# Bisphosphonates and vascular endothelial growth factor-targeted drugs in the treatment of patients with renal cell carcinoma metastatic to bone

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**Skeletal involvement is common in patients with renal cell carcinoma (RCC): ~30% of patients with metastatic RCC (mRCC) will develop bone metastases. Inhibition of vascular endothelial growth factor (VEGF) has been pursued as a therapeutic target in the treatment of metastatic clear-cell RCC (m-ccRCC). Tyrosine kinase inhibitors (TKIs), such as sunitinib, pazopanib, sorafenib, and the monoclonal antibody bevacizumab, became the therapy of choice for patients with m-ccRCC. Besides the undisputed efficacy of TKI in the treatment of m-ccRCC, the problem of metastatic bone disease still remains. There is evidence that the presence of bone metastases in m-ccRCC patients has a significant and clinically relevant negative impact on survival and potentially on the outcome of VEGF-targeted therapy. Also, a relatively common practice in the treatment of such patients is bone-directed therapy with bisphosphonates (BPs). Recent evidence shows a potentially synergistic effect on efficacy but also the potential for increased toxicity of combining TKIs and BPs. This review article highlights the importance of this subject and aims to facilitate further research and optimize the treatment of this important and common group of RCC patients.** ***Anti-Cancer Drugs*** **24:431–440 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

The incidence of renal cell carcinoma (RCC) has been increasing steadily over the past three decades [1]. Worldwide, RCC accounts for ~2–3% of all adult malignancies, with ~209 000 new cases and 102 000 estimated deaths each year [2,3]. Approximately 30% of patients with RCC have metastatic disease at the time of diagnosis [4]. Skeletal involvement is common in patients with RCC: ~30% of these patients will develop bone metastases, of which about 70% are osteolytic lesions [4]. The common approach in the treatment of patients with metastatic RCC (mRCC) in the bone is tyrosine kinase inhibitors (TKIs) and bisphosphonates (BPs) combined. The toxicity and efficacy of this combination is the subject of this article.

### Pathogenesis of renal cell carcinoma

RCC is a heterogeneous disease with different histological types, which is often resistant to chemotherapy and radiation therapy [5,6]. The majority of sporadic RCC tumors are of clear-cell histology (75%), followed in frequency by papillary type I and II tumors (15%), chromophobe tumors (5%), and oncocytomas (5%). Distinct cytogenetic abnormalities have been associated with each type [5].

Major advances have been achieved during the past 15 years in understanding the genetic events that lead to RCC. Frequent and early deletion (loss of heterozygosity) in the Von Hippel–Lindau (VHL) tumor suppressor gene allele has been found in 84–98% of sporadic clear-cell RCC (ccRCC) [7–16]. The VHL protein product, in a complex with other proteins, polyubiquinates hypoxia-inducible factor α (HIF-α) and signals its destruction in the proteasome. In the absence of VHL protein, HIF-α accumulates and binds with HIF-β to form a transcriptional factor complex that induces the transcription of various hypoxia-inducible genes, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), erythropoietin, and transforming growth factor-α (TGF-α) [17–27]. The inactivation of VHL in the majority of ccRCC tumors leads to VEGF overexpression, which drives tumor angiogenesis. Thus, inhibition of VEGF has been pursued as a therapeutic target in RCC [28–30].

### Treatment options for metastatic renal cell carcinoma

Targeted agents now represent the mainstay of systemic treatment for locally advanced and/or mRCC [31,32]. As clear-cell carcinomas constitute the vast majority of all

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RCCs, most clinical studies have been carried out in patients with a clear-cell histology [2,32].

There are several potential strategies of VEGF and angiogenesis inhibition in RCC: small molecules with inhibitory effects on VEGF receptors (VEGFRs), mammalian target of rapamycin (mTOR) inhibitors, and monoclonal antibodies directed against VEGF [33].

On the basis of phase III trials sunitinib, bevacizumab in combination with interferon-α (IFN-α) and pazopanib are recommended in international treatment guidelines as the first-line therapy for mRCC in patients at a favorable or an intermediate prognostic risk according the MSKCC criteria [2,31,32,34–39]. Temsirolimus is an mTOR inhibitor; inhibition of the mTOR kinase pathway dysregulates the cell cycle and angiogenesis by disruption of a number of intracellular signaling pathways. Temsirolimus is recommended in RCC guidelines as first-line treatment specifically for patients at a poor risk [40–48]. Given the efficacy of sorafenib in patients following progression on cytokine-based therapy, sorafenib is recommended in the NCCN and ESMO guidelines as the initial second-line treatment option in this population [49–58]. Everolimus, like temsirolimus, is an mTOR inhibitor, but it is available as an oral formulation for once-daily dosing, which was approved in 2009 for the treatment of mRCC following failure of VEGF-TKI therapy [59]. Recently, axitinib, a potent and selective second-generation inhibitor of VEGFRs, showed efficacy in a randomized phase III study as second-line therapy in patients with mRCC [60]. Table 1 shows the targeted treatment options in mRCC.

**Table 1 Targeted treatment options in metastatic renal cell carcinoma**

| Agents | Indication | RR (%) | PFS (months) | OS (months) |
|---|---|---|---|---|
| Sunitinib [34] | First line | 44 | 11 | 26.4 |
| Bevacizumab + interferon-α [36] | First line | 31 | 10.2 | 23.3 |
| Bevacizumab + interferon-α [37] | First line | 26 | 8.5 | 18.3 |
| Pazopanib [39] | First line | 32 | 11.1 | 22.9 |
| Temisorolimus [48] | First line | 8.6 | 5.5 | 10.9 |
| Sorafenib [58] | Second line | 10 | 5.5 | 17.8 |
| Everolimus [59] | Second line | 5 | 4.9 | 14.8 |
| Axitinib [60] | Second line | 19.4 | 6.7 | NA |

NA, not applicable; OS, overall survival; PFS, progression-free survival; RR, response rate.

## Treatment options for patient with bone metastatic renal cell carcinoma

Optimal management of bone metastases requires a multidisciplinary team. Systemic therapy, radiotherapy (including stereotactic radiosurgery), surgery, radiofrequency ablation, and bone-targeted treatment with the BPs or immunotherapy (denosumab) are combined depending on the biology of the disease, extent of the skeletal involvement (one or multiple sites of bone metastases), presence of symptoms, comorbidities, and the life expectancy of the patient. The goal of such a treatment is to decrease the incidence of skeleton-related events (SREs) and skeletal morbidity and to delay the progression of bone disease and eventually death of the patient [61–68].

## Tyrosine kinase inhibitors and bone metastases of renal cell carcinoma

Besides the undisputed efficacy of TKI and bevacizumab in the treatment of metastatic clear-cell RCC (m-ccRCC), the therapeutic problem of metastatic bone disease still exists. Metastatic bone disease causes significant morbidity through SREs, which include pathological fractures, surgical intervention, palliative radiotherapy to bone lesions, spinal cord compression, and hypercalcemia of malignancy. In the study by Zekri *et al.* [4] on mRCC patients, palliative radiotherapy to bone was required in more than 80% of patients with bone metastases, and long-bone fractures occurred in at least 40% of these patients. Moreover, there is evidence that the presence of bone metastases in m-ccRCC patients has a significant and clinically relevant negative impact on prognosis in general as well as on the outcome of treatment with TKIs [69,70]. Recently, Beuselinck *et al.* [69] have published the results of a retrospective study designed to investigate whether the presence of bone metastases affects outcomes in patients with mRCC receiving sunitinib ($n = 223$). With a median follow-up of 40 months, the median progression-free survival (PFS) and the median overall survival (OS) were significantly shorter in patients with bone metastases compared with those without (8.2 vs. 19.1 months, $P \leq 0.0001$ and 19.5 vs. 38.5 months, $P \leq 0.0001$, respectively). On multivariate analysis, considering platelet count, Eastern Cooperative Oncology Group (ECOG) performance status, number of metastatic sites, neutrophil count, corrected serum calcium, time from diagnosis to systemic treatment, and the presence of bone metastases, bone metastasis was the independent variable most significantly associated with poor PFS ($P \leq 0.0001$) and OS ($P = 0.001$). The conclusion of this study was that the presence of bone metastases in m-ccRCC patients treated with sunitinib has a significant and clinically relevant negative impact on outcome [69]. Also, in line with that study, an analysis of variables among RCC patients receiving first-line therapy with either sunitinib or IFN-α in a randomized trial also confirmed that the presence of bone metastases was a poor prognostic feature in both arms [70]. Moreover, a retrospective review of 58 patients with advanced RCC receiving first-line systemic therapy with sorafenib showed that patients with bone metastases had a poorer prognosis than patients without bone disease. The median PFS was 11.2 months (95% confidence interval 7.4–13.2) for

patients without bone metastases ($n = 36$) versus 4.7 months (95% confidence interval 3.6–7.4) for patients with bone metastases ($n = 22$, log-rank test, $P = 0.002$). Cox regression indicated that the presence of bone metastases was associated with shorter PFS after adjusting for other prognostic factors ($P = 0.02$) [71].

### Effects and toxicities of bisphosphonates in the treatment of bone metastases of renal cell carcinoma

Metastasis to bone occurs through a multistep process, and inhibition of any one of those steps could prevent metastasis to bone or SREs, with consequent improvements in the quality of life of affected patients. Initially, cancer cells form emboli that lodge in capillary beds in bone [72]. As cancer cells enter the bone, they are exposed to factors in the bone microenvironment, such as growth factors released from the bone matrix during osteolysis, which may promote tumor growth [72].

BPs are potent inhibitors of osteoclast-mediated bone resorption and play an important role in the supportive care of patients with bone metastases. Several BPs [clodronate, pamidronate, ibandronate, and zoledronic acid (ZA)] improve clinical outcomes for patients with multiple myeloma and metastatic breast cancer [73–75]. BPs reduce the incidence of SREs, and preclinical and clinical studies, particularly those that have examined ZA, have shown that the combination of BPs and specific systemic oncological therapies may have effect on the outcome of patients with metastatic bone tumors [76–78]. Using a xenograft mouse model, Ottewell *et al.* [76], investigated the effects of clinically effective doses of doxorubicin (Dox) and ZA administered alone, in sequence, and in combination, on the growth of subcutaneously inoculated tumors derived from a human breast cancer cell line. After 6 weeks of treatment, mice treated simultaneously with ZA and Dox had smaller tumors than those treated with Dox alone, with ZA alone, or with ZA, followed 24 h later by Dox. Treatment with Dox, followed 24 h later by ZA almost completely abolished tumor growth. No evidence of bone disease was detected in any of the treatment groups. The authors suggest that patients with early-stage breast cancer may benefit from treatment that combines ZA with cytotoxic agents, administered concomitantly or ZA preceded Dox by 24 h. In another preclinical study, ZA significantly reduced the ability of mesenchymal stem cells to support the migration of breast cancer cells, suggesting an additional mechanism by which ZA may impede tumor metastasis [77]. Moreover, ZA has been shown to decrease the number and persistence of disseminated tumor cells, which are known to promote disease recurrence [78–81].

Aminobisphosphonates induce apoptotic cell death on RCC cell lines, and ZA was consistently more potent in this than pamidronic acid [82–84]. ZA-loaded bone cement also showed marked cytotoxic activity on bone-originated RCC cell cultures in a dose-dependent manner [85]. Under clinical conditions, ZA has been shown to potentiate the effect of radiotherapy to bone metastases from RCC by increasing the response rate, SRE-free survival, and duration of site-specific pain response [86,87]. At least one case study reported that conventional ZA monotherapy itself induced considerable improvement in bone and marked responses in sizes of other metastases for an mRCC patient with bone, lung, pleural, and liver disseminated disease. This was also associated with sustained PFS (more than 20 months [88]. Other BP treatments of RCC patients could also result in an improvement in metastatic disease involving bone and lungs [89].

Compared with bone metastases in breast and prostate cancer, there is a paucity of data on the demographics of bone metastases in RCC and their sequelae in terms of SREs and survival [90]. One of the ZA registrational studies was a placebo-controlled trial in patients with bone metastases from solid tumors other than breast and prostate cancer (10%, i.e. 74 patients, had mRCC). It showed that treatment with 4 mg of ZA significantly extended time to first SRE ($P = 0.007$) and time to first pathologic fracture ($P = 0.004$), with a 58% reduction in the risk of developing SREs for patients with bone metastases from RCC ($P \leq 0.01$) [91].

The results from the subgroup of mRCC patients of this trial have also been published separately [92]. Forty-six RCC patients were treated with either 4 mg of ZA ($n = 27$) or placebo ($n = 19$). ZA treatment significantly extended the median time to progression of bone metastases (586 vs. 89 days, $P = 0.014$). ZA also considerably improved the median OS but this did not reach significance (347 vs. 216 days, $P = 0.104$). ZA is therefore the first BP that significantly reduced skeletal morbidity and delayed the progression of bone lesions in patients with mRCC. Results from a 21-month extension phase of this trial confirmed the benefit of ZA in this population and showed that the median time to first SRE in the 4 mg ZA arm was 442 days (compared with 72 days for placebo, $P = 0.007$) [92].

This subset analysis suggests that ZA is efficacious in RCC patients with bone metastases. The marked reduction in the proportion of patients with an SRE and the increased delay in the time to progression of bone disease suggest that bone metastases of mRCC patients may be sensitive to ZA. The results of this analysis support an expanded role for BPs in the treatment of RCC patients with bone metastases and encourage the exploration of ZA treatment in patients with less advanced disease. Besides the trial results presented above, there are very few data available on the impact of BPs on bone and cancer-specific health of RCC patients with bone metastases. Recently, Woodward *et al.* [93] published a retrospective study on 803 patients with

advanced or mRCC, out of whom 32% of patients ($n = 254$) presented with or subsequently developed bone metastases. Approximately 50% of these patients received BPs treatment, mainly ZA, and 8% were treated with TKI. The skeletal morbidity rate (number of SREs per patient years at risk) for patients who received or did not receive BPs was 1.0 and 1.4, respectively. Overall, for those receiving BPs, 10.7% progressed in the bones compared with 27.1% in those who received no BPs. This phenomenon may be typical of routine clinical practice outside of a clinical trial and points to the need for stronger attention in the internationally guidelines in this indication. The median survival following the diagnosis of RCC was similar in patients who developed bone metastases (20.4 months) and those who did not (20.9 months) [93]. Unfortunately, the authors did not provide data on PFS or OS with respect to the use of BPs in their patients with bone metastases [93]. In a small retrospective study, 45 mRCC patients with bone metastases were included [94]; 23 patients were treated with ZA and 22 were not. The authors found that ZA treatment significantly improved OS (1 year survival was 80.8 vs. 59.1%, $P = 0.0034$) and reduced the SRE rate ($P = 0.0453$).

Ten of the 45 patients also received molecular targeted therapy. Although the compared cohorts were unbalanced in terms of molecular targeted therapies, the OS difference remained significant when time on these drugs was substracted from survival times [94].

A large retrospective study including data of 28 385 ZA-treated patients mined out from two national US managed-care plan databases reported a 56% reduction in risk of mortality as a result of ZA treatment [95]. The greatest benefits were observed for patients treated on a regular basis with ZA for a period beyond 18 months. The authors have concluded that reduced risk of fractures and reduced mortality risk have remained after controlling for other factors such as skeletal complications. Nevertheless, the selection bias, that is longer treatment with ZA could be associated with longer survival, was not sufficiently covered in the article by Henk *et al.* [95].

Another, larger, retrospective study including 71 bone metastatic from 214 mRCC patients also confirmed that ZA and molecular targeted treatments are independent prognostic factors of favorable survival [96].

Table 2 shows the efficacy of BPs in patients with bone metastases of RCC.

It has also been shown that ZA indirectly affects the immunomodulatory effects of γδ T cells. ZA inhibits farnesyl diphosphate synthase (FPPS) in peripheral blood mononuclear cells (PBMCs), causing intracellular accumulation of isopentenyl pyrophosphate (IPP) [99]. Released IPP stimulates the proliferation of γδ T cells and secretion of cytokines, such as interleukin (IL)-4, IL-10, tumor necrosis factor-α (TNF-α), and IFN-γ. These activated γδ T cells are directly cytotoxic to tumor cells, whereas IL-4 and IL-10 stimulate a B-cell (humoral) response to tumor cells, whereas TNF-α and IFN-γ stimulate antigen-presenting cells (e.g. dendritic cells and macrophages) and T helper cells [99,100].

Potentially one of the important effects of ZA on the treatment of patients with m-ccRCC is inhibition of angiogenesis through its inhibition of VEGF production. In a study reported by Santini *et al.* [101], 26 patients with advanced solid cancer and bone metastases received 1 mg of ZA acid weekly for 4 weeks, followed by three cycles of 4 mg of ZA, administered with a standard 28-day schedule. Patients were prospectively evaluated for circulating levels of VEGF just before the beginning of each drug infusion. The median VEGF basal value showed an early statistically significant ($P = 0.038$) decrease 7 days after the first 1 mg infusion of ZA. This effect on VEGF-circulating levels persisted throughout the treatment with ZA [101].

The data on the patients with bone metastases of renal cancer who were treated with BPs, particularly ZA, with a focus on the possible damage to the remaining kidney function are deficient. It has been reported that ZA treatment induces renal failure in patients with bone metastases [102]. In the previously mentioned study by

**Table 2 Efficacy of bisphosphonates in patients with bone metastases of renal cell carcinoma**

| References, type of study | Number of patients | Reduction of SRE proportion (%) | Reduction of SMR (%) | Reduction of risk of developing SRE (%) | Reduction of risk of disease progression (%) | Reduction of risk of death (%) |
|---|---|---|---|---|---|---|
| Lipton *et al.* [92], R | 74 | 50<br>$P=0.015$ | 20<br>$P=0.014$ | 61<br>$P=0.008$ | – | – |
| Woodward *et al.* [93], R[a] | 254 | – | 81<br>$P=$NA | – | – | – |
| Yasuda *et al.* [94], R[b] | 45 | – | – | NA<br>$P=0.0453$ | – | NA<br>$P=0.0034$ |
| Keizman *et al.* [97], R[b] | 76 | – | – | – | 45<br>$P<0.0001$ | 60<br>$P=0.029$ |
| Beuselinck *et al.* [98], R[b] | 76 | – | – | – | 75<br>$P=0.0011$ | 48<br>$P=0.022$ |

BP, bisphosphonate; NA, not available; R, retrospective; SMR, skeletal morbidity rate; SRE, skeletal-related event; TKI, tyrosine kinase inhibitor.
[a]8% of patients treated with TKIs.
[b]Patients treated concomitantly with BP and TKIs.

Rosen *et al.* [91], a 15-min infusion of 4 mg ZA was associated with only a slightly higher risk of increased serum creatinine compared with placebo. In a prospective study by Bujanda *et al.* [103], a notable increase in the serum creatinine level was observed in 9% of patients treated with ZA for bone metastases of different solid tumors and most of them had received BPs for more than 2 years. Elevated serum creatinine levels in the same range (9–12%) have also been found in other sources [104,105]. The author's conclusion was that ZA was safe, with a low rate of reversible renal toxicity [103–105]. In view of the data reported by Bujanda and colleagues and some other authors, patients receiving BPs should be monitored carefully for renal toxicity, especially those with exposure to BPs beyond 2 years [102–105].

### Efficacy and toxicity of sunitinib and zoledronic acid combination

On the basis of the results of trials with BPs, and especially with ZA, the use of these agents together with TKIs is a relatively accepted clinical practice in the treatment of bone m-ccRCC together (50% of patients in the study by Woodword and colleagues and about 30% of patients in the Expended Access Trial, registered at ClinicalTrials.gov as NCT00130897, on the basis of personal information from the current bone substudy analysis) [93,106].

Considering the fact that VEGF could be defined as a biomarker that is modulated (increased) by TKI treatment (class effect of different TKIs, which is one of the potential mechanisms that could lead to the resistance to treatment with TKIs), it is important to discuss the impact of ZA on TKI therapy and highlight potential synergism between TKIs and ZA or other BPs [107]. Theoretically, by decreasing the level of circulating VEGF that had been elevated by TKIs previously, BPs, especially ZA, could prevent the development of resistance to TKI treatment. Knowing the importance of long-lasting VEGFR inhibition in the treatment of mRCC, any improvement in this could result in better treatment efficacy. Consecutively, it can be suggested that BPs, especially ZA, could possibly improve the efficacy of modern VEGFR TKI drugs used in the treatment of mRCC [107,108].

The question is what are the efficacy and toxicity of such combinations? In two published studies, patients who received a combination of TKIs and BPs showed clinically meaningful better efficacy but potentially increased toxicity [97,98]. Both studies were retrospective and not randomized so that selection biases are not excluded. Recently, Keizman *et al.* [97] published data of a multicenter retrospective study that evaluated the effect of BPs on response rate, PFS, and OS of sunitinib-treated mRCC patients with bone metastases. In this analysis, 209 sunitinib-treated mRCC patients were included: 76 patients had bone metastases. Patients were divided into BP users (group 1, $n = 35$) and non-users (group 2, $n = 41$). The groups were balanced in terms of the prognostic factors: previous nephrectomy, clear-cell/non-clear-cell histology, time from initial diagnosis to sunitinib treatment, the presence of more than two metastatic sites, the presence of lung/liver metastases, ECOG performance status, anemia, calcium level greater than 10 mg/dl, elevated alkaline phosphatase, platelet count, pretherapy neutrophil to lymphocyte ratio (NLR) > 3, sunitinib-induced arterial hypertension, and the use of angiotensin system inhibitors. Groups were also balanced with respect to past cytokines/targeted therapy and the mean sunitinib dose/cycle. Disease control rate was 86% in group 1 versus 71% in group 2. Progressive disease was detected in 14 versus 29% [$P = 0.125$, hazard ratio (HR) 2.48], respectively. The median PFS was 15 versus 5 months (HR 0.55, $P \leq 0.0001$) and the median OS was 21 versus 13 months (HR 0.4, $P = 0.029$), in favor of group 1. In a multivariate analysis of the entire patient cohort ($n = 76$), factors associated with PFS were BPs use (HR 2.2, $P = 0.035$) and pretherapy NLR > 3 (HR 0.38, $P = 0.009$). Factors associated with OS were BP use (HR 2.8, $P = 0.008$), elevated alkaline phosphatase level (HR 0.287, $P = 0.0003$), and sunitinib-induced hypertension (HR 5.57, $P \leq 0.0001$). The conclusion of the study was that BPs may improve the outcome of sunitinib therapy in RCC with bone metastases [97]. It is interesting that Keizman and colleagues do not report on the incidence of osteonecrosis of the jaw (ONJ) in their study at all. One possible reason is the short follow-up.

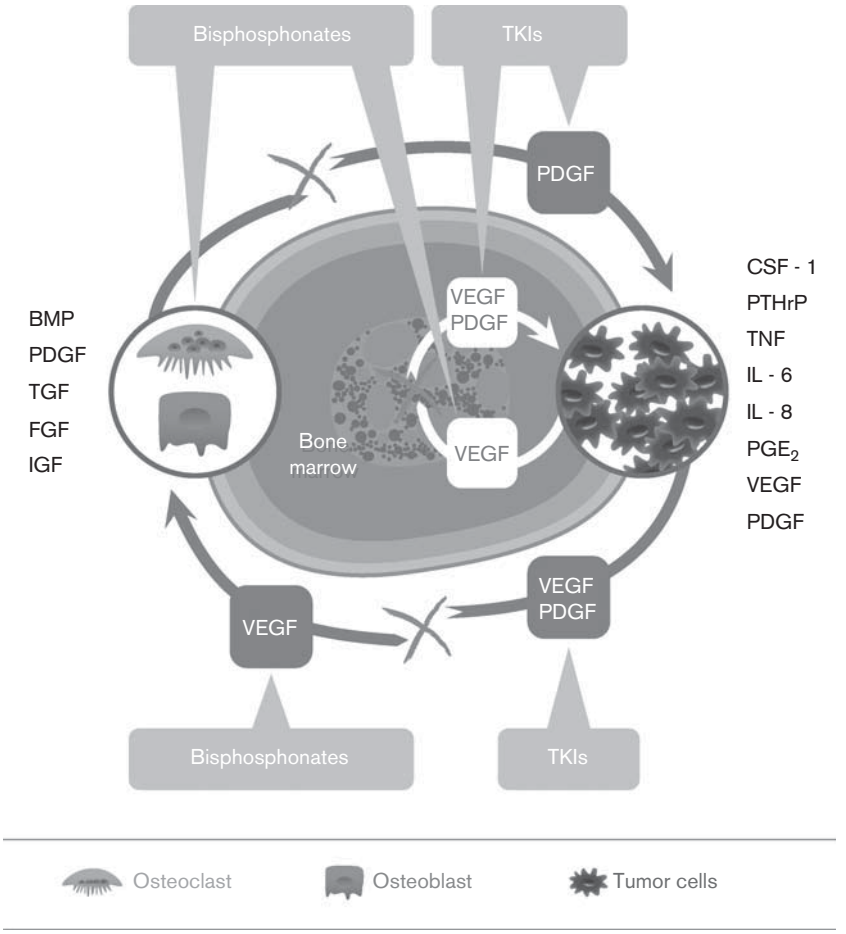
Another data set was published recently by Beuselinck *et al.* [98] on the possible interaction of BP and VEGFR TKI therapy. In this retrospective study, mRCC patients with bone metastases treated with sunitinib and sorafenib have been investigated. Seventy-six patients were included in the outcome analysis: 49 were treated with concomitant BPs and 27 with TKIs alone. Both groups were well balanced in terms of prognostic and predictive markers. The response rate (38 vs. 16% with partial responses, $P = 0.028$), median PFS (7.0 vs. 4.0 months, $P = 0.0011$), and median OS (17.0 vs. 7.0 months, $P = 0.022$) were significantly better in patients receiving BPs. The overall incidence of ONJ was 10% in patients treated with TKIs and BPs, but in patients treated with BPs for more than 12 months, incidence was 17%. The authors concluded that the concomitant use of BPs and TKIs in mRCC patients with bone involvement probably improves treatment efficacy, but is associated with a higher incidence of ONJ [98]. In the absence of a placebo-controlled trial, given the high incidence of SREs, further observations are necessary. It is important to highlight that all toxicities of such treatments generated by the inhibition of VEGF could be potentiated with a combination of VEGFR TKIs and ZA. In particular, the incidence of ONJ could be increased because of its direct causal interaction with vascular inhibition [109–117].

Figure 1 presents the interaction of BPs (ZA) and TKI in bone affected with metastatic tumor.

Osteonecrosis is the death of bone as a result of impaired blood supply. Cancer and its treatment have been described as risk factors for the development of osteonecrosis [111]. Particularly, the use of BPs is associated with ONJ [112–117]. Length of exposure, type of BP used, poor oral hygienic conditions, and previous dental procedures have been recognized as risk factors [112–117]. ONJ occurs in 1–10% of cancer patients treated with intravenous BPs [109]. ONJ is a complication that is correlated with the long-term use of BPs. The mean time of exposure to ZA before a cancer event has been reported to be $\sim$22 months [109].

In a retrospective study, Christodoulou *et al.* [109] reviewed data on 116 patients receiving BPs, 78 ZA and 38 ibandronic acid, with or without antiangiogenic agents for osseous metastases from various tumors. The incidences of ONJ among patients receiving BPs with or without antiangiogenic agents were 16% (four cases) and 1.1% (one case), respectively. The difference was statistically significant ($P = 0.008$). The treatment duration of BPs did not differ significantly between the two groups. The conclusion was that a combination of BPs and antiangiogenic factors induces ONJ more frequently than BPs alone [109]. In a second retrospective study, Bozas *et al.* [110] reviewed data on 77 patients treated with sunitinib for mRCC. Of these patients, 21 had received at least one complete cycle of sunitinib concomitant with ZA. Five of them developed ONJ (24%), resulting in the immediate discontinuation of ZA. Two patients developed ONJ within the first month of concomitant treatment. The mean duration of concomitant treatment with sunitinib and ZA was 5.4 months for the patients who developed ONJ and 7.9 months for those who did not ($P = 0.308$). Life table analysis showed a cumulative

**Fig. 1**




The interaction of bisphosphonates (zoledronic acid) and TKI (sunitinib) in bone affected by metastatic tumor. BMP, bone morphogenetic protein; CSF-1, colony-stimulating factor-1; FGF, fibroblast growth factor; IGF, insulin-like growth factor; IL-6, interleukin-6; IL-8, interleukin-8; PDGF, platelet-derived growth factor; $PGE_2$, prostaglandin $E_2$; PTHrP, parathyroid hormone-related protein; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

hazard of 17% at 6 months of concomitant treatment and 28% at 12 months. Thirteen (62%) of the patients had been exposed to ZA before the initiation of sunitinib. The mean duration of previous exposure to ZA was 13 months for the patients who developed ONJ and 15.7 months for those who did not ($P = 0.452$). The cumulative hazard for ONJ was estimated at 5% for 12 months and 36% for 24 months of ZA exposure. The authors concluded that the risk for ONJ appeared to be higher and possibly accelerated in patients who received a combination of sunitinib and ZA [110]. This suggests a potential synergy of sunitinib with ZA in inducing this debilitating adverse effect, which merits further investigation. This might have implications in the current standards of use of these drugs in cancer patients taking into consideration the natural history of mRCC; this could result in administration of BPs to some patients for several years [117].

The main adverse events of BPs in patients with bone metastases are presented in Table 3.

## Conclusion

Despite the undoubted efficacy of TKIs and bevacizumab in the treatment of patients with m-ccRCC, their efficacy appears to be less pronounced when patients with bone metastases are treated. To provide patients with bone m-ccRCC the best possible care, they are often treated with a combination of TKIs and BPs, in particular ZA. When administered concomitantly, TKIs and ZA can exert a more profound effect on the level of VEGF and with other potential synergistic antitumor activities of BPs, a combination of two agents can increase the efficacy as well as the toxicity of such a treatment. In this review, the authors have attempted to highlight the retrospective evidence of increased efficacy and toxicity of TKIs and BP in combination.

**Table 3 Main adverse events of bisphosphonates in patients with bone metastases**

| References | Hypocalcemia (%) | Blood creatinine increased (%) | Acute renal failure (%) | ONJ (%)[a] | ONJ (%)[b] |
|---|---|---|---|---|---|
| Rosen *et al.* [91][c] | – | 1.8 | – | – | – |
| Lipton *et al.* [92][d] | 19 | 9.5 | 4.8 | – | – |
| Bujanda *et al.* [103][c] | – | 9 | – | 9 | – |
| Christodoulou *et al.* [109][c] | – | – | – | 1 | 16 |
| Bozas *et al.* [110][d] | – | – | – | – | 24 |
| Beuselinck *et al.* [98][d] | – | – | – | – | 17 |

BP, bisphosphonate; ONJ, osteonecrosis of the jaw; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.
[a]Patients treated with BP without TKIs.
[b]Patients treated concomitantly with BP and TKIs.
[c]Patients with bone metastases from different solid tumors.
[d]Patients with RCC bone metastases.

To improve and standardize the treatment of this patient group, we strongly recommend comprehensive retrospective research on this subject or, even better, a prospective randomized study with large cohorts of patients that would examine the efficacy and toxicity of a combination of TKIs and ZA in the treatment of patients with bone mRCC.

## Acknowledgements

### Conflicts of interest

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