The Breast 37 (2018) 28–35

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Therapeutic approaches for protecting bone health in patients with breast cancer

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ARTICLE INFO

Article history:
Received 23 August 2017
Received in revised form
12 October 2017
Accepted 13 October 2017
Available online 23 October 2017

Keywords:
Bone metastasis
Bisphosphonate
Breast cancer
Cancer treatment-induced bone loss
Denosumab
Zoledronic acid

ABSTRACT

Improvements in the survival of patients with breast cancer, together with a better understanding of the pathology of the disease, have led to the emergence of bone health as a key aspect of patient management. Patients with breast cancer are typically at risk of skeletal complications throughout their disease course. The receptor activator of nuclear factor κ B ligand (RANKL) inhibitor denosumab and bisphosphonates (e.g. zoledronic acid) are approved in Europe for the prevention of skeletal-related events (pathologic fracture, radiation or surgery to bone, and spinal cord compression) in adults with bone metastases secondary to solid tumours. These agents are also approved at lower doses for the treatment of patients with postmenopausal osteoporosis, a population largely overlapping with those in the early stages of breast cancer, and those with cancer treatment-induced bone loss, which is caused primarily by aromatase inhibitors. In this review, we consider the evidence supporting the use of therapeutic agents to protect bone health throughout the course of breast cancer. Timing of treatment initiation, dose and treatment duration may prove to be barriers to the optimization of the practical use of these agents in the management of patients with breast cancer. Furthermore, with longer survival times, patients may expect to receive long-term treatment with denosumab or bisphosphonates, therefore consideration must be given to safety. Thus, we aim to summarize the recommendations for the use of these agents in management of patients with breast cancer in Europe. We also discuss the recent evidence for their potential antineoplastic effects.

Contents

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https://doi.org/10.1016/j.breast.2017.10.007
0960-9776/

1. Introduction

Survival for patients with breast cancer in Europe has improved substantially over the past three decades. Between 1989 and 1999, 5-year age-adjusted relative survival increased from 74% to 83% [1], and 5-year survival reached 82% for patients in whom breast cancer was diagnosed between 2000 and 2007 [2]. Recent age-standardized data from the United Kingdom predict 5-year survival of 86.6% for patients diagnosed between 2010 and 2011 [3]. Current levels of expectation for survival are due, in part, to the establishment of European breast cancer screening programmes and improved treatment options [4]. With increased survival comes a greater requirement for the long-term holistic care of patients than ever before [5].

Clinical experience of the long-term management of breast cancer has led to an appreciation of the importance of bone health throughout the disease course. The mean age at breast cancer diagnosis is 62 years [6], and because most patients are perimenopausal or postmenopausal women, they may already have experienced some osteopenic or osteoporotic bone loss. With the onset of menopause, declining oestrogen levels lead to a gradual decrease in bone mineral density (BMD) over time, with the potential for the development of postmenopausal osteoporosis [7]. A decrease in BMD may be exacerbated by the bone-destabilizing effects of certain cancer treatments used in early breast cancer, such as aromatase inhibitors, which can induce a menopause-equivalent state by reducing oestrogen levels, and some chemotherapies. This phenomenon is known as cancer treatment-induced bone loss (CTIBL) [8]. The rate of bone loss in women with breast cancer receiving aromatase inhibitors is at least twice that observed in healthy postmenopausal women [9]. In addition, more than 60% of women initiating chemotherapy are expected to experience ovarian failure within 1 year [10], which is associated with further significant and rapid declines in BMD [11]. Reductions in BMD cause skeletal weakening and increase the risk of pathologic fracture; indeed, the 3-year risk of vertebral fracture is almost fivefold greater in women with newly diagnosed breast cancer than in women in the general population [12]. It is important to note that, even in individuals with normal BMD, the risk of fracture in patients with breast cancer is high. For example, in the placebo arm of the Austrian Breast and Colorectal Cancer Study Group-18 (ABCSG-18) trial in postmenopausal women with early-stage breast cancer, the incidence of pathologic fracture was 10% in individuals with normal BMD and 11% in those with low BMD [13].

Osteoporosis can be treated with low doses of the receptor activator of nuclear factor κ B ligand (RANKL) inhibitor denosumab (60 mg subcutaneously [SC] every 6 months) [14,15] or with bisphosphonates, the most commonly used being zoledronic acid (5 mg intravenously [IV] once per year) [16]. Denosumab offers concurrent benefit to women at risk of CTIBL in the early, hormone-receptor-positive (HR+) stages of breast cancer because these patients are considered at risk for osteoporosis. Evidence suggests that adjuvant use of low-dose denosumab in patients with HR+ breast cancer [13] or adjuvant zoledronic acid in early breast cancer [13,17,18] may positively impact on outcomes in certain populations, although this is not currently reflected in product indications. Disturbances in bone metabolism can be caused by the underlying pathology of the cancer or by bone metastases, and may result in some patients developing hypercalcaemia of malignancy, which is associated with a poor prognosis [19]. With some regional variation, denosumab and zoledronic acid are also approved for the treatment of hypercalcaemia of malignancy [20–22].

As breast cancer progresses, the risk of developing bone metastases increases. For patients with aggressive breast cancer, distant metastases can occur during the 3 years after diagnosis of the primary cancer; however, many patients develop distant metastases as much as 10 years after their initial diagnosis [23]. In Western women with breast cancer, metastases at distant sites are a more common cause of death than the primary tumour itself [23]. Bone is one of the most common sites of metastases from breast cancer, with an incidence of approximately 70% [23,24]. Bone metastases cause complications, commonly referred to as skeletal-related events (SREs; pathologic fracture, spinal cord compression, and radiation or surgery to bone) and are associated with substantial pain and reduced survival [25].

An improved understanding of the importance of bone health in patients with breast cancer has brought about changes in the clinical management of these individuals. For those with breast cancer and bone metastases, denosumab (120 mg SC every 4 weeks) [26] and zoledronic acid (4 mg IV every 3–4 weeks) [21] can prevent SREs [27,28] and offer improvements in quality of life [29,30]. Better detection of bone metastases as a result of improved diagnostic techniques and monitoring [31], and heightened patient awareness through channels such as patient advocacy websites [32], are facilitating earlier intervention with these agents. In this review, we aim to consolidate the latest understanding on the use of denosumab and bisphosphonates for protecting skeletal health in women with breast cancer at all stages of their disease.

2. Early breast cancer

Skeletal weakening due to CTIBL and postmenopausal osteoporosis, as well as the potential for subsequent increases in pathologic fracture risk, are major concerns for patients with early breast cancer. Aromatase inhibitors are routinely used in the adjuvant treatment of HR+ early breast cancer in postmenopausal women; however, through the induction of oestrogen deficiency, the agents can cause a negative bone balance, with increased markers of bone resorption, as well as decreased BMD and increased fracture risk [8]. This has been demonstrated in a prospective substudy of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which had previously demonstrated clinical superiority of the aromatase inhibitor anastrozole over tamoxifen in postmenopausal women with breast cancer [33]. In the substudy, long-term use of anastrozole resulted in median BMD losses from baseline of 6.1% at the lumbar spine and 7.2% from the total hip after 5 years [34]. Increases of 2.8% and 0.7% at the lumbar spine and total hip, respectively, were observed with tamoxifen [34]. Accordingly, the incidence of fractures was significantly lower in those who received tamoxifen than in those prescribed anastrozole (4.4% vs. 7.1%; $p < 0.001$). Although aromatase inhibitors are a common cause of CTIBL, reductions in BMD may also result from treatment with certain chemotherapies, by means of upregulated bone resorption. Drugs likely to produce this effect include taxanes, doxorubicin, 5-fluorouracil, cyclophosphamide, methotrexate and cisplatin [8].

Low-dose denosumab (60 mg SC every 6 months) has been shown to increase BMD compared with placebo at multiple skeletal sites in women with HR+ breast cancer receiving adjuvant aromatase inhibitors [35]. The ABCSG-18 randomized, double-blind, placebo-controlled, phase III trial of denosumab in postmenopausal women with early HR+ breast cancer receiving aromatase inhibitors reported a significantly delayed time to first clinical fracture ($p < 0.0001$) and also significant relative increases in BMD at the lumbar spine, total hip and femoral neck compared with placebo ($p < 0.0001$) [13]. In the Zoledronic Acid – Letrozole Adjuvant Synergy Trial (Z-FAST), treatment with low-dose zoledronic acid (4 mg IV every 6 months) in patients with HR+ early breast cancer receiving letrozole resulted in significant increases from baseline in total hip BMD (+8.9% with upfront treatment; +6.7% with delayed treatment) [36]. Similarly, in the NC03CC (Alliance) randomized, open-label, phase III clinical trial of patients receiving letrozole, a gain in BMD at the total lumbar spine was observed in patients who received upfront zoledronic acid, whereas BMD loss was observed in the delayed treatment arm (+0.58 vs. −0.24, respectively; $p < 0.001$, for change from baseline to 5 years) [37]. Similar patterns were observed for BMD at the femoral neck and total hip [37].

It is well established that fracture risk is reduced in patients with early breast cancer treated with denosumab or bisphosphonates. A meta-analysis of data from postmenopausal women receiving aromatase inhibitors for the treatment of early breast cancer revealed that immediate treatment with denosumab significantly decreased the risk of fractures compared with delayed treatment. There was, however, no decrease in fracture risk when immediate treatment with zoledronic acid was compared with delayed zoledronic acid treatment [38]. Regarding the use of bisphosphonates, in the phase III, randomized, open-label AZURE (does Adjuvant Zoledronate redUce REcurrence in early breast cancer? [BIG 01/04]) trial of adjuvant zoledronic acid in women with stage II or III breast cancer, the study did not meet the primary endpoint (disease-free survival [DFS]), but findings from secondary endpoints showed that the proportion of patients experiencing a pathologic fracture was significantly reduced in those who received zoledronic acid as an adjuvant to systemic treatment compared with those who received systemic treatment alone (6.2% vs. 8.3%; $p = 0.005$) [17]. The development of first and subsequent bone metastases was also significantly reduced in the zoledronic acid group compared with those receiving systemic treatment alone [17]. In a meta-analysis of 18,766 women (premenopausal and postmenopausal) with early breast cancer, conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), the proportion of women experiencing a fracture was significantly reduced in patients receiving bisphosphonates compared with those receiving control treatments (rate ratio: 0.85; 95% confidence interval [CI]: 0.75–0.97; $p = 0.02$) [39]. For the use of denosumab in patients with early breast cancer, the primary endpoint of the ABCSG-18 trial was met, demonstrating that denosumab significantly increased the time to first fracture compared with placebo in patients receiving aromatase inhibitors (hazard ratio [HR]: 0.50; 95% CI: 0.39–0.65; $p < 0.0001$) [13]. The overall cumulative incidence of first fractures in the denosumab group was almost half of that of the placebo group (92 vs. 176). The significant treatment effect of denosumab over placebo was observed in patients who were osteopenic and in individuals who had normal BMD at baseline [13].

In addition to fracture reduction, adjuvant low-dose bisphosphonates or denosumab may confer additional clinical benefit in patients with breast cancer, such as improvements in survival, although results from studies of adjuvant bisphosphonates (clodronate, ibandronate, pamidronate and zoledronic acid) have thus far been mixed [39]. In the large meta-analysis completed by the EBCTCG, significant reductions in breast cancer mortality were observed in postmenopausal women receiving bisphosphonates compared with those receiving control treatment (HR: 0.82; 95% CI: 0.73–0.93; $p = 0.002$). Disease recurrence and bone-specific disease recurrence were also significantly reduced in the bisphosphonate group compared with the control group [39]. For patients receiving endocrine therapy in the earlier ABCSG-12 study, the number of DFS events (primary endpoint) was significantly lower in the adjuvant zoledronic acid group than in the group who did not receive it (HR: 0.77; 95% CI: 0.60–0.99; $p = 0.042$). However, no significant improvements in overall survival (secondary endpoint) were observed when zoledronic acid was added to treatment [18]. In contrast, no improvements in DFS or overall survival were observed for patients receiving or not receiving zoledronic acid in the AZURE study [17]. However, in an exploratory analysis of a subgroup of women who had been postmenopausal for at least 5 years at the start of the study, zoledronic acid improved the rate of invasive DFS events (adjusted HR: 0.77; 95% CI: 0.63–0.96), although this result should be interpreted with caution [17]. Findings from a meta-analysis suggested that adjuvant oral clodronate may improve overall survival and metastasis-free survival compared with placebo in patients with early breast cancer [40].

For denosumab, adjuvant use improved DFS (secondary endpoint) in patients enrolled in the ABCSG-18 trial; however, this result was not statistically significantly different to that seen with placebo in the overall population ($p = 0.051$).

3. Advanced breast cancer

For patients with advanced breast cancer, bone metastases can lead to SREs that can be painful, debilitating and associated with a poor prognosis [41–43]. With breast cancer survival increasing [44], there is an increased probability that patients will experience a SRE. Data from the placebo arms of clinical trials show that patients with bone metastases may experience more than three SREs per year [45]. Furthermore, individuals who have had a SRE are at an increased risk of developing subsequent SREs [46]. Limited data exist on the impact of SREs on survival; however, a large population-based cohort study in Denmark found substantially lower rates of 5-year survival in patients with breast cancer and bone metastases with SREs (8.3%) than in those without SREs (75.8%) [43]. It is clear that SREs impose considerable burdens on patients and healthcare systems alike. High-dose denosumab (120 mg SC every 4 weeks) [26] and zoledronic acid (4 mg IV every 3–4 weeks) [21] are approved in Europe for the prevention of SREs in patients with bone metastases secondary to solid tumours and in individuals with advanced malignancies involving bone, respectively; the clinical evidence supporting these approvals in metastatic breast cancer is well documented [27,28].

Evidence indicates that preventing SREs can lead to improvements in health-related quality of life (HRQoL). In a 12-month randomized controlled trial, 1124 women receiving bisphosphonates for the prevention of SREs experienced an overall increase in HRQoL [30]. In a pooled analysis of three phase III randomized controlled trials in patients with advanced solid tumours ($n = 5544$), significantly fewer individuals receiving denosumab experienced clinically meaningful worsening of HRQoL than did those who were prescribed zoledronic acid ($p = 0.005$) [29]. In the same analysis, denosumab delayed the onset of moderate-to-severe pain by 17% compared with zoledronic acid ($p < 0.001$) [29].

Patients with advanced breast cancer may also be at risk of hypercalcaemia of malignancy, caused by disturbances in bone remodelling. Approximately 10–15% of patients with advanced

cancer may develop this potentially lethal complication [47]. High-dose denosumab (120 mg SC every 4 weeks, with a loading dose of 120 mg on days 8 and 15 of the first month of therapy) is approved for the treatment of hypercalcaemia of malignancy in patients who are refractory to intravenous bisphosphonates in the United States of America, Canada, Russia and Australia [20,22,48,49], and high-dose zoledronic acid (a single 4 mg IV dose) is indicated for patients in Europe [21].

4. Management of bone health in clinical practice: guideline recommendations

It is important that skeletal health is appropriately managed throughout the course of breast cancer. As demonstrated by the supporting clinical data above, denosumab or bisphosphonates can be beneficial to bone health at early and advanced stages of the disease; however, negotiating the various considerations associated with these agents, such as timing of treatment initiation, switching dose, duration of treatment and long-term safety, may prove to be a barrier to the optimization of their use in practice. In this section, we aim to summarize the recommendations for the use of denosumab or bisphosphonates in breast cancer management in Europe.

At the St Gallen International Expert Consensus Conference 2017, the panel members strongly recommended the use of bisphosphonates for the adjuvant treatment of postmenopausal women with breast cancer [50]. Low-dose denosumab or bisphosphonates may be used in the early stages of breast cancer to treat CTIBL; indeed, many women may already be receiving low-dose oral bisphosphonates [51–53], intravenous bisphosphonates [16,54] or denosumab [14] for the treatment of postmenopausal osteoporosis. As breast cancer progresses and metastasizes to bone, treatment may be switched to high doses of these agents to prevent SREs and to treat hypercalcaemia of malignancy. Several factors must be taken into account when considering the switch from low- to high-dose denosumab or bisphosphonates, and these are discussed below.

4.1. Protection against bone loss

Low BMD can affect patients in early and later stages of breast cancer, and predisposes individuals to an increased risk of pathologic fracture. The European Society for Medical Oncology (ESMO) clinical practice guidelines for bone health in patients with cancer advise that patients should be assessed for baseline fracture risk, and that BMD should be measured. Lifestyle changes, such as increasing the amount of weight-bearing exercise and stopping smoking, and dietary measures are recommended, which include ensuring adequate calcium intake (1000 mg/day) and vitamin D supplementation (total intake: 1000–2000 units/day) [55].

These guidelines, together with the ESMO guidelines developed specifically for patients with primary breast cancer, suggest that patients with early or advanced breast cancer at risk of CTIBL and those with low oestrogen status may receive prophylactic bisphosphonates [4]. Patients at risk of CTIBL are identified as those undergoing ovarian suppression and those receiving aromatase inhibitors; periodic BMD assessments are recommended for these individuals [4]. It should be noted, however, that bisphosphonates are not approved for use in this setting.

These recommendations are corroborated by a European consensus guideline, published in 2016, on the use of adjuvant bisphosphonates in patients with early breast cancer [56]. The expert panel advised that bisphosphonates should be considered as part of routine clinical practice for the prevention of CTIBL in all patients with a T-score of less than −2.0 or with two or more fracture risk factors [56]. The panel recommended low-dose intravenous zoledronic acid or oral clodronate [56], although neither agent is approved in Europe for this indication. Denosumab was not discussed at the consensus meeting and therefore does not feature in the guidance. Based on clinical evidence demonstrating a potential benefit in disease outcomes in postmenopausal women, the panel recommended adjuvant bisphosphonates for the prevention of metastases in women aged 55 years or older. For younger patients, adjuvant bisphosphonates were recommended for those who had not had a menstrual period for 12 months or longer, and in premenopausal women whose treatment included ovarian suppression [56].

4.2. Management of the consequences of bone metastases

As soon as bone metastases have been identified, treatment may be switched to higher doses of denosumab or bisphosphonates. The ESMO clinical practice guidelines for bone health in patients with cancer recommend that high-dose zoledronic acid or denosumab therapy should be initiated as soon as bone metastases have been diagnosed, regardless of whether or not there are symptoms such as pain [55]. The European School of Oncology (ESO)–ESMO international consensus guideline for advanced breast cancer recommends that high-dose bisphosphonates or denosumab should routinely be used in combination with other systemic therapy in patients with advanced breast cancer and bone metastases [57]. For patients with persistent and localized pain due to bone metastases, radiological assessment should be performed. In the absence of fracture risk, radiotherapy is recommended for pain palliation [57].

Some trials have also demonstrated that radioisotopes (e.g. strontium-89 chloride) can alleviate pain caused by bone metastases in patients with breast cancer [58]. Such treatments can be of benefit to patients with multiple sites of painful osteoblastic metastases to whom external radiotherapy could not be administered safely [58]. A phase IIa study in 23 patients with advanced breast cancer and bone-dominant disease has indicated that radium-223 dichloride has potential therapeutic benefit [59]. Whilst not approved in patients with breast cancer, radium-223 dichloride is approved for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases [60].

4.3. Considerations for initiation and cessation of treatment with denosumab or bisphosphonates

It is important to consider when to start therapy with denosumab or bisphosphonates, and the duration of treatment. In patients with advanced disease, bone metastases are often asymptomatic and can damage bone structure without causing pain [61]. In an exploratory analysis of patients with breast cancer and bone metastases using data from two phase II clinical trials, the benefit of high-dose zoledronic acid appeared to be greater in patients whose therapy was initiated before the onset of bone pain than in those who received treatment after the onset of bone pain [61]. In another phase III study of denosumab versus zoledronic acid in women with metastatic breast cancer, early intervention with high-dose denosumab or zoledronic acid in patients with advanced cancer reduced pain progression, even in those who had mild or no pain at baseline [62].

There is evidence that early intervention may delay the development of bone metastases. In a study of zoledronic acid for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST), patients were randomly assigned to begin low-dose zoledronic acid 4 mg IV every 6 months immediately, or to start treatment after they had experienced a pathologic fracture

or a decrease in BMD (delayed treatment) [63]. Bone metastases were more common in women who received delayed treatment than in those who started zoledronic acid immediately (4.5% vs. 2.6%) [63]. In the similarly designed Z-FAST trial, a larger proportion of patients in the delayed zoledronic acid group (therapy initiated upon pathologic fracture or a decrease in BMD) than in the upfront treatment group had disease recurrence in the bone (2.3% vs. 1.0%) [36].

The European consensus guideline on the use of adjuvant bisphosphonates in patients with early breast cancer recommends that the duration of low-dose bisphosphonate treatment for premenopausal women should not exceed that of ovarian suppression (3–5 years) unless indicated in patients with low BMD [56]. For postmenopausal women, treatment duration should be 3–5 years, and therapy should only be continued after 5 years if indicated by fracture risk [56]. The ESMO guidelines for bone health in patients with cancer recommend that treatment with high-dose denosumab or bisphosphonates for metastatic disease should continue indefinitely [55], although in clinical practice this may not happen [64].

4.4. Long-term use of denosumab or bisphosphonates

Denosumab and bisphosphonates are generally well tolerated; however, it is important to consider the safety implications of long-term use, particularly if patients are prescribed these agents at early stages of disease. For example, treatment with high-dose denosumab or zoledronic acid is associated with a risk of hypocalcaemia. Denosumab is associated with a higher risk of hypocalcaemia than has been reported for zoledronic acid, consistent with the greater antiresorptive effect of denosumab than of zoledronic acid. A retrospective analysis of data pooled from three phase III trials comparing these two agents (n = 5677) found an overall incidence of hypocalcaemia (grade ≥2) of 12.4% with denosumab compared with 5.3% with zoledronic acid [65]. Long-term data, however, indicate that hypocalcaemia is rare and tends to occur at the start of therapy [66]. The incidence of hypocalcaemia does not increase with cumulative exposure to denosumab [65]. The risk of hypocalcaemia can be minimized through regular monitoring of calcium and vitamin D levels, and dietary supplementation [21,26]. Patients with hypocalcaemia should have their calcium levels corrected before starting treatment with a bisphosphonate or denosumab [21,26]. Denosumab is contraindicated in patients with severe, untreated hypocalcaemia [26].

Zoledronic acid is excreted primarily through the kidneys, so dose reduction is recommended in patients with mild-to-moderate renal impairment. Zoledronic acid is not recommended for the prevention of SREs in patients with severe renal impairment; however, such patients may receive zoledronic acid for the treatment of hypercalcaemia if the risks and benefits of treatment have been considered [21]. It is recommended that serum creatinine is measured before each dose because some patients receiving zoledronic acid may experience reduced renal function. Treatment may be interrupted if renal deterioration is evident [21]. Zoledronic acid accumulates in the bones with repeated dosing. A multivariate analysis showed that the cumulative dose of zoledronic acid in patients with multiple myeloma or solid tumours was an independent predictor of renal impairment [67]. Denosumab is not excreted via the kidneys. Therefore, it is suitable for use in patients with renal impairment; however, individuals with severe renal impairment are at risk of developing hypocalcaemia and should be monitored closely [26].

Development of osteonecrosis of the jaw (ONJ) is an identified risk with zoledronic acid and denosumab treatment [21,26], and this risk rises as treatment duration increases. In an open-label extension study of two phase III studies in patients with metastatic breast or prostate cancer, additional denosumab treatment or switching from zoledronic acid to denosumab at the start of the study extension (total time on denosumab: ≤5.6 years) resulted in 6.9% and 5.5% of patients developing ONJ, respectively, compared with 1.9% and 1.2% of those in the denosumab and zoledronic acid arms, respectively, in the blinded phase of the clinical trial (total time on denosumab: ≤ 7.6 years) [66]. Equivalent data for long-term zoledronic acid treatment are not yet available. For both zoledronic acid and denosumab, treatment should be delayed in individuals with unhealed, open, soft lesions in the mouth. A dental examination with appropriate preventative dentistry, together with a benefit–risk assessment, is recommended before treatment initiation [21,26]. All patients should be encouraged to maintain good oral hygiene and to attend regular dental check-ups. Invasive dental procedures should be avoided during treatment with denosumab or bisphosphonates [21,26].

Elderly patients may have renal impairment, hypertension or diabetes mellitus, and may be taking concomitant medications. This may be of particular importance for patients who may be considered for treatment with zoledronic acid because this agent has been associated with nephrotoxicity. Additionally, an increase in the incidence of ONJ has been reported in patients taking concomitant anti-angiogenic medication [21]. Therefore, in clinical practice, patients with comorbidities should be closely monitored.

Treatment adherence also impacts on outcomes for patients prescribed long-term oral bisphosphonates. Adherence to therapy in real-world practice can be poor, with one database analysis reporting that over 70% of postmenopausal women with osteoporosis had discontinued oral bisphosphonate treatment after 1 year [68]. Postmenopausal women receiving low-dose intravenous bisphosphonates have higher adherence than those prescribed oral bisphosphonates [69]; however, in an analysis of data from a real-world medication claims database, approximately one-third of patients did not return for a second zoledronic acid injection [70]. Adherence to low-dose denosumab treatment is much higher; a real-world study of four European countries found that up to 89% of women with postmenopausal osteoporosis were adherent at 1 year [71].

5. Future perspectives

5.1. Potential antineoplastic effects

Preclinical data suggest that bisphosphonates and denosumab exert anti-tumour activity through direct and indirect mechanisms. An *in vitro* study showed that bisphosphonates inhibit proliferation of tumour cells through the induction of apoptosis [72]. Bisphosphonates have also been shown to inhibit angiogenesis and decrease tumour cells invasion, migration and disorganization of cell cytoskeleton [73]. Preclinical data show that the nuclear factor κ B (RANK)–RANKL pathway plays an important role in tumorigenesis; thus, denosumab, a RANKL inhibitor, may have anticancer effects [74]. Mouse models suggest that RANKL mediates mammary gland development and may facilitate tumour cell growth and migration [75]. The relationship between RANK expression and clinical outcomes in patients with early breast cancer was investigated in a subanalysis of data from the GeparTrio study [76]. Tissue samples were collected by biopsy from 601 patients, of whom 14.5% had elevated levels of RANK expression. The pathological complete response rate was higher among patients with elevated RANK expression than among those with low or no RANK expression; survival outcomes, however, were significantly better among patients with low or no RANK expression (DFS, p = 0.038; overall survival, p = 0.011) [76].

There is increasing evidence that bisphosphonates and denosumab may modulate the immune system, which affects tumour progression. The RANK/RANKL pathway, which is targeted by denosumab, is important for multiple immune system responses including generation of regulatory T cells (Tregs) [77]. The clinical relevance to the immune system of modulating the RANKL pathway is uncertain; however, inhibition of RANKL with denosumab may affect immune responses. For example, treatment with denosumab may reduce Tregs; thereby enhancing anti-tumour immunity. Preclinical data has indicated that bisphosphonates may induce activation of γδ T cells [73]. Bisphosphonates induced a notable increase in sensitivity of tumour cells to lysis by γδ T cells [78].

Clinical evidence has suggested that bisphosphonates may improve long-term survival outcomes in cancer patients with or without bone metastases [73]. As previously mentioned, the EBCTCG meta-analysis demonstrated that patients receiving bisphosphonates showed a significant reduction in breast cancer mortality compared to those receiving control [39]. There is evidence from a large, randomized, phase III study in men with non-metastatic castration-resistant prostate cancer that denosumab may have a beneficial effect on cancer progression. High-dose denosumab significantly increased bone-metastasis-free survival compared with placebo (HR: 0.85; 95% CI: 0.73–0.98; $p = 0.028$) [79]. No studies investigating the antineoplastic effects of denosumab have yet been completed in patients with breast cancer, but the ongoing phase III, randomized, placebo-controlled study of denosumab as adjuvant treatment for women with early breast cancer at high risk of disease recurrence receiving neoadjuvant or adjuvant therapy (D-CARE) is investigating survival with high-dose denosumab (120 mg SC every 4 weeks for 6 months followed by 120 mg SC every 3 months for the next 4.5 years) [80]. The primary outcome (bone-metastasis-free survival) of this trial is due to be reported in late 2017, with overall study completion in 2022 [81]. The potential antineoplastic effects of adjuvant bisphosphonates in breast cancer are under investigation in other ongoing clinical trials (Southwest Oncology Group [SWOG] SO307 [82] and postoperative use of zoledronic acid in breast cancer patients after neoadjuvant chemotherapy [NATAN] [83]). Results of ongoing studies will provide important insights into the clinical role of adjuvant low-dose denosumab or zoledronic acid in early-stage disease.

5.2. Identification of likely responders

Biomarkers of bone metabolism may provide an insight into skeletal metabolism and potentially be used to identify patients at risk of bone metastases, and hence those who could benefit from early initiation of therapy with denosumab or zoledronic acid. In an analysis of data from three phase III trials comparing denosumab with zoledronic acid in patients with advanced cancer and bone metastases, high levels of N-terminal telopeptide and bone-specific alkaline phosphatase were associated with an increased risk of disease progression in bone and reduced overall survival [64]. Circulating RANK, RANKL and osteoprotegerin have the potential to be used as biomarkers for response to treatment of bone metastases. This has been explored in a study of patients with solid tumours and bone metastases in which levels of mRNA for these markers were assessed at baseline and following treatment with zoledronic acid [85]. RANKL mRNA level was found to be the most predictive marker of response to treatment of bone metastases and median baseline values of this marker were significantly higher in responders than in non-responders [85]. Therefore, RANKL is a promising predictor of response to treatment of bone metastases and further research is warranted. Indeed, data from randomized controlled trials assessing the prognostic value of biomarkers of bone metabolism are eagerly awaited.

Concurrently, the identification of individuals who may not derive benefit from early therapy with denosumab or zoledronic acid is also of interest in order to ensure that patients do not receive unnecessary treatment. A recent study of biomarkers of bone metabolism in patients with breast cancer and bone metastases who received zoledronic acid found that levels of urinary N-telopeptide of type I collagen (NTx) were strongly associated with survival [86]. Furthermore, early NTx correction was associated with long-term stabilization of NTx levels, and this might serve as a marker for patients with good prognoses and who may benefit from de-escalation with zoledronic acid [86]. In contrast, patients with extraskeletal metastases had varying levels of NTx, suggesting that the dosing schedule of zoledronic acid was not effective in all patients and may require optimization in certain individuals with more advanced disease [86].

6. Conclusions

The benefits of denosumab or bisphosphonates in patients with advanced breast cancer relating to reductions in SREs and pain are well known. Patients with early-stage breast cancer can use these agents to treat CTIBL, and recent evidence suggests that there may be a potential survival benefit from the adjuvant use of these drugs. Improving our understanding of the appropriate timing of treatment initiation, treatment duration and dose will be important to ensure that bone health in patients with breast cancer is effectively managed throughout the course of their disease.

Conflicts of interest

Diana Lüftner is a member of advisory boards and has attended speaker bureaus for Amgen.

Daniela Niepel is an employee of Amgen and holds stock.

Guenther G. Steger has received honoraria and travel support from Amgen and has attended advisory boards for Amgen.

Acknowledgements

Writing support was provided by Liz Hartfield PhD of Oxford PharmaGenesis, Oxford, and was funded by Amgen (Europe) GmbH. Editorial support was provided by Emma Booth of Amgen (Europe) GmbH.

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