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Correlation of c-Met Expression and Outcome in Patients With Renal Cell Carcinoma Treated With Sunitinib

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Abstract

Prognostic markers for treatment selection in metastatic renal cell carcinoma (mRCC) do not exist. This study evaluates c-Met expression in sunitinib-treated patients with mRCC, and elucidates its role as a possible marker for survival. c-Met expression was analyzed from 137 formalin-fixed paraffin-embedded tumor samples using a validated immunostaining protocol. High c-Met expression is associated with poor survival in patients with mRCC treated with sunitinib.

Background: Treatment of patients with metastatic renal cell carcinoma (mRCC) has improved substantially since the introduction of targeted therapies, but no predictive biomarkers are available. The proto-oncogene c-Met is involved in tumor angiogenesis, development, and metastasis. The main objective was to evaluate c-Met expression in sunitinib-treated patients with mRCC, including patients with bone metastases. **Methods:** c-Met expression was analyzed from 137 formalin-fixed paraffin-embedded tumor samples using a validated immunostaining protocol. **Results:** Patients with low c-Met expression ($n = 78$) had longer progression-free survival (PFS) (median 14.3 vs. 6.5 months; $P < .001$) and overall survival (OS) (median 32.1 vs. 20.1 months; $P = .049$) than those with high expression. High c-Met expression was an independent predictor of unfavorable PFS in a Cox proportional hazards model adjusted for the Heng risk criteria (HR 1.60 [1.09-2.35]; $P = .016$). In a subgroup of patients with no bone metastases ($n = 106$), low c-Met expression was associated with a both longer OS (unadjusted HR 0.63 [95% CI, 0.42-0.95]; $P = .034$) and PFS (unadjusted HR 0.47 [95% CI, 0.31-0.71]; $P < .001$). **Conclusions:** High c-Met expression was associated with poor survival in patients with mRCC treated with sunitinib. Interestingly, the prognostic role may vary based on the location of metastases.

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Keywords: Angiogenesis inhibitor, c-Met inhibitor, mRCC, Prognostic marker

Introduction

Treatment of patients with metastatic renal cell carcinoma (mRCC) has improved substantially since the introduction of targeted therapies, but no biomarkers are available for predicting the efficacy of such therapies.¹ These agents target pathways that are dysregulated in mRCC, namely vascular endothelial growth factor

receptor (VEGFR), platelet-derived growth factor, and PI3K signaling.² Three main classes of approved targeted therapies exist, 7 inhibiting the VEGF pathway and 2 that inhibit the mammalian target of rapamycin (mTOR), and 1 blocking programmed cell death protein 1 (PD-1) activity. Despite the clinical benefit these drugs have achieved, overall survival (OS) benefits are limited and eventually the disease progresses.

Most RCC tumors display defects in the von Hippel-Lindau (VHL) protein due to functional inactivation or mutations in the VHL gene. This in turn leads to the accumulation of hypoxia-inducible factor α (HIF- α), resulting in activation of genes such as VEGF, transforming growth factor β , platelet-derived growth factor, and c-Met.^{3,4} c-Met is a proto-oncogene involved in cell growth, differentiation, cell motility, and tissue repair. Furthermore, c-Met and its ligand hepatocyte growth factor (HGF) have been demonstrated to have a role in angiogenesis, tumor

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Table 1 Patient Characteristics Overall and by c-Met Expression Levels (Low vs. High)			
	c-Met Low vs. High		Total (n = 137)
	Low (n = 78)	High (n = 59)	
Gender			
Male	46 (59.0)	34 (57.6)	80 (58.4)
Female	32 (41.0)	25 (42.4)	57 (41.6)
Age ^a			
Median	66.5	64.0	66.0
Range	24-86	43-80	24-86
WHO			
0-1	69 (88.5)	52 (88.1)	121 (88.3)
>1	9 (11.5)	7 (11.9)	16 (11.7)
Prior nephrectomy			
Yes	76 (97.4)	58 (98.3)	134 (97.8)
No	2 (2.6)	1 (1.7)	3 (2.2)
Histology ^a			
Clear cell	64 (94.1)	43 (79.6)	107 (87.7)
Non-clear cell	4 (5.9)	11 (20.4)	15 (12.3)
Missing	10	5	15
No. of metastatic sites			
0-1	20 (25.6)	19 (32.2)	39 (28.5)
>1	58 (74.4)	40 (67.8)	98 (71.5)
Bone metastasis			
Yes	16 (20.5)	15 (25.4)	31 (22.6)
No	62 (79.5)	44 (74.6)	106 (77.4)
Heng criteria ^a			
Favorable	24 (31.2)	5 (8.8)	29 (21.6)
Intermediate	38 (49.4)	36 (63.2)	74 (55.2)
Poor	15 (19.5)	16 (28.1)	31 (23.1)
Missing	1	2	3

^aPatients with c-Met Low were significantly older compared with patients with c-Met High ($P = .007$). Additionally, patients with low c-Met were significantly more likely to belong to the favorable Heng criteria risk group ($P < .001$) and have a clear-cell histology ($P = .024$).

development, and metastasis.⁵ Interestingly, cancer cells are able to use the HGF-Met axis for invasion and crosstalk among c-Met-VEGFR, and c-Met-EGFR signaling pathways have been detected defining a strong rationale for targeted therapy inhibiting c-Met together with other pathways.^{6,7}

Expression of c-Met has been detected to be higher in tumor than normal tissue, and in RCC, c-Met expression levels seem to be more profound in papillary and sarcomatoid subtypes than in clear-cell carcinoma. More importantly, c-Met expression has been shown to correlate with inferior pathologic features and poor prognosis in RCC.^{8,9} Previous important findings include those of Betsunoh et al,⁸ who established that a higher c-Met mRNA tumor-to-normal renal tissue ratio is related to worse OS, whereas Gibney⁹ confirmed in a 330-patient cohort that c-Met expression is associated with worse disease-specific survival in RCC. Additionally, in prostate carcinoma, research has shown c-Met expression to be greater at metastatic sites as compared with primary tumors,¹⁰ and some evidence suggests increased expression of c-Met in metastatic lesions of the bone in mRCC,¹¹ interesting findings given the dismal prognosis of patients with RCC with bone metastases¹² and the promising results of dual VEGFR and c-MET inhibitors in treatment of mRCC.¹³

The main objective of this study was to evaluate the significance of c-Met in patients with mRCC who have been treated in the modern era of targeted therapy. We analyzed c-Met expression in patients with advanced RCC who received sunitinib as first-line therapy and investigated its relevance as a marker for survival as well as its correlation with bone metastases. To our knowledge, c-Met expression has not previously been evaluated as a biomarker in patients with mRCC treated with first-line VEGFR-targeted agents and its role in the pathogenesis of bone metastases remains unknown.

Materials and Methods

Patients and Clinical Samples

Patients diagnosed with progressive mRCC and treated with sunitinib as the first-line treatment at the Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland, between October 18, 2006, and May 31, 2012, were included in the study. Patients were identified from the hospital registry. The clinical data were captured from the hospital case records. The data-capture cutoff date was set at June 1, 2012. This study included 137 patients of whom clinical data and sufficient histologic specimens could be retrieved. Patient characteristics are described in Table 1. This study was approved by an institutional ethics committee.

Evaluation of c-Met

Tumor c-Met expression was analyzed from formalin-fixed paraffin-embedded samples by using an anti-c-Met rabbit monoclonal ready-to-use antibody (Roche) and a BenchMark XT immunostainer (Ventana Medical Systems). The staining was

Figure 1 c-Met Expression in Metastatic Renal Cell Carcinoma. Examples of Negative, Moderate, Strong, and Very Strong Staining (A-D) of Anti c-Met Antibody With the Magnification 400×

carried out per the manufactures' protocol. c-Met staining intensities were scored according to a 4-tier system (0, no staining; 1+ weak; 2+ strong; 3+ very strong) by 2 independent evaluators who reached good concordance (Kappa value 0.7).

c-Met immunohistochemistry score was determined by assessing both the proportion of stained cells and the intensity of the staining: negative (0): fewer than 50% tumor cells with membrane and/or cytoplasmic staining (any intensity); weak (1): $\geq 50\%$ of tumor cells with weak or higher membrane and/or cytoplasmic staining

but $< 50\%$ of tumor cells with moderate or strong staining intensity; strong (2): $\geq 50\%$ of tumor cells with moderate or strong membrane and/or cytoplasmic staining but $< 50\%$ of tumor cells with strong staining intensity; very strong (3): $\geq 50\%$ of tumor cells with strong membrane and/or cytoplasmic staining intensity.

Assessment of Tumor Response

Response to treatment was assessed by longitudinal computed tomography and physical examinations performed at 8- to 12-week

Figure 2 Kaplan-Meier Survival Curves for c-Met Expression and (A) Progression-Free Survival and (B) Overall Survival

c-Met Expression and RCC

intervals according to standard clinical practice. Radiologists experienced in tumor response evaluation interpreted the imaging results. Treatment efficacy was reported according to Response Evaluation Criteria in Solid Tumors v. 1.0 (RECIST).¹⁴

Statistical Analysis

The association between c-Met expression and clinical variables were assessed by using the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous data. Progression-free survival (PFS) was selected as the primary endpoint. The secondary endpoints were OS and response to treatment. PFS was calculated according to the Kaplan-Meier method from the date of initiation of sunitinib to the date of documented cancer progression or death from any cause, whenever death preceded disease progression. Patients without progression were censored at the time of the last follow-up visit. OS was calculated from the date of sunitinib initiation to death, censoring patients who were alive on the date of the last follow-up visit. Survival between groups was compared with the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model. Statistical tests were 2-sided and $P < .05$ was considered as statistically significant. Statistical analyses were performed with IBM SPSS Statistics for PC version 22.0 (IBM Inc).

Results

c-Met Expression in RCC Tumors

Immunohistochemistry analysis of c-Met expression was evaluated in patients with mRCC who received sunitinib as first-line therapy. Median time on sunitinib treatment was 7.1 months (range 0.3-66.9 months). The tissue samples consisted of either resected primary RCC tumors ($n = 134$) or core needle biopsies ($n = 3$) performed for diagnostic purposes. Sufficient histological samples were available for 137 patients that were all included in the analysis.

A total of 100 (73%) patients had predominantly clear-cell carcinoma and 11 patients (8%) papillary carcinoma. One patient (0.7%) had a sarcomatoid subtype, 1 (0.7%) patient had a collecting duct type, 1 (0.7%) patient had chromophobic subtype, and 1 (0.7%) patient Xp11 translocation. Fifteen (11%) patients could not be classified, leaving the remaining 7 (5%) patients with a combined histology with a clear-cell component.

c-Met expression levels were divided into 4 groups: none, weak, strong, and very strong. Figure 1 displays examples of each category.

c-Met expression was found only in the tumor cell compartment of the samples. Nineteen percent ($n = 26$) of the patients had no c-Met expression, weak expression was found in 38% ($n = 52$), and strong to very strong expression in 43% ($n = 38 + 21$) of the tumor cells. Among the patients with clear-cell carcinoma or predominantly clear-cell, the distribution of c-Met expression was as follows: none 18%, weak 42%, strong 25%, and very strong 15%.

Association of c-Met Expression With Clinical Features

Various clinical variables were tested to investigate a possible correlation with c-Met expression and previously described risk assessment criteria.¹⁵ For these analyses, c-Met expression was divided into 2 groups: low group consisting of expression levels 0 to 1 and high group consisting of levels 2 and 3. Table 1 summarizes the patient characteristics by c-Met expression levels (low vs. high).

This grouping of c-Met expression into low and high groups correlated with age ($P = .007$), histology ($P = .024$), and Heng risk criteria ($P < .001$). Additionally, there was a significant difference in the clinical benefit rate between these groups, because 90.4% ($n = 66$) of the patients within the c-MET low group had a partial response or stable disease as their best response versus 69.2% ($n = 36$) in the high group ($P = .004$).

There was no significant difference in the presence of bone metastases at baseline (before treatment initiation) between low and high c-Met expression groups (20.5% vs. 25.4%, respectively; $P = .54$).

Survival Analysis

Median PFS in the whole patient population was 8.6 months (95% CI, 6.1-11.1 months), whereas OS reached 24.4 months (95% CI, 17.7-31.0 months). Patients with low c-Met expression had longer PFS (14.3 months [95% CI, 11.0-17.6] vs. 6.5 months [95% CI, 5.0-8.0]; $P < .001$, respectively) as well as longer OS (32.1 months [95% CI, 26.3-37.9] vs. 20.1 [95% CI, 13.7-26.6]; $P = .049$, respectively) as compared with patients with high c-Met expression. The Kaplan-Meier survival curves for PFS and OS are shown in Figure 2A and B.

To test whether c-Met expression truly was an independent predictor of sunitinib efficacy, we performed a multivariate survival analysis adjusted for Heng risk criteria and c-Met expression. In this analysis, high c-Met expression predicted worse PFS, but no statistically significant association with OS was seen (Table 2).

Table 2 Multivariate Survival Analyses Adjusted for Heng Criteria and c-Met Expression

Predictor	Progression-Free Survival		Overall Survival	
	HR (95% CI)	P	HR (95% CI)	P
Heng criteria				
Favorable	1.00		1.00	
Intermediate	1.57 (0.97-2.54)	.069	1.28 (0.76-2.16)	.35
Poor	2.37 (1.34-4.19)	.003	2.34 (1.30-4.22)	.005
C-Met expression				
Low	1.00		1.00	
High	1.60 (1.09-2.35)	.016	1.22 (0.81-1.82)	.34

Interestingly, in a subgroup analysis among patients with ($n = 31$) and without ($n = 106$) bone metastases, low c-Met expression was associated with both improved OS (unadjusted HR 0.63 [95% CI, 0.42-0.95]; $P = .034$) and PFS (unadjusted HR 0.47 [95% CI, 0.31-0.71]; $P < .001$) in patients without bone metastases as compared with patients with high c-Met expression. No such association of c-Met expression and outcome was seen among patients with bone metastases (OS; unadjusted HR 0.89 [95% CI, 0.39-2.00]; $P = .77$) (PFS; unadjusted HR 0.62 [95% CI, 0.37-1.23]; $P = .16$). In a multivariate model adjusted for Heng

risk criteria, low c-Met expression remained significantly associated with improved PFS (adjusted HR 0.58 [95% CI, 0.37-0.91]; $P = .017$) in patients with no bone metastases. Survival curves for patients with and without bone metastases are shown in Figure 3.

Discussion

Despite the advances in the treatment of mRCC, resistance to current therapies eventually occurs. The mechanism of resistance to anti-VEGF therapies involves upregulation of alternative angiogenic pathways,¹⁶ and in line with this, HGF/c-Met has been shown to be

Figure 3 Kaplan-Meier Survival Curves for c-Met Expression and (A) Progression-Free Survival and (B) Overall Survival Among Patients With No Bone Metastases Present at Baseline ($n = 106$). (C) Progression-Free Survival and (D) Overall Survival Among Patients With Bone Metastases at Baseline ($n = 31$)

Figure 3 continued

involved in resistance to sunitinib treatment.¹⁷ Research shows that dual inhibition of c-Met and VEGFR signaling prohibits tumor invasion and metastasis,¹⁸ and, for example, cabozantinib has shown clinically meaningful efficacy in anti-VEGFR refractory patients.¹³

The results of this study confirm previous findings that c-Met expression is frequent in RCC of the clear-cell subtype, as most patients in our study population of 137 represent this histological subtype. c-Met expression has been associated with poor prognosis and pathologic features,⁹ but our work is the first to demonstrate that c-Met expression may be associated with poor survival in patients under anti-VEGFR treatment. Patients with tumors expressing high levels of c-Met had significantly shorter PFS and OS

than patients with low c-Met levels, as well as significantly worse clinical benefit rates (90.4% vs. 69.2%). Additionally, high c-Met expression predicted shorter PFS in a multivariate model adjusted for Heng risk criteria.

Previous studies have defined how VHL tumor suppressor loss leads to higher levels of VEGF and c-Met expression and how inhibition of angiogenesis may actually stimulate cancer cell metastasis. In this paradigm, antiangiogenic therapy results in decreased blood flow to the tumor, resulting in hypoxia and upregulation of c-Met. c-Met activation in turn promotes tumor invasion, as cancer cells try to migrate to more oxygen-rich locations.¹⁹ Moreover, HGF treatment has been shown to result in sunitinib

resistance in tumor models.¹⁷ According to our data, higher c-Met expression is linked to a shorter response to sunitinib treatment. Resistance to anti-VEGF therapy, upregulation of c-Met, and early tumor invasion could therefore explain our findings on why patients with mRCC whose tumor cells have high c-Met expression seem to achieve less benefit from sunitinib treatment.

Treatment modalities for advanced RCC are numerous, yet predictive markers for treatment selection remain unknown. According to our results, c-Met expression could serve as a biomarker to define those patients who have worse outcome on first-line anti-VEGFR therapy and who might instead potentially benefit from a dual inhibitor as front-line therapy. Interestingly, a recent phase III clinical study demonstrated that dual inhibitors of VEGF and c-Met signaling have relevant clinical activity, as 19% of patients progressing on/after VEGF/VEGFR targeted therapy had a partial response with cabozantinib as compared with only 3% with everolimus. The trial did not show a correlation, in a subgroup analysis, between c-Met expression and efficacy, but more than a third of the patients (41.5%) could not be evaluated for expression, which might explain the lack correlation to some extent.¹³

In the same phase III METEOR study, patients with bone metastases treated with cabozantinib had a 46% risk reduction for OS and 67% risk reduction for PFS when compared with patients treated with everolimus.¹³ Similar effects of cabozantinib on bone metastases have been reported on other preclinical and clinical studies as well.^{20,21} Recent evidence also has shown that cabozantinib has a beneficial association with bone scan response²² in prostate cancer. We therefore also evaluated whether there is a link between c-Met expression and bone metastases. Although no statistically significant difference was found when comparing c-Met expression levels with bone metastases at baseline, we found that in the subgroup of patients without bone metastases, high c-Met expression predicted worse outcome. This finding of c-Met as a predictive factor only among patients without bone metastases requires further evaluation, especially because the samples used in determining c-Met expression were acquired from primary nephrectomies rather than from biopsies of metastatic lesions.

A potential further limitation of our study is that the expression of c-Met may vary based on the age of the sample. However, no statistically significant association was seen in the frequency of low and high c-Met expression and the age of the analyzed tissue samples ($P = .62$) and there was no significant difference in the median age of tissue samples for low and high c-Met expression (5.1 vs. 5.0 years; $P = .62$), respectively.

Taken together, our results warrant further studies in larger patient populations treated with VEGFR or dual c-Met/VEGFR inhibitors to establish the role of c-Met as a predictive biomarker. The results from the clinical trial, CABOZantinib versus SUNitinib (CABOSUN),²³ are promising, as they demonstrate a role for this dual inhibitor in first-line therapy. However, whether c-Met expression could be predictive in this setting remains to be elucidated.²³

Clinical Practice Points

- mRCC is a disease that is rarely curable. Treatment options include several angiogenesis and mTOR inhibitors yet still prognostic markers for treatment selection do not exist. Cabozantinib is a dual VEGFR and c-Met inhibitor that has been

approved for second-line treatment in mRCC, showing superior efficacy over everolimus. Interestingly, the CABOSUN study demonstrated superior efficacy for cabozantinib over sunitinib in the first-line setting in poor- and intermediate-risk patients.

- According to our results, high c-Met expression is associated with shorter OS and PFS. Interestingly, we also found that high c-Met expression is associated with poor outcome among patients without bone metastases at baseline, suggesting that the prognostic role may vary based on the location of the metastases.
- Our results have been analyzed in patients treated with sunitinib. It would be of high interest to compare these results with the patients treated in the CABOSUN trial and to further elucidate whether c-Met expression could serve as a marker for treatment selection for first-line treatment. Further validation would require prospective studies.

Disclosure

K. Peltola has received honoraria from Novartis, BMS, Pfizer, Amgen, Astellas, Sanofi, Merck, and Eli Lilly. P. Penttilä has received honoraria from Novartis. P. Bono has received honoraria from Pfizer, Novartis, Orion Pharma, BMS, and MSD and research funding from Novartis. The remaining authors declare no conflicts of interest.

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