enrolled 602 patients and showed an overall significant difference in lumbar spine BMD change of 4.4% at 1 year, which increased up to 6.7% at 3 years [65, 69]. Similarly, the ZO-FAST trial (1,066 patients enrolled) showed comparable results, with an overall difference in lumbar spine BMD change of 5.3% after 1 year, and 9.3% after 3 years in favor of immediate concurrent administration of zoledronic acid and letrozole [66–69]. Both Z-FAST and ZO-FAST studies have shown that total hip BMD increased after 3 years in the upfront treatment arm [65, 67]. Moreover, 3-year results from the ZO-FAST study, showed a higher disease-free survival, with a 41% risk reduction of disease recurrence in patients who started concurrently letrozole and zoledronic acid (upfront arm), compared to the delayed treatment arm [67]. This effect is confirmed in the ZO-FAST study 5-year follow-up [70]. The efficacy of zoledronic acid in improving disease-free survival and bone loss was also shown in premenopausal patients in a 3-year study of the Austrian Breast and Colorectal Study Group, involving 1,803 patients with hormone receptor-positive breast cancer [71, 72]. In this open-label randomized trial, concurrent administration of anastrozole or tamoxifen and zoledronic acid 4 mg i.v. every 6 months resulted in a significantly higher bone mineral density (BMD remained stable over 3 years) if compared to that of patients who did not receive zoledronic acid at all (where marked decrease both in lumbar spine and total hip BMD were observed) [71–73]. Interestingly, local and distant recurrences were reduced by zoledronic acid treatment [74], but the results of the AZURE trial showed that adjuvant use of zoledronic acid did not improve disease-free survival (DFS) in stage II/III breast cancer patients, at least in the whole group of randomized patients [75]. The trial included 3,360 patients from 174 centers in England who were randomized to receive adjuvant chemotherapy and/or endocrine therapy with or without zoledronic acid at 4 mg i.v. every 3 to 4 weeks for six doses. The dose was then tapered down to every 3 months for eight doses and then every 6 months for five doses to complete 5 years of treatment. The addition of zoledronic acid to standard treatment did not significantly impact the delivery of chemotherapy [75]. Serious adverse events were similar in both treatment arms, although there were 17 confirmed cases of osteonecrosis of the jaw in the zoledronic acid arm ($P<.0001$) [75]. The median follow-up was 5.9 months, and 752 DFS events (377 in the zoledronic acid group vs. 375 in the control group) have been reported. Overall survival data showed a 15% reduction in risk of dying with zoledronic acid, and this approached statistical

significance (P=.07) [75]. Interestingly, a preplanned analysis indicated that, when considering overall survival, the adjusted Hazard Ratio (HR) was 1.01 for the premenopausal group and 0.71 for the established postmenopausal women with a significant 29% improvement (P=.017) [75].

Several studies have demonstrated the efficacy of other bisphosphonates in preventing AI-associated bone loss, although some of them are very small or present inconclusive results. The ARIBON trial included 131 postmenopausal patients treated for 2 years with anastrozole (plus calcium/vitamin D supplementation) [76]. Fifty osteopenic women were randomized to receive oral ibandronate 150 mg once a month or not. Ibandronate-treated women showed positive BMD changes (+3.0% and +0.6% at lumbar spine and total hip, respectively) when compared to those not receiving ibandronate (−3.2% and −3.9% at lumbar spine and total hip, respectively) [76]. The primary endpoint of the SABRE study was to determine lumbar spine BMD changes from baseline after 1 year of treatment with anastrozole alone or in combination with risedronate (35 mg administered once weekly) in 154 patients [77]. After 2 years, the results of the SABRE study showed a +2.2% and +1.8% BMD increase at lumbar spine and total hip, respectively, in the group treated with risedronate [77]. Similar results were noted in older or smaller trials (Table 2). However, risedronate failed in preventing bone loss in 170 premenopausal women undergoing adjuvant chemotherapy for breast cancer with anthracyclines, taxanes, or cyclophosphamide [78]. Oral clodronate (at the dose of 1,600 mg per day) has been demonstrated to improve BMD at lumbar spine (+2.9%) and femoral neck (+3.7%) in a study on 121 postmenopausal women with breast cancer [79]. Studies with alendronate have been performed on a very small cohort of patients, thus leading to inconclusive results (not significant increase in lumbar spine and hip BMD) [80, 81]. The effects of the new human monoclonal antibody denosumab have also been explored. A trial has randomized 252 AI-treated postmenopausal women with hormone receptor-positive non-metastatic breast cancer to receive placebo or denosumab 60 mg s.c. every 6 months [82]. After 2 years, patients assigned to the treatment with denosumab had a higher BMD than those in the placebo group, both at lumbar spine (+7.6%) and total hip (+4.7%). A significant increase in BMD with denosumab was observed at the lumbar spine after 1 year (+5.5%) and at the radius after 2 years (+6.1%) [82].

Available recommendations

There are few available recommendations. Since 2003, ASCO has issued specific guidelines addressing the issue of fracture prevention in postmenopausal women treated with AIs [15, 83]. ASCO recommends that all patients with T-score <−2.5 should undergo antifracture therapy with bisphosphonates (i.e. alendronate, risedronate, or zoledronic acid), without specific advice on treatment duration. ASCO also recommends that the decision to treat patients with T-scores between −1 and −2.5 should be tailored on an individual basis [83]. The issue of optimal treatment duration has been addressed in 2008 by an international panel of experts [84], which has suggested that patients should be treated for at least 2 years, or possibly as long as AI therapy (up to 5 years), by administering zoledronic acid at the dose of 4 mg i.v. every 6 months together with calcium and vitamin D supplementation. This panel of experts recommended to treat all people with T-score ≤ −2.0, and also those subjects presenting at least two of the following risk factors: T-score <−1.5, age >65 years, BMI <20 kg/m², family history of hip fracture, personal history of fragility fracture after 50 years of age, oral corticosteroid therapy >6 months, and cigarette smoking [84]. A recent revision of these recommendations opens to the possibility of using oral bisphosphonates by evaluating benefits and risks on an individual basis [85]. In addition, denosumab is regarded as a potential treatment option [85]. The international expert panel suggested that the BMD of patients treated with oral

Table 2 Oral bisphosphonates for preventing AI-induced bone loss in postmenopausal women with early breast cancer

Antiresorptive agent (trial)	Reference	Number	BMD study *n*	Dosing	Treatment duration, years	Follow-up, months	Mean change, % BMD	
							Lumbar spine	Total hip
Clodronate	Saarto [79]	61	61	1,600 mg PO/day	3	60	−1.0	−0.1
Risedronate (IBIS II)	Singh et al. [91]	613	59	35 mg PO/week	5	12	+0.3	+0.7
Risedronate	Confavreux [92]	118	11	35 mg PO/week	1	12	+4.1	+1.8
Risedronate	Greenspan [93]	87	87	35 mg PO/week	2	24	+0.4	+0.9
Risedronate (ARBI)	Markopoulos [94]	213	70	35 mg PO/week	2	24	+5.7	+1.6
Risedronate (SABRE)	Van Poznak [95]	154	111	35 mg PO/week	2	24	+2.2	+1.8
Ibandronate (ARIBON)	Lester [76]	131	50	150 mg PO/day	2	24	+3.0	+0.6

PO per os

bisphosphonates should be monitored every 1–2 years, while the decision of the time interval for women undergoing i.v. administration of zoledronic acid has not been clearly defined [84]. On the other hand, postmenopausal women treated with AIs who are not receiving any anti-osteoporotic drug should undergo a BMD measurement after 1–2 years of AI therapy and a regular assessment of their risk status [84, 85]. Therefore, as long as antiresorptive therapy to prevent additional bone loss is initiated, osteoporosis (with or without a history of fractures) is not a contraindication for AI therapy in postmenopausal women with early breast cancer [84, 85]. The panel recommended that antiresorptive therapy should be continued as long as AI therapy is maintained, currently most often 5 years [84, 85]. The preference was given to zoledronic acid 4 mg i.v. every 6 months since it is the only antiresorptive agent with demonstrated efficacy and safety over such a long duration [84, 85].

A consensus of the "Belgian Bone Club" suggested treating all patients with T-score <−2.5 or <−1 who also present other clinical risk factors with i.v. zoledronic acid (as first choice drug), or with oral bisphosphonates, for the duration of AI therapy, providing adequate calcium and vitamin D supplementation at the same time [86]. A UK expert group considered all bisphosphonates as appropriate (zoledronic acid 4 mg i.v. every 6 months, oral ibandronate 150 mg per os every month or 3 mg i.v., oral alendronate 70 mg weekly, oral risedronate 35 mg weekly), with the decision to treat being based on the sole BMD value (T-score <−2.0), or the occurrence of a vertebral fracture, or an annual bone loss >4% (at lumbar spine or total hip) for T-score between −1.0 and −2.0 and the presence of risk factors (i.e., age >65 years; BMI <20 kg/m²; family history of hip fracture; personal history of fragility fracture; corticosteroid therapy >6 months; cigarette smoking). Elderly women (>75 year) with at least one risk factor should be treated with a bisphosphonate irrespective of BMD [87]. According to the same UK expert group, premenopausal women with ovarian suppression undergoing AI therapy should receive a proper antifracture drug if their T-score is <−1.0 or in case of vertebral fracture [87].

ESCEO working group guidance

There is clear evidence for an association between increased bone loss and risk of fragility fractures and the administration of AIs to postmenopausal women with breast cancer. Despite the growing recognition of the frequency and the consequences of AI-induced bone loss, there are currently no therapies specifically approved for its prevention. We recommend that all women starting a therapy with AIs should be carefully assessed for their baseline risk of osteoporotic fractures by performing a DXA examination and a full evaluation of all clinical risk factors (including age, parental fracture history, BMI <20 kg/m², corticosteroid use, cigarette smoking, inadequate nutritional intakes, disuse, tendency to falls, and conditions associated to osteoporosis). A biochemical survey should include determination of calcium, PTH, and vitamin D levels, to exclude primary hyperparathyroidism and to diagnose vitamin D insufficiency or deficiency [53–55]. The role of biochemical markers of bone turnover should be further investigated to assess their ability to predict and possibly monitor bone loss in this setting. General recommendations include an increase in physical exercise and, in most patients, administration of supplemental vitamin D (a weekly dose of up to 10,000 or >800 IU/day) and calcium to maintain a calcium intake of at least 1,000 mg/day.

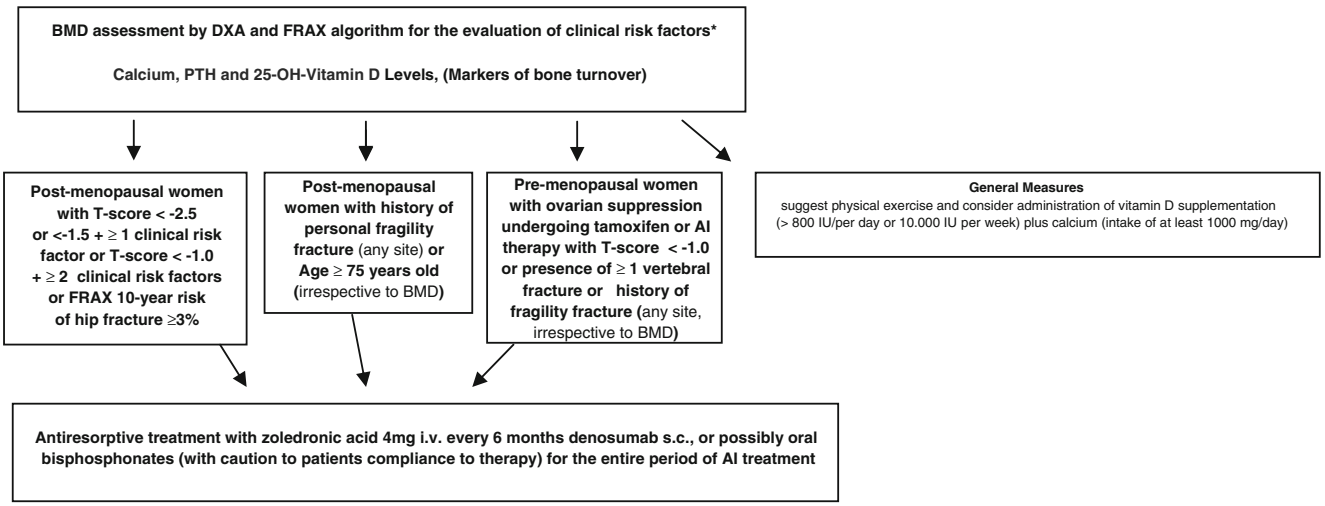

Fig. 1 Algorithm describing the suggested approach to patients with breast cancer treated with AIs

Premenopausal women with ovarian suppression undergoing tamoxifen or AI therapy should also receive antiresorptive therapy if their T-score is <−1.0 or in case of vertebral fracture. However, existing guidelines for antiresorptive therapy in postmenopausal women do not lead to uniform recommendations and are often too complex (including those from the UK expert group). Bisphosphonate therapy is recommended not only in osteoporotic patients, but also in osteopenic patients, if some of the above-mentioned risk factors for fractures are present. BMD measurement by DXA is the cornerstone of all recommendations, but the cutoffs vary. Which risk factors used to help in the therapeutic decision are even more variable, as well as their number. A key advance in predicting fracture risk in postmenopausal women has been the development of the WHO FRAX algorithm, which provides a 10-year fracture probability [88]. However, FRAX is not designed to assess fracture risk in women with breast cancer and indeed may substantially underestimate the effect of AI therapy, as the "secondary osteoporosis" option in the FRAX tool has a much smaller effect on fracture risk than would be expected for AI therapy and is entirely captured in BMD results [80]. Moreover, AIs have a large effect on fracture risk during active treatment, which will be underestimated by FRAX. FRAX is nevertheless useful to assess "baseline" fracture risk in women about to start AI therapy. FRAX-based fracture risk assessment without BMD assessment is markedly influenced by a combination of age and prevalent fragility fracture [89]. On the basis of these considerations, we recommend that antiresorptive treatment should be started in all osteoporotic women and—irrespective of BMD—in all women older than 75 years, and patients with a prevalent fragility fracture. Although the evidence is less strong, postmenopausal women with T-score <−1.5 presenting at least one clinical risk factor (including age, parental fracture history, BMI <20 kg/m², corticosteroids use, cigarette smoking, inadequate nutritional intakes, disuse, tendency to falls, and conditions associated to osteoporosis) should be treated, as well as those with a T-score between −1 and −1.5 presenting at least two clinical risk factors (Fig. 1). Alternatively, therapy could be considered in patients with a FRAX-determined 10-year hip fracture probability ≥3%, which corresponds to the intervention threshold suggested in many countries (or a probability for major osteoporotic fractures of 20%).

Most data have been obtained with zoledronic acid 4 mg i.v. every 6 months [86]. Oral bisphosphonates given at the licensed anti-osteoporotic doses appear to be able to prevent AI-induced bone loss and indeed represent a valid therapeutic option. However, a critical issue is patients' adherence to oral antifracture therapy, and a switch to intravenous therapy is recommended if non-adherence to oral therapy is suspected. Moreover, oral bisphosphonates have been studied in much smaller trials than zoledronic acid. There is also some evidence that zoledronic acid reduces tumor recurrence rate in pre- or postmenopausal women receiving AI therapy [67], and its efficacy in the prevention of AI-induced bone loss is already well documented [65–73]. Such an effect, in terms of recurrence reduction, has not been reported so far in breast cancer for other antiresorptives, notably denosumab, which represents a new effective treatment option more effective than zoledronic acid in patients with bone metastases [90]. The duration of bisphosphonate or denosumab therapy should be as long as that of AI administration, although the prolonged effect of zoledronic acid on bone mass is an argument for a shorter (i.e., 3 years) treatment duration [65–69].

Acknowledgments This work has been promoted and supported by the European Society of Clinical and Economic aspects of Osteoporosis and Osteoarthritis (ESCEO).

Conflicts of interest RR: speaker or scientific board for Amgen, Danone, Nestlè, Novartis, Nycomed, Roche, Servier; JJB: speaker for or consulting fees from Amgen and Novartis; ADC: No-one. JYR: speaker or paid advisory boards for and consulting fees or research grants from Servier, Novartis, Negma, Eli-Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex, UCB Rottapharm, IBSA, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Novo-Nordisk, Nolver, Bristol Myers Squibb, Merck Sharp and Dohme; PP: consulting fees from Amgen, Novartis, Eli-Lilly, Servier. MLB: consulting fees or research grants from Servier, Merck Sharp and Dohme, Novartis, Amgen, Eli-Lilly, Roche.

References

1. Howlader N, Noone AM, Krapcho M et al (2011) SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site 2011.
2. Ferlay J, Shin HR, Bray F et al (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127:2893–2917
3. Goldhirsch A, Wood WC, Coates AS et al (2011) Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 22:1736–1747
4. Dowsett M, Cuzick J, Ingle J et al (2010) Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 28:509–518
5. Mauri D, Pavlidis N, Polyzos NP et al (2006) Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. JNCI 98:1285–1291
6. Cuzick J, Sestak I, Baum M et al (2010) Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol 11:1135–1141
7. Coombes RC, Kilburn LS, Snowdon CF et al (2007) Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 369:559–570
8. Thürlimann B, Keshaviah A, Coates AS (2005) A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. Engl J Med 353:2747–2757
9. Goss PE, Ingle JN, Martino S et al (2005) Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in

receptor-positive breast cancer: updated findings from NCIC CTG MA17. J Natl Cancer Inst 97:1262–1271
10. Smith IE, Dowsett M (2003) Aromatase inhibitors in breast cancer. N Engl J Med 348:2431–2442
11. McCloskey E (2006) Effects of third-generation aromatase inhibitors on bone. Eur J Cancer 42:1044–1051
12. Mouridsen HT, Robert NJ (2005) The role of aromatase inhibitors as adjuvant therapy for early breast cancer in postmenopausal women. Eur J Cancer 41:1678–1689
13. Perez EA (2007) Safety profiles of tamoxifen and the aromatase inhibitors in adjuvant therapy of hormone-responsive early breast cancer. Ann Oncol 18:26–35
14. Body JJ, Bergmann P, Boonen S et al (2007) Management of cancer treatment-induced bone loss in early breast and prostate cancer - a consensus paper of the Belgian Bone Club. Osteoporos Int 18:1439–1450
15. Burstein HJ, Prestrud AA, Seidenfeld J (2010) American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 28:3784–3796
16. Coates AS, Keshaviah A, Thürlimann B et al (2007) Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol 25:486–492
17. Lonning P (2006) Bone safety of aromatase inhibitors versus tamoxifen. Int J Gynecol Cancer 16:518–520
18. Kanis JA, Melton LJ, Christiansen C 3rd et al (1994) The diagnosis of osteoporosis. J Bone Miner Res 9:1137–1141
19. Eastell R, Hannon RA, Cuzick J et al (2006) Effect of an aromatase inhibitor on BMD and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). J Bone Miner Res 21:1215–1223
20. Gnant M, Mlineritsch B, Luschin-Ebengreuth G (2008) Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol 9:840–849
21. Shapiro CL, Manola J, Leboff M (2001) Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. J Clin Oncol 19:3306–3311
22. Chen Z, Maricic M, Pettinger M et al (2005) Osteoporosis and rate of bone loss among postmenopausal survivors of breast cancer. Cancer 104:1520–1530
23. Eastell R, Adams JE, Coleman RE et al (2008) Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol 26:1051–1057
24. Coleman RE, Banks LM, Girgis SI et al (2007) Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. Lancet Oncol 8:119–127
25. Szabo KA, Webber CE, Adachi JD et al (2011) Cortical and trabecular bone at the radius and tibia in postmenopausal breast cancer patients: a Peripheral Quantitative Computed Tomography (pQCT) study. Bone 48:218–224
26. Tang SC (2010) Women and bone health: maximizing the benefits of aromatase inhibitor therapy. Oncology 79:13–26
27. Ghazi M, Roux C (2009) Hormonal deprivation therapy-induced osteoporosis in postmenopausal women with breast cancer. Best Pract Res Clin Rheumatol 23:805–811
28. Lønning PE, Geisler J, Krag LE (2005) Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. J Clin Oncol 23:5126–5137
29. Powles TJ, Hickish T, Kanis JA et al (1996) Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 14:78–84
30. Ettinger B, Black DM, Mitlak BH et al (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 282:637–645
31. Delmas PD, Ensrud KE, Adachi JD et al (2002) Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab 87:3609–3617
32. Freedman AN, Yu B, Gail MH et al (2011) Benefit/Risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. J Clin Oncol 29:2327–2333
33. Hadji P, Ziller M, Albert US et al (2010) Assessment of fracture risk in women with breast cancer using current vs emerging guidelines. Br J Cancer 102:645–650
34. Kanis JA, McCloskey EV, Powles T et al (1999) A high incidence of vertebral fracture in women with breast cancer. Br J Cancer 79:1179–1181
35. Edwards SA, Chiarelli AM, Ritvo P et al (2011) Satisfaction with initial screen and compliance with biennial breast screening at centers with and without nurses. Cancer Nurs 34:293–301
36. Cummings SR, Black DM, Thompson DE et al (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 280:2077–2082
37. Ensrud KE, Black DM, Palermo L et al (1997) Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. Arch Intern Med 157:2617–2624
38. Reginster J, Minne HW, Sorensen OH et al (2000) Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 11:83–91
39. Ettinger B, Black DM, Mitlak BH et al (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 282:637–645
40. Howell A, Cuzick J, Baum M et al (2005) Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 365:60–62
41. Eastell R, Adams J, Clack G et al (2011) Long-term effects of anastrozole on bone mineral density: 7-year results from the ATAC trial. Ann Oncol 22:857–862
42. Joerger M, Thürlimann B (2009) Update of the BIG 1-98 Trial: where do we stand? Breast 18:S78–S82
43. Rabaglio M, Sun Z, Price KN et al (2009) Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. Ann Oncol 20:1489–1498
44. Coombes RC, Hall E, Gibson LJ (2004) A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 350:1081–1092
45. Goss PE, Strasser-Weippl K (2004) Prevention strategies with aromatase inhibitors. Clin Cancer Res 10:372S–379S
46. Coleman RE, Banks LM, Girgis SI (2010) Reversal of skeletal effects of endocrine treatments in the Intergroup Exemestane Study. Breast Cancer Res Treat 124:153–161
47. Chien AJ, Goss PE (2006) Aromatase inhibitors and bone health in women with breast cancer. J Clin Oncol 24:5305–5312

48. Jakesz R, Jonat W, Gnant M et al (2005) Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 366:455–462
49. Cummings SR, Duong T, Kenyon E et al (2002) Serum estradiol level and risk of breast cancer during treatment with raloxifene. JAMA 287:216–220
50. Prentice AM (2008) Vitamin D deficiency: a global perspective. Nutr Rev 66:S153–S164
51. Mithal A, Wahl DA, Bonjour JP et al (2009) Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 20:1807–1820
52. Bertoldo F, Pancheri S, Zenari S et al (2010) Emerging drugs for the management of cancer treatment induced bone loss. Expert Opin Emerg Drugs 15:323–342
53. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B et al (2010) Benefit-risk assessment of vitamin D supplementation. Osteoporos Int 21:1121–1132
54. Peterlik M, Grant WB, Cross HS et al (2007) Calcium, vitamin D and cancer. Anticancer Res 29:3687–3698
55. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281
56. Adami S, Giannini S, Bianchi G et al (2009) Vitamin D status and response to treatment in post-menopausal osteoporosis. Osteoporos Int 20:239–244
57. Bischoff-Ferrari HA, Willett WC, Wong JB (2009) Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med 169:551–561
58. Chen P, Hu P, Xie D et al (2010) Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat 121:469–477
59. Lazzeroni M, Gandini S, Puntoni M et al (2011) The science behind vitamins and natural compounds for breast cancer prevention. Getting the most prevention out of it. Breast 20(Suppl 3):S36-41
60. Garland CF, Comstock GW, Garland FC et al (1989) Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. Lancet 2:1176–1178
61. Tuohimaa P, Tenkanen L, Ahonen M et al (2004) Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer 108:104–108
62. Servitja S, Nogués X, Prieto-Alhambra D et al, Bone health in a prospective cohort of postmenopausal women receiving aromatase inhibitors for early breast cancer. Breast. 2011 Sep 15. [Epub ahead of print]
63. Prieto-Alhambra D, Javaid MK, Servitja S et al (2011 Feb) Vitamin D threshold to prevent aromatase inhibitor-induced arthralgia: a prospective cohort study. Breast Cancer Res Treat 125 (3):869–878
64. Holick MF, Binkley NC, Bischoff-Ferrari HA et al (2011) Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. [Epub ahead of print].
65. Brufsky A, Bossermann L, Caradonna R et al (2009) Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: the Z-FAST study 36 months follow-up results. Clin Breast Cancer 9(2):77–85
66. Bundred NJ, Campbell ID, Davidson N et al (2008) Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women receiving adjuvant letrozole: the ZO-FAST study results. Cancer 112:1001–1010
67. Eidtmann H, de Boer R, Bundred N (2010) Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. Ann Oncol 21:2188–2194
68. De Boer R, Eidtmann H, Lluch A et al (2007) The ZO-FAST trial: zoledronic acid effectively inhibits aromatase inhibitor associated bone loss in post-menopausal women with early breast cancer receiving adjuvant letrozole: 24 month BMD results. Breast Cancer Res Treat 106:S501
69. Brufsky A, Bundred N, Coleman R et al (2008) Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. Oncologist 13:503–514
70. De Boer RH, Bundred N, Eidtmann H et al (2010) The effect of zoledronic acid on aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: the ZO-FAST study 5-year final follow-up. Poster presented at: the 2010 San Antonio Breast Cancer Symposium; December 11, 2010; San Antonio, Texas
71. Gnant MF, Mlineritsch B, Luschin-Ebengreuth G et al (2007) Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. J Clin Oncol 25:820–828
72. Gnant M, Mlineritsch B, Stoeger H et al (2011) Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. Lancet Oncol 12:631–641
73. Gnant M, Mlineritsch B, Luschin-Ebengreuth G et al (2008) Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol 9:840–849
74. Gnant M, Mlineritsch B, Schippinger W et al (2009) Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 360:679–691
75. Coleman RE, Marshall M et al (2011) Breast Cancer Adjuvant Therapy with Zoledronic Acid. N Engl J Med 365(15):1396–1405
76. Lester JE, Dodwell D, Purohit OP et al (2008) Prevention of anastrozole induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. Clin Cancer Res 14:6336–6342
77. Eastell R, Van Poznak CH, Hannon RA et al (2007) The SABRE study (Study of Anastrozole with the Bisphosphonate RisedronatE): 12 month analysis. J Bone Miner Res 22:S113
78. Hines SL, Mincey BA, Sloan JA (2009) Phase III randomized, placebo-controlled, double-blind trial of risedronate for the prevention of bone loss in premenopausal women undergoing chemotherapy for primary breast cancer. J Clin Oncol 27(7):1047–1053, Epub 2008 Dec 15
79. Saarto T, Bloqvist C, Valimaki M et al (1997) Clodronate improbe bone mineral density in postmenopausal breast cancer patients treated with adjuvant antioestrogen. Br Cancer 75:602–605
80. Paterson AHG (2006) The role of bisphosphonates in early breast cancer. Oncologist 11:S13–S19
81. Van den Wyngaert T, Huizing MT, Fossion E et al (2009) Bisphosphonates in oncology: rising stars or fallen heroes. Oncologist 14:181–191
82. Ellis GK, Bone HG, Chlebowski R et al (2009) Effect of denosumab on bone mineral density in women receiving adjuvant aromatase inhibitors for non-metastatic breast cancer: subgroup analyses of a phase 3 study. Breast Cancer Res Treat 118:81–87
83. Hillner B, Ingle J, Berenson J et al (2003) American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in breast cancer. J Clin Oncol 21:4042–4057

84. Hadji P, Body JJ, Aapro MS et al (2008) Practical guidance for the management of aromatase inhibitor- associated bone loss. Ann Oncol 19:1407–1416
85. Hadji P, Aapro MS, Body JJ et al (2011) Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. Ann Oncol. [Epub ahead of print]
86. Body JJ, Bergmann P, Boonen S et al (2007) Management of cancer treatment-induced bone loss in early breast and prostate cancer – a consensus paper of the Belgian bone club. Osteoporos Int 18:1439–1450
87. Reid DM, Doughty J, Eastell R et al (2008) Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. Cancer Treat Rev 34:S3–S18
88. Kanis JA, Johnell O, Oden A et al (2008) FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporos Int 19:385–397
89. Donaldson MG, Palermo L, Schousboe JT et al (2009) FRAX and risk of vertebral fractures: the fracture intervention trial. J Bone Miner Res 24:1793–1799
90. Body JJ (2011) New developments for treatment and prevention of bone metastases. Curr Opin Oncol 23:338–342
91. Singh S, Cuzick J, Edwards R et al. Effect of anastrozole on bone mineral density after one year of treatment. Results from bone substudy of the International Breast Cancer Intervention Study (IBIS-II). Breast Cancer Res Treat 2007; 106(Suppl 1: S9 Abstr 28).
92. Confavreux CB, Fontana A, Guastalla JP et al., Estrogen-dependent increase in bone turnover and bone loss in postmenopausal women with breast cancer treated with anastrozole. Prevention with bisphosphonates, Bone. 2007 Sep;41(3):346-52. Epub 2007 Jun 16.
93. Greenspan SL, Brufsky A, Lembersky BC (2008) Risedronate prevents bone loss in breast cancer, survivors: a 2-year, randomized, double-blind, placebocontrolled clinical trial. J Clin Oncol 26 (16):2644–2652, Epub 2008 Apr 21
94. Markopoulos C, Tzoracoleftherakis E, Polychronis A et al (2010) Management of anastrozole-induced bone loss in breast cancer patients with oral risedronate: results from the ARBI prospective clinical trial. Breast Cancer Res 12((2):R24, Epub 2010 Apr 16
95. Van Poznak C, Hannon RA, Mackey JR (2010) Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. J Clin Oncol 28(6):967–975