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REVIEW-THEMED ISSUE

Clinical and translational pharmacology of drugs for the prevention and treatment of bone metastases and cancer-induced bone loss

Correspondence Luís Costa, Oncology Division, Hospital de Santa Maria, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, 1649-035 Lisbon, Portugal. Tel.: +351 2 1780 5097; Fax: +351 2 1780 5615; E-mail: luiscosta.oncology@gmail.com

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Maria Rita Dionísio[1], André Mansinho[1], Catarina Abreu[1], Joana Cavaco-Silva[1], Sandra Casimiro[2] and Luís Costa[1,2]

[1]Oncology Division, Hospital de Santa Maria – CHLN, Lisbon, Portugal, and [2]Luis Costa Lab, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal

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Bone disease is a frequent event in cancer patients, both due to cancer spread to bone and to cancer therapies. Bone is the organ most frequently affected by metastatic disease when considering the two most frequent cancers in the Western world (breast and prostate cancers). Bone metastases can have a substantial detrimental effect on patients' quality of life, as well as significant morbidity due to complications collectively known as skeletal-related events (SREs), which include hypercalcaemia, pathological fractures, spinal cord compression, and need of radiotherapy or surgery to the bone. These have been successfully mitigated with the development of bone-targeted agents (BTAs; bisphosphonates and denosumab), focused on inhibiting osteoclast activity. The potential direct antitumour effect of bisphosphonates, as well as the impact of osteoclast inhibition with subsequent decrease in bone metabolism, have also propelled investigation on the role of BTAs in preventing cancer relapse in bone. In this review, the authors aimed to discuss the role of BTAs in the treatment and prevention of bone metastases, as well as their potential value in preventing cancer treatment-induced bone loss (CTIBL). The review will focus on breast and prostate cancers, with the aim of providing the most relevant clinical data emerging from bench to bedside translational research in the field of cancer-induced bone disease.

Introduction

In Oncology, the goal of treatments with the potential to change the odds of success between cancer and host competition is mostly dependent on the setting in which they are used. Most of the drugs that can be used in the metastatic disease may provide benefit in the palliative setting but will not cure the patient from cancer. However, under certain circumstances, the same drug(s) used after surgery (i.e. in the adjuvant setting) may prevent cancer relapse for a percentage of patients and offer them a chance of cure.

Because bone is the organ most frequently affected by metastatic disease when considering the two most frequent cancers in the Western world – breast and prostate cancer [1] – it becomes clear why efforts in Oncology research have been largely committed to unraveling the role of bone-targeted agents (BTAs) responsible for inhibition of osteoclast activity in the treatment and prevention of bone metastases (i.e. in the palliative and adjuvant settings, respectively).

It is widely accepted that bone microenvironment is key for cancer cells to successfully thrive in bone [2]. After the visionary 'seed and soil' theory of metastization proposed

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by Stephen Paget in 1889 [2, 3], the work by Gregory Mundy and Theresa Guise was critical to set the foundations for the pathophysiology of bone metastases model known as 'the vicious cycle' [4, 5]. According to this model, cancer cells in bone are able to stimulate osteoclast activity leading to bone osteolysis and, in turn, cancer cells will receive a positive feedback from humoral factors released by the bone matrix during bone destruction and altered remodelling, favouring tumour growth. This concept led to the hypothesis of testing the value of BTAs to treat and prevent bone metastases and, ultimately, to prove that a host-directed therapy (i.e. one targeting osteoclasts and not directly cancer cells) could impact on the outcomes of patients with cancer.

Bone loss is a frequent event in cancer patients, often as a result of cancer therapies – known as cancer treatment-induced bone loss (CTIBL). Indeed, drugs used in cancer treatments (e.g. endocrine therapy, androgen-deprivation therapy and chemotherapy) may induced bone loss and hence increase the risk for fractures [6].

In this review, the authors aimed to discuss the role of BTAs in the treatment and prevention of bone metastases, as well as their potential value in preventing CTIBL. The review will focus on breast and prostate cancer, with the aim of providing the most relevant clinical data emerging from bench to bedside translational research in the field of cancer-induced bone disease.

Classes of BTAs in clinical use for cancer treatment

Osteoclast inhibitors

The current use of BTAs in clinical practice is mainly focused on the inhibition of osteoclast activity by bisphosphonates (BPs) or by **denosumab**, a fully humanized monoclonal antibody that binds to the receptor activator of **nuclear factor kappa-B ligand (RANKL)**, leading to osteoclast inhibition.

BPs display a high affinity for calcium ions, and therefore attach to the hydroxyapatite on bone surface, particularly those undergoing active resorption. All BPs are antiresorptive drugs that block pathologic bone resorption by inducing osteoclast apoptosis. Because of their antiresorptive properties, BPs are used to prevent the hyperactivation of osteoclasts associated with the presence of cancer cells in bone or in the setting of CTIBL.

During bone resorption, BPs are internalized by bone-resorbing osteoclasts, inhibiting osteoclast function [7]. At the cellular level, second- and third-generation nitrogen-containing BPs impair the mevalonate pathway by inhibiting the **farnesyl diphosphate (FDP)** synthase. Consequently, the prenylation of small GTPase signalling proteins is inhibited, ultimately leading to apoptosis. Examples of alkyl-amino BPs are **pamidronate**, **alendronate**, **ibandronate**, whereas heterocyclic BPs include risendronate and **zoledronic acid (ZA)**. First-generation non-nitrogen-containing BPs (**etidronate**, **clodronate [CLO]**, **tiludronate**) lead to intracellular accumulation of cytotoxic non-hydrolysable **adenosine triphosphate (ATP)** analogues. In both circumstances, bone resorption is severely impaired.

Pamidronate and ZA have been approved by both the European Medicines Agency (EMA) (or local European authorities) and the US Food and Drug Administration (FDA) for the treatment of skeletal metastases from breast cancer and multiple myeloma. CLO is not approved in the US but is available in Europe for the treatment of skeletal metastases from breast cancer. Ibandronate is also an option for breast cancer. ZA is the only BP approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) and is also approved for use in other solid tumours, as well as in multiple myeloma.

The receptor activator of nuclear factor kappa B (NFκB) RANK is a transmembrane receptor expressed on the surface of osteoclast precursor cells, and its ligand RANKL is produced by osteocytes, osteoblasts and bone marrow stromal cells. Binding of RANKL to RANK leads to stimulation of RANK signalling, regulating osteoclast differentiation, activity and survival. The soluble decoy receptor for RANKL, **osteoprotegerin (OPG)**, is produced by mature osteoblasts and stromal cells, and binds RANKL, blocking osteoclast differentiation [8, 9]. The anti-RANKL monoclonal antibody denosumab is the most potent osteoclast inhibitor and is approved for use in patients with bone metastases in all solid tumours.

Other BTAs

The radiopharmaceutical agent radium-223 (Ra-223) is considered by several authors as a BTA. Ra-223 has a high affinity to bone and significantly reduces the incidence of bone complications in patients with prostate cancer and bone metastases. Additionally, due to its alpha-emitter properties Ra-223 causes direct cancer cell death by radiation-induced double strand breaks. Ra-223 is probably the first BTA, with unknown target, to show effectiveness in the targeting of osteoblast hyperactivity (as in prostate cancer-associated blastic bone metastases). The most accurate biomarker to predict response to Ra-223 in patients with prostate cancer and bone metastases is the decline of alkaline phosphatase, a biomarker of osteoblast activity [10].

BTAs in the treatment of bone metastases

Whereas the normal physiologic process of bone depends on a strict balance between bone resorption by osteoclasts and new bone formation by osteoblasts, cancer cells growing on bone disrupt this balance, favouring bone resorption. However, osteoblastic bone metastases are the most prevalent form of bone metastases in prostate cancer. In this case, together with the increase in bone resorption due to osteoclastogenesis, also osteoblasts are activated by prostate cancer cells, leading to the accumulation of immature unmineralized bone (osteoid).

Bone metastases are frequent in solid tumours and half of these patients develop one or more complications, collectively termed skeletal-related events (SRE). SREs include bone pain, hypercalcaemia, fractures, spinal cord compression, need of radiotherapy for pain, and need of surgery for pathological fractures [10]. SREs cause significant morbidity, as well

as reduced performance status, quality of life (QoL) and survival [11, 12]. Symptomatic skeletal events (SSEs) differ from the latter for only including symptomatic pathologic fractures.

Real-world evidence continues to support the relevance of SREs as a prevalent clinical event in patients with bone metastases across different solid tumour types [13]. The cumulative incidence of SREs at 24 months in a 15-year study in two large US health systems was 54.2% in breast cancer, 41.9% in prostate cancer, and 47.7% in lung cancer [13].

Bisphosphonates

By disrupting the 'vicious cycle' of bone metastases, BPs are able to prevent bone complications associated with tumour-induced bone osteolysis [13]. Following this rational, ZA, ibandronate, pamidronate and CLO were studied and approved for prevention of skeletal complications in breast cancer patients with bone metastases [14]. However, ZA is the only BP approved for the treatment of bone metastases across all tumour types.

Since the early days of BP investigation in this setting, phase 3 trials assessing their impact on the incidence of SREs have used as endpoints the proportion of patients with at least one SRE, time to the first SRE, and skeletal morbidity rate (mean rate of SREs per person-year). Such trials have sought to compare treatment with BPs versus placebo or treatments with two different BPs [14]. Another approach used to capture the impact of BPs in the incidence of SREs was the Andersen-Gill method, which is a more sensitive means of reporting treatment effects by adjusting for variability in event rates over time and gives an intensity/hazard ratio for recurrent events assuming that events are independent [15].

The efficacy of different BPs in the treatment of patients with breast cancer was assessed in a Cochrane review, which confirmed the value of this drug class to prevent SREs associated with bone metastases [16].

Two phase 3 clinical trials compared the efficacy of different BPs to prevent SREs in patients with breast cancer and bone metastases [17, 18]. In a double-blind randomized trial, intravenous (IV) ZA at 4 or 8 mg was compared to IV pamidronate at 90 mg, and no statistically significant difference was found between these agents concerning number of SREs or time to first SRE [18]. In the non-inferiority ZICE trial, oral ibandronate at 50 mg daily was compared with IV ZA at 4 mg every 3–4 weeks (q3–4w) in patients with breast cancer and bone metastases [17]. In this study, the authors could not reject the hypothesis that ibandronate was inferior to ZA, with an annual rate of SREs of 0.499 (95% CI 0.454–0.549) for ibandronate and 0.435 (0.393–0.480) for ZA.

IV nitrogen-containing BPs are considered the most potent BPs and, among these, ZA combines potency with a shorter time of infusion (15 min). However, the incidence of osteonecrosis of the jaw (ONJ) and renal deterioration rate, two of the most worrisome complications of BPs, are higher with IV compared with oral nitrogen-containing BPs or non-nitrogen-containing BPs, as CLO [19].

The role of BPs in the treatment of patients with prostate cancer and bone metastases is limited to mCRPC, with ZA being the only approved BP in this setting. In a randomized placebo-controlled trial, 643 patients with mCRPC were randomly assigned to IV ZA at 4 or 8 mg or placebo q4w, with a significant reduction in the rate of SREs (49% *vs*. 38%, $P = 0.0029$) and an increase in the median time to first SRE in favour of 4 mg ZA [20, 21].

The role of BPs, including ZA, in the castration-sensitive setting of advanced prostate cancer with bone metastases is yet to be determined. The CALGB 90202 trial, prematurely terminated due to sponsor support withdrawal, reported a median time to first SRE of 31.9 months for ZA *vs*. 29.8 months for placebo (hazard ratio [HR] 0.97; $P = 0.39$) [22].

In other, non-breast or prostate, solid tumours, ZA is the only BP approved to prevent SREs. In the ZA 011 trial, patients were randomly assigned to IV ZA at 8 or 4 mg or placebo q3w with concomitant antineoplastic therapy [23]. Incidence of SREs was reduced in both ZA groups compared with placebo (38% for 4 mg and 35% for 8/4 mg ZA *vs*. 44% for placebo; $P = 0.127$ and $P = 0.023$ for 4 and 8/4 mg groups, respectively) [23, 24]. Additionally, ZA significantly increased time to first SRE in the 4 mg group (median of 230 *vs*. 163 days for placebo; $P = 0.023$). The currently approved dosage of IV ZA to prevent SREs in patients with bone metastases is 4 mg q3–4w.

Denosumab

In two large phase 3 trials, denosumab was superior to ZA in patients with bone-metastatic disease from breast and prostate cancer [25, 26]. Denosumab superiority was evident in the time to first and subsequent SREs, both in breast and prostate tumours. In breast cancer, denosumab delayed time to first SRE compared to ZA (32.4 *vs*. 26.4 months; HR 0.82; $P = 0.01$) [26].

In another phase 3 trial comparing denosumab and ZA in patients with bone metastases from multiple myeloma or solid tumours other than breast or prostate, denosumab was non-inferior to ZA in delaying time to first SRE (20.6 *vs*. 16.3 months; HR 0.84; $P = 0.0007$), but not statistically superior to ZA in delaying time to first SRE ($P = 0.06$) [27].

Approximately 25% of patients receiving nitrogen-containing BPs typically experience events like self-limiting bone pain and flu-like symptoms after the first infusion [28, 29].

In an integrated analysis of 5723 patients from three randomized phase 3 trials, denosumab safety profile on renal function was better than that of ZA, not requiring dose adjustments or renal monitoring [30]. But the incidence of hypocalcaemia was higher with denosumab than with ZA (3.1% *vs*. 1.3% for grade 3–4 toxicities), although most cases were asymptomatic. Importantly, the risk of developing hypocalcaemia was 40% lower in patients treated with denosumab who reported taking calcium/vitamin D supplements at any time during the study, highlighting the importance of adhesion to calcium supplementation in patients receiving denosumab [31].

ONJ is a relevant and potentially serious concern associated with osteoclast-targeting therapies such as ZA and denosumab [32]. ONJ usually manifests as a late adverse event (AE), contrarily to hypocalcaemia, which is an early AE. Median time to ONJ in patients receiving ZA or denosumab is 15 months [33], but the risk of ONJ increases with treatment duration. Therefore, many clinicians consider

stopping BPs or denosumab after 24 months of therapy. In patients receiving treatment at monthly intervals, the incidence of ONJ is similar with ZA and denosumab (1–10%).

Other BTAs

As previously mentioned, Ra-223 is approved for the treatment of mCRPC with bone metastases, being reserved for patients without significant extra-skeletal disease.

The pivotal phase 3 ALSYMPCA trial was a randomized, double-blind, placebo-controlled trial of Ra-223 in 921 patients with symptomatic mCRPC and two or more bone metastases [34]. Men with visceral metastases were excluded from the study. Compared with placebo, Ra-223 was associated with a 30% reduction in the risk of death, longer time to first SSE, and a lower risk of radiotherapy requirement for bone pain and spinal cord compression. Furthermore, a significantly higher percentage of patients receiving Ra-223 had a meaningful improvement in QoL according to the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score during the period of drug administration (25% *vs*. 16% with placebo; $P = 0.002$).

A recent review of Ra-223 data was carried out by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), after results from the phase 3 double-bind clinical trial ERA 223, evaluating Ra-223 or placebo, each in combination with **abiraterone** plus **prednisone**, in patients with mCRPC with bone metastases [35]. The study was prematurely unblinded due to observation of more fractures and deaths in the Ra-223 treatment arm. Based on this, the combination of Ra-223 with abiraterone is now contraindicated [36].

Results from the ERA 223 study indicate that manipulating bone microenvironment can have a positive but also a negative impact on patient outcomes. However, a subgroup analysis of this study suggests that the detrimental effect of combining Ra-223 with abiraterone is not observed in patients concomitantly receiving an anti-osteoclast inhibitor [35].

BTAs are frequently administered as part of the management of patients with bone metastases to delay or prevent SREs. In breast cancer, several BPs and denosumab are approved to treat bone metastases, whereas in prostate cancer the only osteoclast-inhibitors approved are denosumab or zoledronic acid (Figure 1).

Future trends

Several questions remain unanswered regarding the use of BTAs in the treatment of bone metastases. Two of the most relevant are whether it is possible to de-escalate the BTA regimen while maintaining effectiveness with a lower the incidence of ONJ, and what is the optimal duration of BTA therapy.

ZOOM and OPTIMIZE-2 trials evaluated the de-escalation of ZA from an every 4-week to an every 12-week regimen in patients treated with ZA for approximately 12 months, showing that this is a possible treatment option for these patients [37, 38]. This approach was also supported by a meta-analysis in which patients receiving ZA every 12 weeks had a similar risk of SRE as those receiving ZA every 4 weeks [39]. The 12-week administration was subsequently incorporated in the latest guidelines [40].

Since patients with multiple bone metastases and pain have the highest risk for SREs during the first 6–12 months of treatment [30], when ZA is the BP of choice it seems reasonable to start treatment with a monthly regimen for the first 12 months, and then de-escalate to an every 12-week regimen. Importantly, the de-escalation approach is not yet ascertained for patients receiving denosumab. McClung *et al*. [41] reported results from an observational 1-year period after up to 8 years of denosumab treatment in a phase 2 study and showed that eight patients (9.8%) - all having at least one predisposing risk factor - experienced 17 fractures. This included seven patients who experienced one or more vertebral fractures. Clinicians should be aware of the prodromes for atypical fracture of the femur in this context.

Regarding BTA treatment duration, although international guidelines recommend maintaining treatment until evidence of a substantial decline in patient's general performance status or even indefinitely, clinicians often stop BTAs after 2 years. Indeed, pivotal trials arbitrarily determined a BP treatment duration of approximately 2 years, and a denosumab treatment duration of up to 3 years. The rational to stop or de-escalate BTAs after 2 years is mostly dependent on the increased risk of ONJ with prolonged treatment duration.

Drug	Breast cancer	Prostate cancer	Other solid tumours	Multiple myeloma
Clodronate (PO)	X			X
Pamidronate (IV)	X			X
Ibandronate (IV)	X			
Zoledronic acid (IV)	X	X	X	X
Denosumab (SC)	X	X	X	
Radium – 223 (IV)		X		

Figure 1

Current approval status of bone-targeted agents for skeletal-related complications in the oncology setting

BTAs for prevention of bone metastases

BTAs have been investigated in clinical trials to assess the impact of osteoclast inhibition and subsequent decrease in bone metabolism in the prevention of bone metastases (Table 1).

Preclinical data on the potential direct antitumour effect of BPs, particularly nitrogen-containing ones, has raised expectations of a role for BPs in preventing cancer relapse [42, 43]. Either through inhibition of the bone remodelling cycle, or through other potential mechanisms – as a cytotoxic effect on cancer cells, inhibition of angiogenesis or expansion of antitumoral immune cells – BPs became natural candidates to test in the adjuvant setting [42]. Additionally, the pharmacodynamic profile of BPs has a favourable long-lasting effect on bone. This provided a strong reasoning to target dormant residual cancer cells surviving in the bone microenvironment or bone marrow after adjuvant chemotherapy or endocrine therapy with these agents.

Several studies have been conducted in the adjuvant setting aiming to improve recurrence and survival rates by integrating BPs in conventional adjuvant regimens [44, 45]. However, results have been inconsistent or conflicting regarding the value of BPs in preventing breast cancer relapse.

This question was clarified in a study conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [46]. This large patient-level meta-analysis of trials of adjuvant amino and non-amino BPs included 18 776 women with breast cancer. An 18% reduction in the risk of death from breast cancer in the subset of postmenopausal women (HR 0.82 [95% CI 0.73–0.93]; $P = 0.002$) was observed. This effect seemed to stem mainly from the 28% reduction in the risk of bone recurrence (HR 0.72 [95% CI 0.60–0.86]; $P = 0.0002$) rather than from extra-skeletal recurrences. Given these results, several guidelines now advise on the use of ZA and CLO as adjuvant treatment of postmenopausal women with breast cancer [47, 48].

Assessment of the biomarker for bone metastasis MAF status in patients from the phase 3 AZURE trial showed that MAF positivity was predictive of a detrimental effect of adjuvant ZA treatment in non-postmenopausal women with early breast cancer with more relapses outside bone (HR for extraskeletal recurrences, 6.92; 95% CI 2.44–19.6) [49]. These results could explain why only postmenopausal woman achieved benefit with adjuvant ZA in AZURE. However, there is no valid mechanistic explanation for this observation yet.

Denosumab was also investigated as an adjuvant treatment in breast cancer, with the two large phase 3 trials ABCSG-18 [50, 51] and D-CARE [52] evaluating whether denosumab could have a role in the adjuvant setting in this tumour type.

Results from the ABCSG-18 study, in 3425 postmenopausal patients with early hormone receptor-positive breast cancer receiving aromatase inhibitors (AIs) with or without denosumab (60 mg every 6 months), were recently presented [51]. After a median follow-up of 72 months, the disease-free survival (DFS) was significantly improved in the denosumab arm (HR 0.823, 95% CI 0.69–0.98, $P = 0.026$) in a descriptive analysis not controlling for multiplicity.

The D-CARE trial randomized 4509 patients with early breast cancer to standard loco-regional and (neo)adjuvant therapy plus either subcutaneous (SC) denosumab 120 mg or matching placebo monthly × 6 then 3 monthly for up to 5 years [52]. The primary endpoint was bone metastasis-free survival (BMFS), defined as the first bone metastatic event confirmed by central imaging review or death from any cause. DFS and overall survival (OS) were secondary endpoints. No benefit for the addition of denosumab was seen after a median follow-up of 67 months that allowed for the full 5 years of treatment in all patients (HR for BMFS [597 events] 0.97; 95% CI 0.82–1.14; $P = 0.70$). Also, no benefit was observed on DFS (HR 1.04, 95% CI 0.91–1.19, $P = 0.57$). However, exploratory analysis of time to bone metastases as first

Table 1

Studies investigating BTAs in the prevention of bone metastases from breast and prostate cancer (adapted from Casimiro *et al.* [75])

Drug	Number of patients	Bone recurrence	Disease recurrence	Cancer mortality
Breast cancer				
BPs (EBCTCG) [46]	Overall $n = 18\,766$	HR 0.83 (95% CI 0.73–0.94); $P = 0.004$	HR 0.94 (95% CI 0.87–1.01); $P = 0.08$	HR 0.91 (95% CI 0.83–0.99); $P = 0.04$
	Postmenopausal $n = 7388$	HR 0.72 (95% CI 0.60–0.86); $P = 0.0002$	HR 0.86 (95% CI 0.78–0.94); $P = 0.002$	HR 0.82 (95% CI 0.73–0.93); $P = 0.002$
Denosumab (ABCSG-18) [50, 51]	Postmenopausal; $n = 3425$	HR 0.97 95% CI 0.82–1.14, $P = 0.70$	HR 0.82 (95% 0.69–0.98, Cox $P = 0.026$)	HR 1.03 95% CI 0.85–1.25
(D-CARE) [52]	Overall $n = 4509$ Postmenopausal; $n = 2149$	HR 1.04 95% CI 0.91–1.19, $P = 0.57$		
Prostate cancer				
Zoledronic acid (ZEUS) [57]	High risk disease; 1393	14.7 vs. 13.2% in the control group at 4.8 year; (log-rank: $P = 0.65$)		116 vs. 122 deaths in the control group; log-rank $P = 0.76$
(RADAR) [58]	Locally advanced disease treated with RT and ADT ± ZA; $n = 1071$			No difference in prostate cancer-specific mortality

recurrence suggested benefit for denosumab (HR 0.76, 95% CI 0.59–0.97), and time to on-study fracture prior to bone recurrence was also reduced with denosumab (HR 0.76, 95% CI 0.63–0.92). Interestingly, denosumab did not improve BMFS, DFS or OS in the postmenopausal subgroup.

In contrast to the ABCSG-18 study, the D-CARE study recruited patients with a very high risk of distant relapse. It is possible that the rate of distant relapse in visceral organs (such as liver or lung) and earlier death of those patients did not allow differences in BMFS, the primary endpoint of the D-CARE study, to be seen. Bone metastases usually occur later in time when compared to visceral metastases.

Recent attention to a potential role of the RANK/RANKL axis on breast carcinogenesis prompt the development of new clinical trials in the (neo)adjuvant setting. RANKL is the paracrine mediator of progesterone mitogenic action in mammary epithelium and progesterone could also drive mammary stem cell (MaSC) expansion, correlated with increase in RANKL within ER+/PR+ luminal cells [53, 54]. There is also preclinical evidence that RANK/RANKL signalling has a role in *BRCA1*-associated tumours [55], and RANKL inhibition was further shown to reduce proliferation in *BRCA1*-mutated human breast tissue [56].

In prostate cancer, adjuvant BTAs have no well-established role. The adjuvant role of ZA in prostate cancer was tested in the ZEUS and RADAR trials. The ZEUS phase 3 trial recruited 1433 patients with high-risk non-metastatic prostate cancer to receive treatment with or without every 3-month ZA and found no differences in the proportion of patients developing bone metastases (17.1 *vs*. 17.0%; $P = 0.95$) [57]. The RADAR study recruited 1071 men with locally advanced prostate cancer to receive treatment with radiotherapy plus 6 or 18 months of androgen deprivation therapy (ADT) with or without 18 months of ZA and also found no differences in prostate cancer-specific survival between groups [58].

Bone metastases from prostate cancer are often blastic, reflecting a strong paracrine interplay between cancer cells and osteoblasts. This may be a possible explanation for the lack of efficacy of anti-osteoclast agents as the only BTA to prevent disease relapse in bone. It is yet unknown whether a BTA such as Ra-223 alone or in combination with an anti-osteoclast agent could be a valid option to target micrometastases in bone and thus prevent cancer relapse.

BTAs for prevention of cancer treatment-induced bone loss

The diagnosis of cancer is in itself a risk factor for bone loss. However, cancer treatment is also acknowledged as a major driver of bone loss, leading to clinically relevant outcomes of bone frailty even in the absence of bone metastases. In this review, the authors will focus on bone loss associated with therapies frequently used to treat cancer patients, herein designated cancer treatment-induced bone loss (CTIBL) [59].

Drugs used in cancer treatment (like hormone therapy, ADT and chemotherapy) may induce bone resorption, leading to bone loss and a consequently higher risk of bone fractures. Consequently, it is critical to identify which patients are at risk and which preventive measures should be adopted [6].

It is also important to acknowledge the risk for bone loss in other commonly used cancer treatments. For instance, glucocorticoids are used in Oncology as an integral part of anti-emetic chemotherapy regimens, as preventive medications for infusion reactions, and as analgesics. In patients with brain primary and secondary tumours, glucocorticoids are used to manage neurological symptoms associated with peritumoral oedema. Long-term treatment with glucocorticoids can be responsible of iatrogenic osteoporosis.

Chemotherapy is by itself a risk factor for bone loss, independently of subsequent secondary ovarian failure due to chemotherapy. In postmenopausal women, data suggest that patients receiving adjuvant chemotherapy can lose 1–10% of bone mass within 1 year of chemotherapy [60]. Although the World Health Organization (WHO) provides a clinical tool – the Fracture Risk Assessment tool (FRAX) – to evaluate the 10-year probability of major osteoporotic fractures based on several risk factors, anticancer treatments were not included as a specific risk factor [6, 61].

Changes in bone mineral density (BMD) and fracture rates are regarded as the main outcomes to consider in clinical studies of CTIBL. Until now, a dual energy x-ray absorptiometry (DEXA) scan of the hip, lumbar spine, and femoral neck is the best way to determine BMD and a predictor of fracture risk. The necessity of evaluating fracture risk by integrating the determination of BMD is reflected in several guidelines [62, 63]. Periodic BMD evaluations are recommended in women with iatrogenic ovarian failure (those that have treatment-related amenorrhoea for more than 1 year should have BMD assessed), in postmenopausal women treated with AIs, and in all breast cancer patients with fracture risk factors. BMD detection is also recommended in men on ADT. Long-term ADT is associated with significant and progressive BMD decline and fracture events significantly correlate with shorter survival in men with prostate cancer [64].

Prevention and treatment of CTIBL

Adopting healthy lifestyle measures, such as performing weight exercises, avoiding alcohol and tobacco, limiting caffeine consumption, and achieving and/or maintaining a normal body weight, are beneficial to prevent CTIBL [65]. Supplementation with calcium (1200 mg day^{-1}) and vitamin D (800 IU) to reach serum levels of at least 30 ng ml^{-1} of serum vitamin D should also be assured to maintain a healthy bone turnover. Furthermore, maintaining such levels is known to reduce the risk for hip fractures in elderly women [64, 65].

BTAs in CTIBL

Several traditional BTAs (BPs and denosumab) have been investigated to treat patients at risk for bone loss or bone fracture [51, 66–70]. In some of these studies, cancer relapse was a secondary endpoint. Oral BPs such as CLO, alendronate, risedronate and ibandronate can be used to prevent osteoporosis. Concerning oral BPs, patients should be instructed to take these medications on an empty stomach, with plenty of water and in the upright position. Among oral BPs, CLO showed efficacy in preventing bone loss in premenopausal

breast cancer patients with chemotherapy-induced ovarian failure [68].

ZA is the most extensively studied IV BP in clinical trials of CTIBL prevention. One relevant aspect of the BP strategy in this setting was provided by the N03CC (Alliance) trial [66]. This study enrolled 551 postmenopausal women with breast cancer who completed **tamoxifen** and were undergoing daily **letrozole** treatment, who were randomized to upfront (n = 274) or delayed (n = 277) IV ZA 4 mg every 6 months. In the delayed arm, ZA was initiated for post-baseline BMD T-score < −2.0 or fracture. Incidence of a 5% decrease in total lumbar spine BMD at 5 years was 10.2% in the upfront *vs.*

Table 2

Trials of antiresorptive agents for preventing CTIBL in postmenopausal women with breast cancer (adapted from Hadji *et al.* [62])

Antiresorptive agent (trial)	*n*	BMaD study, *n*	Dosing	Treatment duration, years
Zoledronic acid (ZO-FAST)	1065	1065	4 mg iv q6mo	5
Zoledronic acid (Z-FAST)	602	602	4 mg iv q6mo	5
Zoledronic acid (E-ZO-FAST)	527	527	4 mg iv q6mo	5
Zoledronic acid (N03CC)	558	395	4 mg iv q6mo	5
Denosumab (HALT-BC)	252	252	60 mg sc q6mo	2
Denosumab (ABCSG-18)	3425	1872	60 mg sc q6mo	5
Denosumab [72]	1468	1468	60 mg sc q6mo	2
Risedronate (SABRE)	154	111	35 mg po/week	2
Risedronate	87	87	35 mg po/week	5
Clodronate	61	61	1600 mg po/day	3
Risedronate (ARBI)	213	70	35 mg po/week	2
Risedronate (IBIS-II)	613	59	35 mg po/week	5
Ibandronate (ARIBON)	131	50	150 mg po/month	2
Risedronate	118	11	35 mg po/week	1

BMaD: bone mass density; iv: intravenous; sc: subcutaneous; po: per os; q6month: every 6 months

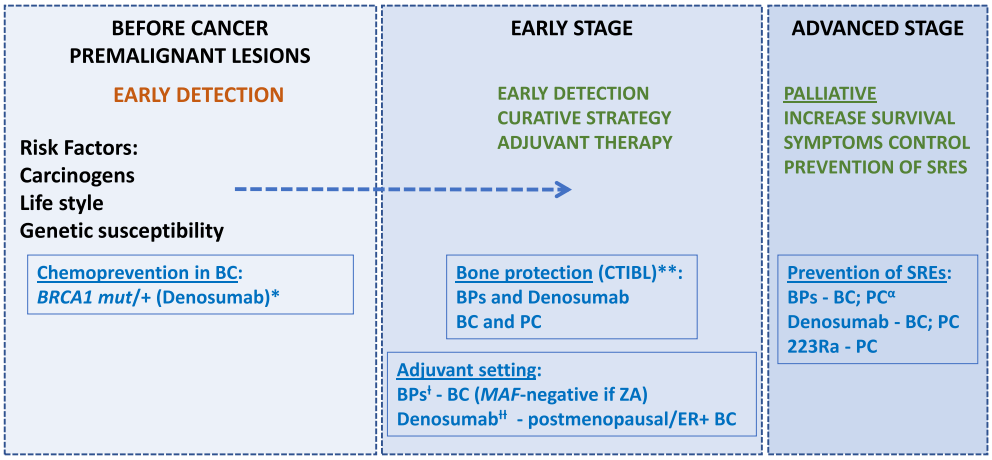

Figure 2

Natural history of breast and prostate cancer: possible time points of clinical intervention and/or research for bone-targeted agents. BC, breast cancer; BRCA1, breast cancer 1; BPs, bisphosphonates; CTIBL, cancer treatment-induced bone loss; ER+, estrogen receptor-positive; MAF, MAF BZIP transcription factor; PC, prostate cancer; ZA, zoledronic acid[a] Investigational data only.[b] Clinical evidence for bone mineral density (BMD) preservation and decreased incidence of fractures (denosumab).[c] In postmenopausal women or associated with ovarian suppression. MAF-negative may have a role in selection of BC patients to ZA.[d] According to ABCSG-18 study (only in postmenopausal women treated with aromatase inhibitors).[e] In PC, ZA is the approved BP with strongest evidence and indication

41.2% in the delayed arm ($P < 0.0001$). Forty-one patients in the delayed arm were eventually started on ZA. However, the number of patients with fractures was not significantly different between the two arms: 24 *vs*. 25 patients in the upfront and delayed arms, respectively. This could be explained by the fact that 41 patients in the delayed arm were "rescued" for having started ZA.

Denosumab at 60 mg every 6 months is approved to increase bone mass in patients with increased risk of fractures in several indications, including postmenopausal women with osteoporosis, men receiving ADT for non-metastatic prostate cancer, and women receiving adjuvant AIs for breast cancer [71].

More recently, updated results of the ABCSG 18 study again reported an important fracture reduction with adjuvant SC denosumab at 60 mg every 6 months in postmenopausal breast cancer patients receiving AIs [51]. In men receiving ADT for non-metastatic prostate cancer, denosumab at 60 mg every 6 months was associated with an increase in BMD and a reduction in new vertebral fractures [72]. Table 2 depicts some of the most representative studies using BTAs to prevent CTIBL.

The incidence of ONJ associated with the use of BTAS in CTIBL is very low, with no cases reported at the ABCSG-18 study. The main reason for this is that in CTIBL, BTA regimens are less intensive due to the most potent anti-osteoclast inhibitors (ZA and denosumab) and prescribed every 6 months instead of monthly as used to prevent SREs in patients with bone metastases.

Conclusions

Bone metastases and SREs are common in patients with advanced solid tumours, and in those who experience SREs the occurrence of pathologic fractures is correlated with a lower survival rate. Understanding the mechanisms associated with increased bone resorption prompt the discovery of the potential benefits of a class of agents known as BTAs.

BPs were the first BTAs to be investigated, becoming the standard of care for SRE prevention in patients with metastatic bone disease. Further knowledge on the role of RANK/RANKL axis on bone osteoclast activation and in the pathophysiology of bone metastases led to the development of a new agent acting as potent osteoclast inhibitor, denosumab. Denosumab provides an effective option for the prevention of SREs in patients with advanced cancer and bone metastases, and more recent investigation suggests that inhibition of RANKL with denosumab may be an interesting strategy to prevent breast cancer in mutated *BRCA1* carriers.

An agent capable of acting as a BTA – Ra-223 – is now approved for the treatment of prostate cancer patients with bone metastases. Importantly, this radiopharmaceutical agent may also act as an anticancer agent by delivering alpha radiation to bone metastases and interfering with the hyperactivation of osteoblasts (a typical feature of bone metastases in prostate cancer).

Investigating a possible role for BTAs in the adjuvant setting was a logical step in cancer research to prevent cancer relapse after surgery. But the need to properly select younger breast cancer women who are candidates for adjuvant BPs is a relevant issue. Although adjuvant BPs are currently reserved for postmenopausal women (either for physiological or surgical reasons or due to ovarian function suppression), extending these agents to younger women is an attractive strategy, namely for those patients at significant risk of (early or late) relapse.

The possible detrimental effect of BPs in premenopause are a matter of concern. If patients with *MAF*-positive breast cancer are acknowledged to have an increased relapse risk outside of bone due to BPs, they will be ineligible for BPs, including if the purpose is to prevent osteoporosis and fractures, two common issues in the CTIBL setting.

The role of denosumab in the adjuvant setting remains unclear. The D-CARE study failed to place this agent as an option for preventing cancer relapse and the ABCSG-18 study is currently the only large trial attesting its use after surgery in postmenopausal women with breast cancer selected to receive AIs.

Until now, there is no evidence for the use of BTAs in prevention of relapse in prostate cancer or any other solid tumours (Figure 2).

In September 2011, denosumab was FDA-approved to treat bone loss in women taking aromatase inhibitors as part of their breast cancer treatment.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [73] and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [74].

Competing Interests

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