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Bisphosphonates combined with sunitinib may improve the response rate, progression free survival and overall survival of patients with bone metastases from renal cell carcinoma

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Abstract ***Background:*** Bisphosphonates are used to prevent skeletal events of bone metastases, and may exhibit antitumour effects. We aimed to evaluate whether bisphosphonates can bring a response rate (RR), progression free survival (PFS) and overall survival (OS) benefit to patients with bone metastasis from renal cell carcinoma (RCC) that is treated with sunitinib.
Methods: We performed a multicentre retrospective study of patients with bone metastases from RCC that was treated with sunitinib. The effect of bisphosphonates on RR, PFS and OS was tested with adjustment for known prognostic factors using a chi-square test from contingency table and partial likelihood test from Cox regression model.
Results: Between 2004 and 2011, 209 patients with metastatic RCC were treated with sunitinib, 76 had bone metastases, 35 bisphosphonates users and 41 non-users. The groups of bisphosphonates users and non-users were balanced regarding known prognostic factors. Objective response was partial response/stable disease 86% ($n = 30$) versus 71% ($n = 29$), and progressive disease 14% ($n = 5$) versus 29% ($n = 12$) ($p = 0.125$, OR 2.48) in users versus non-users, respectively. Median PFS was 15 versus 5 months (HR = 0.55, $p < 0.0001$), and median OS was not reached (with a median follow-up time of 45 months) versus 14 months (HR = 0.4, $p = 0.029$), in favour of users. In multivariate analysis of the entire patient cohort

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($n = 76$), factors associated with PFS were bisphosphonates use (HR = 0.58, $p = 0.035$), and pre-treatment neutrophil to lymphocyte ratio >3 (HR = 3.5, $p = 0.009$). Factors associated with OS were bisphosphonates use (HR = 0.5, $p = 0.008$), elevated pre-treatment alkaline phosphatase (HR = 2.9, $p = 0.003$) and sunitinib induced HTN (HR = 0.63, $p < 0.0001$).
Conclusions: Bisphosphonates may improve the RR, PFS and OS of sunitinib treatment in RCC with bone metastases.

1. Introduction

Renal cell carcinoma (RCC) is the most common cancer of the kidney.[1] Thirty percent of patients present with metastatic disease,[2,3] and recurrence develops in 40% of patients treated for a localised tumour.[2,4] An understanding of the pathogenesis of renal cell carcinoma at the molecular level, and randomised clinical trials, have established the standard role of the orally administered vascular endothelial growth factor receptor and platelet derived growth factor receptor inhibitor sunitinib for the treatment of advanced renal cell carcinoma.[5]

One third of patients with metastatic RCC suffers from bone metastases.[6] Skeletal involvement is commonly aggressive, causing substantial morbidity through the occurrence of skeletal related events (SREs), including pain, pathologic fractures, spinal cord compression and hypercalcemia.[6] Furthermore, data suggest that the presence of bone metastases in RCC has a negative impact on progression free survival and overall survival of patients treated with sunitinib.[7]

In patients with RCC metastatic to bones, bisphosphonates reduce the risk of SREs.[8] Preclinical and clinical data suggest that bisphosphonates may exhibit antitumour effects and prevent tumour progression of RCC.[8–12] A retrospective subset analysis of patients with RCC enrolled in a multicentre, randomised, placebo-controlled study of zoledronic acid indicated that bisphosphonates extended time to disease progression and demonstrated a trend towards improved overall survival compared with the placebo.[12]

The benefit of bisphosphonates in patients with bone metastases from RCC was mainly studied prior to the targeted therapy era. Although suggested by an abstract describing a small patient series,[13] the role and efficacy of bisphosphonates in conjunction with modern targeted agents is currently unknown.[14] In the present study we aimed to evaluate whether bisphosphonates can bring a response rate, progression free survival and overall survival benefit to patients with bone metastases from RCC that is treated with sunitinib.

2. Patients and methods

2.1. Study group

Two hundred and nine patients with metastatic RCC were treated with sunitinib between 1st February 2004 and 31st October 2011, in six centres across two different countries: the United States (Sidney Kimmel Comprehensive Cancer Centre at Johns Hopkins Baltimore, MD) and Israel (Institute of Oncology, Meir Medical Center, Kfar Saba; Department of Oncology, Asaf Harofe Medical Center, Zerifin; Department of Oncology, Rambam Medical Center, Haifa; Department of Oncology, Sheba Medical Center, Tel Hashomer; Department of Oncology, Wolfson Medical Center, Holon). Of these, 76 patients with bone metastases comprised the study group. Patient data were retrospectively and personally collected by the investigator D.K. from electronic medical records and paper charts, including the following clinicopathologic information: age, gender, tumour histology, the time interval from initial diagnosis to sunitinib treatment initiation, Eastern Cooperative Oncology Group (ECOG) performance status, prior treatments for renal cell carcinoma, sites of metastases, laboratory findings, pre-treatment and on treatment blood pressure levels, sunitinib dose reduction and/or interruption and treatment outcomes including objective response rate, progression free survival (PFS) and overall survival (OS). Outcome data were last updated on 31st October 2011. Data on the concomitant use of medications, including angiotensin system inhibitors (angiotensin converting enzyme inhibitors and angiotensin II receptor blockers) and bisphosphonates were gathered from patients electronic medical records and paper charts documenting baseline patient intake and regular on treatment follow-ups, pharmacy records and by contacting patients and other treating physicians as needed.

2.2. Sunitinib treatment

All patients had objective disease progression on scans before starting sunitinib treatment. Sunitinib was prescribed as a part of the standard treatment or clinical trial. It was administered orally, usually at a starting dose of 50 mg once daily, in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment. In patients with significant comorbidities, treatment was initiated at a reduced dose, with subsequent dose escalation if well tolerated. On treatment dose reduction or treatment interruption were done for the management of adverse events, depending on their type and severity, according to standard guidelines. Treatment was continued until evidence of disease

progression on scans, unacceptable adverse events or death. Patient follow-up generally consisted of regular physical examinations and laboratory assessments (haematologic and serum chemical measurements), every 4–6 weeks, and imaging studies performed every 12–18 weeks.

2.3. Treatment outcomes

Follow-up time was defined as the time from sunitinib treatment initiation to 31st October 2011. For the evaluation of response, the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 was applied.[15] In one patient with only bone metastases, only complete response, stable disease or progressive disease were noted, not partial response. The response was assessed by independent radiologists and treating physicians, and personally reviewed by the investigator D.K. Progression free survival was determined by the investigator D.K., and defined as the time from the initiation of sunitinib treatment until evidence of disease progression on scans or death of any cause. Overall survival was defined as the time from the initiation of sunitinib treatment to death of any cause. Treatment associated toxicity was evaluated according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 3.0.

2.4. Statistical analysis

To better elucidate the effect of bisphosphonates use, baseline clinical characteristics and known prognostic factors were compared between bisphosphonates users versus non-users, to identify any potential confounding covariates. Chi-square test was used to compare categorical endpoints, and two-sample *t*-test was used to compare continuous endpoints, after necessary data transformation. Known prognostic factors in metastatic renal cell carcinoma treated with sunitinib[16–22] were included as confounding covariates in the analysis, including past nephrectomy, clear cell versus non-clear cell kidney cancer histology type, time from initial kidney cancer diagnosis to sunitinib treatment initiation, the presence of more than two metastatic sites, lung/liver/bone metastases, ECOG performance status, the presence of anaemia and corrected (for albumin) serum calcium level above 10 mg/dL, platelet count, pre-treatment neutrophil to lymphocyte ratio (NLR) >3, pre-treatment elevated alkaline phosphatase, sunitinib induced hypertension, the use of angiotensin system inhibitors (ASIs), the risk according to the Heng prognostic model, past cytokines and/or targeted treatments, percentage of patients that had dose reduction and/or treatment interruption and mean dose/cycle. Patients who did not progress or die by 31st October 2011 were censored in progression free survival analysis or overall survival analysis, respectively. In addition, for the entire patient cohort, a univariate analysis (unadjusted) of association between each clinicopathologic factor and clinical outcome was performed using logistic regression for response rate and Cox regression model for survival outcomes (PFS and OS). Factors with significant association in the univariate analysis were included in multivariate Cox proportional hazards regression model to determine their independent effects. Survival probabilities and median survival times were estimated from Kaplan–Meier curves. Data were analysed using S-Plus 8.0 for Windows Enterprise Developer.

2.5. Regulatory considerations

The research was carried out in accordance with the approval by the IRB committee of our institutions.

3. Results

3.1. Patient characteristics

Two hundred and nine patients (median age 63 years, 62.4 ± 11.46 mean $\pm$ SD, range 24–87; male 71.3%, $n = 149$) with metastatic renal cell carcinoma were treated with sunitinib between 1st February 2004 and 31st October 2011. Seventy-six patients with bone metastases comprised the study group. Thirty-five patients were bisphosphonates users and 41 nonusers. Among bisphosphonates users, 29 were treated with zoledronic acid and six with pamidronate. The dose and schedule of bisphosphonates were: zoledronic acid 4 mg monthly in 14 patients, zoledronic acid 4 mg q 3 months in 12 patients, zoledronic acid 3.5 mg monthly in three patients with abnormal calculated GFR and pamidronate 90 mg monthly in six patients. Due to the small number of six pamidronate recipients, all analyses were performed only for the combined group of pamidronate and zoledronic acid users. All 35 bisphosphonates users were on bisphosphonates during the entire sunitinib treatment period. No patient required treatment interruption due to osteonecrosis of the jaw. The distribution of clinicopathologic and prognostic factors is shown in Table 1.

3.2. Sunitinib treatment outcomes

Median follow-up time was 38 months (41.2 ± 18.5 mean $\pm$ SD, range 12–82). Objective response at first imaging evaluation within the first three months of sunitinib treatment initiation was complete response 4% ($n = 3$), partial response 29% ($n = 22$), stable disease 45% ($n = 34$) and progressive disease 22% ($n = 17$). Median progression free survival was 8 months (13.3 ± 14.2 mean $\pm$ SD, range 1–73). Median overall survival was 18 months (22.6 ± 18 mean $\pm$ SD, range

Table 1
Distribution of clinicopathologic and prognostic factors, and univariate and multivariate analysis of their association with progression free survival and overall survival.

Factor (n = number of patients with data available)	Distribution	Univariate analysis (HR, p)		Multivariate analysis (HR, p)	
		PFS	OS	PFS	OS
Age (years) ($n = 76$)	60.5 (24–82, 60 ± 11.17) Median (range, mean ± SD)	NS	NS		
Gender ($n = 76$)	Female: 26% ($n = 20$) Male: 74% ($n = 56$)	NS	NS		
Tumour histology ($n = 76$)	Non-clear cell: 16% ($n = 12$)	NS	NS		
ECOG PS ($n = 76$)	0-1: 78% ($n = 59$) >1: 22% ($n = 17$)	0.41, 0.003	0.297, 0.001	NS	NS
Past nephrectomy ($n = 133$)	71% ($n = 54$)	NS	NS		
Time (mos) from dx to sunitinib tx ($n = 76$)	11.5, (1-192, 34.2 ± 47.1) Median (range, mean ± SD)	NS	NS		
Prior systemic tx ($n = 76$)	25% ($n = 19$)	NS	NS		
Lung metastasis ($n = 76$)	75% ($n = 57$)	NS	NS		
Liver metastasis ($n = 76$)	30% ($n = 23$)	NS	NS		
$\geqslant$ 2 metastatic sites ($n = 76$)	99% ($n = 75$)	NS	NS		
Anaemia ($n = 72$)	72% ($n = 52$)	NS	NS		
Platelets count ($n = 72$)	255, (104–595, 273.3 ± 114.3) Median (range, mean ± SD)	NS	NS		
Corrected Ca> 10 mg/dL ($n = 72$)	13% ($n = 9$)	NS	NS		
Elevated pre-treatment AP ($n = 76$)	25% ($n = 19$)	2.7, 0.015	2.8, 0.042	NS	2.9, 0.003
Sunitinib induced HTN ($n = 76$)	43% ($n = 33$)	NS	0.53, 0.04		0.63, <0.001
Sunitinib DR/TI ($n = 76$)	49% ($n = 37$)	NS	NS		
Mean sunitinib dose (mg)/tx cycle ($n = 76$)	48,(12–50, 42.6 ± 10.2) Median, (range, mean ± SD)	NS	NS		
Users of ASIs ($n = 76$)	36% ($n = 27$)	NS	NS		
Heng risk stratification ($n = 75$)	Favourable risk 20% ($n = 15$) Intermediate risk 57% ($n = 43$) Poor risk 23% ($n = 17$)	NS	NS		
Pre-treatment NLR >3 ($n = 76$)	50% ($n = 38$)	4, 0.005	NS	3.5, 0.009	
Bisphosphonates use ($n = 76$)	46% ($n = 35$)	0.55, <0.001	0.4, 0.029	0.58, 0.035	0.5, 0.008

AP = alkaline phosphatase; ASIs = angiotensin system inhibitors; Ca = calcium; DR = dose reduction; Dx = diagnosis; ECOG PS = Eastern Cooperative Oncology Group performance status; HTN = hypertension; Mos = months; NLR = Neutrophil to lymphocyte ratio; NS = non-significant; PFS = progression free survival; OS = overall survival; TI = treatment interruption; Tx = treatment.

2–73). 66 patients (87%) have progressed and 47 patients (62%) died.

3.3. Univariate analysis of factors associated with progression free survival and overall survival (Table 1)

The use of bisphosphonates (HR = 0.55, $p < 0.0001$), ECOG performance status (HR = 0.41, $p = 0.003$), elevated pre-treatment alkaline phosphatase (HR = 2.7, $p = 0.015$) and a high pre-treatment neutrophil to lymphocyte ratio >3 (HR = 4, $p = 0.005$) were associated with progression free survival. The use of bisphosphonates (HR = 0.4, $p = 0.029$), ECOG performance status (HR = 0.297, $p = 0.001$), elevated pre-treatment alkaline phosphatase (HR = 2.8, $p = 0.042$) and sunitinib induced hypertension (HR = 0.53, $p = 0.04$) were associated with overall survival.

3.4. Multivariate analysis of factors associated with progression free survival, and overall survival (Table 1)

Factors associated with progression free survival were the use of bisphosphonates (HR = 0.58, $p = 0.035$), and a high pre-treatment neutrophil to lymphocyte ratio >3 (HR = 3.5, $p = 0.009$). Factors associated with overall survival were the use of bisphosphonates (HR = 0.5, $p = 0.008$), an elevated pre-treatment alkaline phosphatase (HR = 2.9, $p = 0.003$) and sunitinib induced hypertension (HR = 0.63, $0 < 0.0001$).

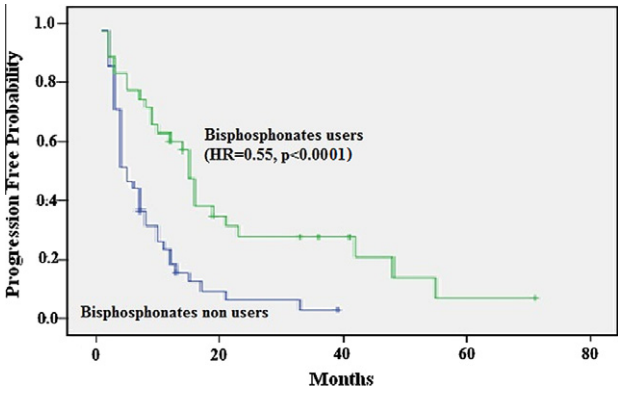

Fig. 1. Kaplan–Meier curves showing progression-free survival, stratified by the use of bisphosphonates.

Bisphosphonates users versus non-users: The groups of bisphosphonates users and non-users were balanced regarding the presence of the above mentioned clinicopathologic and prognostic factors (Table 2). Objective response in bisphosphonates users versus nonusers was partial response/stable disease 86% ($n = 30$) versus 71% ($n = 29$), and progressive disease at first imaging evaluation within the first three months 14% ($n = 5$)

Table 2
Distribution of clinicopathologic prognostic factors stratified by the use of bisphosphonates.

Characteristic	Bisphosphonates users ($n = 35$)	Bisphosphonates non-users ($n = 41$)	*P*
Age (years): median (range, mean ± SD)	64 (39–82, 61.4 ± 11)	60 (24-81, 58.8 ± 11.3)	0.62
Male gender	83% ($n = 29$)	66% ($n = 27$)	0.09
Tumour histology			
Clear cell	86% ($n = 30$)	76% ($n = 31$)	0.1
Non-clear cell	14% ($n = 5$)	24% ($n = 10$)	
ECOG PS: 0–1	86% ($n = 30$)	71% ($n = 29$)	0.18
>1	14% ($n = 5$)	29% ($n = 12$)	
Past nephrectomy	77% ($n = 27$)	66% ($n = 27$)	0.2
Time (months) from dx to sunitinib treatment: median (range, mean ± SD)	13 (1–192, 38 ± 51.9)	8 (1–148, 31 ± 43)	0.08
Prior systemic treatment	26% ($n = 9$)	24% ($n = 10$)	0.6
Lung metastasis	74% ($n = 26$)	76% ($n = 31$)	0.7
Liver metastatis	29% ($n = 10$)	32% ($n = 13$)	0.38
⩾2 metastatic sites	97% ($n = 34$)	100% ($n = 41$)	0.94
Anaemia	79% ($n = 26/33$)	67% ($n = 26/39$)	0.2
Platelets count: median (range, mean ± SD)	239 (114–595, 257 ± 118)	269 (104–577, 286 ± 111)	0.81
Corrected calcium >10 mg/dL	9% ($n = 3/33$)	15% ($n = 6/39$)	0.53
Elevated pre-treatment AP	23% ($n = 8$)	27% ($n = 11$)	0.3
Sunitinib induced HTN	46% ($n = 16$)	41% ($n = 17$)	0.74
Sunitinib dose reduction/treatment interruption	51% ($n = 18$)	46% ($n = 19$)	0.65
Sunitinib dose (mg)/treatment cycle: median(range, mean ± SD)	44 (12–50, 41 ± 11.4)	50 (12–50, 44 ± 9)	0.3
Use of ASIs	43% ($n = 15$)	29% ($n = 12$)	0.07
Subgroups according to the Heng model			
Favourable	17% ($n = 6$)	22% ($n = 9$)	0.22
Intermediate	69% ($n = 24$)	49% ($n = 20$)	
Poor	14% ($n = 5$)	29% ($n = 12$)	
Pre-treatment NLR > 3	49% ($n = 17$)	51% ($n = 21$)	0.7

AP = alkaline phosphatase; ASIs = angiotensin system inhibitors; Dx = diagnosis; ECOG PS = Eastern Cooperative Oncology Group performance status; HTN = hypertension; NLR = neutrophil to lymphocyte ratio.

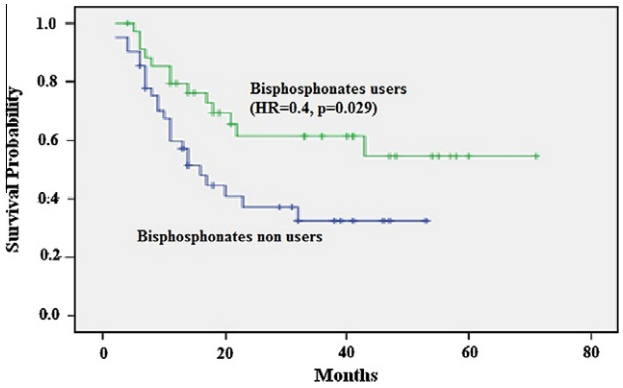

Fig. 2. Kaplan–Meier curves showing overall survival, stratified by the use of bisphosphonates.

versus 29% ($n = 12$) ($p = 0.125$, odds ratio 2.48). Recipients of bisphosphonates had tripling of median progression free survival versus non-recipients (15 versus 5 months, HR = 0.55, $p < 0.0001$, Fig. 1). Median overall survival was not reached (with a median follow-up time of 45 months) versus 14 months (HR = 0.4, $p = 0.029$, Fig. 2) in bisphosphonates users versus non-users, respectively.

In the whole patient cohort, bisphosphonates users ($n = 35$) had a better progression free survival (HR = 0.64) and overall survival (HR = 0.7) than patients without bone metastasis ($n = 133$; PFS 10 months, OS 25 months), although these differences were not statistically significant ($p = 0.09$ and $p = 0.15$, for PFS and OS, respectively) at 0.05 significance level.

4. Discussion

One third of patients with metastatic RCC suffers from bone metastases, [6] whose presence has a negative impact on progression free survival and overall survival with sunitinib treatment.[7] Although suggested by an abstract describing a small patient series,[13] the role and efficacy of bisphosphonates in conjunction with modern targeted agents for RCC metastatic to bones is currently unknown.[14] The present study suggests that concomitant use of bisphosphonates may improve the outcome of sunitinib treatment in renal cell carcinoma and bone metastases. In this retrospective study, after adjustment for other known risk factors for poorer outcome, patients receiving bisphosphonates concomitantly with sunitinib treatment had a significant increase of progression free survival, by 10 months (HR = 0.55, $p < 0.0001$), and overall survival (not reached versus 14 months, HR = 0.4, $p = 0.029$), respectively. Patients using bisphosphonates also had an increase in response rate (86% versus 71%), and a decrease of primary treatment refractoriness (progressive disease at first imaging evaluation within the first three months, 14% versus 29%, odds ratio 2.48), although these were not statistically significant ($p = 0.125$) at 0.05 significance level (might have been in a larger patient cohort). Finally, in a multivariate analysis for the entire group, which included the clinicopathologic prognostic factors mentioned before, the use of bisphosphonates was independently associated with progression free survival (HR = 0.58, $p = 0.035$) and overall survival (HR = 0.5, $p = 0.008$).

The aggressiveness of RCC with bone metastases may be due to the tumour microenvironment. Osteoclast activation due to the presence of malignant cells in the bone may lead to secretion of cytokines such as transforming growth factor-beta, bone morphogenic proteins, insulin-like growth factor, fibroblast growth factor and platelet-derived growth factor, that can not only stimulate the local growth of RCC cells but also circulate and stimulate growth at a distance.[7] Therefore, by inhibiting osteoclasts, bisphosphonates may be additive or synergistic with vascular endothelial growth factor (VEGF) inhibition therapy. In addition to inhibition of osteoclasts, pre-clinical and clinical data suggest that bisphosphonates may directly inhibit RCC growth.[8–12]

Potential direct antitumour effects of bisphosphonates include induction of cancer cells apoptosis, inhibition of angiogenesis, blocking of tumour cells adhesion and immunostimulation.[10,23]

Our study has some limitations. First, this is a multicentre retrospective study that represents an unselected heterogeneous cohort of patients that were treated with sunitinib, including all histologic variants of renal cell carcinoma, and patients who were treatment naïve and those with a history of prior therapy. Nonetheless, the outcome of the present study patient population (i.e. median progression free survival of 8 months, and median overall survival of 18 months) is similar to previously published data on patients with RCC metastatic to bones that are treated with sunitinib.[7] Second, we are unable to exclude the possibility that unequal distribution of unidentified clinicopathologic parameters in our patient cohort may have biased the observed results. Third, the total number of 76 patients, comprising the present study group, is relatively small. Other clinicopathologic factors that were not found to be significantly associated with disease progression in the present study might have been important in a larger patient cohort. Finally, whether our findings are specific to sunitinib or generalizable to other tyrosine kinase inhibitors is not known.

Despite these limitations, our clinical observation that bisphosphonates may improve the outcome of sunitinib treatment in renal cell carcinoma and bone metastases may contribute to treatment decisions, patient selection and clinical trials design. There were no inadvertent interactions observed in patients receiving bisphosphonates concurrently with sunitinib. Because of little side effects, further studies may be warranted, to test and confirm our hypothesis generating observation

in larger patient cohorts, to elucidate the underlying molecular mechanisms and to define which subgroup of patients (e.g. according to risk by prognostic models, clear cell versus non-clear cell histology and first line versus advanced line treatment) will benefit. These may include retrospective subgroup analysis of previously completed large randomised trials of sunitinib or other VEGF inhibitors therapy in metastatic renal cell carcinoma, as well as prospective studies with addition of bisphosphonates to standard antineoplastic targeted therapies.

Conflict of interest statement

None declared.

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