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Bone targeted therapies in advanced breast cancer

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Summary

Bone targeted therapies are of increasing importance, not only for bone health in the clinical course of breast cancer, but recently also in the adjuvant setting as preventative, anticancer and prognosis-improving agents. It is well established that women with advanced breast cancer receive bisphosphonates or denosumab to prevent therapy-related osteoporosis. As many as 70% of these patients suffer from bone metastases and receive bone targeted agents in order to prevent skeletal related events (SREs), which are debilitating or diminish the quality of life.

A number of trials provided guidance, identifying zoledronic acid as the most efficient bisphosphonate, showing that intravenous bisphosphonate administration is superior to oral intake and illustrating the different safety profile of denosumab, which has been reported to be more beneficial than zoledronic acid in delaying the time to first and subsequent (multiple) SREs. New studies have suggested that bone targeted therapies improve rates of overall survival and contribute to preventing recurrence of breast cancer at all sites. Increased bone turnover is both a consequence and a driving factor for tumour growth, expansion, formation of bone lesions and potentially also activation of disseminated tumour cells, leading to bone relapses. We review the current knowledge of bone targeted therapies in advanced breast cancer, with a focus on new insights into their bone-preserving and antitumor activity. Current guidelines, pathology of bone metastasis, mode of action and common side effects have been summarised. We also elaborate on the use of bisphosphonates and denosumab in early breast cancer, during adjuvant therapy with aromatase inhibitors.

Key words: bisphosphonates, denosumab, breast cancer, adjuvant therapy, osteoporosis, bone metastases,

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Background

Breast cancer is the most common cancer in women worldwide and the second most common cancer overall. Despite great progress in therapeutic and diagnostic breast cancer research, 30% of all female cancers are breast carcinoma. The incidence is increasing, which is mostly owing to demographic aging and a manifestation of risk factors in the modern lifestyle. However, recent years brought a decline in mortality and an improvement in survival, probably due to advances in diagnostics, screening and treatment protocols. However, 20 to 30% of patients still relapse after diagnosis. Even late relapses, two decades after diagnosis, are possible.

Breast cancer is one of the most heterogeneous diseases. Personalised management approaches are needed in order to assure the best possible outcome, as well as to avoid over- or undertreatment. Novel endocrine and targeted therapies have the potential to significantly impact both the physiological and psychological health of breast cancer patients and survivors. Only a fraction of treatment strategies are individualised. Individual treatment strategies are based not only on the TNM classification, but also on specific clinicopathological features and a careful risk assessment for each patient, such as specific endocrine and targeted approaches for Her2-positive breast cancers. Over- or undertreatment should be avoided. But whereas there are several recognised prognostic factors (e.g., axillary node status, tumour size/type/grade, lymphatic and vascular invasion, proliferative markers, patient age and status), predictive markers in breast cancer (essential for decision making since they suggest the outcome of patients irrespective of treatment) are limited.

Advanced disease is *per se* very complex and patients face the burden of aggressive therapy with various, sometimes severe, side effects. These include bone thinning with resulting fractures and joint pain. Approximately 70% of patients with advanced breast cancer experience bone metastases, which may produce poor quality of life and some of the highest rates of skeletal-related events (SREs). SREs are defined as pathological fractures (excluding major trauma), radiation therapy to bone, surgery to bone, or spinal cord compression. Although bone metastases do not involve vital organs, they may have deleterious effects and compromise the patient's general state.

Approximately 7% of women with breast cancer are diagnosed before the age of 40 years. Younger age is an independent predictor of adverse outcome and survival rates are worse when compared with those in older women. The proportion of aggressive subtypes, such as triple negative

breast cancer, is higher in younger patients. Neo- and adjuvant chemotherapy, radiotherapy and antihormonal medication are the current standard. Hormone depleting therapies, especially in young women receiving dual blockade with gonadotrophin releasing hormone and aromatase inhibitors, are detrimental to the skeleton. Prevention of resulting bone loss by bone targeted therapies is therefore of utmost importance.

Thus, it is important to study and propose medication for effective and efficient bone targeted therapy. Oral and intravenous formulations of bisphosphonates and denosumab are now successfully used in patients with bone metastatic breast cancer for prevention of SREs such as bone pain, pathological fractures, spinal cord compression and hypercalcaemia of malignancy [1, 2]. Bisphosphonates and denosumab are also used to prevent bone loss associated with antioestrogen therapy [3, 4]. In Switzerland, denosumab is approved as endocrine therapy for patients with breast cancer and prostate cancer, to prevent bone mineral density loss. Both types of substance have been suggested to additionally have antitumour potential. Strikingly, recent research has suggested a beneficial effect for adjuvant use of zoledronate in postmenopausal patients [5–7]. Recently, denosumab also has been shown to have a beneficial effect on disease-free survival in postmenopausal patients with hormone receptor positive breast cancer [8]. The properties of denosumab and of bisphosphonates as a class are summarised in table 1.

Current guidelines

The current American Society of Clinical Oncology (ASCO) evidence-based clinical practice guidelines for the use of bisphosphonates in breast cancer recommend their use only for patients with evidence of metastatic bone destruction. For all patients, and especially for all those with an increased risk of tumour-therapy induced loss of bone mass, the possibilities of osteoprotection should be discussed. All patients should receive a dental examination and appropriate preventive dentistry before and during the therapy to prevent jaw necrosis. The risk for oral necrosis of the jaw is up to 8% in patients with regular bisphosphonate and denosumab treatment, especially in those with risk factors such as extractions or paradontosis.

Life-style factors (physical activity, cessation of smoking, alcohol abstinence), and avoidance of underweight are on the list of nonpharmacological options. Supplements of vitamin D3 and calcium are not contraindicated. However, the approved agents include denosumab (120 mg subcutaneously every 4 weeks), intravenous pamidronate (90 mg over no less than 2 hours) and zoledronic acid (4 mg over no less than 15 minutes every 3–4 weeks). To date, reports suggest that the efficacy of these agents is comparable and modifications in dose, infusion time or dosing interval do not bring further benefits. The dosage must be adjustment according to renal function, measured as serum creatinine levels. Creatinine clearance between 30 and 60 ml/min requires a dose reduction for zoledronate [9, 10]. Monitoring of biochemical markers are not suggested. Similar guidelines have been developed by the National Comprehensive Cancer Network (NCCN) [11–14].

There are a number of open questions in clinical practice, which are still not covered by the guidelines. Firstly, there are no clear recommendations on the treatment duration (to date therapy with bisphosphonates is generally continued for 2–5 years), the cessation time-point, or treatment interval / dose adjustment for patients who receive bone-modifying agents for years. Current guidelines of the Arbeitsgemeinschaft Gynäkologische Onkologie (German Gynaecological Oncology Group, AGO) vaguely suggest interval prolongation from every 4 weeks to every 12 weeks for women who have already been taking zoledronate and who have stable disease [15].

Another important issue, especially in terms of health economics, is the question of administration frequency. Currently, a study of the Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK, Swiss Group for Clinical Cancer Research), called REDUSE, is investigating the 1-monthly versus 3-monthly administration of denosumab.

The adjuvant administration of bisphosphonates is still controversial since the relevant available data are in part contradictory [16–19]. The recommendations in the recent

Table 1: Denosumab and bisphosphonates at a glance.

	Bisphosphonates	Denosumab
Indications	Osteoporosis, hypercalcaemia of malignancy, Paget's disease of bone, multiple myeloma, SREs associated with metastatic bone disease in breast (and other) cancers, adjuvant therapy for postmenopausal breast cancer patients, potentially also in premenopausal patients	Unresectable giant cell tumour of bone in adults and skeletally mature adolescents, to increase bone mass in patients at high risk for fracture including ADT for non-metastatic prostate cancer or adjuvant AI therapy for breast cancer, prevention of SREs in patients with bone metastases from solid tumours, treatment of postmenopausal women with osteoporosis at high risk for fracture
Dosing	Clodronate 1600 mg p.o. daily for 3–9 mo,Pamidronate 300–360 mg p.o. for 18–2 mo or 45 mg i.v. until progression, 90 mg iv every 28 d for 12–24 mo,Zoledronic acid 4 mg i.v. every 28 d for 12 moIbandronate 6 mg i.v. every 28 d or 50 mg p.o. daily	60 mg administered as a single subcutaneous injection once every 6 months
Side effects	Acute-phase-like reaction, renal toxicity, osteonecrosis of the jaw	Acute-phase-like reaction, renal toxicity, osteonecrosis of the jaw
Supplementation of calcium and vitamin D	Vitamin D and calcium supplements must not be routinely given during bisphosphonate administration (supplementation may increase the bone resorption and decrease the efficacy of bisphosphonates).Consider vitamin D supplements in people with, or at risk of, vitamin D deficiency. Consider calcium supplements if patient's dietary intake is low.	At least 500 mg calcium and 400 IU vitamin D daily
Monitoring	Serum creatinine prior to each dose, regular dental examinations, electrolytes/haematocrit/haemoglobin	Electrolytes (incl. phosphate and magnesium), signs of infections or skin rash, regular dental examinations

ADT = androgen deprivation therapy; AI = aromatase inhibitor; i.v. = intravenous; p.o. = oral; SKE = skeletal-related event

version of the AGO guideline include adjuvant administration of bisphosphonates to improve the survival of postmenopausal women, based on a meta-analysis by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) [20–22]. Recent data from the adjuvant denosumab in breast cancer study ABC-SG18 suggest that denosumab can be used for all patients with hormone receptor-positive breast cancer who are receiving adjuvant aromatase inhibitor therapy, irrespective of their bone health status and not only when they have an established osteoporosis [8]. Long-term data on risk profiles, especially for elderly and multimorbid patients, are sparse. Last but not least, potential benefits and risks of the preventive use of these medicines are not yet elaborated.

Pathophysiology of bone metastasis

Metastasis is a consequence of a cascade of events and interactions between the tumour cell and the cellular elements in the bone microenvironment [23]. The complex nature of the latter involves multiple pathways that lead to bone metastasis, for example, via receptor activator of nuclear factor-kappa B (RANK) / RANK ligand (osteolysis in skeletal metastasis), Wnt (wingless int) proteins, endothelin-1, or bone morphogenetic proteins (osteoblastic metastasis) [24, 25]. The simplified description of the process is that of progressive growth at the primary site, a vascularisation phase, invasion, detachment, embolisation, survival in the circulation, arrest at the site of a metastasis, extravasation, evasion of host defence and progressive growth [26–28]. However, at the moment of installation of cancer cells, the normal process of bone turnover is disturbed, leading to lytic, sclerotic or mixed metastases. This causes considerable pain and diminishes the possibility of cure [29, 30]. Metastasising tumour cells mobilise and sculpt the bone microenvironment to enhance tumour growth and to promote bone invasion [31, 32]. Research is continuously aiming to elaborate on the pathophysiology of bone metastasis, which is critical to developing new approaches to prevent bone metastasis or inhibit its progression.

Bone pain

Metastatic bone disease is among the most common causes of cancer pain [33–35]. However, a significant number of bone metastases causes no pain and the intensity or occurrence of pain is often disproportionate to the size or degree of bone involvement.

With expanded understanding of the neurophysiology and related pharmacology of cancer bone pain, clinical approaches to alleviating pain have improved. Newer suitable animal models have provided advanced insight into the mechanisms of cancer pain. It is mostly a neuropathic pain, transmitted by primary peripheral nociceptor afferents. They express a great variety of receptors that detect noxious stimuli, including heat, acidity, lipid metabolites and inflammation molecules. In a metastatic lesion with a persistent acidic, inflammatory environment, sustained stimulation occurs, causing hyperalgesia and allodynia. Thus, any medication that antagonises inflammatory mediating immune cells has a place in the treatment of cancer pain. Tumour growth activates mechanically sensitive ion channels by distension of nerve fibres, frequently entrapping them and possibly causing aberrant regeneration. Primary afferent neurones transmit to the spinal cord segment, which explains the effects of neuromodulating drugs [28, 36–38]. Radiotherapy in low doses given in a single session is a safe and effective cornerstone of pain treatment. Radioisotopes are less precise in delivering specific doses of radiation, but have little toxicity and are easily administrated and effective at subclinical sites of metastases. The use of analgesics according to the World Health Organization ladder is recommended.

Standards of care for management of bone pain from cancer should be employed in conjunction with therapy with bone-modifying agents. These potentiate the effects of analgesics in improving metastatic bone pain.

Mode of action

Zoledronic acid

Zoledronic acid is one of the nitrogen-containing antiresorptive agents, which inhibit osteoclast proliferation. Owing to the chemical similarity to inorganic pyrophosphate, zoledronic acid (and other bisphosphonates) is taken up into the hydroxyapatite elements of the osseous extracellular matrix [39–41]. The exact mechanism of apoptosis induction in osteoclasts is not fully understood. However, animal experiments have suggested that zoledronic acid inhibits specific transferases, such as GGTI-298, leading to loss of protein prenylation in osteoclasts, disrupting their cytoskeleton and inducing programmed death [42–44]. The principal effect is reduced bone resorption, which allows more time for bone rebuilding and remodelling [45, 46]. It has also been hypothesised that zoledronic acid might also stimulate osteoblasts' differentiation and bone mineralisation [47, 48]. Zoledronic acid seems to have the highest potential among the bisphosphonates because of its high affinity to bone, especially bones with an increased turnover, such as in tumour patients [49–51].

Denosumab

Denosumab is a human recombinant monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL). Inhibition of RANKL leads to reduced maturation of preosteoclasts into osteoclasts, osteoclast survival and action. As a result, bone resorption is diminished [52, 53].

Adverse effects of bone targeted therapies and their management

Adverse events associated with bone-targeted agents include osteonecrosis of the jaw, hypocalcaemia and renal insufficiency.

Acute-phase reactions

The commonest side effect is the so-called acute-phase reaction (APR), observed in 10 to 30% of breast cancer patients receiving zoledronic acid and denosumab during the first 3 days after treatment [54–57]. APR is an orchestrated global systemic physiological response to tissue injury, infection or inflammation, mediated by an increase in acute phase proteins, which are involved in the restoration of homeostasis. Clinical features are influenza-like, fever, chills, lethargy, increased catabolism of protein, increase

in slow wave sleep, decreased appetite, hypotension, flushing, bone pain, arthralgia and myalgia. Laboratory results mostly show neutrophilia and leucocytosis, an increase in tumour necrosis factor-alpha and a mild increase in interleukin-6. APRs are not life-threatening, but frequently very distressing for the patients and might lead to poor treatment adherence. Although the exact mechanism is not fully understood, it is suggestive that features such as the presence of nitrogen in the bisphosphonate (zoledronate, ibandronate, pamidronate) and intravenous administration induce APR. Most reactions occur after 72 hours, regress spontaneously or with the aid of nonsteroidal anti-inflammatory drugs and antipyretics, and reappear at subsequent application [58–61].

Nephrotoxicity

Since bisphosphonates are renally excreted, a significant part of the administered dose (40–70%) passes by the renal structures [62–64]. Unmetabolised bisphosphonates diffuse passively into tubular cells and accumulate there, which might lead to apoptosis. The clinical presentation is acute kidney injury due to tubular necrosis. Histologically, focal segmental glomerulosclerosis, acute tubular injury, or minimal change disease without glomerular pathology are observed [65–68]. This type of renal insufficiency is eventually reversible after drug discontinuation (zoledronic acid) but can be irreversible (pamidronate). Denosumab seems to be the bone targeted agent least likely to be linked to renal toxicity, making it a medication of choice for patients with pre-existing renal impairment or dialysis-dependent kidney failure [60, 69, 70].

Simple prevention mechanisms apply: close monitoring of serum creatinine, calcium and phosphate levels; sufficient hydration; avoidance of concomitant nephrotoxic agents; and a temporary interruption of medication if the creatinine level increases by ≥0.5 mg/dl in patients with normal baseline renal function and if the creatinine level increases by ≥1.0 mg/dl in patients with abnormal baseline renal function. Zoledronic acid dose should be reduced in patients with impaired renal function (estimated creatinine clearance 30–60 ml/min) [10].

Hypocalcaemia

Hypocalcaemia is very common during bisphosphonate (3.4–6%) and denosumab (5.5–13%) therapy. Lethargy, fatigue, general weakness or tetany may manifest clinically [71–73]. Fatal cases have been reported [74]. Supplementation of vitamin D and calcium is crucial to prevent hypocalcaemia, especially for patients at risk, such as geriatric patients or those with impaired thyroid or parathyroid function, hypomagnesaemia, pre-existing vitamin D or renal insufficiency, with extensive osteoblastic bone metastases, or after gastric surgery. Serum vitamin D3 and albumin-corrected or ionised calcium levels should be checked before treatment and monitored continually during treatment. Low levels should be adequately corrected. As conversion of vitamin D to its active form is progressively impaired with a creatinine clearance <70 ml/min, calcitriol has been suggested as a better option than vitamin D in denosumab-treated patients with impaired kidney function [75].

Osteonecrosis of the jaw

Defects in vascularisation of the maxilla or the mandibular bone may lead to osteonecrosis of the jaw. Well-established risk factors include head and neck radiotherapy, oral surgical interventions, smoking, diabetes, anaemia, renal insufficiency, and use of glucocorticoids, chemotherapeutic and antiangiogenic agents and bisphosphonates [76–79]. Over the last 10 years, cases of jaw-bone necrosis have been associated with the use of bone targeted therapies: denosumab (2.0% of cases) and zoledronate (1.4%). The American Association of Oral and Maxillofacial Surgeons defined osteonecrosis of the jaw as: (1) the presence of clinically evident necrotic bone exposed through the oral mucosa or facial skin which has persisted despite appropriate management for more than 8 weeks in osteoclast inhibitor-treated patients, with (2) no history of irradiation therapy to the jaw. Careful evaluation of the patients' oral health before and during bisphosphonate and denosumab treatment is mandatory. Invasive dental procedures should be avoided [80, 81].

Very rare side effects

Very rarely, bisphosphonates and denosumab can cause scleritis, uveitis and conjunctivitis [82–87], dermatological conditions such as dermatitis, eczema and rashes [54, 88] or atypical femur fractures [89, 90].

Bone targeted therapies in early breast cancer

Zoledronic acid has been reported as a convenient agent to prevent SREs in postmenopausal women in general. The largest group of patients with breast cancer are postmenopausal women with early stage breast cancer, under oestrogen-depleting treatment. Aromatase inhibitors cause bone loss at a rate of about 1 to 3% per year. Therefore, it is crucial to know whether bone targeted therapies in this specific population are reasonable and beneficial. Hadji et al. developed a score to assess the risks of aromatase inhibitor-associated bone loss and direct treatment [91, 92]. Until now, evidence suggests that twice-yearly zoledronic acid is can be recommended for women at risk of aromatase inhibitor-associated bone loss. Bone targeted therapies for these patients are very strongly recommendable to prevent bone loss and accelerated bone turnover associated with aromatase inhibitor therapy if the T-score is <-2.0 or if at least two fracture risk factors are present. In addition to physical activity and calcium / vitamin D supplements, baseline bone mineral density (BMD) measurement is recommended. Yearly BMD monitoring is advised thereafter. For women over the age of 75 years with one or more major risk factors, bone protection therapy with a bisphosphonate is recommended irrespective of baseline BMD. In the case of noncompliance or worsening BDM, intravenous administration is advocated. The SAMBR trial suggested that risedronate is effective in postmenopausal women at risk of fracture while receiving anastrozole [93]. The ARIBON trial evaluated the impact of ibandronate on the same population of breast cancer patients and showed that monthly oral ibandronate is a comparably efficient alternative to other bisphosphonates [94]. The Zometa-Femara adjuvant synergy trial (Z-FAST) suggested that zoledronic acid, when used concomitantly with letrozole, is able to manage bone loss and reduce osteopathic pain in

this specific group of postmenopausal early breast cancer patients [95–97].

In the ABCSG-18 study, the use of denosumab 60 mg twice per year was examined. Denosumab or placebo were given to postmenopausal women receiving aromatase inhibitor therapy. The risk of osteoporosis was decreased by 50%. Furthermore, there were fewer fractures (92 vs 176 fractures, hazard ratio 0.50). The BMD increased by 6 to 10%. Finally, there was a significant survival benefit for patients receiving denosumab, in particular for patients with tumours large then 2 cm [8].

Antitumour effects of bone targeted agents

Recent preclinical and clinical studies have provided solid evidence that bisphosphonates, especially nitrogen-containing bisphosphonates (N-BPs), have antitumour activity.

In the Breast Cancer in Northern Israel study, the use of bisphosphonates for longer than 1 year was associated with a 28% relative reduction in the risk of postmenopausal breast cancer. The Women's Health Initiative (WHI) confirmed these observations for oral bisphosphonates [98, 99]. In addition to primary preventive functions, bisphosphonates are also potent secondary prevention agents. Recent studies suggest that bisphosphonates reduce the risk of bone metastasis in high-risk breast cancer patients.

For zoledronic acid, the antimetastatic effect might result from a decrease of disseminated tumour cells in the bone marrow of women undergoing neoadjuvant chemotherapy for breast cancer [100]. The antiproliferative and proapoptotic, antiadhesive effects of N-BPs are not well understood. *In vitro* and *in vivo* animal models suggest, that the modulating effects on the immune system via activation of macrophages, endothelial cells and tumour cells, as well as by stimulation of T cells and alteration of the bone microenvironment, are of the utmost importance for anticancer activity [51, 101–103]. N-BPs reduce the levels of hypoxia-inducible factor (HIF)-1α, one of the main proteins of the tumour environment, leading to disturbed anaerobic metabolism in tumour cells and a decrease in vascular endothelial growth factor secretion [104–106]. Since overexpression of HIF-1α is a negative prognostic factor, bone targeted therapies might improve disease-free survival and overall survival in some breast cancer settings. Moreover, N-BPs have been shown to inhibit invasion and angiogenesis, and thus tumour progression and metastatic spread [107]. N-BPs alter the bone marrow microenvironment, making it more hostile toward tumour cells. Thus, dormant micrometastases are less likely to be formed while systemic chemotherapy is being applied, preventing cancer recurrence [108]. Similar anticancer functions have been suggested for denosumab, since RANKL is crucial for proliferation of mammary epithelium and potentially directly contributes to mammary tumourigenesis [109–112].

Evidence-based efficacy of bone targeted therapies in breast cancer

Bone is the most common metastatic site in breast carcinoma [113–115]. Despite a decreasing incidence, bone metastases are extremely relevant for clinical progress and outcome, since the high rate of resultant SREs, such as fractures or hypercalcaemia, reduce quality of life and survival. Bone metastases are associated with more aggressive tumours, occurring primarily in younger women with larger tumour size, higher tumour grade or several positive nodes. Therefore, the life expectancy of patients with bone metastases is approximately 2.3 years, and less than a year if visceral metastases are also present [116–119].

Bisphosphonates are the treatment of choice for the prevention of SREs, for tumour-associated hypercalcaemia and for bone pain.

Meta-analyses of randomised controlled trials in advanced breast cancer with clinically evident bone metastases including patients with bone metastases showed the efficacy of intravenous bisphosphonates in preventing skeletal events (43%) compared with oral bisphosphonates. Zoledronate achieved the best results, followed by pamidronate, ibandronate and clodronate. Significant improvements were also seen in quality of life and in bone pain. Overall, a number of phase III trials demonstrated that bisphosphonates lead to a significant improvement of the quality of life, not only by reducing SREs, bone pain and hypercalcaemia, but also by diminishing the need for radiation therapy [120–124]. As expected, intravenous zoledronic acid was superior to other bone targeted agents [125–128].

Overall survival is not influenced by bisphosphonate use in women with advanced breast cancer. Intriguingly, patients without clinically evident bone metastases did not profit from bisphosphonate therapy in terms of the incidence of skeletal events, but their overall survival was significantly better, even though there was a high variability within the group.

So far, the consensus recommends denosumab as preferred agent owing to its superior efficacy compared with zoledronic acid, and simple subcutaneous route of administration. Since the price difference between denosumab and (now also generic) bisphosphonates is significant, various trials have investigated whether the application intervals can be extended, allowing for a reduced socioeconomic burden and number of adverse events. The Cancer and Leukemia Group B (CALGB) 70604, OPTIMIZE-2, ZOOM, and BISMARK trials showed noninferiority of zoledronic acid administration every 3 months (instead of monthly) for 2 years. Thus, seen from both a clinical and financial perspective, zoledronic acid given every 3 months is a reasonable alternative.

Clinical trials involving bone targeting therapies are summarised in table 2 (metastatic disease) and table 3 (non-metastatic disease).

Markers of bone turnover as tools for monitoring treated patients

Enzymes and protein products released during bone metabolism can be used to noninvasively assess bone turnover [135, 136]. They are still controversial for monitoring therapy in osteoporosis [137–140]. However, they have gained the attention of oncologists, who can track pathological processes that reflect bone destruction through bone metastasis [141–144]. Since bone targeted therapies act on skeletal cells, laboratory values that reflect osteoblastic and osteoblastic activity can suggest the individual effects of

therapeutic agents. This is an elegant method to direct the antiresorptive approach, reduce the number of bone density tests, and detect potential new metastatic events and bone disease progression, since bone turnover markers respond quickly and significantly to bone-targeted (and antineoplastic) therapies, which are associated with a better prognosis [140, 145–147]. So far, there is not enough evidence to determine whether bone turnover markers are valid also for the early diagnosis of bone metastases [148, 149].

In breast cancer patients, bone metastases lead to an increase in bone turnover, which might be a paraneoplastic or/and a neoplastic effect. At the same time, the increased bone resorption leads to skeletal deficits, which are localised diffusely at different bone sites [150, 151].

Markers of bone formation include serum osteocalcin, total alkaline phosphatase, type 1 procollagen and bone-specific alkaline phosphatase. Less well characterised are bone resorption markers: urinary hydroxyproline, total pyridinoline, free deoxypyridinoline, collagen type 1 cross-linked N-telopeptides (NTx), urinary or serum collagen type 1 cross-linked C-telopeptides (CTx), bone sialoprotein and tartrate-resistant acid phosphatase-5b.

The cross-linked NTx are best for predicting skeletal morbidity and death, and monitoring response during zoledronic acid treatment, in patients with bone metastases, but their sensitivity is low (<30%) [148, 152]. To date, bone markers do not have enough power to have diagnostic or prognostic value, but in combination with other diagnostic modalities, they have great potential to improve and to personalise the therapeutic approach.

The important role of general practitioners in antiresorptive therapy of breast cancer patients

The benefits of antiresorptive therapy for breast cancer patients, in both adjuvant and palliative settings, are undeniable, but there is a great number of patients who will not profit from the therapy due to noncompliance (self-induced or due to an inability to understand schedules, dosages, etc.). Elderly patients are especially at risk of limited quality of life due to preventable SREs, simply because they lack support in therapy planning. As oncologists mostly focus on cancer-specific therapies, patients ignore or are less educated about necessary adjacent therapies, such as bisphosphonates or denosumab, including potential supplementations with calcium or vitamin D. In addition, the frequent, mild side effects of the antiresorptive therapies might lead to their discontinuation if the patients are not adequately educated on their importance [153].

The role of the general physician in this specific population is thus crucial, and collaborative efforts lead to an improvement of the quality of life of the patient. Especially in the course of treatment when a stabilisation phase has been reached, frequent contact with the family doctor can assure the continuation of preventive treatment. Proper education and encouragement of the patient to continue antiresorp-

Table 2: Selected phase III trials with bone targeting agents in metastatic breast and other cancer types.

Study	Type of cancer	Drug	Endpoints	Results
Vadhan-Raj et al. 2012 [129]	Advanced cancer (excluding prostate and breast cancer)	Monthly intravenous ZA vs subcutaneous denosumab	Time to first on-study SRE or hypercalcaemia of malignancy, time to first bone radiotherapy; SMR, pain severity	Denosumab better in terms of pain, delaying time until radiation therapy
Stopeck et al. 2010 [54]	Bisphosphonate-naive advanced breast cancer	Monthly intravenous ZA vs subcutaneous denosumab	Time to first on-study SRE, time to first and subsequent (multiple) on-study SREs in terms of toxicity	Denosumab superior to ZA in delaying time to first SRE, time to first and subsequent SREs in terms of toxicity
Costa et al. 2013 [125]	Breast cancer with at least 1 bone metastasis	ZA 4 mg every 3-4 weeks or oral IA 50 mg daily.	One or more SREs, time to first SRE, SMR, in patients with and without baseline pain	IA inferior to ZA for reducing the overall risk of skeletal events; IA noninferior to ZA in delaying the time to the first SRE
Henry et al. 2011 [130]	Bone metastases from solid tumours (apart from breast and prostate) and multiple myeloma	Denosumab vs ZA	Time to first on-study SRE	Denosumab noninferior (trending to superiority) to zoledronic acid in terms of delaying time to first SRE and administration (s.c. vs i.v.)
Berenson et al. 2001 [131]	Solid lung cancer and bone metastases	ZA 4 mg vs placebo 3 weekly for 9 months	Proportion of patients receiving radiation to bone, other SREs, BMD, bone marker, status, pain and analgesic scores, safety	Indifferent for time to progression of bone lesions and survival
Scagliotti et al. 2012 [132]	NSCLC and bone metastasis	Denosumab120 mg every 4 weeks vs ZA 4 mg every 4 weeks	Overall survival	Denosumab significantly improved overall survival
Saad et al. 2012 [133]	Patients with bone metastases secondary to solid tumours or myeloma	Denosumab s.c. 120 mg or ZA i.v. 4 mg, every 4 weeks	Oral adverse events	Osteonecrosis of the jaw did not differ significantly between treatment groups

BMD = bone mineral density; IA = ibandronic acid; i.v. = intravenous; s.c. = subcutaneous; SME = skeletal morbidity rate; SRE = skeletal-related events; ZA = zoledronic acid

Table 3: Phase III trials with bone targeting agents in nonmetastatic breast cancer.

Study	Type of cancer	Drug	Endpoints	Outcome
Gnant et al. 2016 [129]	HR^+ nonmetastatic breast cancer and low bone mass, receiving adjuvant aromatase inhibitor therapy	Placebo vs denosumab 60 mg s.c. every 6 months	Disease-free and overall survival in postmenopausal (natural or induced) breast cancer patients	Denosumab improved overall and disease-free survival of HR+ breast cancer patients receiving aromatase inhibitors
Ellis et al. 2008 [134]	HR^+ nonmetastatic breast cancer treated with adjuvant aromatase inhibitor therapy	Placebo vs denosumab 60 mg s.c. every 6 months	Percentage change from baseline at month 12 in lumbar spine BMD	Denosumab increased lumbar spine BMD

BMD = bone mineral density; HR^+ = hormone-receptor positive; s.c. = subcutaneous

tive therapy, with a recommended lifestyle (proper nutrition with sufficient vitamin D and calcium, physical activity, moderate weight), have a huge impact on final success – the longest possible period without SREs and pain. Jacob et al. were able to demonstrate that women with metastatic breast cancer aged >70 years were at a lower risk of discontinuing treatment with bisphosphonates than younger patients [154]. Partridge et al. found that women aged <45 and >85 were at a higher risk of therapy discontinuation [155]. Although there are several potential reasons explaining this non-linear relation between age and therapy adherence, one is surely the closer and more regular contact with family physicians. Similar conclusions were also reached in other studies [156–159]. Also, the recommended regular dual energy X-ray absorptiometry and dental check-ups, which also influence outcome, are better organised and explained by a trusted general practitioner [160, 161].

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