Review

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Biphosphonates in Advanced Prostate and Renal Cell Cancer – Current Status and Potential Applications

Abstract

Objective: This review summarizes recent findings on the therapeutic benefits of biphosphonates in patients with advanced prostate or renal cell carcinoma (RCC). The role of biphosphonates in ADT-induced osteoporosis and delay of skeletal-related events (SREs) in metastatic bone disease is discussed. A brief overview on the proposed modes of action is given. ***Methods:*** Literature search of PubMed documented publications and abstracts from meetings. ***Results:*** Among the biphosphonates currently available, zoledronic acid is the only one known to be capable of delaying SREs in RCC and prostate cancer patients. Zoledronic acid counteracts cancer treatment-induced osteoporosis in men with prostate malignancies. The antitumor activity of biphosphonates found in vitro and in vivo is intriguing and has to be further assessed in clinical studies. ***Conclusion:*** Due to its unique properties, zoledronic acid is a breakthrough in the management of metastatic bone disease in patients with advanced prostate cancer and RCC. It significantly improves the patients' quality of life, drastically prolongs time to first SRE, and showed a positive but not significant effect on survival.

Introduction

Skeletal complications, such as pathologic fractures, spinal cord compression, bone pain, surgery to bone, and hypercalcemia, are debilitating secondary effects of prostate cancer and renal cell carcinoma (RCC) severely impairing patients' quality of life and dramatically hastening their death. Prostate cancer patients, even in the early stage of the disease, experience osteoporosis and osteopenia more often than their healthy peers with the underlying reasons unknown. Androgen deprivation therapy (ADT), the cornerstone treatment in de novo or recurrent metastatic prostate cancer, markedly aggravates the situation leading to an accelerated decrease of bone mineral density (BMD) [1–3]. With disease progression, bone metastases as one of the most serious complications occur in up to 75% of prostate cancer patients [4]. While bone metastases are with less prevalent in RCC (20–30%) [5], the patients affected by it are confronted with similar devastating skeletal problems. Biphosphonates have been found to counteract the detrimental effects of metastatic bone disease in various cancer types increasing the time to the first skeletal complication, lowering the incidence of pathological fractures and reducing pain [6]. Biphosphonates are distinguished on the basis of potency and chemical structure. The first-generation biphosphonates include etidronate and clodronate. Second-generation aminobiphosphonates, such as alendronate and pamidronate, exceed their predecessors in potency by a factor of 10–100. Risedronate, ibandronate, and zoledronic acid as third-generation biphosphonates with a tertiary nitrogen atom incorporated are as much as 10,000-fold more potent. In addition to their direct action on bone resorption and formation, biphosphonates have been proposed to exhibit antitumor activity. They may reduce tumor burden in the skeleton and probably even in extraskeletal sites [7, 8]. This review provides new

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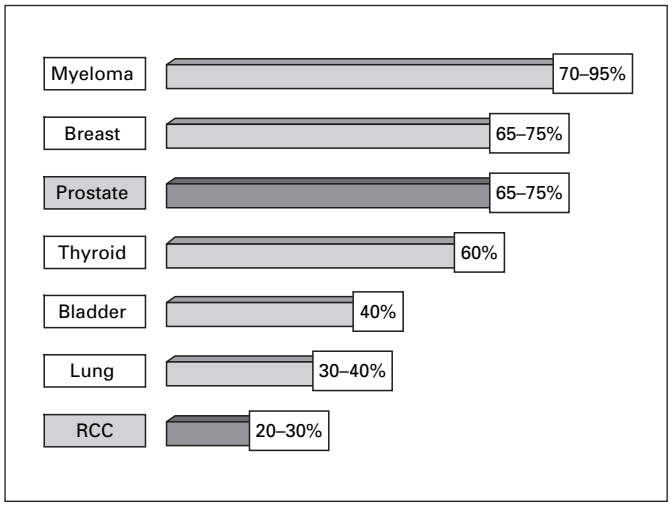

Fig. 1. Incidence rates of various metastatic bone cancers [15].

insights on biphosphonates in the prevention of ADT-induced osteoporosis and the treatment of metastatic bone disease secondary to prostate malignancies and RCC. It introduces the reader to recent clinical studies and theories on the mode of action.

Impact of Skeletal Complications on Patients with Prostate Cancer or RCC

The incidence rates of both prostate cancer as well as RCC have been growing steadily over the last decades. This increase is paralleled by and partly due to earlier diagnosis as a result of annual check-up programs and improved diagnostic procedures, such as ultrasonography and prostate-specific antigen testing in combination with digital rectal examination. It has been observed that patients at all stages of prostate cancer are at elevated risk of osteoporosis and lowered BMD. A considerable proportion of newly diagnosed prostate cancer patients already experiences severe bone loss before cancer treatment has started with 31% of patients having osteopenia in at least one skeletal site [9, 10]. Androgen-deprivation therapy, either by bilateral orchiectomy or treatment with a gonadotropin-releasing hormone agonist (GnRH-A), has been found to further reduce BMD by 4–13% per year [1, 11–14]. ADT is associated with a fourfold increase in the incidence rate of both peripheral and vertebral fractures [15]. Continuous monitoring of BMD and preventive measures against bone loss are strongly recommended. Typically, when the disease progresses to a metastatic stage, the skeleton of prostate cancer patients is already considerably affected and weakened by osteoporosis. The bones represent the first target site for distant metastases in prostate cancer. Correspondingly, the incidence rate of metastatic bone disease in prostate cancer is high and amounts to 65–75% (fig. 1). Prostatic malignancies together with breast cancer account for more than 80% of all cases suffering from bone metastases [16]. With a survival time of 2–3 years after diagnosis of skeletal metastases, prostate cancer patients have to endure a long and heavy burden of repeated fractures and persistent pain constituting an immense challenge for palliative care (fig. 2) [17]. Development of bone metastases in RCC is less common with a prevalence of 20–30% (fig. 1). However, compared with patients having other types of cancer, RCC patients afflicted by metastatic bone disease are at extraordinary high risk of experiencing severe skeletal complications (fig. 2). In an efficacy and safety trial on zoledronic acid in patients with advanced RCC, 74% of patients in the placebo group suffered at least one skeletal-related event (SRE) during the 9 months of the study [18, 19]. In contrast, in a similar study on patients with hormone-refractory, metastatic prostate cancer (duration: 15 months), SREs occurred in 44% of placebo-treated patients. Of those, 29% had to undergo radiotherapy and 22% experienced pathological fractures (fig. 2) [20, 21]. The median time to the first SRE (72 days) was found to be remarkably short in the RCC group treated with placebo (72 days) as compared to the observed time in the prostate cancer study (first SRE: 321 days) [18]. In a 5-year review of 103 patients with metastatic RCC, it was found that >80% of the patients had to undergo palliative radiotherapy to the bone and ≥40% suffered long-bone fractures [5]. It is obvious that skeletal complications have a strong adverse influence on the quality of life [22]. Superimposed on the various problems cancer patients in advanced disease stage have to face, SREs secondary to cancer can be assumed to sap patients' energy and further erode quality of life. Patients are confronted with impaired function and mobility, the necessity of hospitalization and surgical procedures, and the debilitating effects of treatment-refractory pain. Spinal cord compression with high occurrence particularly in prostate cancer patients entails the risk of paraplegia. Analysis of data from a clinical trial on zoledronic acid versus placebo in the treatment of SREs secondary to prostate carcinoma confirms that SREs substantially reduce measures of health-related quality of life as evaluated by the Functional Assessment of Cancer Therapy-General (FACT-G)

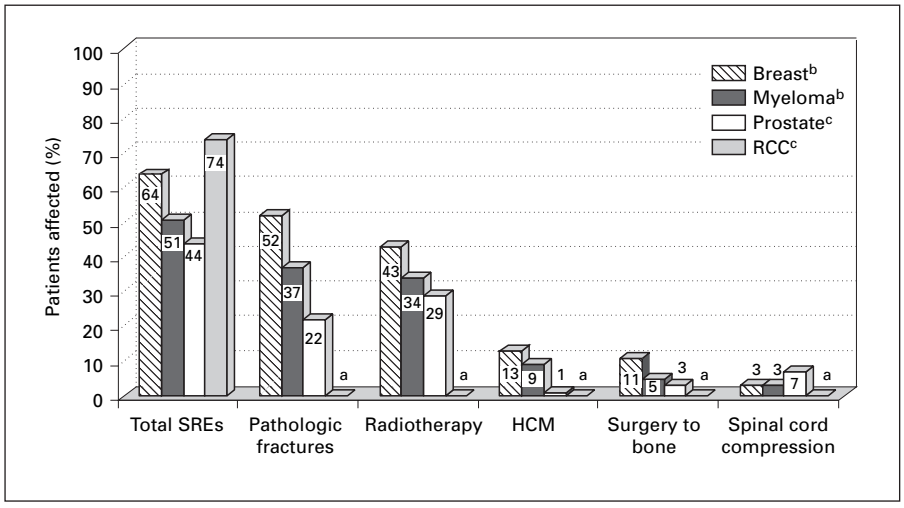

Fig. 2. Skeletal-related event (SREs) in metastatic bone disease: a = data not available; b = pamidronate trial; c = zoledronic acid trial [15, 17]. HCM = Hypercalcemia of malignancy.

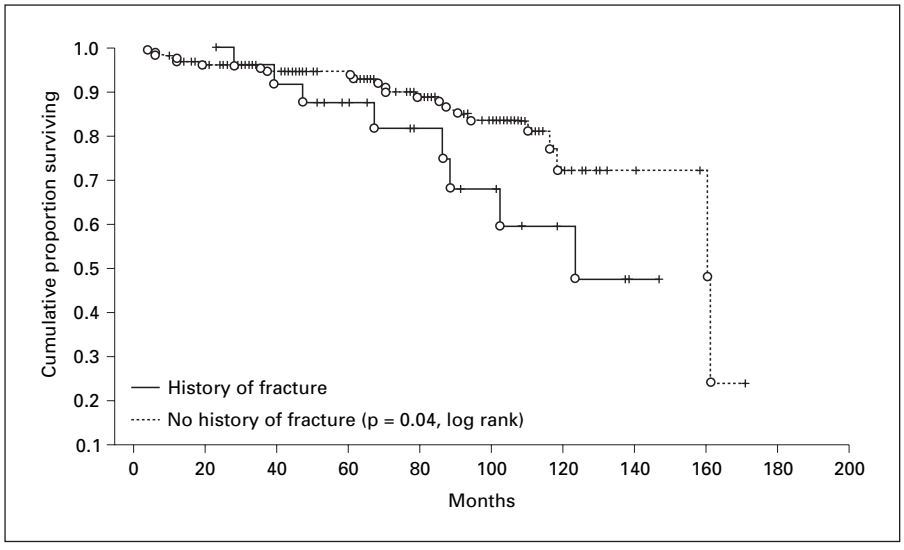

Fig. 3. Negative correlation of overall survival time and a history of skeletal fractures [24].

and EURO-EQ-5D [23]. Even more detrimental, skeletal fractures were found to negatively correlate with survival time. Analyzing the history of 195 patients receiving chronic androgen suppression for prostate cancer, Oefelein et al. [24, 25] observed that median overall survival was significantly lower in patients with cancer-related skeletal fractures (skeletal fractures: 121 months, no skeletal fractures: 160 months). Skeletal fractures are an independent negative predictor of overall survival time (relative risk, 7.4; p = 0.007). The negative impact of SREs on patients with prostate cancer or RCC warrants preventive, therapeutic and palliative care to sustain BMD and to prolong survival by reducing and managing SREs (fig. 3).

Biphosphonates against Cancer Treatment-Induced Bone Loss

Despite conclusive evidence that blockade of androgen signaling by ADT constitutes a major factor for bone loss, screening for osteoporosis is still neglected and low BMD insufficiently treated in patients with prostate carcinoma. In a recently published study (n = 184) aimed to investigate whether physicians are aware of the necessity to monitor, prevent, and treat osteoporosis during ADT, it was found that in only 8.7% (95% confidence interval [CI] = 4.6–13.0%) of patients a DXA scan was performed. Overall, only 14.7% of patients (95% CI = 9.5–20.0%) were treated to maintain physiological BMD. Oral and

intravenous biphosphonates were administered in 4.9% (95% CI = 1.8–8.0%) and 0.5% (95% CI = 0–2.0%) of patients, respectively [26]. This study stresses that, despite conclusive evidence on ADT as a major factor for bone loss, osteoporosis is still underdiagnosed and undertreated in patients with prostate carcinoma undergoing ADT. Further education of physicians on this subject is crucial and still required. Suggested approaches to prevent bone loss include hormonal therapy, dietary supplementation, and treatment with calcitonin or biphosphonates [27]. In a pilot study, an increased bone turnover implied by serum bone and collagen markers was observed in orchiectomized subjects, whereas in estrogen-treated patients bone turnover was reduced suggesting a bone mass-preserving capacity of estrogen [28]. This result is corroborated by another small study with 27 subjects enrolled [11]. However, research on estrogens as preemptive means against ADT-induced bone loss seems to be somewhat abandoned surely in part due to the occurrence of cardiovascular complications in 30% of estrogen-treated men. More research is needed to explore the effect of calcitonin on the course of ADT-induced osteoporosis. In an uncontrolled trial with orchiectomized men (n = 9), intranasal calcitonin treatment was found to partially correct osteoresorption [29]. Results from research on the therapeutic role of oral calcium and vitamin D in ADT-induced bone loss are not conclusive. In a 4-month study on men receiving GnRH-A treatment for prostate cancer, vitamin D supplementation led to prevention of bone loss. However, the observation was not statistically significant when analyzing the 12-month data of the trial [30]. According to two randomized trials with men starting ADT, dietary supplementation based on oral calcium (500 mg/day) and vitamin D (400 IU/day) is inefficient in preventing ADT-induced bone loss [9, 31]. Generally, physicians suggest supplementation with calcium and vitamin D in combination with biphosphonate treatment. Undoubtedly, research on biphosphonates as antiresorptive agents in the prevention and treatment of ADT-induced osteoporosis is most advanced with randomized, placebo-controlled trials performed to evaluate their efficacy [32]. Alendronate is currently the only biphosphonate approved by the FDA for the treatment of male osteoporosis. However, to our knowledge, the beneficiary effects of alendronate against ADT-induced bone loss have not been investigated in clinical trials. Among the various biphosphonates available, pamidronate, etidronate, neridronate, and zoledronic acid have been demonstrated to exhibit a significant protective activity on the bone in prostate cancer patients under ADT. Following adjuvant administration of intermittent cyclic etidronate and calcium supplementation, mean lumbar spine QCT improved by 7.8 ± 3.7% to a final value of 75 mg/cm^3 (95% CI = 48.7–101 mg/cm^3) in men (n = 12) treated with combined androgen blockade. BMD significantly rose in the femoral neck and Ward's triangle, but did not return to baseline [11]. Based on a very recent trial, the authors concluded that neridronate (25 mg i.m. monthly) in combination with calcium and cholecalciferol supplements (500 mg of elemental calcium and 400 IU cholecalciferol, daily) is an effective and safe treatment in preventing bone loss in men receiving ADT for prostate cancer [33]. In a double-blind, randomized, placebo-controlled, crossover study with 22 men receiving gosarelin acetate in combination with flutamide or bicalutamide, it was demonstrated that a single regimen of pamidronate (90 mg in 500 ml of normal saline solution, i.v.) significantly decreased high bone turnover and bone loss compared to placebo [34]. In a 48-week, open-label study with randomly assigned 47 men having advanced or recurrent prostate cancer without bone metastases, leuprolide alone was compared to leuprolide in combination with pamidronate (60 mg i.v. every 12 weeks). Significant differences between the two groups in the mean changes in BMD of lumbar spine ($p < 0.001$), trochanter ($p = 0.003$), total hip ($p = 0.005$), and trabecular bone of the lumbar spine ($p = 0.02$) indicate that pamidronate prevents bone loss [35]. Zoledronic acid, the only biphosphonate approved for the treatment of metastatic prostate carcinoma, was found not only to prevent bone loss, but to preserve bones by increasing mean BMD in lumbar spine, femoral neck, trochanter and hip as shown in a multicenter double-blind, randomized, placebo-controlled clinical study in patients with M0 prostate cancer starting ADT (n = 106). The administered regimen (4 mg, 15-min infusion every 3 months for 1 year) was well tolerated. Recently, recommended treatment algorithms were published for the prevention of cancer treatment-induced bone loss [36, 37].

Clinical Efficacy of Biphosphonates in Metastatic Bone Disease Secondary to Prostate Carcinoma

Initially, biphosphonates have been identified as an efficient therapeutic means against skeletal morbidity secondary to advanced breast cancer and multiple myeloma [38, 39]. Over the last decade, extensive research was performed to expand the clinical utility of biphos-

Table 1. Key mediators of bone remodeling

Activation	Parathyroid hormone (PTH), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-11 (IL-11), tumor necrosis factor α (TNF-α), granulate-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), RANK and RANK-Ligand, prostaglandin E_2 (PGE_2), osteoprotegerin (OPG), 1α,25-dihydroxyvitamin D
Bone resorption	Integrin $\alpha_1\beta_3$, tumor necrosis factor β (TNF-β), fibroblast growth factor (FGF), bone morphogenetic protein (BMP), transforming growth factor β (TGF-β), Ca^{2+}, cathepsin
Bone formation	Parathyroid hormone (PTH), insulin growth factor (IGF-1), core binding factor α1 (Cbfa-1), runt-related transcription factor 2 (Runx-2), 1α,25-dihydroxyvitamin D

phonates into the treatment of skeletal complications in patients with metastatic prostate cancer. Both first- and second-generation biphosphonates were evaluated. Studies on first-generation biphosphonates in prostatic cancer patients with bone metastases mainly evaluated efficacy against bone pain.

Clodronate

In an open multicenter trial, clodronate (300 mg/day i.v. for 10 days) dramatically reduced bone pain assessed by daily consumption of analgesic drugs and by a visual analogue scale in 80 out of 92 patients with bone metastasis due to prostate carcinoma [40]. Several small trials indicated that alleviation of bone pain occurs when clodronate was orally administered with or without preceding intravenous treatment [41–43]. However, this finding could not be confirmed when analyzed in randomized trials. No significant differences were found between the two treatments groups in patients (n = 55) having metastatic prostate cancer randomized either to placebo or to clodronate (300 mg i.v. for 3 days) followed by oral clodronate (3,200 mg for 4 weeks). The authors surmised that the lack of difference could, in part, originate from a substantially lower mean baseline pain in their study groups as compared to previous trials [44]. This theory is corroborated by a study in men randomly assigned to clodronate (1,500 mg i.v. every 3 weeks) or placebo in combination with mitoxantrone (12 mg/m^2 i.v. every 3 weeks) and prednisone (5 mg orally b.i.d.). Subset analysis showed an analgesic benefit in patients with more severe pain. The median duration of response, symptomatic disease progression-free survival, overall survival, and overall quality of life were also examined in this study and were found to be similar between the arms [45]. The effect of oral clodronate (2,080 mg/day) on bone progression-free survival times was determined in a double-blind, placebo-controlled, randomized trial with 311 subjects. Clodronate caused a statistically nonsignificant better symptomatic bone progression-free survival (hazard ratio [HR] = 0.79, 95% CI = 0.61–1.02; p = 0.066) and overall survival (HR = 0.80, 95% CI = 0.62–1.03; p = 0.082) when compared with placebo [46].

Etidronate

Sodium etidronate was found to be ineffective for alleviation of bone pain from prostatic cancer in a study performed by Smith [47].

Pamidronate

Based on two multicenter, double-blind, randomized, placebo-controlled trials, pamidronate (90 mg i.v. every 3 weeks for 27 weeks) was analyzed with bone pain as primary endpoint and proportion of patients with SREs as secondary endpoint. Only a slight analgesic effect was observed and the percentage of patients experiencing SREs was not reduced [48].

Ibandronate

In patients with painful osseous metastases due to prostate carcinoma, ibandronate (6 mg every 4 weeks) significantly reduced pain and daily consumption of analgesics in 92% of the patients [49].

Zoledronic Acid

In a large multicenter, randomized, placebo-controlled trial (n = 643) conducted recently, zoledronic acid has been identified as the only biphosphonate currently available reducing skeletal morbidity secondary to advanced prostate carcinoma and providing durable pain palliation [20]. Patients with hormone-refractory prostate cancer and bone metastases were randomized to a double-blind treatment of zoledronic acid at 4 mg (i.v., n = 214), and at 8 mg (i.v., subsequently reduced to 4 mg due to concerns about renal toxicity, n = 221) given every 3 weeks

for 15 months [50]. 209 patients received placebo. Zoledronic acid significantly reduced the proportion of patients who experienced at least one SRE as compared with placebo (44.2 vs. 33.2%; difference = –11.0%, 95% CI = –20.3 to –1.8%; p = 0.021). Median time to first SRE was not reached at 15 months in the group given a 4-mg dosage of zoledronic acid (placebo: 321 days; p = 0.011 vs. placebo). Biomarkers reflecting bone resorption were significantly lower with zoledronic acid than with placebo. Disease progression, performance status, and quality-of-life scores were similar among the groups. 122 of the patients completed a total of 2 years on study. The results supported the previous findings. 38% of study subjects treated with zoledronic acid experienced ≥ 1 SRE as compared with 49% on placebo (difference = –11.0%, 95% CI = –20.2 to –1.3%; p = 0.028). The annual incidence of SREs was significantly decreased (0.77 for the 4-mg zoledronic acid versus 1.47 for the placebo group; p = 0.005). Median time to the first SRE was determined to be 488 days versus 321 days with placebo. Alleviation of pain was sustained across the 24 months study [20]. Side effects including fatigue, anemia, myalgia, and pyrexia were manageable. In 2002, zoledronic acid was approved by the FDA and EMEA for the prevention of SREs in patients with metastatic bone disease secondary to advanced prostate cancer.

Clinical Efficacy of Biphosphonates in Metastatic Bone Disease Secondary to RCC

The incidence rate of SREs in advanced RCC is extraordinary high. Even so, research data on the efficacy of biphosphonates in the prevention of SRE in RCC is scarce. In a case report on a 47-year-old man having RCC with multiple metastases in bone, lung and lymph nodes, intravenous pamidronate was reported to significantly decrease bone pain and to normalize the serum calcium concentration [51]. Results from a retrospective subset analysis of a larger clinical trial [52] on the efficacy of zoledronic acid against SREs in patients having RCC with bone metastasis are very encouraging. Zoledronic acid (4 mg via 15-min infusions every 3 weeks for 9 months) has been found to exhibit significant benefits. SREs were much less prevalent in zoledronic acid-treated patients (37% patients affected compared with 74% receiving placebo, p = 0.015). A remarkable delay of SREs was observed with a significantly extended median time to the first SRE (median not reached at 9 months vs. 72 days for placebo, p = 0.006) and progression of bone lesion (median not reached at 9 months vs. 89 days for placebo, p = 0.014). Andersen-Gill multiple event analysis showed that zoledronic acid reduces the risk of developing a SRE by 61% [18]. A total of 13 RCC patients were enrolled in the 21-month extension phase of the study. In the zoledronic acid group the median times to first SRE and to bone lesion progression were reached (first SRE: 424 days, p = 0.007; bone lesion progression: 589 days, p = 0.014). Even after 21 months, the median time to first pathological fracture was not attained in patients treated with zoledronic acid. Survival time was improved, but this observation did not reach statistical significance (median: 347 vs. 216 days with placebo, p = 0.104). The study stresses that zoledronic acid has a remarkably positive impact on patients with advanced RCC. Further research on biphosphonates in the prevention of SREs secondary to RCC is ongoing and expected to substantially contribute to the improvement of patients' well-being in the future.

Mechanistic Aspects

Biphosphonates and the Bone Remodeling Process

The continuous turnover of bone matrix and mineral is initiated by activation of osteoclasts to remove old bone and followed by activation of osteoblasts to build new bone. The regulation of osteoclastic and osteoblastic activity depends on a complex and thus far incompletely elucidated interplay of various key mediators (table 1) [53]. Bone-derived growth factors and cytokines released as result of bone resorption can attract malignant cells, which in turn secrete their own osteoblastic and osteoclastic factors. Consequently, disturbance of the dynamic remodeling process occurs leading to loss of bone integrity (osteopenia) and triggering SREs. Based on their radiologic appearance, bone lesions are categorized as osteolytic, osteoblastic, or mixed. Bone lesions in patients with prostate cancer are mainly osteoblastic. However, the underlying biology is more complex, since men with osteoblastic metastases were demonstrated to have increased osteoclast number and activity in skeleton adjacent and distant from the tumor site [54, 55]. RCC is associated with mixed bone lesions [5, 56]. Research has only begun to shed light on the complex cellular and molecular mechanisms by which biphosphonates inhibit bone resorption. In vitro experiments demonstrated that biphosphonates hinder osteoclast recruitment, differentiation and maturation. Being incorporated by osteoclasts, biphosphonates compromise osteoclastic activity

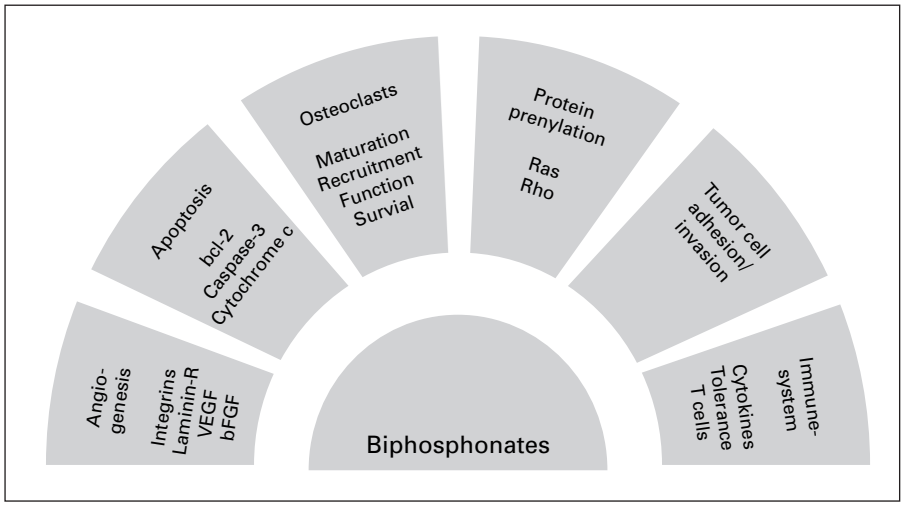

Fig. 4. Modes of action.

and function. Biphosphonates are known to stimulate osteoblasts to release an inhibitor of osteoclast recruitment and survival [57]. Disruption of prenylation essential for the synthesis of Ras and Rho is discussed as one key factor compromising osteoclastic cell function [58]. Pamidronate and zoledronic acid have been found to increase the production of osteoprotegerin (OPG), which antagonizes the maturation of osteoclasts mediated by the nuclear factor-kB ligand (RANKL) [59].

Antitumor Effects of Biphosphonates

Extensive evidence has accumulated that second-generation biphosphonates reduce skeletal tumor burden and exhibit antitumor activity in the bone and on visceral metastases [60, 61]. The newer biphosphonates have been found to block proliferation and induce apoptosis of various tumor cell lines at doses that are likely to be reached in the bone at sites of active bone resorption [62, 63]. Biphosphonates are chelators of zinc and as such inhibit the activity of matrix metalloproteinases thereby interfering with and suppressing tumor cell adhesion to bone, tumor invasion and metastasis [64]. Inactivation of the RANK pathway inhibits myeloma cell growth and survival in the bone [65]. Alteration of bcl-2 expression, activation of caspase-3 and the stimulation of mitochondrial cytochrome c release are discussed as mechanisms underlying the apoptotic effect of biphosphonates [66]. The antiangiogenetic effect of zoledronic acid may be at least in part due to downregulation of anb3 and anb5 integrins and the laminin receptor and modulation of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) [67, 68]. The results on the immunomodulatory effects of biphosphonates as contributing factor for antitumor activity are preliminary. Following administration of biphosphonates to animals, elevated production of inflammatory cytokines by antigen-presenting cells, reduced tolerance to tumor antigens and the formation of cytotoxic T cells were observed [69–71]. It was hypothesized that modulation of cytokines by biphosphonates hinders the growth of cancer cells [72, 73] (fig. 4).

Conclusion

Skeletal complications have a tremendous negative impact on the quality of life and the survival time in patients with metastatic bone disease secondary to carcinomas. Biphosphonates have been demonstrated to be an effective long-term treatment to prevent and delay SREs. Zoledronic acid was found to be superior to other biphosphonates in many aspects. In metastatic bone disease secondary to prostate cancer and RCC, zoledronic acid targeting both osteoblastic as well as osteoclastic lesions has proven to be the only efficacious agent with the additional advantage to be conveniently administered via 15-min infusion. Zoledronic acid is the only biphosphonate with the ability not only to prevent but also to reverse osteoporosis in prostate cancer patients undergoing ADT. Preclinical evidence on the antitumor activity of newer generation biphosphonates has spurred ongoing clinical studies on the capability of biphosphonates to halt disease progression and reduce tumor burden in bone.

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