Translational Oncology
www.transonc.com

Volume 13 Number 2 February 2020 pp. 241–244 241

Does Bone-targeted Therapy Benefit Patients with Metastatic Renal Cell Carcinoma?

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Abstract

INTRODUCTION: In metastatic renal cell carcinoma (mRCC), the bone is the second most common site of metastasis and is associated with increased morbidity and poorer quality of life. Bone-targeted therapies (BTTs) such as denosumab and zoledronic acid may prevent skeletal-related events (SREs). However, the benefit of BTTs in combination with tyrosine kinase inhibitors (TKIs) remains unclear. *METHODS:* We performed a retrospective chart review at the Urologic Cancer Centre for Research and Innovation. Patients with mRCC were included if they had bone metastases treated with TKIs between 2010 and 2017. Our primary outcome was overall survival (OS), defined as the time elapsed from clinical diagnosis of mRCC to death, and modelled using the Kaplan–Meier method. Secondary outcomes included the median time to SRE and the analysis of prognostic factors of OS using Cox proportional hazards regression. *RESULTS:* In total, 230 patients with mRCC were identified; of which, 46 had bone metastases treated with TKIs and were included in the study (TKI-only, $n = 37$; TKI + BTT, $n = 9$). In the TKI + BTT cohort, patients received either denosumab ($n = 5$) or zoledronic acid ($n = 4$). At the time of analysis, 63% of patients were deceased. We observed an OS trend favouring the TKI + BTT cohort (13.8 months [95% confidence interval {CI}: 12.3–15.2] vs. 29.6 months [95% CI: 7.2–51.9], hazard ratio [HR]: 1.66 (95% CI: 0.62–4.45), $P = 0.31$). When patients in the TKI + BTT cohort were stratified by type of therapy (denosumab or zoledronic acid), the median time to SRE was similar between the groups (4.2 months [95% CI: 2.28–6.14] vs. 2.2 months [95% CI: not available], $P = 0.71$]. On univariate or multivariate analysis, it was found that age, gender, comorbidities, International metastatic RCC database consortium (IMDC) prognostic group and pathologic tumour grade were not significant predictors of worse OS. Pathologic stage 3 or 4 was an independent predictor of worse OS (HR: 5.8, 95% CI: 1.41–24.03, $P = 0.015$). *CONCLUSION:* BTTs may have a continued role in the era of targeted therapy and immunotherapy. Further prospective data are required to validate our findings.

Translational Oncology (2020) 13, 241–244

Introduction

In metastatic renal cell carcinoma (mRCC), the bone is the second most common site of metastases, occurring in one-third of patients [1]. Most bone metastases are found in the sacrum, pelvis, spine and proximal extremities [2]. Furthermore, the majority of bone metastases are osteolytic in nature and are particularly destructive [1]. This predisposes patients to skeletal-related events (SREs) such as pathologic fracture, spinal cord compression or radiation or surgery to bone [3]. SREs are associated with increased morbidity and have debilitating effects on the patient's quality of life. In particular, bone pain is the most prevalent type of cancer-induced pain, which may require opiate analgesics and palliative radiation therapy for pain management [4]. Therefore, the prevention of SREs is of paramount importance in this patient population.

Several studies have reported that the median overall survival (OS) after diagnosis of bone metastases in RCC ranges from 12 to 28 months [5,6]. Retrospective series have identified several risk factors to predict the prognosis of patients with mRCC and bone metastases,

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Received 18 July 2019; Revised 16 October 2019; Accepted 16 October 2019

1936-5233/19
https://doi.org/10.1016/j.tranon.2019.10.009

including metachronous bone lesions, extraosseous metastasis, number of bone lesions, increased alkaline phosphatase levels, increased C-reactive protein levels, spinal involvement and sarcomatoid differentiation of the primary tumour [7,8].

Bone-targeted therapies (BTTs) are used to prevent SREs that occur secondary to bone metastases. Denosumab, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, and bisphosphonates such as zoledronic acid are BTTs used for several cancers. However, data on patients with mRCC and bone metastases are limited to a phase II trial ($n = 50$) and a phase III subgroup analysis ($n = 74$), which were both completed before the era of targeted therapies [9−11]. One retrospective analysis of 82 patients with RCC and bone metastases treated with sunitinib found no difference in time to clinical progression between patients with metachronous and synchronous bone lesions, although OS was significantly longer in patients with metachronous bone lesions (38.5 vs. 21.1 months, $P = 0.001$) [12]. However, the benefit of BTTs in combination with targeted therapies such as tyrosine kinase inhibitors (TKIs) remains unclear. To better understand the role of BTTs in the era of targeted therapies, we investigated our institution's experiences with BTTs and TKIs in managing bone metastases from RCC.

Methods

We performed a retrospective chart review at our institution (Urologic Cancer Centre for Research and Innovation) of patients with mRCC and bone metastases treated with TKIs between 2010 and 2017. This study was approved by the Hamilton Integrated Research Ethics Board. Patients were included if they received TKIs and had mRCC with bone metastases confirmed by radiological imaging. We compared two groups: patients with mRCC and bone metastases treated with TKIs (TKI-only) and patients with mRCC and bone metastases treated with TKIs and BTT (TKI + BTT). Our primary outcome was OS, defined as the time elapsed from clinical diagnosis of mRCC to death, and modelled using the Kaplan−Meier method. Our secondary outcomes included median time to SRE, defined as the time elapsed from clinical diagnosis of mRCC to pathologic fracture, spinal cord compression, radiation to bone or surgery to bone, and the analysis of prognostic factors of OS which were defined a priori, using Cox proportional hazards regression. Data were analyzed using IBM® SPSS Statistics version 18.0.

Results

In total, 230 patients with mRCC were identified; of which, 46 had bone metastases treated with TKIs and were included in this retrospective study. These patients were stratified into one of the two groups: TKI-only ($n = 37$) or TKI + BTT ($n = 9$). In the TKI + BTT cohort, patients received either 120 mg of denosumab ($n = 5$) subcutaneously every 4 weeks or 4 mg of zoledronic acid ($n = 4$) intravenously every 4 weeks. Patient and treatment characteristics are demonstrated in Table 1. At the time of analysis, 63% of patients were deceased. All patients received either sunitinib ($n = 28$) or pazopanib ($n = 18$), and 63% had progressive disease while on therapy. In addition, 67% of patients received palliative radiation therapy. When TKI-only and TKI + BTT groups were compared, we observed an OS trend favouring the TKI + BTT cohort (13.8 months [95% confidence interval {CI}: 12.3−15.2] vs. 29.6 months [95% CI: 7.2−51.9], hazard ratio [HR]: 1.66 [95% CI: 0.62−4.45], $P = 0.31$). Furthermore, no significant difference was found in the time to SRE between denosumab and zoledronic acid (4.2 months [95% CI: 2.28−6.14] vs. 2.2 months [95% CI: not available], $P = 0.71$). On univariate or multivariate analysis, it was found that age, gender, comorbidities, eastern cooperative oncology

Table 1. Baseline, Demographic and Treatment Characteristics

Characteristics	Overall ($n = 46$)	TKI-only ($n = 37$)	TKI + BTT ($n = 9$)	*P*-value
Deceased, n (%)	29 (63.0)	23 (62.2)	6 (66.7)	0.80
Median age at mRCC diagnosis, years (IQR)	62.4 (57.5−68.1)	62.4 (58.0−66.2)	63.3 (56.6−70.7)	0.92
Male, n (%)	26 (56.5)	20 (54.1)	6 (66.7)	0.73
History of hypertension, n (%)	23 (50.0)	18 (48.6)	5 (55.6)	0.71
History of cardiovascular disease, n (%)	5 (10.9)	5 (13.5)	0 (0)	0.24
History of diabetes mellitus, n (%)	11 (23.9)	9 (24.3)	2 (22.2)	0.90
ECOG performance status >1	7 (15.2)	5 (13.5)	2 (22.2)	0.95
Karnofsky performance status <80%, n (%)	13/43 (30.2)	10/43 (23.3)	3/43 (7.0)	0.40
Time from mRCC diagnosis to treatment <1 year, n (%)	39/46 (84.8)	33/37 (89.2)	6/9 (66.7)	0.07
IMDC risk group, n (%)				
Favourable	2/40 (5)	1/32 (3.1)	1/8 (12.5)	0.33
Intermediate	23/40 (57.5)	20/32 (62.5)	3/8 (37.5)	
Poor	15/40 (37.5)	11/32 (34.4)	4/8 (50)	
Targeted therapy, n (%)				
Sunitinib	28 (60.9)	22 (59.5)	6 (66.7)	0.69
Pazopanib	18 (39.1)	15 (40.5)	3 (33.3)	
BTT, n (%)				
Denosumab			5 (55.6)	
Zoledronic acid			4 (44.4)	–
Radiation therapy (palliative), n (%)	31 (67.4)	24 (64.9)	7 (77.8)	0.73
Nephrectomy, n (%)	34 (73.9)	27 (73.0)	7 (77.8)	0.09
Grade, n (%)				
1 or 2	15/33 (45.4)	11/26 (42.3)	4/7 (57.1)	0.81
3 or 4	18/33 (54.5)	15/26 (57.7)	3/7 (42.9)	
Median tumour size, cm (IQR)	7.2 (4.9−9.8)	8.0 (5.0−9.5)	6.2 (4.3−9.6)	0.86
Stage, n (%)				
pT1 or 2	14 (30.5)	9 (24.3)	5 (55.5)	0.13
pT3 or 4	16 (34.8)	15 (40.5)	1 (11.1)	

TKI, tyrosine kinase inhibitor; IQR, interquartile range; mRCC, metastatic renal cell carcinoma; BTT, bone-targeted therapy; IMDC, International metastatic RCC database consortium; ECOG, eastern cooperative oncology group.

group (ECOG) performance status, International metastatic RCC Database Consortium (IMDC) prognostic group and pathologic tumour grade were not significant predictors of worse OS. Pathologic stage 3 or 4 was an independent predictor of worse OS (HR: 5.8, 95% CI: 1.41−24.03, $P = 0.015$).

Discussion

Over the past 10 years, mRCC has largely been treated with targeted therapy using TKIs. However, the role of BTTs in the era of targeted therapy remains unclear. In patients with mRCC and bone metastases, recent consensus statements have suggested that bisphosphonates such as zoledronic acid can be used adjunctively with targeted therapy to decrease SREs [13]. However, the paucity of data from trials specifically on mRCC is a particular limitation. A phase II trial published in 2015 randomized 30 patients in a 1:1 ratio to receive everolimus alone or everolimus and zoledronic acid [14]. Compared with everolimus alone, everolimus and zoledronic acid significantly improved the median time to SRE by 4.4 months ($P = 0.03$) and progression-free survival by 2.1 months ($P = 0.009$). While everolimus is no longer the standard treatment for mRCC, zoledronic acid may have a continued role in delaying time to SRE. This is supported by a recent meta-analysis that found zoledronic acid reduced the risk of SREs by 68% (HR: 0.32, 95% CI: 0.19−0.55) compared with placebo or no zoledronic acid [15]. As the meta-analysis only contained two placebo-controlled trials for this comparison, the results from the phase III MOSCAR trial comparing denosumab and zoledronic acid in mRCC may provide further validation [16].

Research on the pathways of bone remodelling discovered RANKL as a key mediator in the development of bone metastases [17,18]. As an inhibitor of RANKL, denosumab disrupts osteoclast activity [19]. Therefore, denosumab offers an alternative for patients with renal impairment or other conditions, limiting the use of zoledronic acid. In a pivotal phase III trial, denosumab was noninferior to zoledronic acid in delaying time to first SRE for various advanced cancers (HR: 0.84, 95% CI: 0.71−0.98) [20]. Although landmark, this study was only powered for noninferiority and lacked a subgroup analysis for RCC as the primary tumour type, precluding any definitive recommendations. Furthermore, a meta-analysis that included a total of 5723 patients from three trials found denosumab significantly improved the time to first SRE by a median of 8.21 months and reduced the risk of a first SRE by 17% compared with zoledronic acid (HR: 0.83, 95% CI: 0.76−0.90, $P < 0.001$) [19]. These findings merit further investigation of denosumab in the mRCC population with bone metastases.

In our study, we found that only 20% of patients with mRCC and bone metastases received BTT in addition to TKIs. A possible explanation for this finding is the lack of public funding for BTT in mRCC. Thus, patients were more likely to only receive publicly funded therapies such as sunitinib or pazopanib to manage bone metastases during the study period. Although rare, osteonecrosis of the jaw may occur when a bisphosphonate or denosumab is used in combination with targeted therapies such as sunitinib or pazopanib [21]. Although this was not observed in our study, this remains an important consideration, and steps should be taken to prevent its occurrence. Although the difference in median OS was not statistically significant, a 16-month improvement in median OS observed in the BTT + TKI group may be clinically significant. Furthermore, the time to SRE between patients receiving denosumab and zoledronic acid was similar between the groups. However, our small sample size and retrospective study design preclude further extrapolation of these findings. We also found that pathologic stage 3 or 4 was a significant predictor for worse OS. In mRCC, high pathologic stage is a well-established predictor of poor OS. Thus, this finding was expected in our study as poor outcomes were anticipated in this patient population regardless of BTT.

Given the resurgence of immunotherapy and development of new targeted therapies for mRCC, the treatment paradigm for bone metastases will continue to evolve. Several ongoing trials investigating emerging treatment options for bone metastases in mRCC may be clinically useful. Results from a phase II trial investigating pembrolizumab, an anti−programmed cell death protein 1 (PD-1) immunotherapy, with denosumab in clear-cell mRCC may shed light on this potential treatment option [22]. Furthermore, cabozantinib, a TKI currently approved in the second-line setting for mRCC, has demonstrated favourable efficacy in mRCC with bone metastases [23]. A phase III trial is investigating its use in combination with nivolumab compared with nivolumab and ipilimumab, two monoclonal antibody immunotherapies [24]. Future studies should consider the type of bone metastases (i.e., osteolytic, osteoblastic or mixed) and RCC subtype to shed light on how the effects of BTTs are modified. In addition, studies should also address vulnerable patient populations who may particularly benefit from BTT.

Conclusions

In summary, we observed an OS trend favouring the TKI + BTT cohort. The renewed interest in BTT and bone metastases in mRCC may help diversify the treatments available to patients in the era of immunotherapy and new targeted therapies. Although our findings are hypothesis generating, further prospective data are required to validate our findings.

Conflicts of interest

None.

Sources of funding

None.

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