Bisphosphonate and Denosumab Therapy: Fields of Application

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Abstract

Bisphosphonates are highly effective in preserving bone mineral density and have a favorable benefit-risk profile. Thereby, bisphosphonates became the preferred antiresorptive drug for malignant and nonmalignant diseases characterized by various kinds of bone loss. In general, bisphosphonates may be considered as treatment option for preserving bone mineral density in any disease accompanied by increased bone resorption, regardless of the pathogenic mechanisms involved. Typical and frequent indications are postmenopausal osteoporosis, breast cancer, prostate cancer, and multiple myeloma.

Bisphosphonates exert beneficial effects beyond their antiresorptive properties and reduce morbidity and mortality in malignant and nonmalignant diseases. Especially, the antitumor activity described in several malignancies is intriguing. The molecular mechanisms generating these additional beneficial effects are still incompletely understood.

Among bisphosphonates, zoledronic acid is the most potent and most thoroughly studied substance. Of all bisphosphonates, zoledronate displays the most beneficial effects in reducing fracture risk, antitumor activity, and additional effects but also the highest risk of adverse events, including BRONJ/MRONJ.

Denosumab has a similarly high antiresorptive capacity as zoledronic acid. In certain settings, it may be a suitable alternative to bisphosphonate therapy.

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Introduction

Due to their effective antiresorptive properties, bisphosphonates are the first-choice treatment in many disorders involving an increase or disruption in bone resorption. Bisphosphonates help to ameliorate quality of life and furthermore have the potential to improve survival in malignant and nonmalignant diseases [1, 2]. The overall good tolerability results in a continuous and prolonged use in many patients. Adverse effects are infrequent and primarily constituted by acute-phase reactions with transient influenza-like symptoms, hypocalcemia, impaired renal function, and complications of the upper aerodigestive tract, such as esophageal ulceration [3]. Additionally, rare cases of atypical femoral fractures have been connected with long-term use of bisphosphonates [4, 5], and an association of atrial fibrillation and esophageal cancer with bisphosphonate use has been suggested [6]. The most problematic adverse event, bisphosphonate-related osteonecrosis of the jaw, has emerged as a severe complication of bisphosphonate therapy [7, 8] and has primarily been described in patients with prolonged intravenous bisphosphonate therapy. Of all available bisphosphonates, the intravenous nitrogen-containing bisphosphonate zoledronic acid displays the most distinct beneficial effects both in reducing skeletal-related events and in improving overall survival in malignant and nonmalignant diseases; however, zoledronic acid is also most frequently associated with adverse events, such as bisphosphonate-related osteonecrosis of the jaw.

Use of Bisphosphonates in Nonmalignant Diseases

Bisphosphonates in Postmenopausal Osteoporosis

Osteoporosis poses a significant public health issue that greatly impacts morbidity and mortality, especially in postmenopausal women. Amino-bisphosphonates exert proven efficacy in reducing fracture risk at the spine, hip, and other nonvertebral skeletal sites and are the most frequently applied treatment strategy with the best cost-to-effectiveness ratio of all therapies for postmenopausal osteoporosis [9]. Women receiving bisphosphonates present decreased bone turnover and serum markers of bone turnover, such as cross-linked C-telopeptides of collagen type I [10]. In excess of their primary function of reducing skeletal-related events, bisphosphonates have also been associated with a significant decrease in morbidity and increase in survival in osteoporosis patients, which is not explainable by the mere effect of preventing fractures. The reasons for this observation are not yet fully understood. Possibly effects of bisphosphonates not directly related to the bone are jointly responsible for this observation, such as the inhibitory effect on the atherosclerotic process demonstrated by experimental evidence [11].

Intravenous zoledronic acid is the most effective bisphosphonate for treating osteoporosis with a 70 % fracture risk reduction, whereas the risk is reduced by 60 % using ibandronate. However, in osteoporosis patients, long-term treatment is frequently required, and oral applications, which are less frequently associated with adverse effects, are often preferred. The nitrogen-containing bisphosphonates alendronate and risedronate are eligible for oral application, are approximately equipotent, and exhibit a log-linear relationship between the dose and the increase in spine bone mineral density in the animal model [12]. Regarding duration of treatment, the benefits of continuing therapy probably outweigh the risk of harm in patients with bone mineral density in the osteoporosis range or previous history of fragility fracture. However, patients who are not at high risk for fracture are candidates for a "drug holiday" in order to minimize the risk of severe side effects [13]. Altogether, it is important to find a rational balance and give continued osteoporosis treatment to those in need, since bisphosphonates prevent many typical hip and vertebral compression fractures, particularly in elderly patients [4].

Bisphosphonates in Chronic Kidney Disease and After Renal Transplantation

Indications for bisphosphonates in chronic kidney disease include hypercalcemia, treatment of

low bone mineral density in all chronic kidney disease stages, and prevention of bone loss after renal transplantation. Renal transplant recipients are at high risk of developing osteoporosis and osteopenia due to underlying renal osteodystrophy, hypophosphatemia, and immunosuppression. Especially, the first year after renal transplantation often entails excessive bone loss, inter alia due to the application of high glucocorticoid doses. Additionally, persistent post-kidney transplant hyperparathyroidism may lead to or exacerbate preexisting bone and cardiovascular disease [14].

In chronic kidney disease, bone biopsy is mandatory before starting a bisphosphonate therapy in case suppressed bone turnover is suspected. Although it has been shown that bisphosphonates can safely be used in all chronic kidney disease stages, including dialysis patients, they must be carefully administered in these patients, because of their urinary elimination and potential renal toxicity. Renal toxicity is associated with infusion velocity and excessive dosage. Therefore, it is important to maintain the time of infusion, and in hemodialysis patients, administration during the hemodialysis session is recommended. A 50 % dose reduction is recommended in chronic kidney disease stage 4 and 5. Renal toxicity is less frequent when using oral bisphosphonate regimens [15]. Oral therapy regimens are also favorable and have been proven to be effective in patients after renal transplantation who are exposed to continuous immunosuppression and thus may have an especially high risk for side effects, such as bisphosphonate-related osteonecrosis of the jaw [16]. Low-dose alendronate or risedronate in addition to vitamin D supplementation given early after renal transplantation prevents early bone loss and is significantly correlated with increased lumbar, spine, and radius bone mineral density 6 months after transplantation when compared to vitamin D supplementation alone [17, 18].

Other Indications

Glucocorticoid-induced osteoporosis is an important indication for bisphosphonate use in various diseases. As an example, Crohn's disease and its therapy affect bone health and result in a high prevalence of low bone mineral density disease such as osteoporosis and osteopenia, which may be ameliorated by bisphosphonate therapy [19]. Furthermore, bisphosphonates are first-choice treatment in Paget's disease, and their efficiency has been proven in osteogenesis imperfecta [20, 21].

Apart from their antiresorptive activity, bisphosphonates may also have specific analgesic or anti-inflammatory effects. Thus, rheumatic diseases associated with systemic and sometimes focal bone loss, such as rheumatoid arthritis, spondylarthritis, or SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome, are candidates for bisphosphonate therapy. Also noninflammatory rheumatic diseases, such as aseptic osteonecrosis, neuropathic osteoarthropathy, algoneurodystrophy, and fibrous dysplasia, are associated with pain and increased focal bone remodeling. Several studies have shown promising therapeutic potential of bisphosphonates in these inflammatory or noninflammatory diseases where therapeutic options are often limited [21, 22].

Preliminary evidence exists that bisphosphonates may furthermore be useful to prevent vascular calcifications and as therapy of calciphylaxis, also known as calcific uremic arteriolopathy. Calciphylaxis is a rare but potentially life-threatening and difficultly treatable condition that almost exclusively affects patients with chronic kidney disease. In a small series of eight patients with calciphylaxis, progression of skin lesions stopped between 2 and 4 weeks after starting bisphosphonate therapy. Within 6 months, wound healing was complete in all patients without recurrence during at least 1 year follow-up [23].

Use of Bisphosphonates in Malignancies

Bisphosphonates are the most common pharmaceutical intervention for prevention of skeletal-related events in patients with malignant skeletal involvement. In principle, bisphosphonates are probably beneficial in any tumor disease metastatic to the bone or in which the treatment causes loss in bone mineral density. Best described are bisphosphonate effects in patients with multiple

myeloma, breast cancer, and prostate cancer, whereas data on the efficiency of bisphosphonate treatment in other malignancies is limited. Bisphosphonates significantly reduce the risk of skeletal complications in multiple myeloma and metastatic bone disease by 30–50 % and prevent cancer treatment-induced bone loss. Osteolytic metastases are primarily caused by excessive bone resorption through osteoclasts with concurrently impaired osteoblast function due to a variety of cytokines produced by metastatic cancer cells, influencing both osteoclast and osteoblast function [24, 25].

Beside the beneficial effects of bisphosphonates on pain and reduction of fractures [26], they also display antimyeloma and antitumor activity with prolonged overall survival reported for various malignancies [27–30]. Several mechanisms by which bisphosphonates exert antitumor effects are proposed. Firstly, bisphosphonates may preserve bone health and delay bone lesion progression by interrupting the vicious cycle of increased osteolysis coupled with increased tumor growth. Metastatic cells in bone secrete cytokines and growth factors, which may promote osteoclast function and survival and thus facilitate bone resorption. Osteoclasts, in turn, release bone-derived growth factors that possibly facilitate tumor cell survival and metastasis growth. Secondly, direct effects on cancer cells may contribute to the antitumor effect. Zoledronic acid inhibits growth, migration, and matrix-associated invasion of breast cancer cells [31]. In vitro, attenuated proliferation of breast cancer cells was demonstrated when treated with ibandronate. Especially, amino-bisphosphonates might have inherent anticancer activities independently of their direct effect on bone [32, 33], which depend on inhibition of protein prenylation through inhibition of the mevalonate pathway, a mechanism not shared by non-nitrogen-containing bisphosphonates [27, 33]. Amino-bisphosphonates inhibit the activity of small GTPases by preventing their posttranslational isoprenylation and thus promote the expression of proapoptotic genes and the upregulation of caspases [34], as activated RAS GTPases downregulate the expression of proapoptotic genes in malignant cells. Thus, nitrogen-containing bisphosphonates may induce apoptosis in neoplastic cells via modulation of the activity of small GTPases [35]. Thirdly, bisphosphonates may stimulate innate antitumor immune mechanisms, such as γδ T cells. In patients with prostate cancer, zoledronate therapy elicited a long-term shift of peripheral γδ T cells towards an activated effector memory-like state associated with improved immune surveillance against transformed or malignant cells [36]. Furthermore, it is suggested that bisphosphonates effect angiogenesis and the stem cell niche by modulation of extracellular matrix gene expression. Hence, bisphosphonates provide more than just supportive care in patients with multiple myeloma or solid tumors with bone metastases.

Bisphosphonates in Multiple Myeloma Patients

Multiple myeloma patients are often affected by pathological fractures early in their disease course but still have a long survival compared to other patients with bone metastases. Due to early and massive bone affection, potent intravenous bisphosphonate regimens are the preferred treatment strategy in multiple myeloma patients. However, the prolonged intravenous bisphosphonate use is probably the reason for a high incidence of bisphosphonate-related osteonecrosis of the jaw (up to 23 % [37]) in these patients. Furthermore, multiple myeloma patients often undergo aggressive high-dose chemotherapy followed by neutropenia and are mostly treated with multiple chemotherapy regimens during their disease course. Chemotherapy generally has immunosuppressant and antivasculogenic properties, and effects of stem cell depletion induced by high-dose chemotherapy on later wound healing capacity may further increase the risk of bisphosphonate-related osteonecrosis of the jaw. Therefore, the Mayo Clinic consensus statement and the IMWG guidelines recommend that bisphosphonate use should be reduced to 1 or 2 years in patients reaching a plateau phase or complete response. For patients with active disease, therapy frequency can be decreased to every

3 months after 2 years [38]. Despite a higher incidence of bisphosphonate-related osteonecrosis of the jaw in patients receiving zoledronic acid, it has to be taken into account that zoledronic acid has been demonstrated to be superior to pamidronate in preventing skeletal-related events at least in certain subsets of patients [39] and superior to non-nitrogen-containing clodronate not only in reducing skeletal-related events but also in improving event-free and overall survival in multiple myeloma patients [32, 40, 41]. Meta-regression analysis has suggested a borderline significant trend for overall survival based on the bisphosphonate potency, although overall survival does not seem to be different comparing zoledronic acid, pamidronate, and ibandronate in the meta-analysis [41]. Data clearly demonstrating the superiority of zoledronic acid compared to ibandronate in multiple myeloma patients is missing; however, ibandronate is not approved for use in multiple myeloma patients, although the incidence of bisphosphonate-related osteonecrosis of the jaw seems to be lower than with zoledronate treatment [37]. Thus, to date, intravenous zoledronate is the preferred bisphosphonate regimen for multiple myeloma patients.

Bisphosphonates in Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women of the western population, and bone loss is common throughout the disease course. About 70 % of patients with advanced breast cancer develop bone metastases, a complication that is often painful and potentially leads to debilitating skeletal-related events. In early breast cancer, accelerated bone mineral density loss frequently occurs in the wake of adjuvant therapy. Rate and extent of chemotherapy or endocrine cancer therapy-induced bone loss are often greater than decreases in bone mineral density during menopause. Bisphosphonates such as zoledronic acid are indicated for the treatment of breast cancer bone metastases and reduce the fracture risk by a third [42]. Zoledronate has been shown to also prevent cancer therapy-induced bone loss and improve bone mineral density in premenopausal women receiving adjuvant endocrine or chemotherapy for breast cancer [43].

The benefits of bisphosphonate therapy in breast cancer go beyond maintaining bone health and include potential anticancer effects [43], which are a desirable treatment quality for this patient population with a good prognosis, but a high risk of recurrent disease. In vitro, zoledronic acid displays a particularly strong antitumor effect on primary breast cancer cells, which may be equal or superior to commonly used chemotherapeutic regimens [44]. Preliminary clinical data suggest that bisphosphonate therapy may reduce circulating tumor cell numbers, which are a negative prognostic indicator of disease-free and overall survival in patients with advanced and metastatic disease [45]. Zoledronic acid demonstrated disease-free survival benefits and a 15 % improvement in overall survival in a meta-analysis including 9,518 breast cancer patients [42]. Notably, not all patient subgroups profit equally by bisphosphonate therapy, but the advantage seems to depend on hormone levels, age, and cancer stage. Especially, patients expected to have low estrogen levels, such as premenopausal patients undergoing ovarian suppression and postmenopausal women who were at least 5 years postmenopause, display significant improvement in overall survival. Thus, reproductive hormones seem to be a treatment modifier to take into account [46]. This might also be the reason for a stronger recurrence risk reduction in older patients (especially older than 60 years) compared to younger patients treated with zoledronate, ibandronate, or clodronate [45]. Patients with early-stage breast cancer clearly profit by zoledronate achieving a reduced risk of recurrence, which persists for years even after cessation of zoledronate treatment [45]. However, data in advanced breast cancer is conflicting, and zoledronate may even increase the risk of recurrence in this setting [42]. Generally, oral bisphosphonates do not seem to affect breast cancer recurrence in premenopausal women and yield inconsistent results in postmenopausal women. Thus, current clinical evidence is insufficient to support the use of oral bisphosphonates as a standard adjuvant breast cancer treatment.

In conclusion, zoledronic acid may be considered as standard of care in adjuvant breast cancer therapy, at least for certain patient subgroups as described above [47]. It stands to reason that an early start of bisphosphonate therapy during breast cancer disease course is advantageous. Treatment duration should not generally be restricted, as persistence with zoledronate therapy for more than 12 months is associated with a substantially greater reduction of skeletal-related events compared with zoledronate treatment for 1–3 months [48].

Bisphosphonates in Prostate Cancer and Other Genitourinary Malignancies

In men, prostate cancer is the most frequent malignancy and the second most common cause of cancer death. Skeletal complications are numerous, either due to bone metastases or as a consequence of androgen deprivation therapy. Complications of bone metastases include bone pain, pathologic fractures, and spinal cord compression [49]. Less common genitourinary malignancies also have a predilection for metastases to the bone. Skeletal metastases have been reported in 20–40 % of patients with stage IV renal cell carcinoma or bladder cancer.

As seen in multiple myeloma and breast cancer patients, positive effects of bisphosphonate therapy in genitourinary malignancies do not only include reduction of skeletal-related events, but also improvement of overall survival. Preclinical studies in models of genitourinary cancers have shown that bisphosphonates can inhibit overall tumor progression, proliferation, invasion, and angiogenesis; activate the immune response against cancer cells; and produce synergistic anticancer effects with cytotoxic agents. Compared to other bisphosphonates, zoledronate demonstrated especially profound direct anticancer activity and synergy with cytotoxic chemotherapy in preclinical studies with prostate cancer cells. The anti-angiogenic effect of zoledronate is especially intriguing in the setting of renal cell carcinoma, characterized by extensive vascularization, and promises to increase the success of anti-angiogenic therapies in metastatic renal cell cancer [36].

Bisphosphonates are frequently used in prostate cancer with bone metastases, although current guidelines recommend their use only in castration-resistant prostate cancer [50]. There is little published guidance for the use of bisphosphonates in renal cell or bladder cancer. Both oral and intravenous bisphosphonates have palliative activity in genitourinary malignancies. Weekly oral alendronate prevents bone loss, increases bone mass, and decreases bone turnover in patients with androgen deprivation therapy for localized prostate cancer [51], and there is evidence that clodronate significantly improves overall survival in patients with prostate M1 disease beginning hormonal therapy. However, to date, zoledronate is the only bisphosphonate having demonstrated significant objective and durable benefits and to have received broad regulatory approval for preventing skeletal-related events in patients with bone metastases from castration-resistant prostate cancer or other genitourinary malignancies. Zoledronate reduces pain scores and proportion of patients with skeletal-related events, prolongs the time to the first skeletal-related event in genitourinary malignancies, and extends the time to disease progression with a trend for prolonged overall survival in renal cell cancer. In patients with bone metastases from bladder cancer, zoledronate increases the 1-year survival rate [36]. There is evidence to apply zoledronate early (i.e., before the first skeletal-related event) in prostate cancer metastatic to the bone, as this strategy is associated with a decreased risk of subsequent skeletal-related events compared to zoledronate treatment started after the first skeletal-related event [52]. Regarding the duration of bisphosphonate therapy, there is no clear recommendation, whether the therapy should be stopped after a finite length of time or extended for as long as it is tolerated. The suspected benefits for overall survival and increased fracture reduction with longer treatment duration revealed in retrospective database analyses argue against general treatment time restrictions in genitourinary malignancies.

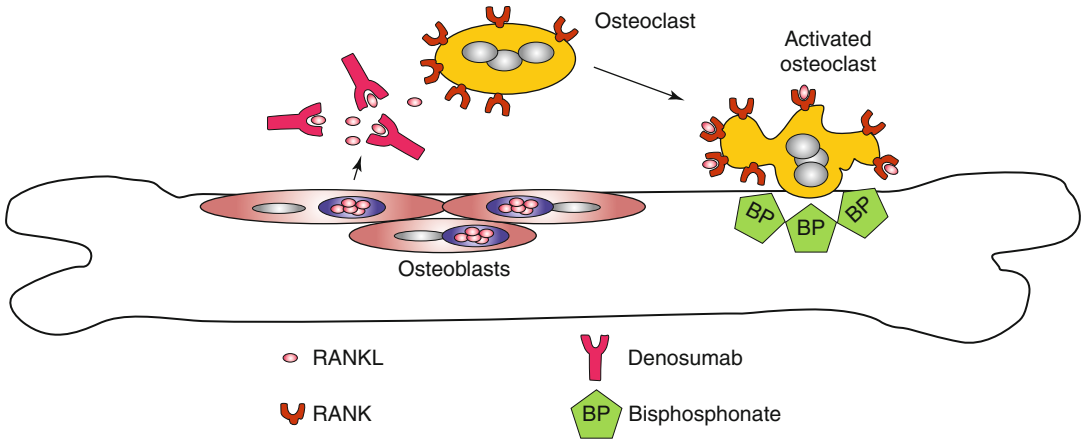

Fig. 2.1 Mechanisms of action of denosumab and bisphosphonates. RANKL is secreted by osteoblasts and binds to the RANK receptor on osteoclasts, promoting osteoclast differentiation and activation. Denosumab binds RANKL and thereby inhibits the RANKL-RANK pathway. Bisphosphonates bind to the bone and enter and thus inhibit resorption by activated osteoclasts (Modified according to Yee and Raje [54] with kind permission of dove medical press)

Denosumab as an Alternative to Bisphosphonate Therapy

Denosumab is a fully human monoclonal antibody that neutralizes the receptor activator of nuclear factor κB ligand (RANKL), a member of the tumor necrosis factor receptor superfamily. RANKL is produced by osteoblasts and activates the RANK receptor on osteoclast precursor cells and osteoclasts. The RANKL-RANK signaling pathway is essential for the differentiation, function, and survival of osteoclasts (Fig. 2.1) [53].

Denosumab is injected subcutaneously. Dosing ranges from 60 mg every 6 months in order to preserve bone density in postmenopausal women to 120 mg every 4 weeks in the setting of malignant disease metastatic to the bone. In contrast to bisphosphonates, denosumab does not accumulate in the bone and its effect is reversible after treatment discontinuation. The circulatory half-life is about 26 days [54].

The indications of denosumab are principally similar to bisphosphonates. However, certain aspects have to be taken into account for the therapeutic decision. The efficacy of denosumab in preventing skeletal-related events was demonstrated to be at least equal to zoledronate [55, 56] but seems to partly depend on the disease type. Denosumab treatment in postmenopausal osteoporosis results in a rapid and sustained reduction of bone turnover markers, a marked increase in bone mineral density and a decrease in fracture risk [57]. In breast [58] and prostate cancer [59] patients, suppression of bone turnover markers is greater than by zoledronic acid. In patients with cancer types other than breast or prostate (mainly lung and multiple myeloma) [55], denosumab was equipotent to zoledronate in preventing skeletal-related events.

The side effect profile of denosumab and bisphosphonates is partly overlapping. Especially adverse effects directly mediated by bone remodeling inhibition, namely, osteonecrosis of the jaw (ONJ), occur with similar frequency under treatment with denosumab and zoledronic acid [55, 56]. Acute-phase reactions, which are frequent after zoledronic acid application, occur rarely after denosumab [55]. Yet it has to be taken into account that the RANKL-RANK signaling pathway is not restricted to osteoclastogenesis: RANKL is a co-stimulatory cytokine for T cell activation [60] and lymphocyte development [61]. Concordantly, an increased infection rate was shown in patients with osteoporosis or early breast cancer treated with denosumab [62]. The interference with the immune system may also increase the risk of neoplasms [57]. Importantly, there is evidence hinting at a worse survival in patients with multiple

myeloma treated with denosumab compared to zoledronate [55]. Thus, denosumab is thus currently not indicated in the setting of multiple myeloma. On the other hand, preclinical data from animal models of breast cancer and melanoma suggest a role of the RANKL-RANK signaling pathway in tumor genesis and metastasis [63, 64], and limited data indicates that denosumab may reduce disease progression in prostate cancer patients [54]. Furthermore, overall survival was not different in breast [58] and prostate cancer [59] patients treated with denosumab or zoledronic acid. Altogether, data concerning the possible antitumor effect of denosumab in comparison with bisphosphonates is still insufficient. The postmarket period of denosumab is still comparably short and yet unknown side effects may emerge. Therefore, vigilance regarding adverse events related to possible effects of RANKL inhibition in tissues other than bone or to bone turnover oversuppression is mandatory [65].

In contrast to bisphosphonate clearance, denosumab clearance is largely independent of renal function, since, similarly to other monoclonal antibodies, denosumab is cleared by the reticuloendothelial system [66]. Subsequently, denosumab does not require dose reduction in case of renal dysfunction, is not contradicted in patients with renal failure [54], and thus seems to be the safest treatment option for patients with impaired renal function [65].

Denosumab is cost-effective compared to no treatment for fracture prevention in postmenopausal women with osteoporosis [57]. However, the estimation of the cost-effectiveness in comparison to bisphosphonates depends on the analytical perspective and model parameters and varies in different economic evaluations [67, 68].

Taken together, denosumab may be a suitable alternative to bisphosphonate therapy in certain settings, for example, for patients with postmenopausal osteoporosis or breast or prostate cancer, who suffer from renal impairment or are unable or refuse to take bisphosphonates.

Conclusions

Bisphosphonates and denosumab are routinely used in the treatment of malignant and nonmalignant diseases with increased osteoclast activity. They effectively reduce skeletal-related events in patients suffering from osteoporosis and metastatic bone disease. Generally, side effects of bisphosphonate and denosumab treatment are infrequent, and they always have to be interpreted with regard to the underlying disease.

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