Expert Opinion

Emerging drugs for the management of cancer treatment induced bone loss

Francesco Bertoldo, Serena Pancheri†, Sonia Zenari & Stefania Boldini
Department of Biomedical and Surgical Sciences, University of Verona, Verona, Italy

Areas covered in this review: We focus our attention on data on the efficacy of currently available and emerging drugs for the management of cancer treatment induced bone loss (CTIBL) found in a PubMed research from 1997 till today.

Importance of the field: One of the most common and severe safety issues of the antihormonal therapy in both sexes is the CTIBL and the related fragility fractures. In postmenopausal women with estrogenic receptor positive breast cancer, the third-generation aromatase inhibitors (AIs) are the standard therapy. Observational retrospective studies have found that AIs treated patients had a high rate of bone loss and fracture risk (RR 1.3). Also in men with prostate cancer receiving androgen deprivation therapy, the increase in bone turnover and the consequent bone loss are very rapid and sustained significantly increasing the fracture risk.

What the reader will gain: The aim of our review is to provide the current evidences for the management of bone loss and fracture risk in this subpopulation.

Take home message: The very high rate of bone loss and the high incidence of fractures indicate that cancer patients at risk of CTIBL need to be carefully monitored and stratified for fracture risk. Although there is a strong evidence of efficacy in prevention of bone loss and reduction of fracture risk for many drugs approved for postmenopausal osteoporosis (PMO) and male osteoporosis, for CTIBL there are actually no drugs approved for this indication.

Keywords: androgen deprivation therapy, aromatase inhibitors, bisphosphonates, cancer treatment induced bone loss, denosumab

Expert Opin. Emerging Drugs (2010) ***15****(2):323-342*

1. Background

Many patients with breast and prostate cancers are treated with antihormonal therapy in order to inhibit disease progression and prevent disease recurrence. Ovarian failure develops within 1 year of therapy in 63 – 96% of premenopausal women with breast cancer who receive post-operative adjuvant chemotherapy mainly with cyclophosphamide, methotrexate and 5-fluorouracil [1,2]. Hormone-ablative therapies and chemotherapy-induced menopause are used to cause a marked and rapid fall of circulating and tissutal sex hormones, particularly useful in hormone-dependent cancer. As a result of earlier diagnosis, more efficacious treatments and longer survival, more patients than in the past are receiving long-term hormonal treatment for breast and prostate cancers. The increasing breast and prostate cancer survivor population, estimated at slightly > 2 million women in the US in 2005 and > 500,000 men a year may be at risk for long-term effects of these beneficial treatments [3-5]. One of the most common and severe safety issues of the antihormonal therapy in both sexes is the so-called cancer treatment induced bone loss (CTIBL) and the related fragility fractures.

10.1517/14728211003631385 © 2010 Informa UK Ltd ISSN 1472-8214

In the evaluation of the impact of the hormonal adjuvant therapies on bone health in cancer patients we should take into account that most patients with breast and prostate cancers are > 65 years old and that the risk of osteoporotic fractures is partially independent of cancer therapies. About 70% of prostate cancer patients have osteopenia or osteoporosis detected by DEXA before starting antiandrogen therapy [4,6,7] and about 20 – 60% of them have a high prevalence of 25(OH)D levels deficiency (< 20 ng/ml) [8] with a significantly increased risk of fragility fractures during the 12 months before androgen deprivation therapy (ADT) [9]. Breast cancer patients have a high prevalence of secondary causes of osteoporosis such as low levels of 25(OH)D, idiopathic hypercalciuria and hyperparathyroidism, excluding aromatase inhibitors (AIs), gonadotropin-releasing hormone (GnRH) and chemotherapy [10]. The hypogonadal state resulting from hormonal adjuvant therapy is more severe and complete than that found in early or late menopause and in aging men [11]. Therefore, the secondary increase of bone turnover, with a negative unbalance between bone formation and bone resorption, induces an impressive high rate of bone loss, exceeding about fivefold that seen in postmenopausal women or in aging men [12]. Thus, accelerated bone loss from CTIBL will be especially concerning in this setting of cancer patients.

In women at the time of the first diagnosis of breast cancer, the incidence of vertebral fractures over the next 3 years was nearly fivefold higher than in the normal population. The risk was > 20-fold greater in women with recurrent breast cancer but no evidence of skeletal metastasis [13]. Interestingly, the prevalence of vertebral fractures was similar in women with breast cancer at the time of the first diagnosis to that in an age-matched sample of the general population [13]. More recently, the prospective analysis on 90,000 postmenopausal women participating to the WHI-OS study confirmed that breast cancer survivors experienced a high yearly rate of any type of fracture with an increase of 31% in fracture risk compared to control subjects [14].

In premenopausal women, chemotherapy-induced menopause, either temporary or permanent, is associated with a rapid bone loss (2 – 4%) within 1 year of initiation of adjuvant chemotherapy for breast cancer [15,16]. In women with persistent menopause after chemotherapy, clinically significant bone loss continued during the following 2 – 5 years [17]. Recently, premenopausal women with endocrine-responsive breast cancer were randomly assigned to receive endocrine therapy alone (GnRH and tamoxifen or letrozole) or endocrine therapy plus upfront zoledronic acid [18,19]. The women with hormonal therapy alone during the 3 years treatment course had a very impressive bone loss both at the lumbar spine (-11.3%) and at the hip (-7.3%) with a mean rate of bone loss of about 3% a year [18,19].

In postmenopausal women with breast cancer and estrogenic receptor positive, the third-generation AIs (anastrozole, letrozole and exemestane) have generally replaced tamoxifen alone because of their better effectiveness in preventing disease recurrence in estrogenic receptor positive early breast cancer [20]. All of these third-generation AIs inhibit aromatase activity by > 98% [20,21]. In the postmenopausal state, unlike tamoxifen, AIs specifically block the conversion of mainly adrenal androgens to estrogens at tissue level, abolishing the protective effects of residual estrogens [21,22]. Moreover, AIs have a favourable side effect profile compared to tamoxifen but because of the well-known relationship between estrogens levels and fracture risk, a negative impact on bone metabolism would be expected. Observational retrospective studies have found that AI treated patients had a higher prevalence of bone loss (8.7%) than not treated patients (7.1%) and a higher prevalence of bone fracture (13.5 vs 10.3%) [23]. The treatment with AI seems to increase 2.5-fold the probability to have a fracture in breast cancer women with respect to tamoxifen [24]. Clinical evidences from randomized controlled trials (RCTs) have shown that AIs are associated with bone loss and increased fracture rates. The rate of bone loss induced by AIs at the lumbar spine and hip ranges from 1.7% to as much as 5.8% a year with an average rate of bone loss of 2% a year [25-31] which significantly exceeds the gradual 1% observed in PMO women [29,32-34]. The high rate of bone loss is maintained through a rapid and sustained increase of bone turnover during AI treatment, with serum levels of N-terminal propeptide of collagen type 1 (P1NP), N- and C-terminal crosslinking telopeptides of type I collagen (NTX and CTX, respectively) that significantly exceed the levels observed in control group from 20 to 45% [25-31,35-38]. The increases in annual fracture rate are similar for all three AIs [39].

In the Anastrazole, Tamoxifen, Alone or in Combination trial a 43% increase was reported in fracture rate for women receiving anastrazole compared with tamoxifen therapy (annual fracture rate 2.9% for anastrazole vs 1.9% for tamoxifen). Similar increases in fracture rate versus tamoxifen were reported with letrozole (48%) and exemestane (40%) [18,26,39-44].

Androgen deprivation therapy (ADT) is commonly used in advanced prostate cancer and is increasingly used before the development of bone metastasis, particularly as additional therapy to radiation or prostatectomy in high-risk or locally advanced disease [45].

In aging men, the decrease of sex steroids results in a gradual bone loss of 0.5 – 1% a year [46]. In men with prostate cancer receiving ADT, as in AI treated women, the increase in bone turnover and the consequent bone loss are very rapid and sustained during hormonal adjuvant therapy. Prospective longitudinal studies have reported decreases in bone mineral density (BMD) after 1 year of ADT ranging from no significant decrease to -4.8% at the spine and to -3.8% at the total hip [47-59]. In RCTs studing the preventive role of bisphosphonates (BPs), the annual rates of bone loss ranging from no significant changes to 5.7% at the spine and 2.8% at the hip are confirmed [45]. Significant changes are already detectable at 6 months after the beginning of ADT in non-metastatic prostate cancer and are characterized by an increase in bone markers [58,60]. The rate of bone loss per year of

treatment was irrespective to the type of ADT (GnRH agonist alone or plus antiandrogen, GnRH agonist plus antiandrogen and orchiectomy, intermittent ADT plus antiandrogen) ranging from -1.4 to -4.6% [46]. Other cross-sectional studies confirm progressive reduction in BMD with increasing duration of ADT [61-63]. However, fractures remain the most significant clinical problem related to CTIBL induced by ADT, influencing, as independent predictor, the survival of these patients [64].

The fracture rate due to ADT in prostate cancer patients has not yet been established with prospective studies. However, several retrospective studies provide significant evidences of increased fracture risk [45]. An analysis of 15,716 men with fractures and 47,149 matched controls in a nationalwide population-based case control study found an increased fracture risk for GnRH agonist treated patients, with or without antiandrogen therapy (odds ratio (OR) 1.7; 95% CI, 1.2 – 2.5) or orchiectomy (OR 1.7; 95% CI, 1.2 – 2.4) adjusting values for prior fractures, age and prostate cancer [65]. A pharmaceutical claims-based analysis of 12,120 men with prostate cancer reported a risk fracture rate of 7.91 versus 6.55 per 100 person/year at risk in GnRH group and ADT naive control, respectively [66]. A review of the records of 50,613 men having received a diagnosis of prostate cancer during a 5-year period showed that 19.4% of those who received ADT had fractures, as compared with the 12.6% of those who did not receive ADT [9,67]. Furthermore, a significant relation between the number of received doses of GnRH agonist during 1 year and the subsequent fracture risk was found, the treatment duration independently predicting fracture risk. A Medicare claims analysis of 10,617 men reported for men receiving GnRH agonists compared with controls a fracture risk of 7.88 versus 6.51 per 100 person/year at risk, respectively, with a significant relationship with the duration of ADT treatment [68].

However, it should be noted that the real rate of fracture in CTIBL could be underestimated because in RCTs and in epidemiological studies only clinical fractures are captured not taking into account that about 50% of the fragility fractures are morphometric vertebral fractures that are completely asymptomatic and are assessed only with a preplanned sequential spine X-rays. Actually, there are no RCTs planned to measure morphometric fractures of the spine. Furthermore, the use of BMD T-score as surrogate parameter of fracture risk in CTIBL could induce an additional underestimation of the real risk of fragility. BMD T-score threshold for the diagnosis of osteoporosis is validated by the WHO only for PMO osteoporosis and not for other conditions. This is not totally reassuring [28,69]. The high bone turnover and the high rate of bone loss, characterizing the CTIBL, predict fracture risk independently from BMD, probably reflecting bone microarchitecture deterioration [70]. It is likely that cancer patients with CTIBL have a different BMD fracture threshold if compared to other types of osteoporosis.

2. Medical need

There are strong evidences that both in breast and prostate cancers, adjuvant hormonal therapy increasing survival and inducing bone loss impacts significantly on bone health of survivors increasing their susceptibility to fragility fractures.

The very high rate of bone loss and the high incidence of fractures persisting for the duration of the endocrine adjuvant therapy and beyond indicate that cancer patients at risk of CTIBL need to be carefully monitored, correctly stratified for fracture risk and properly treated.

Recently, expert panels and position papers have suggested a new approach to assess fracture risk and to establish the treatment threshold, which integrates better levels of BMD (T-score lower of -1 DS) with independent predictors of fracture (age, previous fractures, familial history of fractures, corticosteroids therapy), similar to what has happened to the fracture risk assessment in postmenopausal osteoporosis [71-74]. Therefore, the last version of the ASCO guidelines (2003) for women with breast cancer and the expert panels for prostate cancer men [75,76] on the basis of recent evidences should not be followed because they potentially exclude a portion of patients with CTIBL at risk of fracture from therapeutic attention.

Although all guidelines and expert panels regarding CTIBL indicate the necessity to prevent and treat CTIBL, currently there are no approved therapies. All guidelines and position papers suggest the use of inhibitors of bone resorption, mainly bisphosphonates (BPs). BPs are currently proposed because of their effect on BMD and their efficacy in reducing fracture risk. They are the gold standard in PMO, glucocorticoid-induced and male osteoporosis. In addition, consistent data suggest that BPs can largely prevent CTIBL as indicated by BMD measurements [45]. However, several questions remain regarding which therapy may be more suitable in CTIBL setting, that is, BPs or raloxifene, or other new drugs approved for PMO and male osteoporosis. Actually, the evidences of risk fracture reduction in CTIBL setting with BPs treatment are surprisingly lacking and only a few data with new antiresorptive therapies, that is, denosumab, have been recently published [77]. Furthermore, available guidelines on the use of BPs in CTIBL do not indicate which BP is the most appropriate, which route of administration (oral or intravenous) is more convenient, which is the right dose and how long BP therapy should be continued [71,72]. However, the strongest evidences in treatment of CTIBL in breast cancer are obtained with zoledronic acid 4 mg every 6 months that is about twofold the dose approved for PMO (zoledronic acid 5 mg yearly) [45,78].

In conclusion, actually the growing evidences that indicate the need to manage the long-term complications arising from endocrine adjuvant therapies in cancer patients conflict with the scarce evidences of efficacy on fracture risk of the current treatments, mainly BPs.

3. Existing treatments

Regarding the pathophysiologic and molecular pathways of bone loss in postmenopausal osteoporosis and CTIBL, there are apparently no reasons to consider that these two conditions are different. Therefore, it should be a logical consequence that the same drugs used in PMO would also be useful in CTIBL.

The currently used drugs for PMO and aging men act in one of these three ways: as inhibitors of bone resorption (antiresorptive drugs); as stimulators of bone formation (anabolic drugs) and by a combination of both mechanisms, that is, dual-acting agents.

The standard treatment for PMO is the inhibition of bone resorption with BPs, selective estrogen receptor modulators (SERMs) and estrogens [79,80]. BPs actually are the first-line therapy in PMO for their safety and efficacy profile.

The anabolic therapy with teriparatide (1 – 34) or parathormone (1 – 84) has recently proved to be effective in severe osteoporosis with an impressive increase in bone mass in a relative short treatment time [81].

Finally, strontium ranelate has been recently introduced in PMO therapy for the proven efficacy in preventing both vertebral and non-vertebral fractures [82]. Its mechanism of action is not fully explained even if there are sparse evidences of a mixture of antiresorptive and anabolic effect (dual-acting agent) [83].

Although teriparatide, parathormone and strontium ranelate are not officially contraindicated in cancer patients, there are some concerns in their use in CTIBL regarding their mechanism of action. In fact, recent data about the role of bone turnover in homing of cancer cells into the bone raise questions about the safety profile of these drugs in this setting of patients. Moreover, the molecular similarity of teriparatide and parathormone 1 – 84 with parathyroid hormone-related protein (PTHrp) could not exclude potential direct effects on cancer cells via the interaction with the parathyroid hormone (PTH) receptor, as proven in animal studies [84].

These concepts explain why only the inhibitors of bone resorption are studied and developed in CTIBL.

3.1 Therapeutic class review

3.1.1 Bisphosphonates in breast cancer treatment induced bone loss

Several BPs are currently available for the treatment of age related or menopausal osteoporosis, as well as treatment and prevention of skeletal metastasis in solid tumours (**Table 1**). Although not approved for bone loss associated with cancer treatments, BPs have shown significant benefits in clinical trials. The magnitude of prevention of BMD losses and even some increases in BMD achieved with BPs suggest that a proactive approach with this drug class may decrease fracture risk among patients with breast cancer [85].

We will, therefore, examine the most important studies for each type of BP in the setting of breast and prostate CTIBL (**Tables 2** and **3**).

3.1.1.1 Clodronate

Clodronate (both oral and intravenous (i.v.)) has been investigated in CTIBL. Saarto *et al.* [86] conducted a 3-years RCT with 1600 mg of oral clodronate daily or placebo of 121 postmenopausal breast cancer women without skeletal metastasis during adjuvant treatment with SERMs demonstrating that oral clodronate significantly increased BMD at lumbar spine (+2.9%) and femoral neck (+3.7%) at 2 years. Two studies have also been performed in premenopausal women with chemotherapy-induced ovarian failure. In the first one [15], 2-years of oral clodronate treatment reduced the mean BMD loss at the lumbar spine from -5.9 to -2% and at the femoral neck from -2.2% to +0.9% ($p = 0.0005$ and 0.017, respectively). In the second study, there was no difference in bone loss of lumbar spine BMD between seven cycles of 1500 mg of clodronate i.v. for 1 year or placebo [87].

3.1.1.2 Risedronate

Delmas *et al.* [88] performed a randomized, placebo-controlled study of 53 women with breast cancer and artificially induced menopause, 36 of them were taking tamoxifen 20 mg/day. They have evidenced that oral risedronate therapy (8 cycles oral risedronate 30 mg/day or placebo daily for 2 weeks followed by 10 weeks of no drug, 12 weeks per cycle) in premenopausal women with chemotherapy or radiotherapy-induced ovarian failure after breast cancer surgery reduced mean BMD loss at the lumbar spine by 2.5% ($p = 0.041$), at the trochanter by 3.1% (0.002) and at the femoral neck by 2.6% ($p = 0.029$) compared with placebo. Risedronate has also been investigated in postmenopausal women during anastrozole therapy for early breast cancer (SABRE study) [89,90]. The primary end point of the study was lumbar spine BMD change from baseline at 12 months. At 1 year, BMD increased by 1.7 and 1.3% at lumbar spine and total hip, respectively; however, in the placebo group, BMD decreased by 0.4 and 0.1%, respectively. Greenspan *et al.* [91] confirmed in a cohort of 87 postmenopausal women with breast cancer with or without AI therapy randomly assigned to once-weekly risedronate 35 mg or placebo for 24 months that oral risedronate was beneficial for spine and hip BMD (difference of 1.6% at the spine and 2.5% at the hip, $p < 0.05$) and reduced bone turnover.

On the other hand, the group of Hines *et al.* [92] evidenced in a randomized placebo-controlled study in 216 premenopausal women undergoing adjuvant chemotherapy for breast cancer that risedronate 35 mg/weekly did not prevent bone loss.

3.1.1.3 Alendronate

Two studies have evaluated the effects of oral alendronate on BMD in postmenopausal women with breast cancer. Improvements were noted in spine and hip BMD but the number of patients was too small to perform statistical analyses demostrating a significant difference from placebo [93].

Table 1. Currently available drugs for the treatment of cancer treatment induced bone loss.

Compound	Company	Indication	Stage of development	Mechanism of action
Alendronate	Merck & Co.	Osteoporosis	Marketed	Inhibition of farnesil pirophosphate synthase in the mevalonate pathway
Risedronate	Procter & Gamble	Osteoporosis	Marketed	Inhibition of farnesil pirophosphate synthase in the mevalonate pathway
Clodronate	Abiogen	Osteoporosis	Marketed	Induction of osteoclast apoptosis
Pamidronate	Generics	Bone metastases	Marketed	Inhibition of farnesil pirophosphate synthase in the mevalonate pathway
Ibandronate	Roche	Osteoporosis	Marketed	Inhibition of farnesil pirophosphate synthase in the mevalonate pathway
Zoledronate	Novartis	Osteoporosis, bone metastases	Marketed	Inhibition of farnesil pirophosphate synthase in the mevalonate pathway
Lasofoxifene	Pfizer	Hormone replacement therapy, menopausal symptoms, osteoporosis	Marketed	Agonist/antagonist action on estrogen receptor
Raloxifene	Eli Lilly	Osteoporosis, hormone replacement therapy, breast cancer	Marketed	Agonist/antagonist action on estrogen receptor
Bazedoxifene	Wyeth	Menopausal disorders, osteoporosis	Marketed	Agonist/antagonist action on estrogen receptor
Toremifene	Orion Pharma	Treatment of hormone receptor positive breast cancer in postmenopausal women	Marketed	Agonist/antagonist action on estrogen receptor
Fulvestrant	AstraZeneca	Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression after antiestrogen therapy	Marketed	Estrogen receptor antagonist with no estrogen agonist effect

Pharmaprojects – Copyright to Citeline Drug Intelligence (an Informa business). Readers are referred to Pipeline (http://informa-pipeline.citeline.com) and Citeline (http://informa.citeline.com).

3.1.1.4 *Ibandronate*

Monthly oral ibandronate (150 mg) has also been evaluated for preventing bone loss in a randomized, placebo-controlled study of 131 postmenopausal women with early breast cancer receiving anastrozole 1 mg/day. After 2 years, osteopenic patients treated with ibandronate gained +2.98 and +0.60% at the lumbar spine and hip, respectively. Patients treated with placebo, however, lost -3.22% at the lumbar spine and -3.9% at the hip ($p = 0.01$ at both sites). Urinary n-telopeptides, serum c-telopeptide and serum bone-specific alkaline phosphatase levels decreased in patients receiving ibandronate of 30.9, 26.3 and 22.8%, respectively, at 12 months and increased in those taking placebo (40.3, 34.9 and 37%, respectively) [94].

3.1.1.5 *Zoledronate*

Recently, trials have examined the preventive role of the BPs among PMO women receiving AIs. The largest of these trials, the Zometa-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST), an open-label, multi-center, randomized study, evaluated i.v. zoledronic acid administered at a dose of 4 mg every 6 months in 602 women receiving adjuvant letrozole with baseline T-score > -2.0 DS. In one treatment arm, zoledronic acid was initiated concurrently with letrozole, whereas in the other arm treatment was delayed until BMD loss. One-year results from the Z-FAST trial showed an increase in mean lumbar spine BMD of 1.9% from baseline in the upfront zoledronic acid arm compared with a mean decrease of 2.4% with delayed administration with an overall difference of 4.4% ($p < 0.0001$) [27]. A report after 36 months of follow-up indicated that the absolute difference in lumbar spine BMD between the arms increased to 6.7% ($p < 0.001$), with more fractures in the delayed arm versus the concurrent arm (6.3 vs 5.6%, respectively), although the study was not powered to detect differences in fracture [95]. One-year results from the ZO-FAST trial are comparable, with an overall difference of 5.7% between the study arms in favour of upfront administration [96]. Preliminary findings after 24 months of follow-up continue to demonstrate a significant difference in BMD in favour of upfront zoledronic acid [97]. In the Austrian Breast and Colorectal Study Group-12 (ABCSG-12), a well-known randomized, open-label, Phase III, four-arm trial they have compared tamoxifen and goserelin (a GnRH agonist) versus anastrozole and goserelin both with or without zoledronic acid for 3 years in 1803 premenopausal women with endocrine responsive breast cancer. In all, 404 patients were prospectively included in the bone substudy and randomly assigned to

Table 2. Bisphophonates in breast cancer treatment induced bone loss.

Study	Drug	BMD changes	Time	Bone turnover markers changes
Saarto *et al*. 1997 [86]	Clodronate 1600 mg/day	LS + 2.9% vs placebo FN + 3.7% vs placebo	2 years	Not available
Saarto *et al*. 1997 [15]	Clodronate 1600 mg/day	LS + 3.9% vs placebo FN + 3.1% vs placebo	2 years	Not available
Vehmanen *et al*. 2004 [87]	Clodronate 7 cycle of 1500 mg i.v. for 1 year	No significant change vs placebo	1 year	Not available
Delmas *et al*. 1997 [88]	Risedronate 30 mg/day for 8 cycles	LS + 2.5% vs placebo Hip + 3.1% vs placebo FN + 2.6% vs placebo	2 years	Not available
Eastell *et al*. 2007 [89]	Risedronate 35 mg/weekly	LS + 1.7% vs basal FN + 1.3% vs basal	1 year	Not available
Greenspan *et al*. 2008 [91]	Risedronate 35 mg/weekly	LS + 1.6% vs placebo Hip + 2.5% vs placebo	2 years	Not available
Hines *et al*. 2008 [92]	Risedronate 35 mg/weekly	Does not prevent bone loss vs placebo		
Sawka *et al*. 2005 [93]	Alendronate 70 mg/weekly	No significant difference vs placebo		
Lester *et al*. 2008 [94]	Ibandronate 150 mg/month	LS + 2.98% vs basal Hip + 0.60% vs basal	2 years	u-NTX -30.9% s-CTX -26.3% BALP -22.8% vs basal
Brufsky *et al*. 2007 [27,95]	Zoledronate 4 mg/6 months	LS + 1.9% vs basal LS + 6.7% vs no treatment	1 year 3 years	Not available Not available
Bundred *et al*. 2008 [96]	Zoledronate 4 mg/6 months	LS + 5.7% vs no treatment	1 year	Not available
Gnant M *et al*. 2008 [19]	Zoledronate 4 mg/6 months	Stable vs basal	3 years	Not available

Pharmaprojects – Copyright to Citeline Drug Intelligence (an Informa business). Readers are referred to Pipeline (http://informa-pipeline.citeline.com) and Citeline (http://informa.citeline.com).
BALP: Bone alkaline phosphatase; BMD: Bone mineral density; FN: Femoral neck; i.v.: Intravenous; LS: Lumbar spine; s-CTX: Serum c-telopeptide; u-NTX: Urinary n-telopeptide.

receive or not zoledronic acid 4 mg every 6 months. After 3 years of treatment, patients who received zoledronic acid had stable BMD both at the lumbar spine and at the hip versus a decrease of 11.3 and 7.3%, respectively, in the control group [19].

3.1.2 Bisphosphonates in prostate cancer treatment induced bone loss

3.1.2.1 Alendronate

Once weekly oral alendronate resulted to be effective in reducing bone loss in 112 men with non-metastatic prostate cancer receiving ADT. This randomized, double-blind, placebo-controlled, partial crossover trial demonstrated that in men treated with alendronate 70 mg/weekly BMD increased over 1 year by 3.7% ($p < 0.001$) at the spine and by 1.6% ($p = 0.008$) at the femoral neck. Men in the placebo group had losses of 1.4% at the spine and 0.7% at the femoral neck. Bone turnover statistically significantly decreased in the alendronate group compared with placebo [98].

3.1.2.2 Risedronate

Ishizaka *et al*. evaluated 61 prostate cancer patients who had received ADT for about 40 months and treated with 2.5 mg of risedronate daily for 6 months. BMD remained stable in the femoral neck and radius during risedronate therapy. In contrast, the BMD of the lumbar spine showed a gain of 4.9 + 8.9%. Urinary N-telopeptide of type I collagen decreased significantly after 3 months of treatment [99]. Moreover, Izumi *et al*. demonstrated in a prospective observational study of 60 Japanese patients with prostate cancer who were receiving ADT that oral administration of risedronate is effective for the recovery of ADT-induced bone loss [100].

3.1.2.3 Pamidronate

Diamond *et al*. conducted a double-blind, randomized, placebo-controlled, crossover study. A single infusion of pamidronate in 21 men receiving ADT for prostate cancer resulted in a significant increase of 2% in femoral neck BMD and of 7.8% in lumbar spine (assessed with QCT) in a 1 year period [101]. Smith *et al*. conducted an open-label study in which they randomly assigned 47 men with prostate cancer and no evidence of bone metastases to receive either leuproline (a GnRH agonist) alone or leuproline and pamidronate (60 mg intravenously every 12 weeks). The group treated with leuproline experienced a significant

Table 3. Bisphosphonates in prostate cancer treatment induced bone loss.

Study	Drug	BMD changes	Time	Bone turnover markers changes
Greenspan *et al*. 2007 [98]	Alendronate 70 mg/week	LS + 3.7% vs basal FN + 1.6% vs basal	1 year	Not available
Ishizaka *et al*. 2007 [99]	Risedronate 2.5 mg/day	LS + 4.9% vs basal FN stable vs basal	6 months	Not available
Diamond *et al*. 2001 [101]	Pamidronate 60 mg i.v. only one infusion	LS + 7.8% vs basal FN + 2% vs basal	1 year	Not available
Smith *et al*. 2001 [102]	Pamidronate 60 mg i.v. every 12 weeks	Stable vs basal	6 months	Not available
Bhoopalam *et al*. 2009 [104]	Zoledronate 4 mg every 3 months	LS + 5.95% vs placebo	1 year	Not available
Casey 2007 [108]	Zoledronate 4 mg every 3 months	LS + 3.3% FN + 0.7%	1 year	Not available
Smith *et al*. 2008 [109]	Zoledronate 4 mg every 3 months	LS + 5.6% FN + 1.6%	1 year	Not available

BMD: Bone mineral density; FN: Femoral neck; i.v.: Intravenous; LS: Lumbar spine.

decrease in BMD at any site in a 48 week period of time whether the mean BMD in the group treated with pamidronate did not change significantly in the same time period [102].

3.1.2.4 Zoledronate

Israeli *et al*. evaluated the efficacy of zoledronic acid in preventing BMD loss and suppressing bone marker in patients with locally advanced prostate cancer during ADT treating 200 patients randomly assigned them to receive either zoledronic acid 4 mg every 3 months or placebo. At week 52, the least squares mean BMD percentage differences were 6.7% for lumbar spine and 3.7% for total hip ($p < 0.0001$ for both) [103]. Bhoopalam *et al*. investigated the efficacy of zoledronic acid in 93 patients with prostate cancer who were on ADT for 1 year in mean. They were assigned to receive either zoledronic acid 4 mg every 3 months for four treatments or i.v. placebo. They demonstrated that zoledronic acid significantly improved lumbar spine BMD of 5.95% versus placebo [104]. Zoledronic acid administered at a dose of 4 mg every 3 months for 1 year is the most commonly investigated BP in prostate cancer with several RCTs reporting significantly increased BMD ranging from 3.3 to 5.6% in the spine and 0.7 to 1.6% in the total hip, regardless of whether the patients were already receiving ADT [103,105-107] or starting ADT at study enrolment [108,109].

Finally, we should discuss a little about the fact that BPs dose-finding studies in CTIBL have not been performed. Alendronate, risedronate and ibandronate in CTIBL have been studied at doses with evidences of antifracture efficacy in postmenopausal osteoporosis (PMO), glucocorticoid and male osteoporosis, while in the majority of zoledronic acid studies it has been used at a higher dose, almost double than that approved for prevention of fractures in PMO and male osteoporosis (5 mg/year). If the primary end point is the prevention of bone loss, probably all the doses tested are adequate but if the primary end point is the fracture risk reduction we can only speculate that the doses used for PMO and male osteoporosis can be adopted in CTIBL supposing that CTIBL is biologically similar to PMO and male osteoporosis. In other words, we do not know which is the correct dose for the fracture risk reduction in CTIBL.

3.1.3 Denosumab

Bone loss is mediated by osteoclasts, whose formation, function, and survival depend on receptor activator of NF-κB ligand (RANKL). RANKL binds to its receptor RANK on preosteoclasts and mature osteoclasts and activates and maintains osteoclast-mediated bone resorption [110-113]. Denosumab is a fully human mAb that specifically inhibits RANKL, and suppresses bone resorption [113]. The effects of denosumab on BMD have been explored also in the setting of CTIBL (**Table 4**).

Denosumab increased lumbar spine BMD versus placebo ($p < 0.05$) in a 2 year randomized, placebo-controlled, Phase III study of 252 patients with hormone receptor positive, non-metastatic breast cancer and low bone mass who were receiving adjuvant AI therapy. Denosumab treatment was associated with statistically significant gains in lumbar spine BMD compared with placebo. The treatment effect of denosumab on BMD was maintained at 24 months. The observed differences in BMD between denosumab and placebo groups were statistically significant ($p < 0.05$) across all skeletal sites and subgroups, except for radial BMD in patients who had received steroidal AI [114].

Ellis *et al*. conducted a randomized, placebo-controlled Phase III study over a 24 month period. They studied 252 patients during AI therapy who were randomly assigned to receive placebo or subcutaneous denosumab 60 mg every

Table 4. Other drugs tested in cancer treatment induced bone loss.

Study	Drug	BMD changes	Time	Bone turnover markers changes
Ellis *et al*. 2008 [113]	Denosumab 60 mg/6 months	LS + 5.5% vs placebo LS + 7.6% vs placebo	1 year 2 years	-91% vs basal Not available
Smith *et al*. 2009 [77]	Denosumab 60 mg/6 months	LS + 5.6% vs basal	2 years	Not available
Smith *et al*. 2008 [157]	Toremifene 80 mg/day	LS + 2.3% vs placebo FN + 1.5% vs placebo Hip + 2% vs placebo	1 year	Not available

BMD: Bone mineral density; FN: Femoral neck; LS: Lumbar spine.

6 months. At 12 and 24 months, lumbar spine BMD increased by 5.5 and 7.6%, respectively, in the denosumab group versus placebo ($p < 0.0001$ at both time points). Increases were observed as early as 1 month and were not influenced by duration of AIs therapy. Markers of bone remodeling were rapidly reduced with a median percentage reduction from baseline of 91% compared with 9% in the placebo group ($p < 0.0001$) [113]. Smith *et al*. conducted a double-blind multi-center study in which 1468 patients with CTIBL in prostate cancer were randomly assigned to receive either denosumab 60 mg subcutaneously every 6 months or placebo. At 24 months, the denosumab group experienced a gain of 5.6% in lumbar spine BMD versus a decrease of 1% in the placebo group ($p < 0.001$) and the difference between the two groups remained significant through 36 months. Furthermore, patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5 vs 3.9% with placebo; $p = 0.006$) [77].

3.1.4 Selective estrogen receptor modulators

3.1.4.1 Raloxifene

Raloxifene resulted effective in preventing PMO bone loss over a 3 year period in the MORE trial, a multi-center randomized, blinded, placebo-controlled trial of 7705 women who were randomized to receive 60 mg/day of raloxifene or placebo [115]. BMD gained after 3 years amounted to 2.1% at the spine and to 2.6% at the femur. Raloxifene reduced vertebral fractures over 3 years by 30 and 55% in women with and without prevalent fractures, respectively [115-118]. The RUTH clinical trial, an international multi-center, randomized, placebo-controlled trial of 10,101 PMO women who were randomly assigned to receive 60 mg/day of oral raloxifene or placebo, clearly demonstrated the benefits of raloxifene in the prevention of clinical fractures (33% reduction, $p = 0.007$) [119]. Despite the strong rationale of using raloxifene in CTIBL, this compound has not been tested in this setting.

3.2 Calcium and vitamin D supplementation

Calcium and vitamin D supplementations alone or combined with antiresorptive therapies are critical in the management of CTIBL. There are many arguments in favour of this.

First of all, the prevalence of vitamin D deficiency (25(OH)D serum values below 30 ng/ml) or insufficiency (25(OH)D below 20 ng/ml) are very common in almost every region of the world studied, being particularly frequent in Southern European countries [120]. Risk factors of vitamin D deficiency include elderly, female sex, overweight, dark skin pigmentation, winter season and reduced sun exposition, dietary habits and national policies of vitamin D fortification [120]. However, it has been recently discovered that vitamin D deficiency is pandemic, involving also children and healthy adults across the world [121-123]. Therefore, it is not surprising that a high proportion of patients with breast and prostate cancers have low or very low plasma 25(OH)D levels [124,125], a condition of particular concern in these patients, not only for their bone health but also for the strong association with risk of cancer incidence and mortality [126]. Recent meta-analysis evidenced that vitamin D and calcium supplementation have chemopreventive effects against breast and prostate cancers, even if in the latter the data are conflicting [126-129]. Secondary hyperparathyroidism is a direct consequence mainly of low 25(OH)D levels rather than low calcium intake [128,130]. PTH elevation due to low 25(OH)D levels impairs the efficacy of the antiresorbing agents, mainly BPs, by three to fivefold lower BMD changes and by 1.5-fold increased risk of incidence of fracture, in vitamin D insufficient as compared to vitamin D repleted postmenopausal women [131]. However, in cancer patients, secondary hyperparathyroidism is of particular concern because PTH may have promotional activity on cancer progression directly binding the PTHrp on cancer cells (PTH1R) and indirectly enriching bone microenvironment of cytokines and growth factors favoring the development and progression of bone metastatic disease [132]. Therefore, optimal vitamin D repletion seems to be necessary in cancer patients to maximize the response to antiresorbing agents and probably to obtain an anticancer effect. It is noteworthy that adequate vitamin D doses (greater than 400 IU daily of cholecalciferol) exert an additional antifracturative effect compared to antiresorptive agents, reducing the nonvertebral fractures by at least 20% and the hip fractures by at least 18%, independently of additional calcium supplementation [133]. Serum 25(OH)D levels of 75 nmol/l (30 ng/ml) or higher can be considered appropriate [134]. These levels provide optimal benefits beyond

bone health (e.g., on hypertension, cardiovascular diseases, falls, cancer, mortality) [134], and they could be influenced by calcium intake, being somewhat lower with a high calcium intake or higher with a very low calcium intake [135]. The evidences from randomized trials suggest that the dose of vitamin D supplementation needed to bring the large majority of people to the optimal range of values of serum 25(OH)D is far greater than that suggested by guidelines and administered in almost all trials regarding BPs for the treatment of osteoporosis, CTIBL or bone metastases (about 400 – 600 IU daily of cholecalciferol) [136]. Currently, a dose > 800 – 1000 IU daily, probably comprised between 1800 and 4000 IU per day, is suggested [134]. Daily doses of 10,000 IU for 4 months appear safe in breast cancer patients with bone metastases [137]. Among the available types of vitamin D, the inactive forms, such as cholecalciferol, should be preferably used, as more safe, cheap and usefully utilized by almost all tissues throughout autocrine hydroxylation, rather than activated metabolites that should be reserved to chronic renal failure [133].

3.3 Adherence and duration of therapy

About 50% of patients with postmenopausal osteoporosis fail to comply or persist with anti-osteoporosis treatment regimens within 1 year [138]. Poor compliance is associated with higher fracture rates and increased morbidity, mortality and costs [139,140]. Annually or biannually, i.v. BPs or subcutaneous denosumab administered every 6 months could potentially ameliorate this Achilles' heel of osteoporosis treatment.

The optimal duration of treatment to prevent CTIBL could be only speculative. There are data that indicate that the high bone turnover, high rate of bone loss and the fracture risk persist during endocrine adjuvant treatment with a significant fall of fracture risk after the withdrawal in the subsequent years [141].

On the other hand, BPs and denosumab maintaining the bone turnover adequately suppressed induced a continued improvement of BMD [113,142]. Therefore, the minimum treatment period should cover the duration of endocrine adjuvant treatment. At withdrawal of hormonal suppression, the risk of fracture should be re-assessed and the antiresorbing agents, without the emerging of new fracture risks, could be withdrawn. Furthermore, there are consistent evidences that the benefits of amino-BPs, mainly of the ones with higher bone affinity such as zoledronic acid and alendronate, probably could not be limited to the treatment course, the protective effects on BMD and fractures potentially extending through some years after cessation [143]. The use of BPs and denosumab in the future in CTIBL setting requires further studies to more clearly define the most appropriate timing and length of therapy as well as the long-term efficacy and safety.

3.4 Safety/tolerability of antiresorbing agents

BPs are the most commonly prescribed medications for the treatment of osteoporosis and actually represent the gold standard for the treatment of bone metastases. Although evidence supports a good safety profile for these agents, numerous tolerability issues have been associated with their use. Evaluating the safety and the tolerability of oral and particularly i.v. BPs should be considered in that there are consistent differences mainly in the schedules of administration between their use in bone metastatic, osteoporosis or CTIBL setting, with annual cumulative doses about 12-fold higher in the former setting. The major concerns for oral amino-BPs are upper gastrointestinal (UGI) adverse events including esophagitis, esophageal ulcer and erosive esophagitis without apparently significant differences among BPs (alendronate, ibandronate, risedronate) and placebo. In the 'real life', the issue of UGI tolerability is strongly linked with the correct following of the administration instructions. In CTIBL setting, administration of zoledronic acid appears to be well tolerated and the most frequent adverse event is the influenza-like illness [25,144,145]. Its incidence ranges in about 10 – 50% of patients treated for the first time and can be treated or prevented with acetominophene. Recently, it has been found that a determinant of developing the acute phase response are low pretreatment levels of 25(OH)D [146].

Osteonecrosis of the jaw (ONJ) has also been associated with the use of amino-BPs. The ONJ associated with oral BPs in osteoporosis is rare with an estimated prevalence of 0.7/100,000 patients/year [147]. One case of ONJ in the zoledronic acid group and one patient in the placebo group are reported in the pivotal trial for the prevention of osteoporotic fractures [148]. Out of a total of 2195 patients with CTIBL treated with zoledronic acid [27,144,145], 6 cases of ONJ have been reported and only 1 (< 0.005%) case has been confirmed by the ONJ adjudication committee. Only three patients had impaired renal function suspected to be related to BP treatment [27,144,145]. Recently, a significantly higher incidence of atrial fibrillation (1.3% in zoledronic group vs 0.5% in placebo group) has been reported associated with the annual infusion of zoledronic acid for osteoporosis in a pivotal trial [149] and afterwards suspected for oral BPs. Actually, the heterogeneity and the paucity of the existing data preclude any definitive conclusion on the exact nature of the risk of this side effect [150]. In general, adverse events due to oral and i.v. BPs used at low doses as in osteoporosis and CTIBL setting are mild and easily manageable.

For denosumab (60 mg every 6 months), the most common adverse effects in Phase III trials in prevention of CTIBL in breast and prostate cancer patients were arthralgia, pain at the extremities, back pain and fatigue with a similar incidence in the placebo group [77,113]. In breast cancer patients, serious AEs were reported in the 15% in the denosumab group and in the 9% of the placebo group but none was considered to be treatment related. Infections were reported in the 2% of the denosumab group and in the 1% of the placebo group.

In prostate cancer patients, serious adverse events related to infections were reported in the 5.9% of patients receiving

Table 5. Emerging drugs for the treatment of cancer treatment induced bone loss.

Compound	Company	Indication	Stage of development	Mechanism of action
Denosumab	Amgen	Osteoporosis cancer, bone cancer, prostate cancer, breast	Pre-registration Phase III clinical trials	Specifically inhibits RANKL and suppresses bone resorption
Balicatib	Novartis	Osteoporosis	Discontinued	Cathepsin K inhibitor
Odanacatib	Merk & Co.	Osteoporosis	Phase III clinical trials	Cathepsin K inhibitor
Arzoxifene	Eli Lilly	Osteoporosis,hormone replacement therapy, breast cancer	Phase III clinical trials	Agonist/antagonist action on estrogen receptor
Antibodies to sclerostin			In development	Interferes in the signaling cascade leading to an increased number of activated osteoblasts
Antibodies to Dkk-1			In development	Interferes in the signaling cascade leading to an increased number of activated osteoblasts
SARMs			In development	SARMs

RANKL: Receptor activator of NF-κB ligand; SARM: Selective androgen receptor modulator.

denosumab and in the 4.6% of those receiving placebo. One patient receiving denosumab had hypocalcemia whereas all receiving placebo had it [77]. No cases of ONJ were reported in both studies. A single case of ONJ has been recently reported in a patient with prostate cancer and bone metastases participating in a Phase III study with denosumab (120 mg/every 4 weeks) compared with zoledronic acid (4 mg/every 4 weeks). He completed a course of chemotherapy with docetaxel and prednisone and his current medication was LHRH, stilboestrol and doxazosin [151].

4. Competitive environment

4.1 Selective estrogen receptor modulators

4.1.1 Bazedoxifene

Bazedoxifene is an indole-based estrogen receptor (ER) ligand which exerts significant estrogenic and antiestrogenic activity both *in vitro* and *in vivo* targeting any tissue that has ERs (**Table 5**). Phase III studies of bazedoxifene, particularly a 3 year, randomized, double-blind placebo-controlled study of 6847 subjects treated with bazedoxifene or placebo, proved a significant relative risk reduction of new vertebral fractures in the group treated with bazedoxifene versus placebo [152]. Clinical studies of bazedoxifene in combination with estrogens (randomized, placebo-controlled, Phase III studies with daily bazedoxifene combined with conjugate estrogens compared with raloxifene or placebo) evidenced better increases in lumbar BMD for this treatment regimen (range 1.15 – 2.61%) compared with placebo (-1.92%). In this trial among women within 5 years from menopause, the mean increase from baseline in lumbar spine BMD at 2 years was significantly greater for all bazedoxifene/conjugate estrogen doses (range 1.15 – 2.61%) compared with raloxifene (0.15%; $p < 0.05$) [153,154].

4.1.2 Lasofoxifene

The PEARL [155] study, a Phase III RCT, compared 3 years of lasofoxifene 0.25 or 0.5 mg/daily versus placebo demonstrating that it improves significantly lumbar spine and femoral neck BMD and reduces the risk of vertebral fractures by 31 and 42% ($p < 0.002$), respectively.

4.1.3 Arzoxifene

The FOUNDATION study, a Phase III, 2 years, randomized, placebo-controlled trial including 331 postmenopausal women with normal to low bone mass, evaluated the effects of arzoxifene 20 mg/day on BMD. BMD resulted significantly increased in the arzoxifene group both at the lumbar spine (1.63%; $p < 0.001$) and at the total hip (1.08%; $p < 0.001$) versus a significant decrease in BMD at the same sites in the placebo group. Between groups, BMD comparisons showed significant increases in the arzoxifene group at all time points when compared with placebo. Moreover, in the arzoxifene group, biochemical markers of bone metabolism resulted significantly decreased versus placebo at each visit ($p < 0.001$) [156].

4.1.4 Toremifene

Toremifene is a second generation SERM that is currently in clinical development for the prevention and treatment of osteoporosis in men receiving ADT for hormone sensitive prostate cancer. Smith *et al.* have recently published an interim analysis of 197 subjects of a multi-center, Phase III fracture prevention study of 1392 men with prostate cancer receiving ADT. They were randomized to receive either toremifene 80 mg/day or placebo. The group treated with toremifene had significant increase in BMD at each skeletal site compared with placebo, after 1 year of treatment. Between group differences in BMD from baseline to month 12 were 2,

3% at lumbar spine, 2% at total hip and 1, 5% at femoral neck (**Table 4**) [157].

4.2 Cathepsin K inhibitors

Two cathepsin K inhibitors, balicatib and odanacatib, are tested in humans and shown to reduce markers of bone resorption and increase bone mass. A multi-center, randomized, placebo-controlled dose-finding study including 675 postmenopausal women treated with balicatib 50 mg daily has been conducted by Adami *et al*. Markers of bone resorption declined by > 55% and BMD increased by 4.46% at the lumbar spine and by 2.25% at the total hip [158,159]. McClung *et al*. conducted a randomized, controlled trial of 399 postmenopausal women, which evaluated the effects of four oral doses of odanacatib given weekly on BMD and bone markers. It showed dose-dependent increases in spine and hip density (+5.5 and +3.2%, respectively), and a significative decline of urine N-telopeptide of type I collagen and bone specific alkaline phosphatase (-52 and -13%, respectively) compared with a much smaller decline in the placebo group (-3%) [160].

4.3 Antibodies to sclerostin

Antibodies to sclerostin have shown to increase bone formation in osteopenic estrogen-deficient rats. A single subcutaneous dose of an antibody to sclerostin in postmenopausal women resulted in an increase in N-terminal propeptide of type I collagen levels of 60 – 100% at the 84th day of treatment, no increase in serum C-telopeptides and a 6% increase in lumbar spine BMD [161].

4.4 Antibodies to dikkopf 1

Dikkopf 1 (Dkk1) antibodies preventing binding of dikkopf-1 to lipoprotein-receptor-related protein 5/6 have shown to increase bone mass, bone volume and bone formation in rodents. Antibodies to dikkopf-1 could be used as anabolic agents for the treatment of patients with low bone mass [162].

4.5 Fulvestrant

Fulvestrant is an antagonist of the ER without agonist effects. It is a specific drug in the class of the antiestrogenic therapies. In all, 14 postmenopausal women with locally advanced or metastatic breast cancer received fulvestrant (250 mg monthly intramuscular) as their first-line endocrine therapy in an open-label prospective clinical trial. In this study, they analyzed the mean percent changes of bone specific alkaline phosphatase, N-terminal propeptide of procollagen type 1 and C-terminal telopeptide at 0, 1, 6, 12 and 18 months. This study, by evidencing the stability of bone turnover markers, suggested an apparent lack of effects of fulvestrant on bone turnover [163].

4.6 Selective androgen receptor modulators

Selective androgen receptor modulators (SARMs) largely remain in the discovery and development stage, with a number of agents in preclinical development, and only a few drugs completing Phase I or II clinical trials up to now. No SARM has been approved yet for clinical use [156].

5. Current research goals

At present, the use of endocrine adjuvant therapies improves survival outcomes in breast and prostate cancers. In this population of patients, the increasing awareness of CTIBL, particularly of the fragility fractures risk, and effective strategies to manage these adverse effects are required to maintain good quality of life (QoL). The evidences of efficacy of lifestyle modifications and pharmaceutical interventions proven to reduce the fracture risk in postmenopausal women and aging men are not directly applicable in CTIBL. The discovery of new molecular targets in the cellular mechanisms regulating bone turnover (e.g., RANKL/RANK/OPG axis, Wnt-B catenin signaling) drives the research of new classes of drugs. In this way, being the molecular mechanisms of imbalance between osteoclasts and osteoblasts activity involved in bone loss common to different conditions, such as osteoporosis, CTIBL or bone metastasis, it is reasonable that drugs with innovative mechanisms of action (e.g., denosumab) need to be tested in RCTs in many conditions characterized by disturbance of bone turnover. Nevertheless, the evidences of efficacy concerning specific end points, for example, reduction of fracture risk, obtained in one disease, could not be considered suitable for other diseases. In fact, rate of bone loss, incidence and type of fractures are probably quite different among distinct conditions and, therefore, the doses, the schedules of administration, the duration of the effects and the safety should be tested for the specific indications. For example, in CTIBL there is evidence that BPs, the standard treatment for fracture risk reduction in postmenopausal osteoporosis, can prevent and partially recover bone loss (given in different doses than osteoporosis), while the reduction of fracture risk is not yet proven. There are a number of ongoing studies with both oral and i.v. BPs, mainly in CTIBL, which have not yet generated data. These studies will provide evidences for the optimal strategy for reducing bone loss and perhaps the resulting fractures.

A further intriguing field of research in emerging therapies for CTIBL is the exploration of the combined use as well as the sequential use of drugs with different molecular and/or cellular targets in bone (e.g., BPs and denosumab) searching an additive effect or a more convenient schedule or a longer lasting effect. Finally, an important research goal should be the comparison of efficacy, safety profile and compliance among drugs with proven efficacy to define the best choice and offer the best chance of therapy for CTIBL.

6. Scientific rationale

The scientific rationale for the use of these compounds in the setting of the CTIBL is based on the mechanisms of action of these drugs and on their capability of reducing bone turnover.

We, therefore, briefly analyze the single role of each drug in bone metabolism.

6.1 Bisphosphonates

BPs are stable analogues of pyrophosphate in which the oxygen atom linked to two phosphate groups is replaced by a germinal central carbon atom. They bind avidly to hydroxyapatite bone mineral surfaces, especially within resorption cavities. Subsequently, they are taken up by local osteoclasts, primarily through endocytosis [164]. Nitrogen-containing BPs inhibit the mevalonate pathway, the main target being farnesyl diphosphate synthase. Inhibition of the mevalonate pathway leads to a loss of important prenylated proteins which are required for the survival of the cell, finally inducing osteoclasts apoptosis. In addition, build up of proximal metabolites in the mevalonate pathway may have positive effects on immune function including the expansion of $\gamma\delta$ T cells [110,164-168].

6.2 Denosumab

Bone loss is mediated by osteoclasts, whose formation, function and survival depend on the RANKL. RANKL binding to its receptor RANK on preosteoclasts leads to the development and activation of osteoclasts which maintain bone resorption [110-112]. Denosumab, a fully human mAb, specifically inhibits RANKL and suppresses bone resorption.

6.3 Selective estrogen receptor modulators

SERMs are drugs with mixed agonist/antagonist action on ERs in different tissues. In clinical trials, they have shown to prevent bone loss and to lower serum cholesterol levels, without stimulating the endometrium.

6.4 Cathepsin K inhibitors

Bone resorption by osteoclasts comprises both demineralization of inorganic bone components and removal of organic bone matrix. Demineralization requires acid secretion by osteoclasts into resorption lacunae, whereas matrix degradation is accomplished by cysteine proteases including cathepsin B, L, S and K [130]. Cathepsin K has high collagenase activity and at the acidic pH present in the resorption lacunae dissolves type I collagen. Elimination of cathepsin K in osteoclasts results in inhibition of bone resorption.

6.5 Antibodies to sclerostin and Dkk1

The exploration of the mechanisms by which the formation of bone is regulated during embryogenesis has clearly established a role for members of the hedgehog family of proteins and their receptors as well as for bone morphogenetic proteins and their receptors [168-171]. Several marker genes of the osteoblast lineage are now identified, and the picture that emerges is that of a cascade of signaling pathways each of which activates the expression of a few genes characteristic of the osteoblast lineage as well as the expression of the ligand for the following signaling cascade, ultimately leading to the expression of the full set of genes characteristic of a mature, bone matrix secreting osteoblast [172]. Antibodies to sclerostin and to Dkk1 interfere in one of the numerous key points of this signaling cascade leading to an increased number of activated osteoblasts and, therefore, to an increase of the entire bone mass. This effect is the base of a strong rationale for their use in conditions of bone loss as PMO, male and glucocorticoid osteoporosis. However, in cancer patients, the key roles of osteoblasts in the bone homing of cancer cells and in the creation/mainteinance of premetastatic niche raise some concerns on their use in this setting of patients.

6.6 Fulvestrant

Fulvestrant is a new ER antagonist with no estrogen agonist effect and has a novel mode of action. It binds, blocks and increases degradation of ER protein leading to an inhibition of estrogen signaling through the ER. It was recently approved for the treatment of hormone receptor positive (HR^+) metastatic breast cancer in postmenopausal women with disease progression after antiestrogen therapy [173]. Fluvestrant seems to reduce the trabecular bone loss in animal models after ovariectomy [174]. However, the results of a small clinical pilot study show a modest effect on bone resorption, lower than expected [163].

7. Potential development issues

Prevention of CTIBL has become an important issue and many BPs and denosumab are investigated in clinical trials evaluating their effects on bone loss in this setting. Recent guidelines and recommendations on management of CTIBL [71-73] suggest the use of bone-targeted treatments (mainly BPs) in patients with breast or prostate cancer at very conservative BMD levels (for a T-score ranging between -1 and -2) or in presence of other BMD-independent fracture risk factors, regardless of BMD. This preventive approach is based on the evidences of a better preservation of BMD if BPs are started in the early stage of bone loss rather than delayed after fractures or after significant bone loss has occured [27]. The potentially greater benefits of this approach on fracture risk in CTIBL are based on the likely rationale that better BMD (a surrogate end point of efficacy) probably corresponds to a better bone quality and to a low risk of fracture. Only recently, the preliminary evidences of the beneficial effects of zoledronic acid in preventing not only bone loss but more intriguingly the development of skeletal and non-skeletal metastasis may suggest more specific indications for the clinical use of BPs and potentially of other inhibitors of bone turnover in the cancer setting. The goal of the therapeutic approach will shift from bone mass preservation to prevention of metastasis (skeletal and possibly nonskeletal). Bone is not only the most frequent site of metastasis for breast and prostate cancers, but as a great number of preclinical data indicate, bone marrow microenvironment acts as a niche for dormant cancer cells attracted through the release of bone-derived cytokines and growth factors, till their

development in bone metastasis or dissemination to extra-osseus sites. Potent amino-BPs, as zoledronic acid, alone or in combination with chemotherapy, could have a direct or indirect antineoplastic effect, influencing bone microenvironment and the survival of dormant cancer cells. Zoledronic acid in two pilot studies significantly reduced at 1 year the number of marrow disseminated tumor cells after adjuvant chemotherapy suggesting an antitumor effect within the bone microenvironment [175-177]. Recenly, in the ABCSG-12 study, the administration of zoledronic acid 4 mg every 6 months primarily to prevent endocrine adjuvant bone loss was associated with 35% improvement in disease free survival (DFS) with a significant reduction of nonskeletal metastasis and locoregional recurrence rate, too [178]. Similar improvements in DFS have been presented from Z-FAST/ZO-FAST studies and the results of ongoing trials using zoledonic acid, clodronate and ibandronate with DFS and bone metastasis free survival as primary end points (AZUR, SWOG, GAIN, SUCCESS) are expected in the next year [179]. Other developing drugs, that is, denosumab, interfering with bone turnover and modulating bone microenvironment could potentially be effective in the adjuvant setting.

We can suppose that if the antitumoral effect and the improving of DFS of BPs are confirmed, their adjuvant role should overcome the effects on bone mass preservation in endocrine adjuvant treated patients becoming the primary indication, anyway assuring the bone-sparing effect.

8. Conclusions

The hormone deprivation therapy is the standard therapy in prostate cancer and recently the AIs showed a clear superiority compared to tamoxifene in hormonal adjuvant therapy of early breast cancer. Both the treatments are associated with an increasing bone loss and fracture risk. CTIBL does not seem to be determined through different pathogenic and molecular mechanisms from PMO or aging male osteoporosis, even if it shows about twofold higher rate of bone loss and fracture. At the present, there are no available drugs registered to treat or prevent CTIBL. Potentially all antiresorptive drugs, mainly BPs, registered for PMO or male osteoporosis could be used, even if none have demonstrated fracture risk reduction in this specific setting of patients. Among these, zoledronic acid 4 mg every 6 months has the largest body of evidences in the prevention of CTIBL. Emerging drugs in this setting with antiresorptive activity include denosumab, a fully human mAb that specifically inhibits RANKL, cathepsin K inhibitors, antibodies to sclerostin and Dkk1 and SERMs, which selectively modulate the activity of ERs. These drugs are in parallel developed for PMO but the dose, the schedule, the antifracture efficacy and the safety profile in this setting could not be directly bridged to CTIBL. There is the necessity, for the oncology community, of agents with efficacy and safety profile specifically proven for CTIBL. The development of new drugs for the market will require not only a challenge on the efficacy and safety profile, which should be superior to BPs but also on economic profile, considering the availability now of inexpensive generic alendronate and in the next few years of all generic BPs.

9. Expert opinion

In recent years, bone health is becoming a central issue in cancer patients, mainly in breast and prostate cancers. The bone is involved at many stages of the natural history of the cancer disease. Soon after chemotherapy in premenopausal women or during endocrine adjuvant therapy, the increase of bone turnover induces a rapid bone loss (and probably a rapid deterioration of bone quality) that in turn increases the risk of fragility fracture. Bone is a preferred site involved in metastatic disease, with pain, skeletal related events (SREs: pathological fractures, hypercalcemia, spinal compression, radiotherapy, surgery) and loss of QoL that deeply impact on survival. Finally, there are increasing evidences that a high bone turnover is associated with a bone marrow microenvironment enriched of cytokines and growth factors that attract cancer cells, thus, creating a pre-metastatic niche promoting the survival of dormant cells with a subsequent dissemination to extra-skeletal sites. In the last 10 years, the increasing scientific advances in understanding the molecular mechanism of bone turnover and the close molecular cross-talk among cancer cells, osteoblasts, osteoclasts, osteocytes and bone marrow cells have revealed an intriguing pathophysiologic and clinical network among the apparently separate clinical conditions that involve the skeletal in cancer patient. So, high bone turnover induces bone loss and bone fragility, promotes the homing of cancer cells in bone and the development of metastasis, increases the risk of SRE and is associated with poor survival. Finally, it is likely that a frail osteoporotic bone is more prone to an SRE than a healthy one. On this basis, the normalization of bone turnover, recovering the normal balance between osteoblasts and osteoclasts functions, seems to be the key to interrupt this vicious cycle that globally affects many aspects of bone heath in cancer patients.

Among the antiresorptive drugs, the most potent inhibitors of bone turnover are the amino-BPs, and among amino-BPs, zoledronic acid is by far the most potent. In this category of drugs, it is unlikely that greater significant benefit could come from developing additional agents. For example, denosumab, with the limit of the lack of head to head comparison among antiresorptive drugs in CTIBL and in PMO, suppresses bone turnover at the same level (-90%) of zoledronic acid and reduces the incidence of vertebral and non-vertebral fracture of the same extent (-70 and -30%, respectively) [113].

Although for all amino-BPs nowadays there are evidences of reducing fracture risk in different types of osteoporosis and across a wide range of risk classes, data on the reduction of fracture risk are lacking in CTIBL and there is no therapy approved for this condition. However, recently, expert panels

recognizing the necessity to address accelerated bone loss in these at-risk populations and taking into account the negative impact of fractures on patient independence and QoL, combining the large body of evidences on prevention of CTIBL, mainly using zoledronic acid, recommend that all patients treated with endocrine adjuvant therapy should be evaluated for the risk of CTIBL and eventually treated with BPs [72,73]. Recent analysis of the Z-FAST trial demonstrates that zoledronic acid is cost-effective in the prevention of fractures in women with early breast cancer treated with AI, particularly when the treatment is started before bone loss has occurred [180].

Despite the above evidences, some questions remains undetermined: which patients may benefit mostly from preventive BPs and what are the optimal dose and frequency of administration. In parallel, preliminary evidences support an exciting new field of utilization of zoledronic acid: the possibility of preventing skeletal and nonskeletal metastases. The adjuvant role will be confirmed through the several ongoing trials which have event-free survival and DFS as primary end points. These trials could also demonstrate whether treatment with adjuvant BPs has a class effect and whether it is specific of certain agents. Awaiting the confirmation of the adjuvant role of zoledronic acid or other BPs, at present the use of zoledronic acid in prevention of CTIBL is useful because of the additional benefits that overcome BMD, covering all the targets of bone health in a cancer patient. In this landscape, the development of new drugs in the bone health field, as denosumab, with good evidences in preventing bone loss in CTIBL and also in reducing SRE in metastatic bone diseases, should be evaluated not only for their efficacy differences, convenient administration or cost, but for their ability to prevent skeletal and nonskeletal metastases.

Clearly, although there may be little added benefits from developing additional agents of the antiresorptive category for this setting of patients, new drugs with different mechanisms of action and differently targeted on bone could offer the opportunity to explore new strategies such as a combined use with the new end point of preventing bone metastasis.

Declaration of interest

F Bertoldo has received financial support: i) as grants for research support: Novartis, Nycomed, Procter & Gamble; ii) as a consultant, advisory board member on the speakers bureau or at sponsored speaking events: Merck, Eli Lilly, Novartis, Procter & Gamble, Sanofi-Aventis, Roche, GlaxoSmithKline, Nycomed.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Pfeilschifter J, Dieli IJ. Osteoporosis due to cancer treatment: pathogenesis and management. J Clin Oncol 2000;18:1570-93
2. Mincey BA. Osteoporosis in women with breast cancer. Curr Oncol Rep 2003;5:53-7
3. American Cancer Society. Breast Cancer Facts & Figures 2005 – 2006. Available from www.cancer.org
4. Smith MR. Therapy insight: osteoporosis during hormone therapy for prostate cancer. Nat Clin Pract Urol 2005;2:608-15
5. Smith MR, McGovern FJ, Fallon MA, et al. Low bone mineral density in hormone naïve men with prostate carcinoma. Cancer 2001;91:2238-45
6. Hussain SA, Weston R, Stephenson RN, et al. Immadiate dual energy Xray absorptiometry reveals a high incidence of osteoporosis in patients with advanced prostate cancer before hormonal manipultion. BJU Int 2003;92:690-4
7. Ryan CW, Huo D, Stallings JW, et al. Lifestyle factors and duration of androgen deprivation affect bone mineral density of patients with prostate cancer during first year of therapy. Urology 2007;70:122-6
8. Li H, Stampfer MJ, Hollis JB, et al. A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. PLos Med 2007;4 (3):e103
9. Shahinian VB, Kuo YF, Freeman JL, et al. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154-64
10. Camacho P, Dayal A, Diaz J, et al. Prevalence of secondary causes of bone loss among breast cancer patients with osteopenia and osteporosis. J Clin Oncol 2009;26;33:5380-5
11. Khosla S, Melton LJ III, Atkinson EJ, O'Fallon WM. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 2001;86(8):3555-61
12. Hirbe A, Morgan EA. Skeletal complication of breast cancer therapies. Clin Cancer Res 2006;12(Suppl 20):6309-14
13. Kanis JA, McCloskey EV, Powles T, et al. A high incidence of vertebral fracture in women with breast cancer. Br J Cancer 1999;79:1179-81
14. Chen Z, Maricic M, Bassford TL, et al. Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study. Arch Intern Med 2005;165:552-8
15. Saarto T, Blomqvist C, Valimaki M, et al. Chemical castration induced by adjuvant cyclophosphoamide, methotrexate, and fluorouracil chemotherapy causesrapid bone loss that is reduced by clodronate: a randomized study in premenopuasal breast cancer patients. J Clin Oncol 1997;15:1341-7
16. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. J Clin Oncol 2001;19:3306-11
17. Vehmanen L, Saarto T, Elomaa I, et al. Long term impact of chemotherapy induced ovarian failure on bone mineral density (BMD) in premenopausal breast

cancer patients. The effect of adjuvant clodronate treatment. Eur J Cancer 2001;37:2373-8

18. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial and ARNO 95 trial. Lancet 2005;366:455-62
19. Gnant M, Milneritsch B, Luschin-Ebengreuth G, et al. 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 2008;9:840-9
20. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor positive breast cancer: status report 2004. J Clin Oncol 2005;23:619-29
21. Osborne C, Tripathy D. Aromatase inhibitors: rationale and use in breast cancer. Ann Rev Med 2005;56:103-16
22. Riggs BL, Khosla S, Melton LJ. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev 2002;23:279-302
23. Mincey BA, Duh MS, Thomas SK, et al. Risk of cancer treatment associated bone loss and fractures among women with breast cancer receiving aromatase inhibitors. Clin Breast Cancer 2006;7:127-32
24. Carney JF, Davis J. Emerging bone health issues in women with breast cancer in Hawai'i. Hawaii Med J 2007;66:164-66
25. Coleman RE, Banks LM, Girgis SI, et al. 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 2007;8:119-27
26. Perez EA, Josse RG, Pritchard KI, et al. Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study of NCIC CTG MA.17. J Clin Oncol 2006;24:3629-35
27. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole induced bone loss in postmenopausal women with early breast cancer. J Clin Oncol 2007;25:829-36
28. Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-years results from the Arimidex, Tamoxifen, alone or in combination (ATAC) trial 18233230. J Clin Oncol 2008;26:1051-7
29. Eastell R, Hannon RA, Cuzick J, et al. Effect of an aromatase inhibitor on BMD and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen Alone or in combination (ATAC) trial. J Bone Miner Res 2006;21:1215-23
30. Gnant MFX, Milneritsch B, Luschin-Ebengreuth G, et al. 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 2007;25:820-8
31. Lonning PE, Geisler J, Krag LE, et al. 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 2005;23:5126-37
32. Reid IR, Brown JP, Burckhardt P, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med 2002;346:653-61
33. Warming L, Hassager C, Christiansen C. Changes in bone mineral density with age in men and women: a longitudinal study. Osteoporos Int 2002;13:105-12
34. Lindsey R, Christiansen C, Einhorn TA. Consensus development statement: who are candidates for prevention and treatment for osteoporosis? Osteoporos Int 1997;7:1-6
35. Coleman R, Banks LM, Hall E, et al. Intergroup Exemestane study: 1-year results of the bone subprotocol [abstract]. Breast Cancer Res Treat 2005;87:S35
36. Gonnelli S, Cadirni A, Caffarelli C, et al. Changes in bone turnover and in bone mass in women with breast cancer switched from tamoxifen to exemestane. Bone 2007;40:205-20
37. Heshmati HM, Khosla S, Robins SP, et al. Role of low levels of endogenous estrogen in regulation of bone resorption in late menopausal woman. J Bone Miner Res 2002;17:172-7
38. Banerjee S, Smith IE, Folkerd L, et al. Comparative effects of anatsrozole, tamoxifen alone and in combination on plasama lipids and bone-derived resorption during neoadjuvant therapy in the impact trial. Ann Oncol 2005;16:1632-8
39. Coleman RE, Body JJ, Gralow JR, Lipton A. Bone loss in patients with breast cancer receiving aromatase inhibitors and associated treatment strategies. Cancer Treat Rev 2008;34:S31-42
40. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081-92
41. Kristensen B, Ejlertsen B, Mouridsen HT, et al. Bisphosphonate treatment in primary breast cancer: results from a randomised comparison of oral pamidronate versus no pamidronate in patients with primary breast cancer. Acta Oncol 2008;47(4):740-6
42. Howell A, Cuzick J, Baum M, et al. Results of the ATAC trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60-2
43. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozol and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353:2747-57
44. Forbes JF, Cuzick J, Buzdar A, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 2008;9:45-53
45. Saad F, Adachi JD, Brown JP, et al. Cancer treatment induced bone loss in breast and prostate cancer. J Clin Oncol 2008;26:5465-76
46. Higano CS. Understanding treatments for bone loss and bone metastasis in patients with prostate cancer: a practical review and guide for the clinician. Urol Clin North Am 2004;31:331
47. Morote J, Orsola A, Abascal JM, et al. Bone mineral density changes in patients with prostate cancer durino the first 2 years of androgen suppression. J Urol 2006;175:1679-83
48. Greenspan SL, Coates P, Sereika SM, et al. Bone loss after initiation of androgen

deprivation therapy in patients with prostate cancer. J Clin Endocrinol Metab 2005;90:6410-17

49. Sieber PR, Keiler DL, Kahnoski RJ, et al. Bicalutamide 150 mg maintains bone mineral density during monotherapy for localized or locally advanced prostate cancer. J Urol 2004;171:2272-6

50. Smith MR, Goode M, Zietman AL, et al. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Oncol 2004;22:2546-53

51. Bergstrom I, Gustafsson H, Sjoberg K, et al. Changes in bone mineral density differ between gonadotropin releasing hormone analogue and surgically castrated men with prostate cancer: a prospective controlled, parallel group study. Scand J Urol Nephrol 2004;38:148-52

52. Higano C, Sheilds A, Wood N, et al. Bone mineral density in patients with prostate cancer without bone metastasis treated with intermittent androgen suppression. Urology 2004;64:1182-6

53. Miyaji Y, Saika T, Yamamoto Y, et al. Effects of gonadotropin releasing hormone agonists on bone metabolism markers and bone mineral density in patients with prostate cancer. Urology 2004;64:128-31

54. Prerston DM, Torrens JI, Harding P, et al. Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. Prostate Cancer Prostatic Dis 2002;5:304-10

55. Berruti A, Dogliotti L, Terrone C, et al. Changes in bone mineral density, lean body mass and fat contenta s measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastasis given androgen deptivation therapy. J Urol 2002;167:2361-7

56. Mittan D, Lee S, Miller E, et al. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. J Clin Endocrinol Metab 2002;87:3656-61

57. Daniell HW, Dunn SR, Ferguson DW, et al. Progressive osteoporosis during androgen deprivation therapy for prostate cancer. J Urol 2000;163:181-6

58. Maillefert JF, Sibilia J, Michel F, et al. Bone mienral density in men treated with synthetic gonadotropin releasing hormone agonists for prostatic carcinoma. J Urol 1999;161:1219-22

59. Eriksson S, Eriksson A, Stege R, et al. Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens. Calcif Tissue Int 1995;57:97-9

60. Hoff AO, Gagel RF. Osteoporosis in breast and prostate cancer survivors. Oncology 2005;19:651-8

61. Stoch SA, Parker RA, Chen L, et al. Bone loss in men with prostate cancer treated with gonadotropin releasing hormone agonists. J Clin Endocrinol Metab 2001;86:2787-91

62. Kiratli BJ, Srinivas S, Perkash I, et al. Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer. Urology 2001;57:127-32

63. Wei JT, Gross M, Jaffe CA, et al. Androgen deprivation therapy for prostate cancer results in significant loss of bnone density. Urology 1999;54:607-11

64. Oefelein MG, Ricchiuti V, Conrad W, et al. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. J Urol 2002;168:1005-7

65. Abrahamsen B, Nielsen MF, Eskildsen P, et al. Fracture risk in Danish men with prostate cancer: a nationwide register study. BJU Int 2007;100:749-54

66. Smith MR, Boyce SP, Moyneur E, et al. Risk of clinical fractures after gonadotropin releasing hormone agonist therapy for prostate cancer. J Urol 2006;175:136-9

67. Eastham JA. Bone health in men receiving androgen deprivation therapy for prostate cancer. J Urol 2007;177:17-24

68. Smith MR, Lee WC, Brandman J, et al. Gonadotropin releasing hormone agonists and fracture risk: a claims based cohort study of men with non metastatic prostate cancer. J Clin Oncol 2005;23:7897-903

69. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002;359:1929-36

70. Seeman E, Delmas PD. Bone quality-the material and structural basis of bone strength and fragility. N Eng J Med 2006;354:2250-61

71. Body JJ, Bergmann P, Boonen S, et al. Management of cancer treatment induced bone loss in early breast and prostate cancer- a consensus paper of the Belgian Bone Club. Osteoporos Int 2007;18:1439-50

- **Focus on a new approach and on a new way of management of CTIBL.**

72. Reid DM, Doughty J, Eastell R, et al. Guidance for the management of the breast cancer induced bone loss: a consensus position statement from a UK expert group. Cancer Tret Rev 2008;34:S3-18

- **Focus on a new approach and on a new way of management of CTIBL.**

73. Hadji P, Body JJ, Aapro MS, et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. Ann Oncol 2008;19:1407-16

- **These three articles are of particular interest because they focus on a new approach and on a new way of management of CTIBL.**

74. Kanis JA, Burlet N, Cooper C, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2008;19:399-428

75. Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003;21:4042-57

76. Diamond TH, Higano CS, Smith MR, et al. Osteoporosis in men with prostate carcinoma receiving androgen deprivation therapy: recommendations for diagnosis and therapies. Cancer 2004;100:892-99

77. Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen deprivation therapy for prostate cancer. N Engl J Med 2009;361:745-55

78. Black DM, Delmas PD, Eatsell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22

79. Graham R, Russell G, Espina B, Hulley P. Bone biology and the pathogenesis of osteoporosis. Curr Opin Rheumatol 2006;18(Suppl 1):S3-S10

80. Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodelling. J Bone Miner Res 2005;20:177-84

81. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1 – 34) on fractures and bone mineral density in

postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41

82. Meunier PJ, Slosman DO, Delmas PD, et al. Strontium ranelate: dose-dependent effects in estabilished postmenopausal vertebral osteoporosis: a 2-year randomized placebo controlled trial. J Clin Endocrinol Metab 2002;87:2060-6

83. Hamdy NA. Strontium ranelate improves bone microarchitecture in osteoporosis. Rheumatology 2009;48:9-13

84. Schneider A, Kalikin LM, Mattos AC, et al. Bone turnover mediates preferential localization of prostate cancer in the skeleton. Endocrinology 2005;146 (4):1727-36

85. Perez EA, Serene M, Durling FC, Weilbacher K. Aromatase inhibitors and bone loss. Oncology 2006;20(9):1029-48

86. Saarto T, Blomqvist C, Valimaki M, et al. Clodronate improves bone mineral density in post-menopausal breast cancer patients treated with adjuvant antioestrogens. Br J Cancer 1997;75:602-5

87. Vehmanen L, Saarto T, Risteli J, et al. Short-term intermittent intravenous clodronate in the prevention of bone loss related to chemotherapy-induced ovarian failure. Breast Cancer Res Treat 2004;87:181-8

88. Delmas PD, Balena R, Confraveux E, et al. Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double blind, placebo controlled study. J Clin Oncol 1997;15:955-62

89. Eastell R, Van Poznak CH, Hannon RA, et al. The SABRE (Study of Anastrozole with the Bisphosphonate RisedronatE) study: 12 month analysis. J Bone Miner Res 2007;22(Suppl 1):S113

90. Van Poznak CH, Hannon RA, Clack G, et al. Markers of bone metabolism in postmenopausal women with hormone receptor positive early breast cancer [abstract 156]: SABRE. Presented at 2007 ASCO breast cancer symposium; 7 – 8 September 2007; San Francisco, CA, USA

91. Greenspan SL, Brufky A, Lembersky BC, et al. Risedronate prevents bone loss in breast cancer survivors: a 2-year, randomized, double-blind, placebo-controlled clinical trial. J Clin Oncol 2008;26:2644-52

92. Hines SL, Mincey BA, Sloan JA, et al. Phase III randomized, placebo-controlled, double-blind trial of risedronate for the prevention of bone loss in premenopuasal women undergoing chemotherapy for primary breast cancer. J Clin Oncol 2008;27:1047-53

93. Sawka AM, Ioannidis G, Papaioannou A, et al. Are oral bisphosphonates effective inimproving lumbar bone mineral density in breast cancer survivors with osetopenia or osteoporosis? J Obstet Gynaecol Can 2005;27:759-64

94. Lester JE, Dodwell D, Purohit OP, et al. Prevention of anastrozole induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. Clin Cancer Res 2008;14(19):6336-42

95. Brufsky A, Bossermann L, Caradonna R, et al. The effect of zoledronic acid on aromatase inhibitor associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: the Z-FAST study 36-month follow-up. Breast Cancer Res Treat 2007;106:27

96. Bundred NJ, Campbell ID, Davidson N, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST study results. Cancer 2008;112:1001-10

97. De Boer R, Editmann H, Lluch A, et al. 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 2007;(Suppl 1):106:501

98. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. Ann Intern Med 2007;146(6):416-24

99. Ishizaka K, Machida T, Kobayashi S, et al. Preventive effect of risedronate on bone loss in men receiving androgen-deprivation therapy for prostate cancer. Int J Urol 2007;14:1071-5

100. Izumi K, Mizokami A, Sugimoto K, et al. Risedronate recovers bone loss in patients with prostate cancer undergoing androgen deprivation therapy. Urology 2009;73:1342-6

101. Diamond TH, Winters J, Smith A, et al. The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade. A double-blind, randomized, placebo-controlled crossover study. Cancer 2001;92(6):1444-50

102. Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen deprivation therapy for prostate cancer. N Engl J Med 2001;345:948-55

103. Israeli RS, Rosenberg SJ, Saltzstein DR, et al. The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy. Clin Genitourin Cancer 2007;5(4):271-7

104. Bhoopalam N, Campbell SC, Moritz T, et al. Intravenous zolerdronic acid to prevent osteoporosis in a veteran population with multiple risk factors for bone loss on androgen deprivation therapy. J Urol 2009;182:2257-64

105. Michaelson MD, Kaufman DS, Lee H, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin releasing hormone agonist induced bone loss in men with prostate cancer. J Clin Oncol 2007;25:1038-42

106. Ryan CW, Huo D, Bylow K, et al. Suppression of bone density loss and bone turnover in patients with hormone sensitive prostate cancer and receiving zoledronic acid. BJU Int 2007;100:70-5

107. Ryan CW, Huo D, Demers LM, et al. Zoledronic acid initiated during the first year of androgen deprivation therapy increases bone mineral density in patients with prostate cancer. J Urol 2006;176:972-8

108. Casey R. Zoledronic acid reduces bone loss in men with prostate cancer receiving goserelin: 12-month results. Presented at the American Society of Clinical Oncology Prostate Cancer Symposium; 22 – 24, February 2007; Orlando, FL, USA

109. Smith MR, Eastham J, Gleason DM, et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol 2003;169:2008-12

110. Burgess TL, Qian Y, Kaufman S, et al. The ligand for osteoprotegerin (OPG) directly activates mature osteoclasts. J Cell Biol 1999;145:527-38

111. Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998;93:165-76

112. Yasuda H, Shima N, Nakagawa N, et al. Osteoclast differentiation factor is ligand for osteoprotegerin/osteoclastogenesis inhibitory factor and is identical to TRANCE/RANKL. Proc Natl Acad Sci USA 1998;95:3597-602

113. Ellis G, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol 2008;26:4875-82

114. Ellis G, Bone HG, Chlebowski R, et al. Effect of denosumab in 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 2009; doi: 10.1007/s10549-009-0352-y

115. Ettinger B, Black DM, Mitlack BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. J Am Med Assoc 1999;282:637-45

116. Siris ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after 8 years: results from the Continuing Outcomes Relevant to Evista (CORE) study. J Bone Miner Res 2005;20:1514-24

117. Lee WL, Chao HT, Cheng MH, Wang PH. Rationale for using raloxifene to prevent both osteoporosis and breast cancer in postmenopausal women. Maturitas 2008;60:92-107

118. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: 4-year results from a randomized clinical trial. J Clin Endocrinol Metab 2002;87:3609-17

119. Barrett-Connor E. raloxifene use for the heart (RUTH) trial investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006;355:125-37

120. Mithal A, Wahl DA, Bonjour JP, et al.; IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. Global vitamin D status and determinants of hypovitaminosis D. Osteoporosis Int 2009;20(11):1807-20

121. Adami S, Bertoldo F, Braga V, et al. 25-hydroxy vitamin D levels in healthy premenopausal women: association with bone turnover markers and bone mineral density. Bone 2009;45:423-6

122. Glover S, Gall M, Schoenborn-Kellenberger O, et al. Establishing a reference interval for bone turnover markers in 637 healthy young, pre-menopausal women from UK, France, Belgium and the USA. J Bone Miner Res 2009;24:389-97

123. Holick MF. The vitamin D deficiency pandemic and consequences for nonskeletal health: mechanism of action. Mol Aspects Med 2008;19(6):361-8

124. Crew KD, Shane E, Cremers S, et al. High prevalence of vitamin D deficiency despite supplementation in premenopausal women with breast cancer undergoing adjuvant chemotherapy. J Clin Oncol 2009;27:2151-6

125. Li H, Stampfer MJ, Hollis JB, et al. A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms and prostate cancer. PLoS Med 2007;4(3):e103

126. Peterlik M, Grant WB, Cross HS, et al. Calcium, vitamin D and cancer. Anticancer Res 2009;29:3687-98

127. Chen P, Hu P, Xie D, et al. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat 2009; doi 10.1007/s10549-009-0593-9

128. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81

129. Yin L, Raum E, Haug U, et al. Meta-analysis of longitudinal studies: serum vitamin D and prostate cancer risk. Cancer Epidemiol 2009;33:435-45

130. Kawahara M, Iwasaki Y, Sakaguchi K, et al. Predominant role of 25(OH)D in the negative regulation of PTH expression: clinical relevance for hypovitaminosis D. Life Sci 2008;82:677-83

131. Adami S, Giannini S, Bianchi G, et al. Vitamin D status and response to treatment in post-menopausal osteoporosis. Osteoporos Int 2009;20(2):239-44

132. Berruti A, Tucci M, Generali D, et al. Management of the side-effects of intravenous bisphosphonates: targeting the serum parathyroid hormone elevation. Ann Oncol 2006;17(12):1854-55

133. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency. A meta analysis of randomized controlled trials. Arch Intern Med 2009;169:551-61

134. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, et al. Benefit-risk assessment of vitamin D supplementation. Osteoporos Int 2009; doi: 10.1007/s00198-009-1119-3

135. Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? J Steroid Biochem Mol Biol 2004;89-90:611-14

136. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy Press. Washington, DC, USA; 2000

137. Amir E, Simmons CE, Freedman OC, et al. A phase 2 trial exploring the effects of high-dose (10000 IU/day) vitamin D3 in breast cancer patients with bone metastases. Cancer 2009; doi: 10.1002/cncr.24749

138. Seeman E, Compston J, Adachi J, et al. Non-compliance: the Achilles' heel of antifracture efficacy. Osteoporos Int 2007;18:711-19

139. Gallagher A, Rietbrock S, Olson M, et al. Fracture outcomes related to persistence and compliance with oral bisphosphoantes. J Bone Miner Res 2008;23:1569-75

140. Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphopshonates therapy and fracture rates in osteoporotic women: relationship to vertebral and non vertebral fractures from 2 US claims database. Mayo Clin Proc 2006;81:1013-22

141. Forbes JF, Cizick J, Buzxdar A, et al. Effects of anastrozole and tamoxifene as adjuvant treatment for early-stage breast cancer: 100 month analysis of the ATRAC trial. Lancet Oncol 2008;9:45-53

142. Burkiewicz JS, Scarpace SL, Bruce SP. Denosumab in osteoporosis and oncology. Ann Pharmacother 2009;43:1445-55

143. Bertoldo F, Tonini G, Vincenzi B. Medical oncology: zoledronic acid prevents bone loss in early stage breat cancer. Nat Rev Clin Oncol 2009;6:192-2

144. Gnant MF, Milneritsch B, Luschin-Ebengreuth G, et al. Zoledronic acid effectively 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 2007;25:820-8

145. Brufsky A, Lund K, Cobb P, et al. Twenty-four month follow-up of the effect of zoledronic acid (ZA) on aromatase innibitor associated bone loss (AIBL) in postmenopausal women (PMW) with early breast cancer (EBC) receiving adjuvant letrozole (LET) [abstract 5060]. Breast Cancer Res Treat 2006;100(Suppl 1):S233

146. Bertoldo F, Pancheri S, Zenari S, et al. Serum 25(OH)D modulate the acute phase response associated to the first nitrogen containing bisphophonate infusion. J Bone Miner Res 2009, doi: 10.1359/jbmr.090819

147. Khosla S. Bisphosphonates-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. ASBMR Task Force on Bisphosphonate-Associated ONJ. J Bone Miner Res 2007;22(10):1479-91

148. Grbic JT, Landesberg R, Lin SQ, et al. Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in the health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial. J Am Dent Assoc 2008;139(1):32-40

149. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22

150. Mak A, Cheung MWL, Chun-Man Ho R, et al. Bisphosphonates and atrial fibrillation: Bayesan metanalysis of randomized and observational studies. BMC Muscoloskelet Disord 2009;10:113

151. Taylor KH, Middlefell LS, Mizen KD. Osteonecrosis of the jaws induced by anti-RANK ligand therapy. Br J Maxillofac Surg 2009; doi: 10-1016/j.bjoms.2009.08.030

152. Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture fracture risk in postmenopausal women with osteoporosis: results from a 3 year, randomized, placebo and active controlled clinical trial. J Bone Miner Res 2008;23(12):1923-34

153. Gallagher JC, Lindsay R, Dietrich J, et al. Smart trials: effects of a tissue selective estrogen complex (TSEC) comprised of bazedoxifene (BZA) and conjugated estrogens (CEs) on bone mineral density (BMD) in postmenopausal women. Fertil Steril 2007;88:S241

154. Lindsay R, Ronkin S, Constantine G, et al. A double-blind, placebo-controlled, phase 3 study of bazedoxifene/conjugated estrogens in postmenopausal women: effects on BMD. Presented at ENDO; June 4 2007; Toronto

155. Cummings SR, Eastell R, Ensrud K, et al. The effects of lasofoxifene on fractures and breast cancer: 3-year results from the PEARL trial. J Bone Miner Res 2008;23(Suppl 1):S81

156. Bolognese M, Krege JH, Utian WH, et al. Effects of arzoxifene on bone mineral density and endometrium in postmenopausal women with normal or low bone mass. J Clin Endocrinol Metab 2009;94(7):2284-9

157. Smith MR, Malkowicz SB, Chu F, et al. Toremifene increases bone mineral density in men receiving androgen deprivation therapy for prostate cancer: interim analysis of a multicenter phase III clinical study. J Urol 2008;179:152-5

158. Adami S, Supronik J, Hala T, et al. Effect of one year treatment with the cathepsin-K inhibitor, balicatib, on bone mineral density in postmenopausal women with osteopenia/osteoporosis. J Bone M iner Res 2006;21(Suppl 1):S24

159. Deal C. Future therapeutic targets in osteoporosis. Curr Opin Rheumatol 2009;21:380-5

160. McClung M, Bone H, Cosman F, et al. A randomized, double-blind, placebo-controlled study of odanacatib (MK-822) in the treatment of postmenopausal women with low bone mineral density: 24-month results. J Bone Miner Res 2008;23:S82

161. Padhi D, Stouch B, Fang L, et al. Antisclerostin antibody increases markers of bone formation in healthy postmenopuasal women. J Bone Miner Metab 2007;22(Suppl 1):S37

162. Voorzanger-Rousselot N, Journe F, Doriate V, et al. Assessment of circulating Dikkopf-1 with a new two-site immunoassay in healthy subjects and women with breast cancer and bone metastases. Calcif Tissue Int 2009;84(5):348-54

163. Agrawal A, Hannon RA, Cheung KL, et al. Bone turnover markers in postmenopausal breast cancer treated with fulvestrant. A pilot study. Breast 2009;18:204-7

164. Russell RG, Rogers MJ. Bisphosphonates: from the laboratory to the clinic and back again. Bone 1999;25:97-106

165. Coleman RE. Adjuvant bisphosphonates in breast cancer: are we witnessing the emergence of a new therapeutic strategy? Eur J Cancer 2009;45(11):1909-15

166. Monkkonen H, Auriola S, Lehenkari P, et al. A new endogenous ATP analog (ApppI) inhibits the mitochondrial adenine nucleotide translocase (ANT) and is responsible for the apoptosis induced by nitrogen containing bisphosphonates. Br J Pharmacol 2006;144:437-45

167. Woodward J, Coleman RE, Holen I. Preclinical evidence for the effect of cisphosphonates and cytotoxic drugs on tumor cell invasion. Anticancer Drugs 2005;16:11-9

168. Chen D, Zhao M, Mundy GR. Bone morphogenetic proteins. Growth Factors 2004;22:233-41

169. Chung U-ki, Schipani E, McMahno AP, Kronanberg HM. Indian hedgehog couples chondrogenesis to osteogenesis in endochondral bone development. J Clin Invest 2001;107:295-304

170. Long F, Chung U-I, Ohba S, et al. Ihh signalling is directly required for the osteoblast lineage in the endochondral skeleton. Development 2004;131:1309-18

171. Wan M, Cao X. BMP signaling in skeletal development. Biochem Biophys Res Commun 2005;328:651-7

172. Baron R, Rawadi G. Minireview: targeting the WNT/beta-catenin pathway to regulate bone formation in the adult skeleton. Endocrinology 2007;148(6):2635-43

173. Faslodex (fulvestrant). AstraZeneca Pharmaceuticals LP; Wilmington, DE, USA; 2004

174. Lea CK, Flanagan AM. Ovarian androgens protect against bone loss in rats made oestrogen deficient by treatment with ICI 182,780. J Endocrinol 1999;160:11-7

175. Mundy GR, Yoneda T, Hiraga T, et al. Preclinical studies with zoledronic acid and other bishosphonates: impact on the bone microenvironment. Semin Oncol 2001;28:35-44

176. Li A, Park J, Melisko M. Zledronic acid as adjuvant therapy for women with early stage breast cancer and occult tumor cells

in bone marrow. Cancer Res 2007:68: abstract 510

177. Rack B, Schindelbeck C, Strobol B, et al. Efficacy of zoledronate in treating persiting isolate tumor cells in bone marrow in patients with breast cancer. A phase II pilot study. Dtsch Med Wochenschr 2008;13(7):285-9

178. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopuasal breast cancer. N Engl J Med 2009;360(7):679-91

179. Freedman OC, Amir E, Clemons MJ. Adjuvant bisphosphonate therapy for breast cancer patients: standard of care or future direction? Crit Rev Oncol Hematol 2009;72(1):56-64

180. Logman F, Heeg B, Botteman M, et al. Cost effectiveness of zoledronic acid in the prevention of fractures in postmenopausal women with early breast cancer receiving aromatase inhibitors: application to the United Kingdom [abstract 1146]. 14th European Cancer Conference (ECCO); September 23 – 27 2007; Barcellona, Spain

Affiliation

Francesco Bertoldo MD, Serena Pancheri[†] MD, Sonia Zenari MD & Stefania Boldini MD
[†]Author for correspondence
Department of Biomedical and Surgical Sciences,
University of Verona,
Verona, Italy
Tel: +39 045 8124262;
Fax: +39 045 8027496;
E-mail: serenapancheri@virgilio.it