Original Study

Metformin Use and Outcome of Sunitinib Treatment in Patients With Diabetes and Metastatic Renal Cell Carcinoma

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Abstract

We analyzed the effect of metformin use on sunitinib treatment outcome in diabetic patients with metastatic renal cell carcinoma. In metformin users versus nonusers, clinical benefit was 96% versus 84% ($P = .054$), median progression-free survival was 15 versus 11.5 months ($P = .1$), and median overall survival (OS) was 32 versus 21 months ($P = .001$). In multivariate analyses of the entire patient cohort, metformin use was associated with OS.

Background: Although studies in several cancer types suggest that metformin has antitumor activity, its effect on the outcome of targeted therapies in metastatic renal cell carcinoma (mRCC) is poorly defined. We aimed to analyze the effect of metformin use on the outcome of sunitinib treatment in diabetic patients with mRCC. **Patients and Methods:** We performed a retrospective study of diabetic patients with mRCC, who were treated with sunitinib in 8 centers across 2 countries. Patients were divided into metformin users and nonusers. The effect of metformin use on response rate, progression-free survival (PFS), and overall survival (OS), was tested. Furthermore, univariate and multivariate analyses of the association between clinicopathologic factors and metformin use, and outcome were performed using the entire patient cohort. **Results:** Between 2004 and 2014, 108 diabetic patients with mRCC were treated with sunitinib. There were 52 metformin users (group 1) and 56 nonusers (group 2). The groups were balanced regarding clinicopathologic factors. Clinical benefit (partial response + stable disease) in group 1 versus 2 was 96% versus 84% ($P = .054$). Median PFS was 15 versus 11.5 months ($P = .1$). Median OS was 32 versus 21 months ($P = .001$). In multivariate analyses of the entire patient cohort (n = 108), factors associated with PFS were active smoking and pretreatment neutrophil to lymphocyte ratio > 3. Factors associated with OS were metformin use (hazard ratio, 0.21; $P < .0001$), Heng risk, active smoking, liver metastases, and pretreatment neutrophil to lymphocyte ratio > 3. **Conclusion:** Metformin might improve the OS of diabetic patients with mRCC who are treated with sunitinib.

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Introduction

Renal cell carcinoma is the most common cancer of the kidney.[1] Of patients with the disease, 20% to 30% are diagnosed with metastatic disease, and 70% to 80% of patients present with localized or locally advanced disease at diagnosis, which is potentially curable by radical surgical resection alone.[2] Among patients

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who undergo radical resection for localized disease, future metastatic disease develops in 20% to 40%.[3]

An understanding of the pathogenesis of renal cell carcinoma at the molecular level, and randomized 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.[4]

The oral hypoglycemic agent metformin is widely used in the treatment of diabetes.

Data suggest that metformin might have antineoplastic properties. It might affect cancer cells indirectly by decreasing insulin levels or directly by inhibiting cancer cell proliferation and apoptosis.[5] Metformin is a potent adenosine monophosphate–activated protein kinase (AMPK) activator.[6] When activated, AMPK inactivates enzymes involved in adenosine triphosphate consumption such as fatty acid and protein synthesis.[6] Furthermore, AMPK activation inhibits the mammalian target of rapamycin (mTOR) complex 1 pathway and S6K1 phosphorylation implicated in the tumorigenesis process.[7] Metformin might also induce autophagy and apoptosis mechanisms.[8] Although some data suggest that metformin inhibits renal cell carcinoma cell proliferation in vitro,[9] its effect on the outcome of targeted therapies in metastatic renal cell carcinoma is poorly defined.

In the present study we sought to determine the effect of concomitant metformin use on the outcome of diabetic patients with metastatic renal cell carcinoma who are treated with sunitinib.

Patients and Methods

Study Group

We reviewed the records of patients (unselected cohort, international multicenter database) with evidence of metastatic renal cell carcinoma, who were treated with sunitinib, between February 1, 2004 and December 31, 2014, in 8 centers across 2 different countries: the United States (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD) and Israel (Institutes of Oncology at Meir Medical Center, Kfar Saba; Asaf Harofe Medical Center, Zerifin; Rambam Medical Center, Haifa; Sheba Medical Center, Tel Hashomer; Soroka Medical Center, Beer-Sheva; Rabin Medical Center, Petach Tikva; Tel Aviv Sourasky Medical Center, Tel Aviv). Diabetic patients identified and comprised the study group. Patient data were retrospectively collected from electronic medical records and paper charts, including the following clinicopathologic information: age, sex, tumor histology, the time interval from initial diagnosis to sunitinib treatment initiation, Eastern Cooperative Oncology Group performance status, previous treatments for renal cell carcinoma, sites of metastases, laboratory findings, blood pressure levels during treatment, sunitinib dose reduction and/or treatment interruption, and treatment outcomes including objective response rate, progression-free survival (PFS), and overall survival (OS). Outcome data were last updated on December 31, 2014. Data on the concomitant use of medications, including angiotensin system inhibitors (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) and metformin, were gathered from patient electronic medical records and paper charts documenting baseline patient intake and regular follow-ups during treatment, pharmacy records, and by contacting patients and other treating physicians as needed. Patients were divided into 2 groups: (1) metformin users; and (2) metformin naive.

Sunitinib Treatment

All patients had objective disease progression on scans before starting sunitinib treatment. Sunitinib was prescribed as a part of 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, or in 3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment. In patients with significant comorbidities, treatment was initiated at a reduced dose, with subsequent dose escalation if well tolerated. 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 (hematologic and serum chemical measurements), every 4 to 6 weeks, and imaging studies performed every 12 to 18 weeks.

Treatment Outcomes

Follow-up time was defined as the time from sunitinib treatment initiation to December 31, 2014. For the evaluation of response, the Response Evaluation Criteria in Solid Tumors version 1.1 was applied.[10] The response was assessed by independent radiologists and treating physicians. PFS was defined as the time from the initiation of sunitinib treatment until evidence of disease progression on scans or death from any cause. Overall survival was defined as the time from the initiation of sunitinib treatment to death from any cause.

Statistical Analysis

The group of metformin users included patients who started taking metformin before or within 1 month after beginning sunitinib treatment. To better elucidate the effect of metformin use, baseline clinical characteristics and known prognostic factors were compared between metformin users versus nonusers, to identify any potential confounding covariates. The χ^2 test was used to compare categorical end points, and 2-sample t test was used to compare continuous end points, after necessary data transformation. Baseline clinical characteristics and known prognostic factors in metastatic renal cell carcinoma treated with sunitinib[11-18] were included as confounding covariates in the analysis, including age, sex, pretreatment smoking status (active vs. past/never), histology (clear cell vs. nonclear cell), past nephrectomy, previous systemic therapies, number of metastases sites, presence of lung/liver/bone metastases, pretreatment neutrophil to lymphocyte ratio (NLR) $>$ 3, sunitinib-induced hypertension, sunitinib dose reduction or treatment interruption, mean sunitinib dose per treatment cycle, the use of angiotensin system inhibitors, and the risk according to the Heng prognostic model. Patients whose disease did not progress or who died by December 31, 2014 were censored in PFS analysis or OS analysis, respectively. PFS time and OS time were analyzed using Cox proportional hazards

regression model. Finally, to determine if the use of metformin is independently associated with outcome, data of the entire patient cohort were analyzed using a univariate analysis (unadjusted) of association between each clinicopathologic factor and clinical outcome, 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 the multivariate Cox proportional hazards regression model to determine their independent effects. A P value of $\leq .05$ was considered statistically significant. Survival probabilities and median survival times were estimated from Kaplan–Meier curves.

Regulatory Considerations

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

Results

Patient Characteristics

Between February 1, 2004 and December 31, 2014, 108 diabetic patients with metastatic renal cell carcinoma were treated with sunitinib. There were 52 metformin users (group 1) and 56 nonusers (group 2). The median daily dose of metformin was 850 mg (mean, 1200 ± 500 mg; range 500-2350 mg). The distribution of clinicopathologic and prognostic factors is shown in Table 1. The groups were balanced regarding the following clinicopathologic factors: age, sex, Heng risk, past nephrectomy, metastatic renal cell carcinoma histology (clear cell vs. nonclear cell), presence of ≥ 2 metastatic sites, lung/liver/bone metastasis, previous targeted therapy, smoking status, use of angiotensin system inhibitors, pretreatment NLR > 3, sunitinib-induced hypertension, and sunitinib dose reduction/treatment interruption, and sunitinib mean dose per cycle.

Sunitinib Treatment Outcomes

In the entire patient cohort (n = 108), best objective response was complete response in 6 patients (5%), partial response in 47 patients (44%), stable disease in 44 patients (41%), and progressive disease (within the first 3 months of therapy) in 11 patients (10%). Median PFS was 13 months (mean, 18.3 ± 17.4 months; range, 1-77 months). Median OS was 25 months (mean, 30.7 ± 23 months; range, 1-96 months).

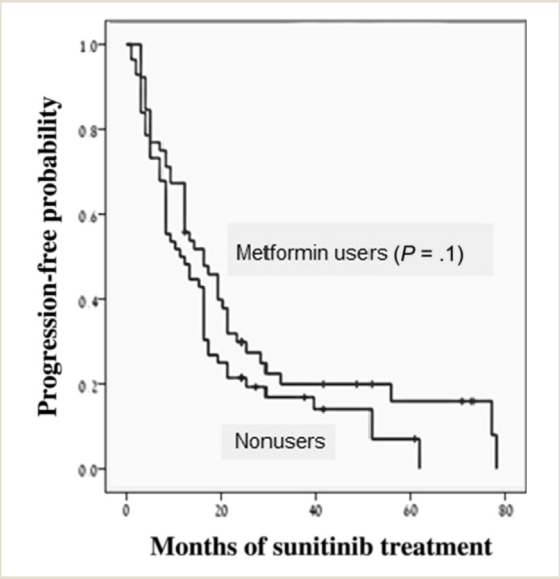
In group 1 versus 2, clinical benefit (partial response + stable disease) was 96% (n = 50) versus 84% (n = 47), and 4% (n = 2) versus 16% (n = 9) had disease progression within the first 3 months of therapy ($P = .054$). A complete response was noted in 12% (n = 6) versus 0% (n = 0). Median PFS (Figure 1) was 15

Table 1 Baseline Patient Characteristics Stratified According to Metformin Use

Characteristic	Metformin Users (n = 52)	Metformin Nonusers (n = 56)	*P*
Median Age (Mean ± SD; range), Years	67 (66 ± 8; 48-84)	66 (65 ± 8; 48-81)	.81
Sex			.49
Male	62 (32)	68 (38)	
Female	38 (20)	32 (18)	
Tumor Histology			.45
Clear Cell	87 (45)	91 (51)	
Nonclear Cell	13 (7)	9 (5)	
Past Nephrectomy	85 (44)	86 (48)	.87
Previous Systemic Therapy	0 (0)	0 (0)	1
Lung Metastasis	73 (38)	80 (45)	.37
Liver Metastasis	25 (13)	27 (15)	.83
Bone Metastasis	42 (22)	41 (23)	.9
Metastatic Sites ≥2	87 (45)	84 (47)	.7
Sunitinib-Induced HTN	60 (31)	61 (34)	.91
Sunitinib Dose Reduction/Treatment Interruption	50 (26)	48 (27)	.85
Mean Sunitinib Dose per Treatment Cycle ± SD (Range; Median), mg	42 ± 5.5 (20-50; 48)	45 ± 4 (18-50; 50)	.6
Users of ASIs	69 (36)	66 (37)	.73
Heng Risk Stratification			
Favorable	12 (6)	27 (15)	.052
Intermediate	60 (31)	59 (33)	
Poor	29 (15)	14 (8)	
Pretreatment NLR >3	52 (27)	43 (24)	.35
Smoking Status			
Active	19 (10)	21 (12)	.78
None/Past	81 (42)	79 (44)	

Data are presented as percentages (n), except where otherwise stated.
Abbreviations: ASIs = angiotensin system inhibitors; HTN = hypertension; NLR = neutrophil to lymphocyte ratio.

Figure 1 Kaplan–Meier Estimates of Progression-Free Survival Stratified According to Status of Metformin Use



versus 11.5 months (hazard ratio [HR], 0.71; $P = .1$). Median OS (Figure 2) was 32 versus 21 months (HR, 0.42; $P = .001$; Table 2).

Univariate Analysis (Entire Patient Cohort, n = 108) of Factors Associated With PFS and OS

Smoking status (HR, 2.55; $P < .0001$ for active vs. never/past smokers), the Heng risk (HR, 1.12 and 2.45; $P = .69$ and .006, for favorable and intermediate vs. poor risk, respectively), the use of angiotensin system inhibitors (HR, 0.58 for yes vs. no; $P = .016$), sunitinib-induced hypertension (HR, 0.56 for yes vs. no; $P = .006$), and NLR > 3 before sunitinib treatment (HR, 2.1 for > 3 vs. ≤ 3; $P = .001$) were individually associated with PFS. Status of metformin use (yes vs. no) was not associated with PFS (HR, 0.71; $P = .1$).

Figure 2 Kaplan–Meier Estimates of Overall Survival Stratified According to Status of Metformin Use

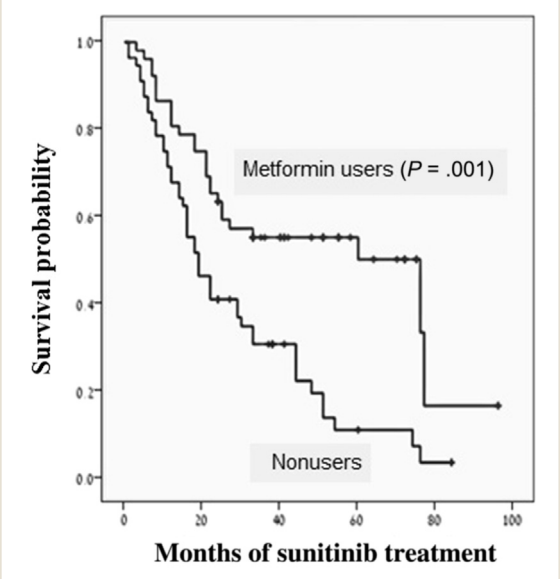


Table 2 Sunitinib Treatment Outcome Stratified According to Status of Metformin Use

Treatment Outcome	Metformin Users (n = 52)[a]	Metformin Nonusers (n = 56)[a]	Value[b]
Response Rate			
Complete Response	12 (6)	0 (0)	.054, OR 4.8 (0.9-13.3)
Partial Response	38 (20)	48 (27)	
Stable Disease	46 (24)	36 (20)	
Disease Progression Within 12 Weeks of The Start of Sunitinib Treatment	4 (2)	16 (9)	
Median PFS, Months	15	11.5	.1, 0.71 (0.47-1.08)
Median OS, Months	32	21	.001, 0.42 (0.26-0.69)

Abbreviations: HR = hazard ratio; OS = overall survival; PFS = progression-free survival.
[a]Data are presented as percentage (n).
[b]Data are presented as *P*, HR (95% CI), except where otherwise noted.

Status of metformin use (yes vs. no; HR, 0.43; $P = .001$), smoking status (HR, 3.34; $P < .0001$ for active vs. never/past smokers), the Heng risk (HR, 1.1 and 2.9; $P = .82$ and .003, for favorable and intermediate vs. poor risk, respectively), past nephrectomy (HR, 0.51 for yes vs. no; $P = .027$), presence of liver metastases (yes vs. no; HR, 1.8; $P = .019$), and NLR > 3 before sunitinib treatment (HR, 2.51 for > 3 vs. ≤ 3; $P < .0001$) were individually associated with OS.

Multivariate Analysis (Entire Patient Cohort, n = 108) of Factors Associated With PFS and OS

Factors independently associated with PFS were smoking status (HR, 2.66; $P < .0001$, for active vs. never/past smokers), and NLR > 3 before treatment (HR, 1.83 for > 3 vs. ≤ 3; $P = .012$). Factors independently associated with OS were status of metformin use (yes vs. no; HR, 0.21; $P < .0001$), smoking status (HR, 2.87; $P < .0001$, for active vs. never/past smokers), Heng risk (HR, 1.46 and 3.34; $P = .28$ and .008, for favorable and intermediate vs. poor risk, respectively), presence of liver metastases (yes vs. no; HR, 1.79; $P = .037$), and NLR > 3 before treatment (HR, 3.3 for > 3 vs. ≤ 3; $P < .0001$).

Other Treatments for Diabetes at Time of Initiation of Sunitinib Treatment

In the group of metformin nonusers, 93% (n = 52) were given diabetic treatment (insulin and/or an oral treatment, eg, thiazolidinediones, glyburide, repaglinide, glipizide), and 7% (n = 4) were not given any diabetic therapy. In metformin users versus non users,

21% (n = 11) versus 27% (n = 16; $P = .6$) were treated with insulin, and 62% (n = 32) versus 59% (n = 33; $P = .9$) were treated with ≥ 2 diabetic therapies.

Discussion

Results of the present study suggest that concomitant use of metformin might improve the outcome of sunitinib treatment in diabetic patients with metastatic renal cell carcinoma. In this retrospective study, diabetic patients who received metformin, had a significant (HR, 0.42; $P = .001$) 11-month increase of OS, after adjustment for other known risk factors for poorer outcome. Patients using metformin also had an increase in clinical benefit (96% vs. 84%; 12% vs. 0% complete response), a decrease of primary treatment refractoriness (progressive disease at first imaging evaluation within the first 3 months, 4% vs. 16%), and a better (by 3.5 months) PFS (HR, 0.71), although these were not statistically significant at the 0.05 significance level (although it might have been significant in a larger patient cohort). Finally, in a multivariate analysis for the entire group, which included the clinicopathologic prognostic factors mentioned previously, the use of metformin was independently associated with OS (HR, 0.21; $P < .0001$).

The present study observation is supported by existing preclinical and clinical data suggesting that the oral hypoglycemic agent metformin might have antineoplastic properties.

Metformin might affect cancer cells indirectly by decreasing insulin levels or directly by inhibiting cancer cell proliferation and apoptosis.[5,8] The mTOR is a therapeutic target for metastatic renal cell carcinoma.[19] One putative antineoplastic mechanism of metformin, is through inhibition of the AKT/mTOR signaling pathway, via activation of AMPK, a negative regulator of the mTOR pathway.[6,7,9] Because some of these antineoplastic effects of metformin might be mediated by mechanisms that are independent of sunitinib action, metformin might be additive or synergistic with vascular endothelial growth factor inhibition therapy, and not be specific to sunitinib treatment.

Our study has some limitations. First, this was a retrospective study representing a heterogeneous group of patients, including all histologic variants of renal cell carcinoma. Second, the total number of 52 patients treated with metformin is relatively small. Thus, other clinicopathologic factors that were not found to be significantly associated with OS in the present study might have been important in a larger patient cohort. Third, all users in the present study started metformin use before initiation of sunitinib treatment, and the analysis did not take into consideration the duration of metformin therapy before and during sunitinib treatment.

Therefore, the benefit of initiating metformin use after initiation of sunitinib therapy, and the effect of metformin treatment duration remain open questions. Finally, the present study lacked an assessment of the severity and control of diabetes (eg, hemoglobin A1c level) at the start of sunitinib treatment. Because metformin is generally considered the first-line agent to treat diabetes, patients in the nonmetformin arm could have had more severe diabetes and therefore could have had a reduced survival because of a greater severity of diabetes. Nonetheless, the incidence of a significant cardiovascular event (significant decrease of left ventricular ejection fraction, acute coronary syndrome, cerebrovascular accident) during therapy was similar between the groups (15% [n = 8] vs. 13% [n = 7]). Moreover, regarding the disease severity, the improved outcome with metformin use was seen despite a higher incidence of Heng poor risk patients and a lower incidence of favorable risk patients among users versus nonusers (difference close to being significant, $P = .052$).

Despite these limitations, our clinical observation that metformin use seems to improve the outcome of sunitinib treatment in diabetic patients with metastatic renal cell carcinoma might contribute to treatment decisions, patient selection, and clinical trials design. Metformin is generally considered safe with a large therapeutic window, and rare cases of hypoglycemia and lactic acidosis have been reported. Thus, further studies might 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 (eg, according to risk using prognostic models, clear cell vs. nonclear cell histology) will benefit.

Conclusion

Concomitant use of metformin might improve the outcome of sunitinib therapy in metastatic renal cell carcinoma.

Clinical Practice Points

- Although studies in several cancer types suggest that metformin has antitumor activity, its effect on the outcome of targeted therapies in metastatic renal cell carcinoma is poorly defined.
- In diabetic patients with metastatic renal cell carcinoma, who used metformin versus those who did not, clinical benefit (partial response + stable disease) was 96% versus 84% ($P = .054$), median PFS 15 versus 11.5 months ($P = .1$), and median OS was 32 versus 21 months ($P = .001$). In multivariate analyses of the entire patient cohort (metformin users vs. nonusers), metformin use was associated with OS.
- If the present study results were validated prospectively, diabetic patients with metastatic renal cell carcinoma might be treated with metformin concomitantly with targeted therapy.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Li L, Kaelin WG Jr. New insights into the biology of renal cell carcinoma. *Hematol Oncol Clin North Am* 2011; 25:667-86.
2. Massari F, Bria E, Maines F, et al. Adjuvant treatment for resected renal cell carcinoma: are all strategies equally negative? Potential implications for trial design with targeted agents. *Clin Genitourin Cancer* 2013; 11:471-6.
3. Herrmann E, Weishaupt C, Pöppelmann B, et al. New tools for assessing the individual risk of metastasis in renal cell carcinoma. *Clin Exp Metastasis* 2013; 30: 215-24.
4. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; 356:115-24.
5. Margel D, Urbach DR, Lipscombe LL, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. *J Clin Oncol* 2013; 31: 3069-75.
6. Zakikhani M, Dowling R, Fantus IG, Sonenberg N, Pollak M. Metformin is an AMP kinase-dependent growth inhibitor for breast cancer cells. *Cancer Res* 2006; 6:10269-73.
7. Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA. The antidiabetic drug metformin suppresses HER2 (erbB-2) oncoprotein overexpression via inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells. *Cell Cycle* 2009; 8: 88-96.
8. Tomic T, Botton T, Cerezo M, et al. Metformin inhibits melanoma development through autophagy and apoptosis mechanisms. *Cell Death Dis* 2011; 2:e199.

9. Liu J, Li M, Song B, et al. Metformin inhibits renal cell carcinoma in vitro and in vivo xenograft. *Urol Oncol* 2013; 31:264-70.
10. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228-47.
11. Patil S, Figlin RA, Hutson TE, et al. Prognostic factors for progression-free and overall survival with sunitinib targeted therapy and with cytokine as first-line therapy in patients with metastatic renal cell carcinoma. *Ann Oncol* 2011; 22: 295-300.
12. Motzer RJ, Bukowski RM, Figlin RA, et al. Prognostic nomogram for sunitinib in patients with metastatic renal cell carcinoma. *Cancer* 2008; 113:1552-8.
13. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol* 2008; 26: 127-31.
14. Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 2011; 103:763-73.
15. Heng DY, Xie W, Regan M, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009; 27:5794-9.
16. Keizman D, Huang P, Eisenberger MA, et al. Angiotensin system inhibitors and outcome of sunitinib treatment in patients with metastatic renal cell carcinoma: a retrospective examination. *Eur J Cancer* 2011; 47:1955-61.
17. Keizman D, Ish-Shalom M, Huang P, et al. The association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression-free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma. *Eur J Cancer* 2012; 48:202-8.
18. Keizman D, Gottfried M, Ish-Shalom M, et al. Active smoking may negatively affect response rate, progression-free survival, and overall survival of patients with metastatic renal cell carcinoma treated with sunitinib. *Oncologist* 2014; 19:51-60.
19. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; 372:449-56.