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Bone-Targeted Therapy in Metastatic Breast Cancer – All Well-Established Knowledge?

Simon P. Gampenrieder Gabriel Rinnerthaler Richard Greil

IIIrd Medical Department with Hematology, Medical Oncology, Hemostaseology, Infectious Diseases and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute (SCRI) with Laboratory of Immunological and Molecular Cancer Research (LIMCR) and Center for Clinical Cancer and Immunology Trials (CCCIT), Paracelsus Medical University Salzburg, Salzburg, Austria

Keywords

Metastatic breast cancer · Bone metastasis · Bone-targeted therapy · Bisphosphonates · Denosumab

Summary

Bone-targeted therapies like bisphosphonates (zoledronic acid or pamidronate) or denosumab are recommended in all patients with metastatic breast cancer and bone metastases, whether they are symptomatic or not. The choice between these 2 different agents, however, remains open. In this review, we critically discuss the emerging evidence for direct anti-tumor activity of bone-targeting agents, the utility of bone turnover markers for treatment decision and efficacy prediction, as well as the safety and financial aspects of bisphosphonates and denosumab. Furthermore, we provide a possible therapeutic algorithm, and present new pharmacologic agents which are being investigated for the treatment of metastatic bone disease.

Introduction

Accelerated bone loss is a frequent problem in patients with breast cancer. Besides treatment-induced bone loss due to endocrine therapies, approximately 70% of patients with advanced disease experience bone metastases [1], which can lead to so-called skeletal-related events (SREs) defined as pathological fractures, hypercalcemia, spinal cord compression, and the need for surgical intervention and/or radiation therapy. SREs are associated with shortened survival, deterioration of quality of life, and significant medical care costs [2–4]. Bisphosphonates (BPs) are the most frequently used pharmacologic agents to prevent SREs and treatment-induced bone loss in patients with metastatic breast cancer [5, 6]. Better understanding of bone remodeling led to the development of denosumab, a fully human monoclonal antibody against receptor activator of NFκB ligand (RANKL). Denosumab shows even higher efficacy in the prevention of SREs and treatment-induced bone loss than BPs [7, 8]. Despite the beneficial effects of BPs and RANKL-targeting agents, these agents are both associated with significant side effects, and the treatment of bone resorption and its deleterious clinical consequences in metastatic breast cancer still require further improvement. In this review, we critically discuss the emerging evidence for direct anti-tumor activity of bone-targeting agents, the utility of bone turnover markers for treatment decision and efficacy prediction, as well as the safety and financial aspects of BPs and denosumab. Furthermore, we present new pharmacologic agents which are being investigated for the treatment of metastatic bone disease.

Bone-Targeted Effects of Established Antiresorptive Agents

Bisphosphonates

Mode of Action

BPs are synthetic analogues of naturally occurring pyrophosphates, and based on their activity and chemical structure they are chronologically classified into 3 generations (table 1). BPs form bonds with crystal surfaces and inhibit hydroxyapatite crystal dissolution in bone tissue. In addition to this physicochemical stabilization of the bone structure, BPs are inter-

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Richard Greil, MD
IIIrd Medical Department
Salzburg Cancer Research Institute (SCRI)
Paracelsus Medical University Salzburg
Müllner Hauptstraße 48, 5020 Salzburg, Austria
r.greil@salk.at

Table 1. The 3 generations of bisphosphonates

1st Generation	2nd Generation	3rd Generation
clodronate	alendronate	zoledronat
etidronate	ibandronate	minodronate
	pamidronate	risedronate

nalized by endocytosis from osteoclasts and metabolically incorporated into nonhydrolyzable analogues of adenosine triphosphate (ATP). These metabolites accumulate within osteoclasts, inhibit their absorption capacity, and induce apoptosis by inhibiting ATP-dependent enzymes. Nitrogen-containing BPs (N-BPs), second- and third-generation BPs, furthermore inhibit farnesyl diphosphate (FPP) synthase, a key enzyme of the mevalonate pathway. This capacity makes zoledronic acid (ZA) in some preclinical experiments up to 10,000-fold more potent than the first generation BP clodronate. Loss of FPP synthesis and its downstream metabolites prevents posttranslational modifications of small GTPases such as Ras, Rab, Rho, and Rac. These crucial signaling proteins regulate a variety of cell processes important for osteoclast function. Furthermore, disruption of the mevalonate pathway leads to an accumulation of isopentenyl pyrophosphate (IPP) in osteoclasts, which is converted to a cytotoxic ATP analogue called ApppI.

Clinical Activity

Several phase III trials demonstrated the ability of BPs to prevent and delay SREs in women with advanced breast cancer and clinically evident bone metastases [9–13]. A recent meta-analysis summarized 9 trials including 2,806 breast cancer patients comparing BPs with placebo or no BP, showing that BPs reduced the SRE risk by 15% (relative risk (RR) 0.85, 95% confidence interval (CI) 0.77–0.94; p = 0.001) [14]. In addition, BPs significantly reduced bone pain in 6 out of 11 studies, and improved global quality of life in 2 out of 5 studies; however, no effect on survival was observed in breast cancer patients with bone metastases [14]. As expected from preclinical studies [15], intravenous ZA showed the highest efficacy in reducing the risk of skeletal complications when compared to other BPs [16–20], representing therefore the most commonly used drug in oncological settings. The OPTIMIZE-2 trial, a phase III trial presented at the ASCO annual meeting 2014, demonstrated that after 1 year of treatment the dosing frequency of ZA can be reduced to 1 administration every 12 weeks without compromising effectiveness in women with breast cancer and bone metastases. The difference in SRE rate between the 2 arms was 1.2% (p = 0.724), and the frequency of adverse events (AEs) was lower in the 12-week arm; however, this was not statistically significant (renal AEs 7.9 vs. 9.6%, and osteonecrosis of the jaw (ONJ) 0 vs. 1.0%) [21].

Denosumab

Mode of Action

Denosumab is a fully humanized IgG_2 monoclonal antibody against RANKL. RANKL is a member of the tumor necrosis factor (TNF) superfamily, and is expressed on the surface of osteoblasts. Soluble RANKL is released into the bone microenvironment where it binds to and activates its receptor RANK on immature osteoclasts, acting as a key factor for osteoclast differentiation and activation. The expression level of RANKL is influenced by different hormones and cytokines such as macrophage-colony stimulating factor, TNF, prostaglandins (e.g. PGE2), steroids, parathyroid hormone (PTH), PTH-related protein (PTHrP), and interleukins (IL)-1, -6, -8 and -11 [22]. In bone metastases, these and other factors like macrophage inflammatory protein (MIP) 1α are secreted by tumor cells as well, leading to increased osteoclast activity. Furthermore, tumor cells excrete factors like Dickkopf-1 (DKK-1) and activin A that inhibit osteoblast differentiation. On the other hand, bone resorption releases growth factors (transforming growth factor β, insulin-like growth factors, fibroblast growth factors, and platelet-derived growth factor) from the bone matrix that stimulate tumor growth [23]. The monoclonal antibody denosumab binds RANKL and prevents bone resorption by inhibiting both mature osteoclast function and osteoclast differentiation, thereby interrupting this vicious cycle of bone destruction [7].

Clinical Activity

Three double-blind, phase III, registration trials with identical study design compared subcutaneous denosumab (120 mg, every 4 weeks) with intravenous ZA (4 mg adjusted for creatinine clearance, every 4 weeks) in patients with bone metastases secondary to breast cancer (n = 2,046), castration-resistant prostate cancer (n = 1,901), and other tumors including non-small cell lung cancer (n = 702), myeloma (n = 180) and other types of solid tumors (n = 894) [24–26]. In breast cancer patients, denosumab was superior to ZA in delaying time to first SRE, which represented the primary study endpoint. In addition, the secondary endpoint, time to first and subsequent SREs, was favoring denosumab [25]. Similar results were reported in patients with hormone-refractory prostate cancer [26]. In patients with bone metastases secondary to advanced-stage solid tumors and myeloma, however, denosumab failed to demonstrate superiority over BPs [24]. When excluding the myeloma cohort (representing 10% of the study population), an ad hoc analysis showed finally that denosumab was superior also in the solid tumor subset of this study [27] (table 2). The overlapping design of the 3 trials allowed a preplanned, integrated analysis of safety and efficacy data [8]. Overall, denosumab was superior to ZA in delaying time to first on-study SRE by a median of 8.2 months and reducing the risk of a first SRE by 17% (hazard ratio (HR) 0.83, 95% CI 0.76–0.90; p < 0.001). This superiority was consistent in various patient sub-

Table 2. Phase III trials comparing zoledronic acid (4 mg every 4 weeks intravenously) with denosumab (120 mg every 4 weeks subcutaneously)

Author, year [ref.]	Patients, n	Population	Results (primary endpoint)
Stopeck et al., 2010 [25]	2,046	breast cancer	delayed time to first on-study SRE (HR 0.82, p < 0.001 non-inferiority, p = 0.01 superiority)
Fizazi et al., 2011 [26]	1,901	prostate cancer	delayed time to first on-study SRE (HR 0.82, p = 0.0002 non-inferiority, p = 0.008 superiority)
Henry et al., 2011 [24]	1,776	solid tumors (except breast or prostate) and multiple myeloma	delayed time to first on-study SRE (HR 0.84, p = 0.0007 non-inferiority, p = n.s. superiority)
Henry et al., 2014 [27]	1,597	solid tumors (except breast or prostate) with multiple myeloma excluded	delayed time to first on-study SRE (HR 0.81, p = 0.017 superiority)

SRE = Skeletal-related events; HR = hazard ratio; n.s. = not significant.

groups (prior SRE status, age). Denosumab was also superior to ZA in reducing the risk of multiple SRE by 18% (RR 0.82, 95% CI 0.75–0.89; p < 0.001) [8]. Based on the clinical activity, denosumab is approved not only for treatment of osteoporosis in postmenopausal women with high risk of fracture but also for bone loss in patients with cancer and bone metastases.

Markers of Bone Turnover as Surrogate Endpoints

Biochemical markers of bone formation and resorption, termed as bone turnover markers, are reflecting tumor-induced changes of bone metabolism. One of the most intensively investigated markers is urine amino-terminal cross-linked telopeptide of collagen type I (uNTx). Patients with high or moderate levels of uNTx have a 2-fold increased risk of skeletal complications and disease progression compared to patients with low uNTx levels (p < 0.001) despite treatment with ZA (n = 1,462) or pamidronate (n = 362) [28]. Furthermore, persistently elevated uNtx after 3 months of ZA correlates with worse overall survival (OS) [29].

In a phase II trial conducted in patients with bone metastases caused by various tumor types, only patients with uNTx levels above the normal range (> 50 nmol/l/mM creatinine) despite ongoing intravenous BP treatment for at least 8 weeks were included [30]. Patients were randomly assigned to continue BPs or receive subcutaneous denosumab (180 mg every 4 weeks or 180 mg every 12 weeks) for 25 weeks. A normalization of uNTx levels at week 13, the primary endpoint of this study, was achieved by 71% of patients in the denosumab arms, compared with 29% of patients in the BP arm (p < 0.001) translating into lower SRE rates during the treatment phase in denosumab-treated patients. Additionally, in a retrospective analysis of the ZA phase III database, a normalization of initially elevated uNTx levels correlated with improved OS [27].

Other bone turnover markers under investigation are serum C-telopeptide (sCTx), aminoterminal propeptide type-1 procollagen (P1NP), osteocalcin, bone-specific alkaline phosphatase (BSAP), and tartrate-resistant acid phosphatase 5b (TRAP-5b).

Since bone lesions are generally considered non-measurable according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors version 1.1), the assessment of therapy response in the case of bone-only disease is frequently difficult. There therefore exists a great clinical need for bone turnover markers corresponding to treatment response, especially if tumor markers like CA15–3 are not elevated.

Antitumor Effects of Bone-Targeted Agents: Preclinical Evidence

Bisphosphonates

There is growing preclinical evidence that the new generation of N-BPs harbor antitumor activity in addition to their effect on bone mineral density, while for denosumab similar data are missing.

BPs interact with macrophages, endothelial cells, and tumor cells, and stimulate the cytotoxicity of γδ T-lymphocytes, a subset of human T cells that exhibits anticancer activity [31]. In a variety of cancer cell lines, BPs have demonstrated the ability to induce apoptosis as well as the capacity to decrease tumor cell adhesion, migration, and invasion [32].

Inhibition of the FPP synthetase seems to be the most important underlying antitumor mechanism of N-BPs. Disruption of the mevalonate pathway not only prevents posttranslational modifications (prenylation) of the small GTPases Ras, Rab, Rho, and Rac in tumor cells, but also leads to intracellular accumulation of IPP [33], mediates immuno-controlling effects on γδ T-lymphocytes, and promotes antiangiogenic activity [34]. BPs also directly influence angiogenesis by degradation of hypoxia-inducible factor (HIF)-1α, leading to a decrease in vascular endothelial growth factor secretion in vitro [35].

Moreover, ZA inhibits tumor proliferation and migration by affecting the interaction between bone marrow-derived

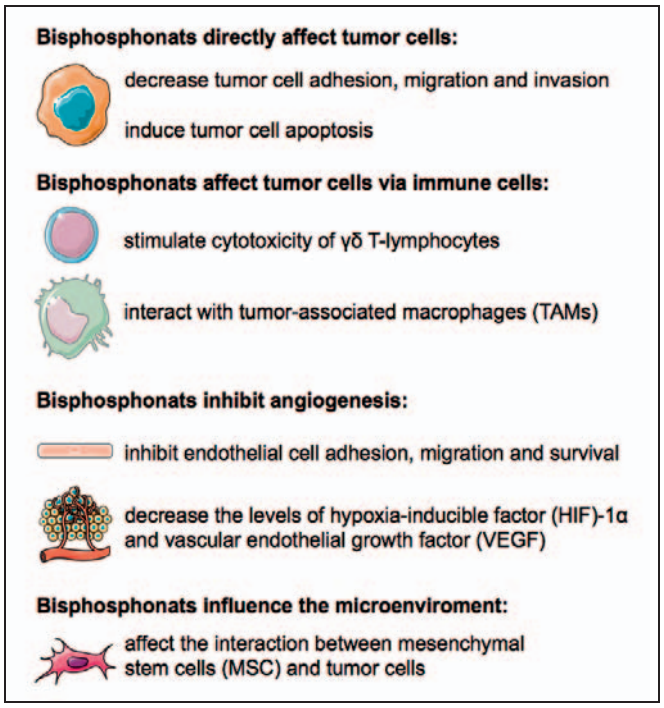

Fig. 1. Potential mechanisms of anti-tumor activity of bisphosphonates (drawings generated using Servier Medical Art; *www.servier.com*).

mesenchymal stem cells (MSCs) and breast cancer cells in vitro [36]. By affecting the recruitment of MSCs by primary tumors, ZA might influence an important mechanism of tumor progression. In addition, ZA sensitizes endothelial cells to TNF-induced (caspase-independent) apoptosis through inhibition of the FAK-PKB/Akt pathway [31] (fig. 1).

Denosumab

Whether denosumab harbors anticancer activity as well is largely unknown. RANKL and RANK are known to play an important role in mammary gland development [37], and studies in mouse models have shown that the RANKL-RANK pathway is directly involved in mammary tumorigenesis [38, 39]. In addition, RANKL production by tumor-infiltrating regulatory T cells promoted the development of pulmonary metastases in a RANK-positive breast cancer model [39]. Recent microarray analysis in human breast cancer biopsies showed that low RANK messenger RNA (mRNA) levels correlated with longer OS and disease-free survival, and, interestingly, a relatively increased expression of RANK mRNA was found in the basal-like breast cancer subtype when compared with non-basal-type tumors [40].

Data from a preclinical study in breast cancer cell lines and umbilical vein endothelial cells (HUVECs) as well as in vivo vascularization models supported the potential antiangiogenic and anticancer activity of ZA in vitro and in vivo but failed to demonstrate a similar effect of denosumab [41]. Additional studies are clearly warranted to elucidate the potential anticancer activity of denosumab.

Antitumor Effects of Bone-Targeted Agents: Clinical Evidence

Bisphosphonates

Clinical data supporting an antitumor effect of BPs are primarily derived from cancer prevention studies and adjuvant trials. Both the Women's Health Initiative Observational Study and the Breast Cancer in Northern Israel Study showed a significant reduction in the risk for breast cancer in women who received BPs (32 and 28% RR reduction, respectively) [42, 43]. Furthermore, it has been shown that ZA given as a monthly dose in combination with chemotherapy reduced the number of disseminated tumor cells in the bone marrow of early breast cancer patients more efficiently than chemotherapy alone [44–47]. This effect might explain the results of the recently presented meta-analysis of 22 trials including almost 18,000 early breast cancer patients, where the addition of BPs to standard adjuvant treatment significantly reduced the risk for distant recurrence and breast cancer death [48].

In the metastatic setting, ZA seems to prolong OS in patient with metastatic bone disease from different solid tumors only in patients with high uNTx levels at baseline, but these data have to be interpreted with caution because of their exploratory nature [49]. A meta-analysis of 9 trials including 2,806 metastatic breast cancer patients comparing BPs with placebo or control revealed no effect on OS in the overall population [14], while in lung cancer or prostate cancer such an effect was observed [50, 51].

Denosumab

Denosumab significantly increased bone metastases-free survival compared with placebo in a phase III trial including 1,432 men with non-metastatic castration-resistant prostate cancer at high risk of bone metastasis (prostate-specific antigen (PSA) ≥ 8.0 μg/l or PSA doubling time ≤ 10.0 months, or both) by a median of 4.2 months (HR 0.85, 95% CI 0.73–0.98; p = 0.028). However, no influence on OS was seen when compared to placebo (HR 1.01, 95% CI 0.85–1.20; p = 0.91) [52]. A meta-analysis summarizing trials comparing denosumab with ZA in patients with bone metastases secondary to breast cancer, prostate cancer, other solid tumors, or multiple myeloma neither showed any difference in OS (HR 0.99, 95% CI 0.91–1.07; p = 0.71) nor in disease progression (HR 1.02, 95% CI 0.95–1.08; p = 0.63) [8].

Safety of Bone-Targeted Therapies

Bisphosphonates

The most frequent side effects from intravenous BPs are fever and myalgias (acute-phase reactions, APR), which may occur in up to 55% of cases mostly within 24 h of the first infusion. Antipyretic and anti-inflammatory agents usually provide easy relief [53]. Importantly, not all BPs induce APR to the

same extent (ZA more than the others). Pathophysiologically, APR is attributed to a transient release of pro-inflammatory cytokines (mostly TNF-α, IL-6, interferon-γ) from γδ T-lymphocytes, which are activated in response to BPs.

Electrolyte alterations, including hypophosphatemia, hypocalcemia, and hypo- or hypermagnesemia, are other known disturbances associated with intravenous BPs. Therefore, prophylactic substitution of calcium and vitamin D are recommended [53].

Renal toxicity is a major issue with intravenous N-BPs. An increase in creatinine levels from baseline is reported in about 10% of patients receiving BP treatment, but the frequency varies depending on the specific BP, the dose schedule, the duration of administration, and concomitant medications. Creatinine clearance should be measured prior to administration of intravenous BPs, and dose adjustments according to treatment guidelines as well as prolonged infusion times may help to reduce this problem [53].

ONJ is an infrequent AE reported in 1.3% of patients with bone metastases receiving ZA [8]. Risk factors for the development of this serious side effect are poor oral hygiene, history of dental extraction or use of dental appliance, preexisting dental or periodontal disease, usage of glucocorticosteroids and antiangiogenic agents, or radiation therapy [53, 54]. Therefore, before starting intravenous N-BP treatment, patients should have a dental examination, and surgical dental procedures, if required, should ideally be completed before initiation [55].

Oral BPs like ibandronate or clodronate may in addition provoke esophageal or gastric irritation and diarrhea [16].

Denosumab

Renal AEs and APR occur significantly less frequently with denosumab when compared with ZA [8]. Unlike BPs, denosumab is not excreted via the kidneys but is eliminated by intracellular catabolism in phagocytes, similar to the clearance mechanism of other therapeutic monoclonal antibodies, and can therefore be safely used in patients with chronic kidney disease [56, 57].

In the registration trials, hypocalcemia of any grade was 2-fold higher in the denosumab group compared to ZA, and severe hypercalcemia (< 1.75 mmol/l) was reported in 3.1 versus 1.3% [8]. Several case reports of prolonged severe hypocalcemia, consistent with our own experience, are reported in the literature [58, 59]. Elucidation of predictive factors for this high bone turnover state caused by denosumab is therefore greatly needed. Baseline calcium serum levels within the normal range, as recommended in the prescribing information, should be a mandatory prerequisite.

In a meta-analysis comparing denosumab with ZA, ONJ occurred at a higher rate in the denosumab arm; however, the difference was not statistically significant (1.8 vs. 1.3%; p = 0.13) [8]. In contrast to BPs, dental procedures are thought to be safe after a therapy pause of only 26 days (compared to 6 months with N-BPs) because of the much shorter half-life of denosumab.

A statistically increased risk of pancreatitis and serious infections, including endocarditis, erysipelas, and infectious arthritis, has been reported with this drug as well [53].

Economic Considerations

SREs are associated with relevant medical care costs. A retrospective study in metastatic breast cancer in the US showed that the average cost of treatment of an SRE was $13,940 (95% CI $11,240–16,856) [2]. Although denosumab has demonstrated benefit over ZA in preventing or delaying SREs in different phase III trials, ZA is less expensive, and the higher efficacy of denosumab has to be weighed against the incremental costs. On the other hand, the ease of subcutaneous injection and the lack of a need to closely monitor creatinine levels have to be taken into account. The economic point of view becomes even more important since the economic pressure on healthcare systems all over the world is growing, and ZA became generic in the EU in November 2013.

Future Perspectives

Targeting Signaling Pathways

A number of new compounds are under investigation for the treatment of metastatic bone disease (fig. 2). Agents targeting the Src family kinases (e.g. dasatinib, saracatinib, KX2–391, and bosutinib) showed promising preclinical and early-phase clinical data. A recently presented phase II trial of dasatinib in combination with letrozol in metastatic breast cancer not only showed a reduced percentage of patients with a T-score < –1.5 but also a significantly longer progression-free survival (PFS) in the combination arm compared with letrozol alone [60]. A phase II trial investigating bosutinib, which inhibits the Src/Abl tyrosine kinase as well as many other kinases, showed promising antitumor activity as single agent as well; however, no consistent changes in the levels of bone turnover markers were seen [61].

Odanacatib (MK-0822), an inhibitor of cathepsin K, suppressed uNTx similarly to ZA after 4 weeks of treatment in women with breast cancer and bone metastases [62]. A phase III trial in metastatic prostate cancer, however, has been withdrawn prior to enrollment for administrative reasons (NCT00691899), and further development of odanacatib in the oncology field is on hold.

Exploratory analyses from the BOLERO-2 trial in metastatic breast cancer showed that the mTOR inhibitor everolimus may have beneficial effects on bone metabolism, potentially reducing bone resorption and contributing to a bone-protective effect [63].

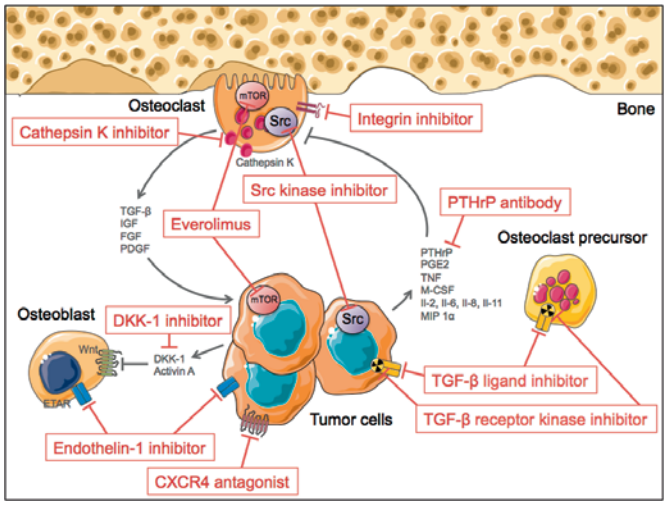

Fig. 2. Promising compounds under investigation for the treatment of metastatic bone disease (drawings generated using Servier Medical Art; *www.servier.com*).

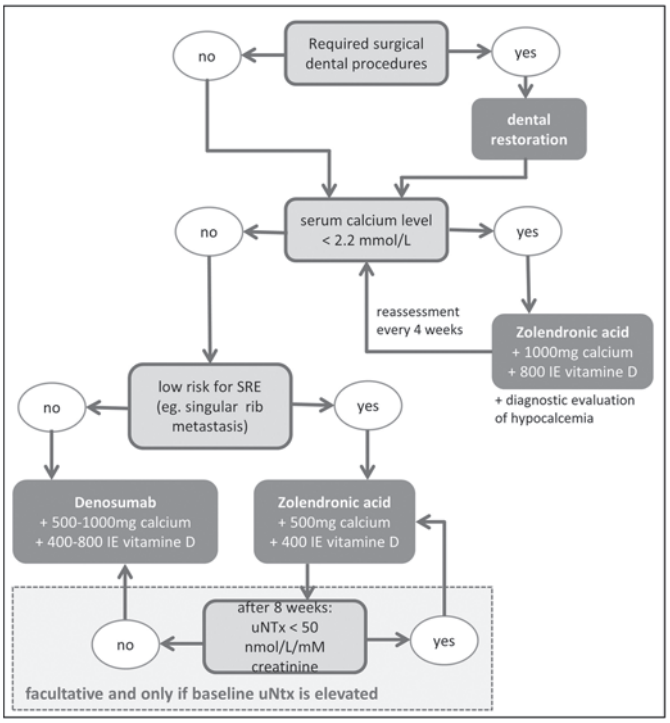

Fig. 3. Proposed treatment decision algorithm.

Other promising targets like chemokine receptor 4 (CXCR4), parathyroid hormone-related peptide (PTHrP), transforming growth factor β (TGF-β), DKK-1, integrins, or endothelin-1 are under investigation, but clinical data in breast cancer are still missing [64, 65].

Radiopharmaceuticals

Radium-223 (Xofigo®, Bayer Healthcare, Leverkusen, Germany), a first-in-class alpha-emitting radiopharmaceutical, acts by delivering cytotoxic alpha-particle radiation to sites of bone metastasis. This highly targeted cytotoxic effect on bone metastases has led to the approval for the treatment of patients with castration-resistant prostate cancer and symptomatic bone metastases with no known visceral metastatic disease. A phase III trial in this population (n = 921) showed that radium-223, compared with placebo, significantly improved median OS by 3.6 months (HR 0.70, 95% CI 0.58–0.83; $p < 0.001$), significantly delayed the time to first SRE (HR 0.66, 95% CI 0.52–0.83; $p < 0.001$), and improved quality of life [66]. In breast cancer, only phase II data are available: 21 patients with advanced bone-dominant disease not being candidates for further endocrine therapy received radium-223 (50 kBq/kg intravenously) every 4 weeks for 4 cycles [67]. Therapy resulted in a significant reduction in uNTx and BSAP, and the metabolic response rate (defined as ≥ 25% reduction in maximum standardized FDG uptake value from baseline in positron emission tomography/computed tomography) was 32% at week 9 and 42% at week 17. Treatment was generally well-tolerated, and most AEs considered to be possibly or probably treatment-related were mild and reversible, with nausea, diarrhea, anorexia, vomiting, constipation, fatigue, and bone pain being the most frequently reported (mostly grade 1–2; grade 3 AEs occurred in only 5 patients). Grade 3 hematologic AEs were infrequent as well, with 1 case of anemia and 1 case of neutropenia [67]. Further studies with radium-223 in this patient population are being planned.

Other bone-seeking radiopharmaceuticals like phosphorus-32, strontium-89, rhenium-186, rhenium-188, and samarium-153 have shown promising results in terms of reducing pain from diffuse skeletal metastases [68], but further data are needed to assess their effect on disease progression.

Conclusion – All Well-Established Knowledge?

Bone-targeted therapies are of undisputed importance in the multimodal therapy of metastatic breast cancer involving the bone. Initiation of an N-BP (ZA or pamidronate) or denosumab is recommended in all patients with metastatic breast cancer and bone metastases, whether they are symptomatic or not [69]. The best choice between these 2 different agents, however, remains open. The guidelines from the American Society of Clinical Oncology (ASCO) state that there is insufficient evidence to demonstrate greater efficacy of one bone-modifying agent over another [70]. The greater efficacy, demonstrated in clinically relevant endpoints like time to first and subsequent SRE in a prospective double-blind phase III trial [25], might be considered in favor of denosumab. The ease of subcutaneous injection and the lack of a need to closely monitor creatinine levels are further advantages. The lack of differences in PFS and OS as well as in the rate of ONJ, the significantly higher costs, and the higher rate of grade 3 hypocalcemia may, however, influence treatment

choice in favor of BP, especially if the risk for an SRE is low. Another possible clinical strategy could be to reserve denosumab for patients whose uNTx levels failed to normalize after BP treatment. A possible algorithm for treatment choice is provided in figure 3.

Many questions still remain. What is the optimal treatment duration? What is the role of newer bone-targeting agents? How should radiopharmaceuticals be included into the therapeutic algorithm? Ongoing studies will answer some of these questions, and future research efforts may provide additional encouraging treatment options for patients with metastatic bone disease.

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