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Breast Cancer: Rank Ligand Inhibition

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Key Words

Bisphosphonates · Bone metastases · Denosumab · Osteoporosis · Cancer treatment-induced bone loss

Summary

Breast cancer and bone health are closely linked. Early menopause induced by gonadotropin-releasing hormone analogues or chemotherapy as well as aromatase inhibitors reduce oestrogen levels, thereby causing cancer treatment-induced bone loss (CTIBL). Furthermore, bone metastases are commonly found in advanced disease. Current treatment options for bone lesions comprise systemic anti-tumour therapy, irradiation, surgery and bisphosphonates. The main mechanism of osteolysis, osteoclast activation, is induced by the RANK ligand and suppressed by osteoprotegerin (OPG). A human antibody targeting the RANK ligand, denosumab, had superior activity compared to OPG and was therefore further developed in the clinical setting. This article reviews clinical data on denosumab. Data were obtained by searching the Medline database and abstracts from the ASCO annual meeting, ASCO breast meeting, ECCO, ESMO, and the San Antonio Breast Cancer Symposium. Clinical trials have demonstrated that denosumab reduces markers of bone turnover, and suggest equal efficacy to bisphosphonates in reducing the rate of skeletal-related events. While overall fewer side effects were observed, a numerically increased rate of osteonecrosis of the jaw was reported. Denosumab was well tolerated, and clinical activity was similar to bisphosphonates in metastatic disease. Trials of denosumab in the prevention of CTIBL are ongoing.

Schlüsselwörter

Bisphosphonate · Knochenmetastasen · Denosumab · Osteoporose · Therapiebedingter Knochenverlust

Zusammenfassung

Brustkrebs und Knochengesundheit sind eng verbunden. Vorzeitige Menopause durch GnRH (gonadotropin-releasing hormone)-Analoga oder Chemotherapie sowie Aromatasehemmer führen über reduzierte Östrogenspiegel zu therapiebedingtem Knochenverlust (cancer treatment-induced bone loss, CTIBL). Auch sind Knochenmetastasen beim metastasierten Brustkrebs häufig. Derzeitige Behandlungsoptionen umfassen systemische Antitumortherapien, Bestrahlung, orthopädische Eingriffe sowie Bisposphonate. Die Osteoklastenaktivierung, die zum Knochenabbau führt, wird durch den RANK-Liganden vermittelt und durch Osteoprotegerin (OPG) gehemmt. Ein Antikörper gegen den RANK-Liganden, Denosumab, erwies sich im klinischen Einsatz OPG überlegen. Dieser Artikel fasst klinische Daten zu Denosumab zusammen. Dazu wurden die Pubmed Medline, sowie Abstracts vom ASCO Annual Meeting, ASCO Breast, ECCO, ESMO, sowie dem San Antonio Breast Cancer Symposium durchsucht. Ergebnisse zeigen, dass Denosumab die Marker des Knochenumsatzes reduzieren kann. In Bezug auf die Vermeidung von Knochenkomplikationen war die Wirksamkeit mit Bisphosphonaten vergleichbar. Insgesamt traten weniger Nebenwirkungen auf, die Anzahl an Kieferosteonekrosen war jedoch numerisch erhöht. Denosumab zeichnete sich durch gute Verträglichkeit und Wirksamkeit bei Knochenmetastasen aus. Aktuell wird die Rolle von Denosumab zur Prävention von CTIBL in klinischen Studien untersucht.

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Introduction

Breast Cancer and Bone Health

Breast cancer and osteoporosis are among the most prevalent diseases in women [1, 2]. They are closely linked to cancer-treatment induced bone loss (CTIBL) [3]. Furthermore, breast cancer commonly metastasizes to bone [1, 4]; indeed, bone metastases are found in up to 60% of all patients with advanced stage disease [4].

Cancer Treatment-Induced Bone Loss

In premenopausal women, chemotherapy may induce ovarian failure [5]. Likewise, adjuvant endocrine therapy with gonadotropin-releasing hormone (GnRH) analogues suppresses ovarian function. Eventually, this early reduction of normal oestrogen levels increases bone loss [6]. In postmenopausal women, aromatase is the main source of oestrogen production [7]; inhibition of aromatase with aromatase inhibitors (AIs) is superior to tamoxifen in the adjuvant setting [8]. Reduction of oestrogen blood levels by aromatase inhibition, on the other hand, confers bone loss [9]. This eventually translates into a higher fracture rates (11% with AIs compared to 8% with tamoxifen) [10]. With growing awareness of those facts, clinical trials of CTIBL prevention with bisphosphonates were initiated. By now, it is well established that bisphosphonates inhibit CTIBL [6, 11]. This effect, however, might not translate into a reduction of fracture rates [12]. Denosumab, a monoclonal antibody targeting receptor activator of nuclear factor-kappaB ligand (RANKL), was found to reduce the incidence of new vertebral fractures in patients on androgen deprivation for prostate cancer [13]. Trials of denosumab for prevention of CTIBL in breast cancer are currently ongoing [14].

Bone Metastases in Breast Cancer

As outlined, bone metastases are common in breast cancer; they are classified according to radiographic appearance as osteolytic, osteoblastic, or mixed [15], with the majority being osteolytic [16]. Possible complications such as hypercalcaemia, fractures, or spinal cord compressions may therefore occur. As a consequence of this, an increased need for local treatment such as surgery or radiotherapy to bone arises [17]. Complications and the need for local interventions are summarized by the term skeletal-related events (SREs) [18]. In clinical studies, biomarkers of bone turnover predicting for SREs (e.g. urinary-N-telopeptide/creatinine ratio, uNTx/Cr) are measured in order to assess activity of bone disease; their respective decrease is commonly used as surrogate for treatment efficacy [19].

Current Treatment Options for Bone Metastases

Besides local interventions, current treatment strategies for bone metastases comprise systemic anti-tumour therapy and bisphosphonates. Bisphosphonates block osteolysis by directly inhibiting osteoclasts, highly specialized cells of bone resorption [20]. Due to its antiresorptive properties, bisphosphonates reduce SREs and cancer-associated bone pain [21].

Regulation of Bone Metabolism

Regulation of Bone Resorption

Bone resorption necessitates osteoclast activation. As early as 1980, it was suggested that osteoblasts might be involved in osteoclastogenesis [22]. An 'osteoclast-activating factor' produced by osteoblasts was hypothesized, whose nature remained elusive up until 1998 when RANKL was identified [23]. Osteoclasts themselves derive from osteoclast precursors (OCPs), cells of the mononuclear linage [24] and derivatives of pluripotent precursors in the bone marrow [25]. Increased numbers of such OCPs are responsible in part for bone resorption in multiple myeloma [26]. Bone resorption, as understood today, is regulated by the RANK/RANKL/OPG pathway consisting of 3 proteins: RANK, RANKL (which activates OCPs by binding to membrane-bound RANK), and its antagonist, osteoprotegerin (OPG) [27]. Those proteins are members of the tumour necrosis factor (TNF) receptor family of cytokines. Osteoblasts as well as bone marrow stromal cells secrete RANKL and monocyte colony-stimulating factor (M-CSF) [28]. M-CSF is constitutively expressed; the relative levels of RANKL and OPG expression therefore control osteoclastogenesis [29].

RANK Pathway in Osteolytic Metastases of Solid Cancers

Complex interactions between tumour cells, bone matrix, and bone cells occur in lytic bone lesions, resulting in a vicious cycle of bone destruction [30]. In breast cancer, tumour cells secrete cytokines and growth factors such as parathyroid hormone-related peptide (PTHrP), IL-1, IL-6, IL-8, IL11, and TNF-α, triggering upregulation of RANKL expression in osteoblasts and stromal cells [31–33]. In other malignancies (prostate cancer, multiple myeloma), tumour cells were found to express RANKL directly [34, 35]. Furthermore, some cytokines (IL-1, IL-6, IL-8, TNF-α) can stimulate osteoclastogenesis in a RANKL-independent manner [36, 37]. Resulting bone resorption again mobilizes growth factors from bone matrix (TGF-β, insulin-like growth factor, basic fibroblast growth factor, bone morphogenetic protein (BMP)) which in term promote tumour growth and support tumour cell survival [15, 16, 38] (fig. 1). Indeed, an animal model revealed that tumour cells directly adjacent to bone had a significantly higher proliferation rate [39]. OPG, on the other hand, was found to reduce osteoclastogenesis [35]. This was observed in co-culture systems wherein cancer cells induced other cells to express RANKL [32, 40]. Therefore, it seemed reasonable to develop compounds inhibiting the RANK/RANKL pathway.

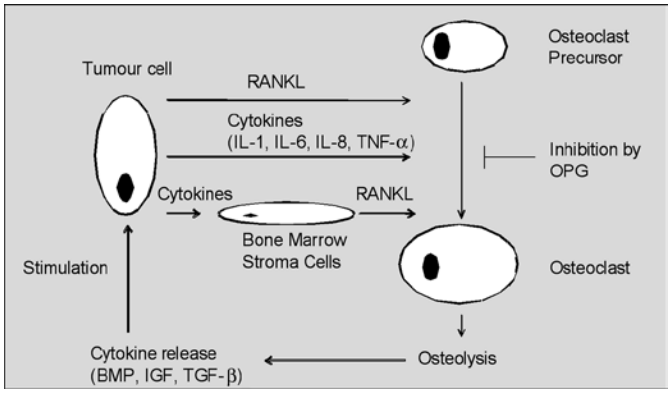

Fig. 1. Osteoclast activation in bone metastases (BMP = bone morphogenetic protein; IGF = insulin-like growth factor; IL = interleukin; OPG = osteprotegerin; RANKL = receptor activator of nuclear factor-kappaB ligand; TGF-β = transforming growth factor β; TNF-α = tumour necrosis factor α).

Denosumab

Early Development

Development of drugs targeting the RANK/RANKL pathway started with recombinant OPG (AMGN-0007). OPG was active and well tolerated in women with osteoporosis and lytic bone lesions [41, 42]. Yet denosumab (AMG162), a fully human antibody targeting RANKL, reduced levels of bone turnover markers to a greater extent. Therefore, further development of OPG was discontinued [43]. In phase I trials, different doses and schedules of denosumab and their respective effects on pharmacodynamics (PD), parmacokinetics (PK), as well as uNTX were evaluated. In patients with postmenopausal osteoporosis, effects of denosumab were sustained for up to 6 months, allowing for an administration schedule similar to intravenous bisphosphonates [43]. Further studies were conducted in patients with breast cancer and multiple myeloma. No drug-related serious adverse events or antibodies against denosumab were observed [44, 45]. Based upon those early data, phase II studies of denosumab in postmenopausal osteoporosis, multiple myeloma, and metastatic solid tumours were initiated.

Phase II Clinical Trials of Denosumab in Malignancies

In a randomized phase II trial, 255 patients with metastatic breast cancer received different doses and schedules of denosumab or zoledronic acid. Primary study endpoint was reduction of uNTX/Cr. Denosumab and zoledronic acid yielded similar results; serious adverse events were reported in 9% of patients treated with denosumab as compared to 16% in the bisphosphonate group. According to PK/PD simulations, a dose of 120 mg administered every 4 weeks was reported as the optimal schedule [46]. A recent update once again concluded that denosumab suppressed uNTX/Cr to the same extent as zoledronic acid [47]. Another phase II study was conducted in a mixed cancer population already receiving bisphosphonates for bone metastases. A total of 111 patients were randomized to denosumab or bisphosphonate continuation. The percentage of patients reaching uNTx levels < 50 nmol/l at week 13 was defined as primary study endpoint. This level was reached by 71% of patients on denosumab, as compared to 29% in the group with ongoing intravenous bisphosphonates ($p < 0.001$). Rates of adverse events were similar between treatment groups [48].

Phase II Clinical Trial of Denosumab in CTIBL

In a trial of denosumab for the prevention of CTIBL, 252 patients with reduced bone mass receiving AIs for early breast cancer were randomized to denosumab (60 mg subcutaneously every 6 months) or placebo. Primary study endpoint was lumbar spine bone mineral density (BMD) after 1 and 2 years. In the denosumab group, BMD increased significantly over time (5.5 and 7.6% at 12 and 24 months, respectively; $p < 0.0001$ both time points). Treatment was well tolerated, and adverse events were similar between the denosumab and placebo group [49]. Based upon these results, phase III trials of denosumab in malignant bone disease were initiated. Other studies evaluated the role of denosumab in postmenopausal osteoporosis and CTIBL [14].

Phase III Clinical Trials of Denosumab in Malignancies and CTIBL

Currently, two phase III trials of denosumab in patients with bone metastases have reported respective results. In a trial of denosumab in a mixed cancer population (patients with breast or prostate cancer were excluded), the primary study endpoint, non-inferiority to zoledronic acid, was reached (hazard ratio (HR) 0.84; 95% confidence interval (CI) 0.71–0.98; $p = 0.0007$) [50]. In a second large study conducted in breast cancer patients (Amgen 20050136; NCT00321464) who had not received prior treatment with intravenous bisphosphonates, a total of 2,046 patients were randomized to denosumab 120 mg every 4 weeks or zoledronic acid. Preliminary results were presented at the 2009 European Cancer Conference and updated at the 2009 San Antonio Breast Cancer Symposium [51, 52]. Time to first SRE was significantly longer in the denosumab group (HR 0.82; 95% CI 0.71–0.95; $p< 0.0001$ non-inferiority; $p = 0.001$ superiority). Denosumab was also significantly superior in delaying time to first radiation to bone (HR 0.74; 95% CI 0.59–0.94; $p = 0.01$) and time to first event of hypercalcaemia of malignancy (HR 0.82; 95% CI 0.70–0.95; $p = 0.007$). Overall, less adverse events were observed in the denosumab group, although, in contrast to phase II data, a similar rate of ONJ was reported. Results of NCT00321464 are summarized in table 1. As preclinical as well as limited clinical data suggested a direct anti-tumour effect of zoledronic acid, it was carefully observed if denosumab had a detrimental effect on tumour progression.

Table 1. Comparison of denosumab versus zoledronic acid in metastatic breast cancer (n = 2,046)

Endpoint	Hazard ratio	95% CI	p
Primary endpoint			
Time to first on-study SRE, non-inferiority	0.82	0.71–0.95	>0.0001
Secondary endpoints			
Time to first on-study SRE, superiority	0.82	0.71–0.95	0.01
Time to first and subsequent on-study SRE	0.77	0.66–0.89	0.001
Time to first radiation to bone	0.74	0.59–0.94	0.01
Time to first on-study SRE or HCM	0.82	0.70–0.95	0.007
Time to experiencing moderate or severe pain	0.87	0.79–0.97	0.009
Overall disease progression	1.00	0.89–1.11	n.s.
Overall survival	0.95	0.81–1.11	n.s.
Skeletal-related events	**Denosumab**	**Zoledronic acid**	**p**
Total number of SREs, n	491	623	n.a.
Skeletal morbidity rate, mean (SREs per year, n)	0.45	0.58	0.004
Adverse events	**Denosumab**	**Zoledronic acid**	
Overall AEs, n (%)	977 (96)	985 (97)	
Severe AEs, n (%)	453 (44)	471 (46)	
Acute phase reactions[a], n (%)	106 (10.4)	277 (27.3)	
AEs related to renal toxicity, n (%)	50 (4.9)	86 (8.5)	
Osteonecrosis of the jaw, n (%)	20 (2.0)	14 (1.4)	
Toothache, n (%)	57 (5.6)	37 (3.7)	
Hypocalcaemia, n (%)	56 (5.5)	34 (3.4)	

95% CI = 95% Confidence interval; SRE = skeletal-related event (pathologic fracture, irradiation to bone, surgery to bone, spinal cord compression); AE = adverse event; HCM = hypercalcaemia of malignancy; n.s. = not significant; n.a. = not applicable.
[a]Pyrexia, bone pain, chills, arthralgia, influenza-like illness, myalgia, flushing.

While the studies were not powered for such endpoint analysis, available clinical data do not suggest impairment of oncologic outcomes in the respective denosumab groups.

In a randomized trial of denosumab versus placebo in patients on androgen deprivation therapy for prostate cancer, denosumab was associated with increased BMD and a lower rate of vertebral fractures, therefore preventing CTIBL [13]. A study of denosumab for the prevention of CTIBL in breast cancer conducted by the Austrian Breast and Colorectal Cancer Study Group (ABCSG-18; NCT00556374) is currently ongoing. Patients on adjuvant AIs without prior bisphosphonate exposure are randomized to denosumab or placebo; results of this trial will eventually clarify the role of denosumab in CTIBL prevention [14].

Tolerability

Denosumab was well tolerated in clinical trials, and side effects were in general mild and manageable (table 1). Still, due its specific mechanism of action, a number of concerns were raised. As the RANK pathway is a co-stimulatory pathway for T-cell activation, a higher risk for infectious diseases was anticipated [53]. In vivo studies, however, revealed no increased risk of bacterial infections [54] or altered virus clearance in response to influenza infections [55].

ONJ is a rare yet problematic side effect of bisphosphonate therapy. The highest incidence occurs with nitrogen bisphosphonates in cancer patients, although a number of cases have been reported in women on oral bisphosphonates for osteoporosis. Importantly, it was observed that dental surgical procedures further increase the risk. ONJ therefore may be caused by complete inhibition of normal bone turnover in conjuncture with traumatic bone lesions or infection [56]. In early clinical studies of RANKL inhibition, no cases of ONJ were observed. Phase III clinical trials, however, reported a numerically increased number of ONJ in the respective denosumab groups [52]. Therefore, the same safety recommendations apply.

Repeatedly, a direct anti-tumour effect of zoledronic acid was suggested in preclinical models [57]. In ABCSG-12, premenopausal patients on adjuvant endocrine therapy were randomly assigned to zoledronic acid or control. Here, significantly fewer recurrence events were observed in the bisphosphonate group [58]. Those findings are meanwhile supported by data from postmenopausal bone protection trials (ZO-FAST; NCT00171314) [59]. Currently, there are no data on the effect of denosumab on breast cancer recurrence or progression; results from phase III trials, however, do not suggest an increased risk for tumour progression. An ongoing study (ABCSG 18; NCT00556374) is evaluating the role of denosumab in the prevention of CTIBL in postmenopausal patients receiving adjuvant endocrine therapy with AIs [14]. In this randomized phase III trial, recurrence-free survival is assessed as secondary endpoint. The D-CARE trial (study of denosumab as adjuvant treatment for women with high risk early breast cancer receiving neoadjuvant or adjuvant therapy; NCT01077154) even defined bone metastasis-free survival as primary study endpoint [14]. Together, those two trials will yield important insights into whether inhibition of the RANK pathway can ultimately improve recurrence-free survival.

Conclusion

Currently, bisphosphonates are the standard of care for the treatment of breast cancer patients with bone metastases. Those drugs effectively reduce the number of SREs. Still, many patients will eventually develop SREs despite treatment; therefore, alternative treatment approaches are of value. Denosumab is a fully human antibody targeting RANKL. Phase III clinical trials suggest at least equal efficacy of denosumab and zoledronic acid. Denosumab was well tolerated and side effects were mild; still, the incidence of ONJ was numerically increased. Ongoing clinical studies are evaluating the potential role of denosumab for the prevention of CTIBL and its effect on tumour progression. In conclusion, inhibition of osteoclast activation by denosumab offers an effective and well tolerated treatment option in patients with bone metastases from breast cancer and other malignancies.

Conflict of Interest

Rupert Bartsch: advisory board Amgen; lecture honoraria: Novartis. Guenther G. Steger: advisory board Amgen; travel support: Amgen; Michael Gnant: advisory board Amgen, Novartis; consultant with Amgen, Novartis; lecture honoraria: Amgen, Novartis; research support: Amgen, Novartis.

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