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CONSENSUS STATEMENT

Management of cancer treatment-induced bone loss in early breast and prostate cancer - a consensus paper of the Belgian Bone Club

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Abstract Cancer treatment-induced bone loss (CTIBL) is one of the most important side effects of adjuvant antineoplastic treatment in hormone-dependent neoplasms. Chemotherapy, GnRH analogs and tamoxifen can induce marked bone loss in premenopausal women with early breast cancer. Aromatase inhibitors (AIs) are replacing tamoxifen as the preferred treatment for postmenopausal women. As a class effect, steroidal (exemestane) and non-steroidal (anastrozole and letrozole) AIs increase bone turnover and cause bone loss (4%–5% over 2 years). When compared to tamoxifen, the risk of getting a clinical fracture under AI treatment is increased by 35%–50%. In patients with prostate cancer, androgen deprivation therapy (ADT) increases bone turnover, reduces bone mass (4%–5% per year) and increases the fracture rate depending on the duration of therapy. Zoledronic acid can prevent accelerated bone loss induced by goserelin in premenopausal women, by letrozole in postmenopausal women and by ADT in men. More limited data indicate that weekly alendronate or risedronate could also be effective for preventing CTIBL. Initiation of therapy early, prior to the occurrence of severe osteoporosis, rather than after, may be more effective. Bisphosphonate treatment should be considered in osteoporotic but also in osteopenic patients if other risk factor(s) for fractures are present.

Keywords Adjuvant cancer treatment · Androgen deprivation · Aromatase inhibitor · Bisphosphonate · Bone loss · Osteoporosis

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Introduction

Besides the direct effect of metastatic cancer on bone, several anticancer treatments have the potential to damage the skeleton. Patients with cancer are, thus, at increased risk for developing osteoporosis as a complication from their anti-cancer treatment [1]. A variety of hormonal and non-hormonal treatments can promote bone loss by inducing hypogonadism. Osteoporosis will ensue in a large percentage of patients unless hormone replacement is carried out without delay [2]. Hypogonadism occurs in two different settings. First, hypogonadism may occur in hormone-dependent tumors, such as breast and prostate cancers, as part of the treatment strategy. Secondly, hypogonadism may be a consequence of cancer therapy in hormone-dependent tumors for which replacement therapy is generally contraindicated, or in non-hormone-dependent tumors, such as lymphoma, in which hypogonadism is an undesirable effect of anticancer treatment [1]. The first situation has been the subject of several recent developments that will be reviewed in this article focused on hormone therapy-induced bone loss.

Cancer treatment-induced bone loss (CTIBL) can lead to osteoporosis, which is associated with decreased bone strength, increased fracture risk, diminished quality of life, and increased mortality [2, 3]. Hip or vertebral fractures are associated with a 20% increase in expected mortality rate after 5 years. Substantial negative effects of osteoporotic fractures have been shown on morbidity, mortality and overall healthcare costs [3]. CTIBL is generally more rapid and severe than age-related bone loss. Bisphosphonates are the mainstay for the treatment of postmenopausal bone loss, male osteoporosis and corticosteroid-induced osteoporosis but no oral or intravenous medication has been approved yet to prevent CTIBL.

Methods

We included descriptive, cross-sectional and prospective studies related to the pathogenesis, monitoring, treatment and prevention of CTIBL in breast and prostate cancer. Review articles and available guidelines were also included. We searched MEDLINE from 1966 to March 2007, and databases such as the Cochrane Controlled Register, for citations of relevant articles. After this extensive search of the literature, a critical appraisal of the data was obtained through a consensus experts meeting.

Breast cancer

Premenopausal women

In patients who undergo ovarian ablation therapy — either by surgery, chemotherapy or use of GnRH agonists such as goserelin — losses in bone mass as high as 13% have been reported within the first year of treatment [4]. Chemotherapy-induced ovarian dysfunction accelerates the onset of menopause by an average of 10 years [5]. Ovarian failure develops within 1 year of therapy in 63%–96% of premenopausal women with breast cancer who receive postoperative adjuvant chemotherapy [1].

GnRH analogs are an effective form of endocrine therapy for premenopausal women with breast cancer [6]. The long acting agonist GnRH analogs continually stimulate the gonadotropic cells in the pituitary, leading to downregulation of GnRH receptors, inhibition of LH secretion and ovarian insufficiency [7]. Within the first 6 months of goserelin treatment, more than 95% of premenopausal women experience amenorrhea, and estrogen deficiency induces loss of both cortical and trabecular bone [8]. For instance, in the Zoladex Early Breast Cancer Research Association (ZEBRA study), assessing the effect of goserelin administration for 2 years with six monthly cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) adjuvant chemotherapy in premenopausal women with early breast cancer, mean decreases from baseline BMD were −10.5% for goserelin-treated and −6.5% for CMF-treated patients at the spine ($P<0.001$) and −6.4% and −4.5% ($P<0.05$) at the hip, respectively [8, 9]. BMD was partially recovered 1 year later after stopping goserelin therapy and the return of ovarian function in most of the patients. In contrast, among patients in the CMF group in whom early menopause was induced, ovarian function did not return, and these patients had persistent bone loss [9].

Depending on the tissue and prevailing estrogen levels, tamoxifen exhibits a range of biologic activity from full estrogen antagonism to partial agonism. Randomized placebo-controlled trials of predominantly postmenopausal patients have shown that adjuvant tamoxifen at a dose of 20 to 30 mg/d over 2 years is associated with an increase in BMD in the lumbar spine [10]. Despite acting as a partial estrogen agonist on the skeleton, tamoxifen causes bone loss in the spine and hip in premenopausal patients, probably because it acts as an estrogen antagonist in the presence of premenopausal levels of estrogens. In a placebo-controlled tamoxifen chemoprevention trial, the mean annual loss in lumbar BMD per year over the 3-year study period in tamoxifen-treated compliant women who remained premenopausal throughout the study period was 1.44% compared with a small gain of 0.24% per year for women on placebo ($P<0.001$). Tamoxifen had the opposite effect in postmenopausal women, as the mean annual increase in BMD for postmenopausal women on tamoxifen was 1.17% in the spine ($P<0.005$) and 1.71% in the hip ($P<0.001$) as compared with a insignificant loss in the placebo group [11].

Postmenopausal women: effects of aromatase inhibitors on bone

Until recently, the selective estrogen receptor modulator tamoxifen had been the mainstay for the treatment of hormono-dependent advanced and early breast cancer. Due to their improved efficacy, aromatase inhibitors (AIs) are replacing tamoxifen as the preferred treatment for postmenopausal patients with both early and advanced estrogen-dependent breast cancer [12]. However, this major change in the therapy of breast cancer has led to concerns about the potential short- and long-term effects of AIs, notably on bone health [13]. The aromatase enzyme converts androgens to estrogens and is the main source of endogenous estrogen in postmenopausal women [14]. As a class effect, AIs cause bone loss by lowering the levels of endogenous estrogen. In contrast, at least in postmenopausal women, tamoxifen acts as a weak estrogen to preserve bone mass and has been shown in some studies to decrease fracture rate [10, 11, 15].

There are two types of AIs, steroidal (or "irreversible", substrate-site binding type I) and non-steroidal (heme-binding, type II). Steroidal inactivators are structurally similar to androstenedione and act as competitors for binding with aromatase. Non-steroidal imidazole-based agents interact reversibly with the cytochrome P450 moiety of aromatase. Both the non-steroidal AIs, anastrozole and letrozole, and the steroidal AI exemestane have been approved for use in adjuvant treatment of early breast cancer, which usually entails treatment for up to 5 years. Trials examining their use beyond 5 years and their role as preventatives agents in healthy women are underway. This makes it essential to evaluate the long-term effects of these agents on bone health [16].

Animal data

Some preclinical data have suggested that differences might exist between exemestane and the non-steroidal AIs. Rather than increasing bone turnover in ovariectomized rats, exemestane was shown to prevent loss of BMD and to reduce markers of bone turnover. In this setting of complete estrogen deficiency in the rat, letrozole had no impact on bone turnover or bone mineral density, whereas exemestane decreased bone turnover, increased bone density and bone strength, suggesting that androgenic effects of this steroidal inhibitor can indeed be observed in this animal model [17].

Exemestane is structurally related to androstenedione and its major metabolite, 17-hydro-exemestane, is androgenic as well, which probably explains these protective effects on bone. However, the use of much higher doses, on a weight for weight basis, than the doses used in humans must be taken into account. In contrast, letrozole and anastrazole are non-steroidal reversible inhibitors devoid of androgenic activity.

Effects on bone turnover, bone loss and fracture incidence

The reported discrepancies between the effects of the three currently available AIs may relate to the short duration (≤6 months) of studies including most often small numbers of subjects. Anastrozole and letrozole were reported to have neutral effects on biochemical markers of bone resorption and formation, while exemestane increased PINP and serum CTX [18]. On the other hand, increases in bone resorption markers have been reported with letrozole. In a 6-month, double-blind, placebo-controlled study in 42 healthy volunteers with a mean age of 69 years, letrozole significantly increased urinary crosslinks excretion by 14% ($P<0.05$) without a compensatory increase in the bone formation markers BAP or osteocalcin. Serum PTH also decreased by 22% ($P<0.005$), in agreement with an increase in bone resorption [19]. These data indicate that, in late postmenopausal women, even the low circulating estrogen levels exert a restraining effect on bone turnover and support the concept that variations in these low concentrations may contribute to differences in the rate of bone loss with ageing.

More recently, all three AIs were compared in an open, randomized, multicenter pharmacodynamic study [20]. Healthy postmenopausal volunteers were randomized to receive anastrozole (1 mg/day), letrozole (2.5 mg/day), or exemestane (25 mg/day) daily for 6 months. In the 90 evaluable subjects, markers of bone resorption and formation increased with all three agents (by 2–28%), but no statistically significant differences were observed between the three AIs. Similar effects have been observed in 1–2 years studies evaluating anastrozole and exemestane in early breast cancer [21, 22]. It is reasonable to conclude that the three currently available AIs are associated with increased bone turnover and that steroidal and non-steroidal AIs thus appear to have similar effects on bone turnover in human subjects.

No available head-to-head studies comparing the three AIs are yet available regarding their effects on bone loss and fracture rate. Moreover, AIs have been compared to tamoxifen or evaluated after tamoxifen. This is critical since tamoxifen is known to exert a protective effect on the skeleton. Although the anti-fracture effect of tamoxifen remains controversial and has not been found in the IBIS-1 study [23], 5 years of tamoxifen treatment has been shown to reduce the incidence of osteoporotic fractures by 32% (RR=0.68; 95%CI=0.51–0.92) in a large primary prevention breast cancer study after an average of 7 years follow-up [24]. In sequential or cross-over studies where AIs are administered after tamoxifen, the withdrawal of tamoxifen may, thus, contribute to bone loss and increased fracture incidence.

Trials comparing AIs and tamoxifen

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) and Breast International Group (BIG) 1–98 trials have demonstrated that adjuvant therapy with an AI (anastrozole or letrozole) is superior to treatment with tamoxifen in women with hormone receptor-positive disease in terms of breast cancer outcome [25, 26]. The ATAC trial has been the largest trial conducted in the adjuvant setting, including 9,366 patients treated for 5 years. Anastrazole had a better overall safety profile than tamoxifen with respect to endometrial cancer, vaginal bleeding and discharge, cerebrovascular events, venous thromboembolic events and hot flushes but was associated with a significant increase in musculoskeletal disorders and fractures as compared with tamoxifen [25]. In a subgroup of non-osteoporotic patients evaluated for bone loss, the 81 women who received anastrozole had only a modest increase in bone turnover but lost about 4% of bone mass in the lumbar spine or the total hip after 2 years [21]. After a median follow-up of 68 months, the overall fracture rates were 11.0% and 7.7% in the anastrozole and tamoxifen groups, respectively ($P<0.0001$). The incidence of hip fractures was similar and very low in both groups but there were significantly more vertebral fractures in the AI group, 1.5% versus 0.9% ($P<0.05$) [27]. Similarly, in the BIG 1–98 trial comparing letrozole with tamoxifen, after a median follow-up of 26 months, clinical fractures occurred more frequently in the AI group than in the tamoxifen group, 5.7% versus 4.0% ($P<0.001$) [26].

Trials of AIs after tamoxifen therapy

Letrozole has been compared to placebo in women with breast cancer who had completed the classical five years of tamoxifen therapy (MA-17 trial) [28]. The study was stopped after a median follow up of 2.4 years due to a significant improvement in breast cancer outcomes in the letrozole group. Within this time frame, there was a trend for more new diagnoses of osteoporosis in the letrozole group as compared to the placebo group, 5.8% versus 4.5% ($P=0.07$), but fracture risk was not significantly increased (3.6% versus 2.9%, $P=0.24$). In a bone subprotocol of this trial including 226 patients, significantly more bone loss occurred after 2 years in the letrozole group than in the placebo group, −3.6% versus −0.7% at the total hip, and −5.4% versus −0.7% at the lumbar spine. This was accompanied by a significant increase in NTX levels in the letrozole group [29].

Exemestane has been studied in 4,742 postmenopausal women with primary breast cancer who had received 2–3 years of tamoxifen therapy [30]. At this time point, women were randomized to complete 5 years of tamoxifen or to switch to exemestane for the remainder of the 5 years (the Intergroup Exemestane Study or IES). After a median follow-up of 30 months, there were more clinical fractures in the exemestane group than in the tamoxifen group, although the difference was not statistically significant (3.1% vs. 2.3%, $P=0.08$). More exemestane-treated patients had newly diagnosed osteoporosis (7.4% vs. 5.7%; $P=0.05$) than patients who continued on tamoxifen. Follow-up of this trial has shown a significant increase in the fracture rate in exemestane treated women but full publication is awaited. These data suggest that despite its steroidal structure and putative androgenic activity, exemestane does not have a bone sparing effect in patients with breast cancer. In a similar trial using anastrozole, after a median follow-up of 28 months, there were significantly more clinical fractures in patients who switched to anastrozole than in those who continued on tamoxifen, 2% versus 1%, respectively ($P<0.05$) [31].

AIs versus placebo

Lönning et al. conducted a 2-year randomized controlled trial of exemestane versus placebo in low risk receptor-positive postmenopausal women with early-stage breast cancer [32]. The primary endpoint was not anti-tumor efficacy, but rather BMD. The authors found that the "bone-losing" properties of exemestane predominate, though the magnitude of the annual bone loss in the lumbar spine was small and insignificant, but bone loss was statistically significant in the femoral neck. By chance or for other unknown reasons, placebo-treated women experienced higher bone loss than expected. This may have contributed to smaller differences in BMD between exemestane and placebo, especially at the lumbar spine. Exemestane significantly increased markers of bone turnover. These results are consistent with those of the IES trial mentioned above [31].

A recent observational study based on medical claims databases also found that AIs are associated with an increase in risk for bone loss and clinical fracture. Despite the limitations inherent to this type of study, patients were carefully selected and the sample size was large, 1354 patients receiving an AI (mostly anastrozole) being compared to 11014 controls. The prevalence of bone fracture was significantly increased in the AI group compared with the control group with a relative risk of 1.35 (95% CI, 1.16–1.58; $P=0.001$). After adjusting for age, comorbidities and other possible confounding factors, the relative risk of clinical fracture was 1.21 (95% CI, 1.03–1.43; $P=0.02$) [33].

In summary, results of available clinical studies suggest that all three third-generation AIs affect bone turnover, BMD and fracture risk. There is a critical need, however, for comparative data from prospective, randomized trials

that would directly assess the clinical impact of AIs on bone. One such trial (MA-27), a head-to-head comparison of anastrozole and exemestane, will shortly complete recruitment.

Diagnosis and monitoring of bone loss

Consequences of bone fractures include chronic pain, loss of functional independence, financial problems, decreased quality of life, increased morbidity and mortality [34]. Besides preventing fractures, treatment of CTIBL may have additional benefits. There is preclinical evidence supporting a correlation between an increase in bone turnover and an increased risk of developing bone metastases [35], suggesting that treating, or better preventing, CTIBL in patients with early stage breast cancer might also decrease the risk of bone metastasis. Along the same line, oral clodronate may delay bone metastasis in patients with early breast cancer [36]. Early diagnosis and treatment of CTIBL, thus, appear to be of prime importance, especially that treatment may be more efficacious in patients with earlier stages of bone loss. The goal is to detect bone loss early and to intervene appropriately so that fractures can be avoided. However, osteoporosis often remains undetected in patients with cancer until bone fracture occurs. Bone density testing is performed in only 3%–32% of high-risk patients [37]. Several organizations, therefore, have developed clinical guidelines for screening cancer patients for bone loss.

Current guidelines from the International Society for Clinical Densitometry (ISCD) recommend BMD assessment in patients at risk for bone loss because of age (women aged ≥65 years and men aged ≥70 years), postmenopausal status with other risk factors, prior fragility fracture, medication use or disease or medical condition that is associated with low bone mass or bone loss [38]. Moreover, BMD assessments are recommended in patients for whom treatment decisions may be affected by bone health status and to monitor treatment effects in patients who are being treated for bone loss [38]. Patients receiving adjuvant therapy for breast cancer typically fall into several of these categories. More specifically, the American Society of Clinical Oncology (ASCO) has established guidelines for breast cancer patients, recommending that all women considered at high risk for osteoporosis should be evaluated for BMD. This includes all women >65 years of age; those 60–64 years of age and with a family history of fractures, body weight <70 kg, or prior non-traumatic fracture; postmenopausal women receiving AI therapy; and premenopausal women with ovarian failure secondary to cancer treatment [39]. Subsequent monitoring for bone loss is recommended based on baseline T-score and the presence of confounding risk factors [39].

Prevention and treatment of CTIBL in breast cancer

There are currently no treatments approved specifically for prevention of CTIBL. Because CTIBL is typically more rapid and severe than age-related bone loss, it is likely that only the most potent agents will display sufficient activity in this setting. Bisphosphonates are promising agents for prevention of CTIBL during adjuvant therapy for breast cancer. The oral bisphosphonates clodronate and risedronate have shown activity in limiting CTIBL after adjuvant chemotherapy. Saarto et al. investigated the effects of 1600 mg/day clodronate versus no additional therapy for 2 years in patients who received adjuvant CMF for breast cancer (n=148). In the 39 evaluable patients who developed amenorrhea, clodronate significantly reduced bone loss at the lumbar spine and prevented it at the femoral neck [40]. Delmas et al. compared 2 years of cyclic risedronate with placebo in patients with chemotherapy-induced ovarian dysfunction (n=53). Risedronate prevented bone loss at the spine and at the hip. At 2 years, the mean difference between groups was 2.5% at the spine and 2.6% at the femoral neck [41]. The interpretation of the study results is, however, complicated by the fact that two thirds of the women were under tamoxifen therapy.

Intravenous bisphosphonates might provide improved efficacy and convenience compared with oral bisphosphonates in the setting of CTIBL. Several trials are ongoing with zoledronic acid. The Austrian Breast and Colorectal Cancer Study Group is conducting a 3-year randomized trial (ABCSG-12) to investigate the effects of zoledronic acid (4 mg via 15-min infusion every 6 months) on bone loss in premenopausal women receiving adjuvant therapy with goserelin in combination with either anastrozole or tamoxifen. Planned accrual of 1,800 patients is complete and 401 of them have been evaluated in a bone density subprotocol. The results indicate that zoledronic acid could completely prevent accelerated bone loss during 3 years in the anastrozole and in the tamoxifen groups. Without bisphosphonate, bone loss was significantly greater at the lumbar spine in the anastrozole/goserelin group than in the tamoxifen/goserelin group, −17.3% and −11.6%, respectively [42].

Bisphosphonate therapy is designed to prevent or slow the rate of bone loss in patients receiving cancer treatment to reduce fracture risk. Initiation of therapy early, prior to the occurrence of severe osteoporosis or fracture, rather than late may therefore be more effective. This is supported by recently published results from the Zometa-Femara Adjuvant Synergy Trial (Z-FAST), in which zoledronic acid was evaluated for prevention of CTIBL in 602 postmenopausal women with early breast cancer receiving adjuvant letrozole. Zoledronic acid (4 mg via 15-min infusion every 6 months) was administered either upfront or delayed (until post-baseline T-score declined <−2 SD or

occurrence of fracture). At 1 year, per protocol criteria, 12.6% of the patients in the delayed group had to start zoledronic acid therapy after a median time of 6.9 months. Overall BMD differences between both groups at 1 year were 4.4% at the lumbar spine and 3.3% at the total hip ($P < 0.001$). Upfront treatment, thus, increases BMD and can prevent AI-induced bone loss with 1 year of follow-up [43]. Lastly, the SWOG 0307/Intergroup trial is planned to compare intravenous zoledronic acid with oral clodronate or ibandronate. Although the primary endpoint of this trial will be disease-free survival, BMD assessments have also been planned. This trial will provide important insight into the relative efficacy of bisphosphonates for preventing CTIBL. At the time of this writing, it is unknown if other less potent and less costly bisphosphonates than intravenous zoledronic acid can prevent AI-induced bone loss. The attractive hypothesis that bisphosphonates regimens used in osteoporotic patients are sufficient to prevent CTIBL is currently investigated using oral weekly risedronate or monthly ibandronate.

Prostate cancer

Effects of androgen deprivation therapy on bone loss and fracture rate

Options for androgen deprivation therapy (ADT) include bilateral orchidectomy, administration of a gonadotropin-releasing hormone (GnRH) analogue, or complete androgen blockade with a GnRH agonist and an antiandrogen [44]. Most men prefer treatment with a GnRH agonist because of the psychological implications of orchidectomy; especially that orchidectomy and treatment with GnRH agonists have equivalent response rates and duration of response. GnRH agonists decrease serum concentrations of testosterone by more than 95% and estrogen by approximately 80% [45]. Bone loss that occurs with ADT is generally more rapid and severe than that associated with normal age-related bone loss and at least comparable to the rate associated with menopause [46]. In normal men, BMD has been reported in some studies to decrease at a rate of 0.5%–1.0% per year starting in mid-life [47]. Several studies have prospectively evaluated BMD changes during initial ADT for non-metastatic prostate cancer. Significant changes are already detectable at 6 months after initiation of ADT and are accompanied by an increase in bone turnover markers [2, 48]. Most studies reported 4%–10% decreases in BMD as measured by DXA during the first year of ADT and, with continued therapy, at a rate of up to 4%–5% per year. BMD appears to decline steadily during long-term treatment [48–50].

A few retrospective studies reported that ADT increases fracture risk in men with prostate carcinoma [51–53]. In one study, 14% out of 235 men who had been castrated experienced at least one clinical osteoporotic fracture compared with only 1% of prostate carcinoma patients without a history of ADT ($P=0.001$) [51]. In another study with a median duration of GnRH agonist treatment of 22 months, 9% of men had at least one fracture and the median interval between initiation of ADT and fracture was 22 months [52]. Two more recent studies shed more light on the risk of fractures in patients on ADT for prostate cancer.

The first is a claims-based cohort study from a 5% national random sample of Medicare beneficiaries ($n=3779$) treated with GnRH agonists and compared to men with early prostate cancer who were followed for 7 years and did not receive GnRH agonist treatment ($n=8341$) [54]. The clinical fracture rate was 7.91 per 100 person-years at risk among GnRH agonist users as compared with 6.55 per 100 person-years in matched controls (relative risk, 1.21; 95% CI, 1.09–1.34, $P<0.001$). Rates of vertebral fractures (relative risk, 1.18; 95% CI, 0.94–1.48) and hip fractures (relative risk, 1.76; 95% CI, 1.33–2.33) were also higher in men treated with a GnRH agonist. GnRH agonist treatment remained an independent predictive factor for fracture risk in a multivariate analysis. Treatment-related increases in fracture risk seemed to be restricted to men with at least one year of GnRH agonist exposure [54]. This study was designed to provide conservative estimates of fracture risk in men with prostate cancer. Patients with incident GnRH agonist treatment were included in the study group regardless of treatment duration, and 35% of men received less than 1 year of therapy and no more than one fracture was assigned to any patient. Other limitations of this claims-based analysis may contribute to an underestimation of fracture risk, including the inability to exclude patients receiving treatment for osteoporosis. The study design may, thus, have underestimated the effect of GnRH agonist on fracture risk.

In the second study, Shahinian et al. reviewed the records of 50,613 men who were listed in the linked database of the Surveillance, Epidemiology and End Results program of Medicare as having received a diagnosis of prostate cancer during a 5-year period [55]. Of men surviving at least 5 years after diagnosis, 19.4% of those who received ADT had a fracture, as compared with 12.6% of those who did not receive ADT ($P<0.001$). In the Cox proportional-hazards analysis, adjusted for characteristics of the patient and the tumor, there was a statistically significant relation between the number of received doses of GnRH agonists during one year and the subsequent fracture risk. Treatment duration independently predicted the fracture risk. The curves for the groups that underwent

orchidectomy or received 5–8 doses or ≥9 doses of GnRH agonists diverged from that for the group that did not receive ADT over the entire period of follow-up. Those who underwent orchidectomy and those who received ≥9 doses of GnRH agonists in the year after diagnosis had the shortest fracture-free survival. Men who received ≥9 doses of GnRH agonists had a relative risk of fracture of 1.45 (95% CI, 1.36–1.56), which was comparable to the risk observed in the orchidectomy group [55]. ADT has other adverse effects on body composition including a decrease in lean body mass and muscle size [56]. Treatment-related frailty may increase the risk of falls in older men. ADT may, thus, increase fracture risk by decreasing both BMD and lean body mass.

The relative risks of fracture associated with ADT are of the same magnitude as those reported for patients treated with other high-risk medications, such as oral corticosteroids. For example, the General Practice Research Database reported that patients treated with oral corticosteroids have a relative risk for non-vertebral fractures of 1.33 (95% CI, 1.29–1.38), for hip fractures of 1.61 (95% CI, 1.47–1.76) and for vertebral fractures of 2.60 (95% CI, 2.31–2.92) [57].

Other hormonal therapies for prostate cancer do not appear to be harmful for the skeleton.

Estrogens play an important role in male bone metabolism. In older men, serum bioavailable estradiol levels are significantly correlated with baseline BMD at different skeletal sites and high levels are associated with less bone loss at the hip [58]. Moreover, estradiol levels are inversely correlated with vertebral fracture risk [59]. Severe osteoporosis and delayed skeletal maturation were also observed in a man with severe estrogen deficiency due to an inactivating mutation in the aromatase gene and estrogen therapy markedly increased his BMD [60]. In contrast to standard ADT by orchidectomy or administration of a GNRH agonist, medical castration with estrogens is not associated with bone loss in men with prostate cancer. In a small nonrandomized study, changes in BMD were evaluated in 27 men with non-metastatic prostate cancer treated with either bilateral orchidectomy or estrogens. Orchidectomy decreased BMD of the hip by 10% after 1 year, whereas ADT with estrogens decreased BMD by only 1% [49]. Larger randomized studies are required to confirm this preliminary observation.

Bicalutamide is a non-steroidal antiandrogen that competitively inhibits the action of androgens by binding to androgen receptors in target tissues. Bicalutamide is indicated for use in combination with a GnRH agonist to treat men with metastatic prostate carcinoma and, more recently, has been approved in many countries for the treatment of men with early-stage prostate carcinoma. Bicalutamide increases serum concentrations of estradiol [61]. Because estrogens are important determinants of BMD and fracture risk in men, bicalutamide monotherapy appears to maintain or even increase BMD when compared to treatment with a GnRH agonist [62].

Prevention and treatment of CTIBL in prostate cancer

No consensus exists for BMD testing in men with prostate cancer, although an expert panel recently issued screening recommendations [63]. The panel proposed that all men at increased fracture risk (defined as those on ADT and/or with a history of fracture) should have routine BMD assessment. Patients with a T-score ≥−1 should be monitored and screened every 2 years whereas those with a T-score of −1 to −2.5 should have BMD testing repeated after 6–12 months of ADT.

The initial treatment considerations are similar to the ones used to treat postmenopausal women. Factors such as vitamin D deficiency or inadequate calcium intake should be corrected as they may contribute to bone loss in men with prostate carcinoma. Dietary calcium intake should be maintained at 1200–1500 mg per day and supplemental vitamin D intake should be 400–800 IU per day [64]. Although calcium and vitamin D are recommended, they are not sufficient to prevent ADT-induced bone loss.

The effects of raloxifene have been tested in a limited open-label trial including 48 patients on ADT. Patients were randomized between 60 mg raloxifene daily or observation for 1 year. Mean BMD increased by about 1% in the raloxifene group and, according to the measured site, decreased by 1% to 2.6% in the observation arm [65]. On the other hand, low dose estrogen can also inhibit bone resorption in men receiving ADT [66].

There are three randomized studies in patients with prostate cancer demonstrating that the bisphosphonates pamidronate and zoledronic acid can prevent bone loss under ADT.

In a placebo-controlled study, Smith et al. treated 47 patients with locally advanced disease and no evidence of bone metastases with leuprolide alone or in combination with pamidronate 60 mg every 3 months. After 1 year, the control group without bisphosphonates showed a decrease of bone mass at the lumbar spine (−3.3%) and at the hip (−1.8% for total hip) whereas there were no significant changes of BMD at any skeletal site in the group receiving pamidronate [67]. Diamond et al. performed a crossover study of pamidronate in 21 men with prostate carcinoma and bone metastases after at least 6 months of ADT [68]. Patients were randomly assigned to either pamidronate 90 mg or placebo administered once and were crossed over to the other treatment after 6 months. Primary study end points were BMD by DXA and quantitative CT scan. Pamidronate significantly reduced bone loss at the lumbar spine and at the hip for at least 6 months [68]. More recently, Smith et al. treated 106 men with localized disease

at the beginning of ADT either with 4 mg zoledronic acid every 3 months or with placebo infusions. After 1 year, there was a significant reduction of BMD in the placebo group (−2.0%), whereas patients treated with zoledronic acid achieved a significant increase of bone mass at the lumbar spine (5.3%). Mean bone mineral density of the femoral neck, trochanter and total hip also increased in the zoledronic acid group and decreased in the placebo group. Benefit was seen across all groups, including patients with a T-score between −1 and −3 [69]. However, less frequent dosing might be sufficient. Michaelson et al. randomized 40 men with non-metastatic prostate cancer under GnRH agonist therapy between a single 4-mg zoledronic acid infusion and a placebo infusion. All patients had baseline T-scores above −2.5. At 12 months, BMD increased and bone turnover was reduced in men treated with zoledronic acid compared with placebo. Between-group BMD differences at 12 months were 7.1% (95% CI, 4.2–10.0%; $P<0.001$) at the lumbar spine, 2.6% (0.9–4.3%; $P<0.005$) at the total hip and 2.1% (−0.1 to 4.4%; $P=0.06$) at the femoral neck [70]. The improvement in BMD after a single annual dose of zoledronic acid is thus similar to that reported with quarterly dosing [69]. However, osteoporotic patients were excluded from the trial and patients were on ADT since an average of 1 year which is different than in the initial zoledronic acid trial where patients were treated within 1 month after starting ADT. It is unknown if these differences have influenced the results. According to these results, zoledronic acid cannot only prevent bone loss but also increase BMD in prostate cancer patients under ADT. This greater efficacy of zoledronic acid compared to pamidronate might be explained by the higher potency of zoledronic acid and the relatively low dose of pamidronate (60 mg) used in Smith's study, in agreement with the fact that bone resorption increased before each pamidronate infusion in that trial [67].

Oral alendronate is an approved therapy for men with osteoporosis and normal to moderately low serum testosterone concentrations [70]. Greenspan et al. postulated that bone loss due to ADT could also be reversed with the same therapy. To address this hypothesis, 112 men with non-metastatic prostate cancer on ADT for at least 6 months were enrolled in a 2-year, double-blind, placebo-controlled, randomized clinical trial. After 1 year of alendronate (70-mg once weekly) therapy, bone mass increased significantly by 3.7% at the spine and 0.7% at the total hip, respectively. In contrast, men on placebo had significant decreases of bone mass of 1.3% and 0.7%, respectively [71]. In a retrospective cohort study of 47 men treated with ADT since more than 2 years on average, bone loss at the spine and hip was also prevented in alendronate users ($n=22$) versus non users [72]. These data suggest that the bisphosphonate scheme used for the treatment of age-related osteoporosis could also be a valid therapy for bone loss due to ADT.

These considerations for the prevention of CTIBL in breast and prostate cancer patients should not lead to an indiscriminate use of bisphosphonates, especially that these drugs are not without side effects. Characteristic adverse effects of oral bisphosphonates are gastrointestinal, such as epigastric pain and esophagitis. Intravenous infusions can be associated with renal safety issues, injection site reactions, and flu-like syndromes [73]. Most cases of renal function deterioration in cancer patients are mild and reversible but the Food and Drug Administration has reported 72 cases of renal failure with zoledronic acid observed in clinical practice [74]. Serum creatinine should be monitored before each dose of zoledronic acid, and its use is not recommended in patients with severe renal insufficiency and those taking nephrotoxic medications. Renal safety monitoring with intravenous ibandronate is not mandatory, because no cases of renal failure have been reported so far but the activity of ibandronate is still unknown in the setting of CTIBL.

Recently, osteonecrosis of the jaw (ONJ) was reported to occur with prolonged bisphosphonate therapy even if the exact pathogenesis needs further investigation. Although sometimes devastating, it was believed to be an extremely rare complication essentially seen after dental extraction and concomitant corticosteroid therapy. Recent series suggest that the incidence has been under-evaluated in cancer patients. In a prospective evaluation of more than 250 cancer patients treated with monthly bisphosphonates infusions for up to 6 years, the incidence of ONJ was 6.7% overall (17 patients), 9.9% in myeloma, 6.5% in prostate cancer, and 2.9% in breast cancer [75]. The median number of infusions was 35 in the patients who developed ONJ compared with 15 for patients without ONJ ($P<0.001$). There may be a greater risk with zoledronic acid than with pamidronate that ONJ will develop sooner [75]. From a recent systematic review, Woo et al. concluded that the prevalence of ONJ in cancer patients might reach 6%–10% but, even if a few cases have been reported, its incidence is likely to be considerably lower in osteoporosis. The median duration of drug use in affected cancer patients ranged from 22 to 39 months. The authors suggested that bisphosphonate-associated ONJ results from marked suppression of bone turnover leading to accumulation of physiologic microdamage in the jawbones and compromising biomechanical properties. The antiangiogenic property of bisphosphonates and other medications may increase its risk [76]. Other comorbid conditions and other medications, such as chemotherapy and cortcosteroids, are likely to play an important contributory role. Therapeutic schemes used to treat osteoporotic patients are also quite different than the ones used to control metastatic bone disease. Bisphospho-

nate dosages utilized to treat metastatic bone disease are about five to tenfold higher than the ones apparently needed to prevent or treat CTIBL, even if the Z-FAST study used a dose about two times higher than the one tested in postmenopausal osteoporotic women. The incidence of ONJ in patients receiving oral bisphosphonates for osteoporosis is extremely low. Considering that not all reported cases have been confirmed to be ONJ, and on the other hand, that there may be underreporting, the incidence has been estimated at 1 in 100,000 patient-years [77]. However, there is currently no evidence that a causative link can be established and no case of ONJ has been reported in the Z-FAST trial in patients under letrozole therapy. In the phase III placebo-controlled study (2301 trial) testing the value of yearly 5-mg zoledronic acid infusions for 3 years in osteoporotic women (and overall in the HORIZON clinical development program in Paget's disease and osteoporosis), no spontaneous cases of ONJ have been reported. Independent and blinded review and adjudication of maxillofacial events in the 2301 trial was based on a database search for possible maxillofacial events and identified only two cases, one on placebo and one on zoledronic acid. The observed cases were consistent with established risk factors like local infection and the condition resolved with antibiotic therapy [78]. These findings support the concept that ONJ is uncommon in the osteoporosis population, that ONJ does occur in individuals not receiving bisphosphonates and that risk assessment guidelines should distinguish between osteoporosis and oncology populations. However, the risk of ONJ in the specific setting of CTIBL will have to be carefully evaluated and monitored.

Specific recommendations

Our approach is summarized in Table 1. We recommend that all women starting medical castration therapy or AI therapy and all men starting ADT should be assessed for their risk of osteoporosis and undergo BMD measurement by DXA. Professional guidelines recommend only high-risk breast cancer patients with T-score between −1 and −2.5 to undergo monitoring on an annual basis for changes in BMD. However, the prevalence of CTIBL in the setting of adjuvant therapy for breast or prostate cancer suggests that all patients should be monitored for bone loss. Currently, DXA is the most reliable method for assessing BMD [39]. The role of markers of bone resorption, such as the cross-linked N-telopeptide of type I collagen (NTX) or the C-telopeptide (CTX), should be investigated to assess their ability to predict bone loss in cancer patients receiving AIs or ADT. Bone loss increases fracture risk and has long-term implications with respect to function and quality of life. Despite the growing recognition of this problem [39, 79], there are currently no therapies specifically approved for preventing CTIBL in patients who are receiving adjuvant therapy for breast or prostate cancer.

Since cancer therapy-associated bone loss is largely preventable, an aggressive approach to preserve bone health should be implemented. Attention should be paid to bone health through lifestyle modifications including smoking cessation, moderation of alcohol consumption and regular weight-bearing exercise. Supplemental vitamin D (400–800 IU per day) and supplemental calcium to maintain a calcium intake of 1200–1500 mg per day are also recommended. Patients with existing osteopenia and osteoporosis should be evaluated for conditions which further deteriorate skeletal health, such as vitamin D deficiency, hyperparathyroidism, hyperthyroidism and hypercalciuria. Preserving BMD should be an important part of cancer therapy and not simply considered as supportive care when a fracture occurs.

Although available drugs for treating osteoporosis have not been considered yet for reimbursement in the specific indications of prevention and treatment of CTIBL, existing professional guidelines already recommend bisphosphonate

Table 1 Recommendations for the management of CTIBL in breast and prostate cancer in the adjuvant setting

Recommendations
Measurement of BMD by DXA and evaluation of specific risk factors for osteoporotic fractures in all patients.
BMD monitoring every 1–2 years of osteoporotic and osteopenic patients. Monitoring every 2–5 years in patients with normal baseline BMD according to the presence of other risk factors.
Adequate lifestyle modifications and calcium and vitamin D intakes.
Consider bisphosphonate therapy for:
- Osteoporotic patients (T-score <−2.5 or history of fragility fracture).
- Osteopenic patients (T-score between −1.0 and −2.5) considering the severity of osteopenia and the presence of other risk factors.
Regular measurement of BMD in untreated patients and initiation of therapy if significant bone loss is detected in osteopenic patients.
Proposed therapy:
- Breast cancer (aromatase inhibitor therapy): 4 mg zoledronic acid every 6 months (based on the results of the Z-FAST trial). Other regimens of bisphosphonate treatment are under evaluation and may be considered.
- Prostate cancer (androgen deprivation therapy): 4 mg zoledronic acid once a year or weekly alendronate.

therapy, along with annual BMD testing, only for those subjects with T scores ≤−2.5 (or −2.0 according to the National Osteoporosis Foundation guidelines). Treatment for bone loss is also indicated when the patient experiences a fragility fracture. It is unknown whether osteopenic patients should be treated as well. Double-blind placebo-controlled trials in osteopenic patients using monthly oral ibandronate and weekly risedronate are ongoing. In the meantime, we recommend that patients with T-scores between −1 and −2.5 be considered for treatment with bisphosphonates if other risk factor(s) for fractures are present. Besides BMD, several risk factors for osteoporotic fractures independent of BMD have been identified. They include older age, a prior history of fracture, a family history of hip fracture, previous and/or current use of systemic corticosteroids, a low body mass index, premature menopause, current smoking and a high intake of alcohol. It has been proposed that the contribution of these risk factors should be integrated to calculate a 10-year risk of fracture probability, similarly to the absolute risk approach already successfully applied in the management of coronary heart disease. However, the use of multiple risk factors has to be applied cautiously until interrelationships are determined and validated [80]. The decision to initiate therapy must also be based on the degree of osteopenia. We thus propose a selective approach based on BMD and the presence of major risk factors other than AI therapy in osteopenic patients (Table 1). Our recommendations are in agreement with other recently proposed guidelines [81, 82]. In women with risk factors, Chien and Goss thus recommend to start bisphosphonates if their T-score is −1.5 or below [82].

It must, nevertheless, be pointed out that available studies and recommendations are based on prevention of bone loss but that no fracture data are available yet. This is even more important taken that, besides for estrogens, anti-fracture efficacy of available drugs for treating postmenopausal osteoporosis has been demonstrated in osteoporotic but not in osteopenic women. However, as mentioned above, it appears that bone loss due to CTIBL is often more dramatic than age-related bone loss and that an early intervention is probably justified in most cases. The optimal duration of bisphosphonate therapy is unknown. They should probably be administered as long as AI therapy is continued although it can be argued that their prolonged inhibitory activity on bone resorption would allow a shorter treatment, especially for intravenous therapy whose duration of evaluation is limited to 3 years. The results of ongoing trials evaluating the benefits of bisphosphonates in patients at risk for CTIBL will provide important insights into the optimum strategy to maintain bone health during adjuvant therapy for breast cancer. Oral and intravenous ibandronate have recently been approved in Europe for the treatment of breast cancer metastatic to bone [83], and the utility of oral ibandronate in the CTIBL setting is currently evaluated. Zoledronic acid is the most potent bisphosphonate available [84], has the shortest approved infusion time of all intravenous bisphosphonates and has been shown to prevent bone loss with infrequent intravenous administration (every 6 months) in premenopausal women receiving GnRH agonist and in postmenopausal women receiving letrozole. Initial results of the Z-FAST trial suggest that patients at increased risk of fracture may benefit from upfront bisphosphonate therapy.

There is limited information about the prevention or treatment of osteoporosis in men with prostate carcinoma. Pamidronate (60 mg intravenously every 3 months) prevents bone loss during ADT. Zoledronic acid (4 mg intravenously every 3 months) increases BMD during ADT. A yearly infusion of zoledronic acid may, however, be sufficient (Table 1). Alendronate and other oral bisphosphonates may be effective, but further experience is needed. Osteoporotic patients should be treated and a recent review concurs with our recommendations that osteopenic patients on prolonged ADT therapy should be treated on an individual basis, notably as a function of the presence of additional risk factors [85]. Such a proactive rather than reactive approach to bone health will help to maintain BMD, minimize fracture risk and improve quality of life in patients receiving adjuvant therapy for breast and prostate carcinomas [81, 82, 85].

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