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ORIGINAL PAPER

The correlation between the incidence of adverse events and progression-free survival in patients treated with cabozantinib for metastatic renal cell carcinoma (mRCC)

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Abstract

Clinical practice shows significant differences in treatment outcomes across patients treated with cabozantinib for metastatic renal cell carcinoma (mRCC). It is not known whether cabozantinib-induced adverse events are predictive factors of survival as in case of drugs such as sunitinib or axitinib. The study participants were 30 adult patients with mRCC treated with cabozantinib as a second- or further line setting. All adverse events were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Progression-free survival (PFS) values were calculated by taking the beginning of cabozantinib treatment as the start date and either disease progression or death as the end date. PFS were estimated using the Kaplan–Meier method, and compared using the log-rank test. We identified independent PFS predictors using multiple Cox proportional hazards models and reported hazard ratios (HR) with 95% confidence intervals. The median observation time cabozantinib treatment was 7.5 months, with a range of 2–15 months. During that time, 11 (37%) of the patients had mRCC progression. Median PFS on cabozantinib was not reached, and lower quartile was 6 months. All patients developed at least one adverse event in the course of cabozantinib therapy. Hypertension, hypothyroidism and HFS were observed most frequently, in about two-thirds of the patients. The co-incidence of multiple adverse events was common. Hypertension, hypothyroidism, diarrhea and liver toxicity were significantly associated with longer PFS values. Patients with three or more side effects had significantly longer PFS than those with two or fewer. Even though this study was conducted in a small patient sample and the observation time was relatively short our results confirm the predictive value of the incidence of adverse events during cabozantinib treatment in mRCC patients. To the best of our knowledge, this is the first study of this kind conducted in this group of patients.

Keywords Renal cell carcinoma · Cabozantinib · Predictive factors · Progression-free survival

Introduction

Recent years have witnessed constant progress and improved patient outcomes in the treatment of metastatic renal cell carcinoma (mRCC). Better understanding of RCC biology and advancements in the basic sciences have led to the introduction of new treatment strategies in clinical practice. One example of this is immunotherapy, nivolumab as second- and further lines of treatment [1]; or ipilimumamb and nivolumab as first-line treatment for patients with intermediate or poor prognosis according to MSKCC criteria [2]. Established mRCC treatment strategies, like those targeting VEGFR, have also been developed and improved in recent years. Cabozantinib is one of the new drugs approved for the treatment of mRCC. It is a tyrosine kinase inhibitor with a specific activity profile. It inhibits not only VEGF receptors kinases but also MET, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT3 and TIE-2 [3]. This is particularly important because the AXL and MET pathways are related to resistance to TKI treatment [4]. In the registration study, the effectiveness of cabozantinib was compared to that of

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Table 1 Baseline characteristics of patients treated with cabozantinib

Patient characteristics	Values observed in mRCC patients ($N=30$)
Male sex, *N* (%)	18 (60)
Median age (range) (years)	64 (44–75)
Median BMI (range) (kg/m^2)	27 (18–46)
Clear cell histology, *N* (%)	29 (97)
Prior nephrectomy, *N* (%)	29 (97)
Fuhrman grade	
1, *N* (%)	2 (7)
2, *N* (%)	12 (40)
3, *N* (%)	11 (37)
4, N (%)	5 (16)
MSKCC, points	
0, *N* (%)	8 (27)
1, *N* (%)	15 (50)
2, *N* (%)	6 (20)
3, *N* (%)	1 (3)
Heng Prognostic Score, points	
0, *N* (%)	8 (27)
1, *N* (%)	15 (50)
2, *N* (%)	4 (13)
3, *N* (%)	2 (7)
4–6, *N* (%)	1 (3)
Metastases	
Liver, *N* (%)	5 (17)
Bone, *N* (%)	13 (43)
Lungs, *N* (%)	22 (73)
Pancreas, *N* (%)	4 (13)
Other sites, *N* (%)	20 (67)
Median number of sites (range)	3 (2–6)
ECOG	
0, *N* (%)	7 (23)
1, *N* (%)	13 (43)
2, *N* (%)	9 (30)
3, *N* (%)	1 (4)
4, *N* (%)	0 (0)
Karnofsky Performance Score	
100, *N* (%)	2 (7)
90, *N* (%)	6 (20)
80, *N* (%)	19 (63)
$\leq$70, *N* (%)	3 (10)
First-line treatment	
Sunitinib, *N* (%)	22 (73)
Pazopanib, *N* (%)	5 (17)
Sorafenib, *N* (%)	2 (7)
Pembrolizumab, *N* (%)	1 (3)
Second-line treatment	
Axitinib, *N* (%)	7 (23)
Everolimus, *N* (%)	15 (50)
Sorafenib, *N* (%)	1 (3)
Cabozantinib in second-line treatment, *N* (%)	7 (23)

Table 1 (continued)

Patient characteristics	Values observed in mRCC patients ($N=30$)
Cabozantinib in third- or further line treatment, *N* (%)	23 (77)

everolimus in a group of patients who experienced progression while being treated with VEGFR-TKI. The study found significant improvement of progression-free survival (PFS) and overall survival (OS) in the cabozantinib group [5].

Clinical practice shows significant differences in treatment outcomes in mRCC patients, and there is a need to identify predictive factors that can help optimize treatment. So far, studies have not provided definitive answers but in case of VEGFR-targeted agents, the incidence of adverse events related to the mechanism of actions of these drugs can have predictive value for the treatment outcomes. Studies of groups of patients treated with sunitinib have shown, that side effects such as hypertension, hypothyroidism and the hand-foot syndrome (HFS) are markers of sunitinib activity in the body. They are correlated with treatment outcomes such as ORR, PFS, and OS [6–10]. Similar findings were obtained for the incidence of hypertension in axitinib treatment [11]. Other studies suggest that the co-incidence of various side effects can itself be a predictive factor since patients who experience more adverse events during treatment tend to have better treatment outcomes [12, 13]. There are currently no studies of the relationship between the incidence of adverse events and treatment outcomes in the course of cabozantinib treatment. The goal of this study was to evaluate the relationship between the incidence of side effects and PFS in patients treated with cabozantinib as second- or further line treatment for mRCC patients.

Materials and methods

The retrospective study included 30 adult patients with mRCC treated at the Department of Uro-oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology with cabozantinib as a second- or further line of treatment (Table 1) between 2017 and 2018. Patients were included in the study if they met two inclusion criteria: diagnosis of metastatic RCC and previous anti-VEGF TKI treatment. The initial dose of cabozantinib was 60 mg daily. Permission to conduct this study was granted by the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology Bioethics Committee (permission number 38/2018).

Our data set consisted of patient demographics, cabozantinib dose and dose reductions log, adverse events, treatment delays, and treatment outcomes. Performance scores were evaluated with the ECOG and Karnofsky Scale. Data on objective adverse events included hypertension, HFS, hypothyroidism, liver toxicity (serum aspartate transaminase and/or alanine transaminase elevation), asthenia, and diarrhea.

Table 2 Adverse events observed during treatment with cabozantinib

Adverse event	*N* (%)
Hypertension	22 (73)
Hypothyroidism	21 (70)
HFS	20 (67)
Asthenia	18 (60)
Diarrhea	15 (50)
Liver toxicity	7 (23)
Number of adverse events	
1–2	9 (30)
3–4	14 (47)
5–6	7 (23)

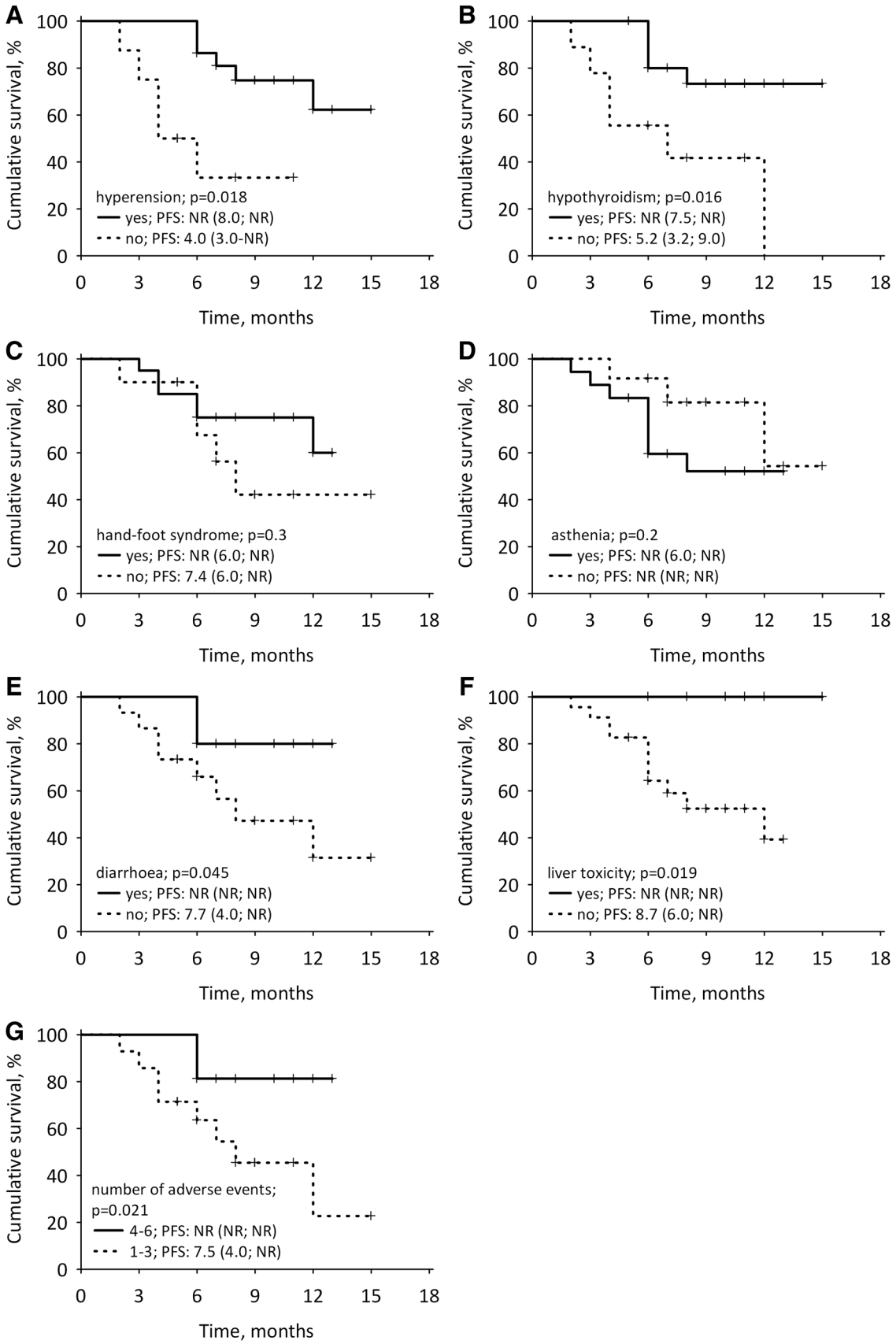
Blood pressure (BP) was measured during outpatient clinic visits, and patients were also asked to monitor their BP at home. Patients with systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg, as well as those who had pre-existing medication-controlled arterial hypertension and required additional antihypertensive medication during treatment, were classified as having developed cabozantinib-induced hypertension.

All adverse events were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Clinical and laboratory evaluation was performed every 4 weeks and included a physical examination and blood tests. Response to therapy was evaluated every 12 weeks using the RECIST 1.1 criteria.

Statistical analysis

Nominal variables are summarized as the number of patients (percentage of the group) in each group, and continuous variables are provided as medians (lower/upper quartile). PFS values were calculated by taking the beginning of cabozantinib treatment as the start date and either disease progression or death as the end date. We estimated PFS values using the Kaplan–Meier method, and compared them using the log-rank test. We identified independent PFS predictors


A
Cumulative survival, %
hyperension; p=0.018
yes; PFS: NR (8.0; NR)
no; PFS: 4.0 (3.0-NR)
Time, months
B
Cumulative survival, %
hypothyroidism; p=0.016
yes; PFS: NR (7.5; NR)
no; PFS: 5.2 (3.2; 9.0)
Time, months
C
Cumulative survival, %
hand-foot syndrome; p=0.3
yes; PFS: NR (6.0; NR)
no; PFS: 7.4 (6.0; NR)
Time, months
D
Cumulative survival, %
asthenia; p=0.2
yes; PFS: NR (6.0; NR)
no; PFS: NR (NR; NR)
Time, months
E
Cumulative survival, %
diarrhoea; p=0.045
yes; PFS: NR (NR; NR)
no; PFS: 7.7 (4.0; NR)
Time, months
F
Cumulative survival, %
liver toxicity; p=0.019
yes; PFS: NR (NR; NR)
no; PFS: 8.7 (6.0; NR)
Time, months
G
Cumulative survival, %
number of adverse events;
p=0.021
4-6; PFS: NR (NR; NR)
1-3; PFS: 7.5 (4.0; NR)
Time, months

◂**Fig. 1** Kaplan–Meier curves showing PFS among mRCC patients treated with cabozantinib. Patients with (solid lines) and without (dashed lines) adverse events: hypertension (**a**), hypothyroidism (**b**), hand-foot syndrome (**c**), asthenia (**d**), diarrhea (**e**), liver toxicity (**f**), and number of adverse events below or above the median value (**g**). Median PFS (lower; upper quartile) in months and *p* values in log-rank test are shown in the graphs

using multiple Cox proportional hazards models and reported hazard ratios (HR) with 95% confidence intervals.

Results

The median observation time cabozantinib treatment was 7.5 months, with a range of 2–15 months. During that time, treatment was discontinued in 11 (37%) of the patients, due to mRCC progression. In further follow-up, six of those patients died. Two patients (7%) were lost to follow-up. Seventeen patients (57%) were still in cabozantinib therapy at the end of the study. Median PFS on cabozantinib was not reached, lower quartile was 6 months. The best response during cabozantinib treatment was partial response in 12 patients (40%), stable disease in 14 (47%), and progression in 4 (13%).

All patients developed at least one adverse event in the course of cabozantinib therapy (Table 2). Hypertension, hypothyroidism and HFS were observed most frequently, in about two-thirds of the patients. The co-incidence of multiple adverse events was common, with nearly half of the group developing three to four adverse events (Table 2). Seventeen patients (57%) required dose reduction because of side effects. Hypertension, hypothyroidism, diarrhea and liver toxicity were significantly associated with longer PFS values (Fig. 1). Patients with three or more side effects had significantly longer PFS than those with two or fewer. Dose reduction was not significantly associated with PFS ($p=0.2$).

Among baseline characteristics of patients presented in Table 1, only the Heng Prognostic Score was significantly associated with PFS (Table 3). Hypertension and hypothyroidism positively predicted PFS independently of Heng scores (Table 3). As there were no uncensored cases among patients who developed liver toxicity, it was impossible to calculate Cox regression including this variable as a predictor. However, we carried out this analysis for liver toxicity or diarrhea (i.e., the occurrence of least one of the two). Liver toxicity or diarrhea predicted PFS independently of hypertension and hypothyroidism, but not of Heng Scores (Table 3). However, the total number of adverse events (excluding HFS and asthenia) positively predicted PFS independently of Heng Scores (Table 3). In a multiple Cox regression analysis including various adverse events, hypertension and liver toxicity or diarrhea were identified as independent predictors of PFS (Table 3).

Discussion

Even though this study was conducted in a small patient sample and the observation time was relatively short (median PFS for the group was not reached), our results confirm the predictive value of the incidence of adverse events during cabozantinib treatment in mRCC patients. To the best of our knowledge, this is the first study of this kind conducted in this group of patients. Similar to what has been reported in studies of sunitinib [7–10, 12, 13], we found correlations between individual adverse effects (hypertension, hypothyroidism and liver toxicity or diarrhea) and PFS, and between the co-incidence of multiple adverse effects and PFS. The independent predictive value of liver toxicity is especially interesting. It might be the result of cabozantinib's action on the MET pathway. Some studies suggest a hepato-protective influence of the activation of this pathway, and by inhibiting this pathway cabozantinib may lead to the appearance of laboratory signs of liver toxicity [14–16]. As we mentioned in the introduction, the MET pathway is one of the pathways activated in course of developing resistance to antiangiogenic treatment. It, therefore, seems that the incidence of liver toxicity might attest to the effective inhibition of the MET pathway. It is also worth emphasizing that cabozantinib proved to be highly active in patients who had already received mutiple lines of treatment. Even though 77% of

Table 3 Simple and multiple cox regression to predict PFS

Predictor variable	Odds ratio for progression (95% confidence interval); *p* value		
	Simple	Adjusted for Heng Prognostic score	Multiple
Heng Prognostic Score > 1 point	5.50 (1.66–18.05); $p=0.005$	Not applicable	Not included
Hypertension	0.19 (0.05–0.67); $p=0.010$	0.14 (0.03–0.60); $p=0.008$	0.12 (0.02–0.69); $p=0.018$
Hypothyroidism	0.24 (0.07–0.78); $p=0.018$	0.56 (0.11–2.99); $p=0.5^{NS}$	0.52 (0.14–1.90); $p=0.3^{NS}$
Liver toxicity or diarrhea	0.20 (0.05–0.77); $p=0.019$	0.36 (0.08–1.71); $p=0.2^{NS}$	0.14 (0.03–0.73); $p=0.020$
Number of adverse events excluding HFS and asthenia, per 1	0.28 (0.13–0.57); $p<0.001$	0.28 (0.11–0.69); $p=0.005$	Not included

NS not significant

our patients received cabozantinib as a third- or higher line of treatment, the ORR for the group as a whole was about 40%; and with a median observation period of 7.5 months the median PFS value for the group was not reached. 57% of the patients in our sample needed dose reductions, the observed adverse events were manageable, and no patients stopped treatment because of toxicity or treatment-induced complications.

Compliance with ethical standards

Conflict of interest Jakub Kucharz has received research grant from Novartis, travel grants and speakers' honoraria from Pfizer, Bayer, Novartis and IPSEN. Pawel Wiechno has received speakers' honoraria and travel Grants from Pfizer, Bayer, Novartis and IPSEN. Other authors declare no conflicts of interest.

References

1. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373(19):1803–13. https://doi.org/10.1056/NEJMoa1510665.
2. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, et al. Nivolumab plus Ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277–90. https://doi.org/10.1056/NEJMoa1712126.
3. Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis,angiogenesis, and tumor growth. Mol Cancer Ther. 2011;10:2298–308.
4. Zhou L, Liu XD, Sun M, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene. https://doi.org/10.1038/onc.2015.343.
5. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, Hammers HJ, Donskov F, Roth BJ, Peltola K, Lee JL, Heng DYC, Schmidinger M, Agarwal N, Sternberg CN, McDermott DF, Aftab DT, Hessel C, Scheffold C, Schwab G, Hutson TE, Pal S, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17(7):917–27. https://doi.org/10.1016/S1470-2045(16)30107-3.
6. Ravaud A, Schmidinger M. Clinical biomarkers of response in advanced renal cell carcinoma. Ann Oncol. 2013;24(12):2935–42.
7. Rini BI, Tamaskar I, Shaheen P, Salas R, Garcia J, Wood L, et al. Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst. 2007;99(1):81–3.
8. Rini BI, Cohen DP, Lu DR, Chen I, Hariharan S, Gore ME, et al. Hypertension as biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst. 2011;103(9):763–73.
9. Buda-Nowak A, Kucharz J, Dumnicka P, Kuzniewski M, Herman RM, Zygulska AL, Kusnierz-Cabala B. Sunitinib-induced hypothyroidism predicts progression-free survival in metastatic renal cell carcinoma patients. Med Oncol. 2017;34(4):68. https://doi.org/10.1007/s12032-017-0928-z.
10. Pusanov I, Michaelson D, Cohen D, et al. Evaluation of hand-foot syndrome (HFS) as a potential biomarker of sunitinib efficacy in patients with metastatic renal cell carcinoma (mRCC) and gastrointestinal stromal tumour (GIST). ECCO16-ESMO36- ESTRO30 2011 (Abstract 1444).
11. Rini BI, Garrett M, Poland B, et al. Axitinib in metastatic renal cell carcinoma: results of a pharmacokinetic and pharmacodynamic analysis. J Clin Pharmacol. 2013;53:491–504.
12. Kucharz J, Dumnicka P, Kuzniewski M, Kusnierz-Cabala B, Herman RM, Krzemieniecki K. Co-occurring adverse events enable early prediction of progression-free survival in metastatic renal cell carcinoma patients treated with sunitinib: a hypothesis-generating study. Tumori J. 2015;101:555–9. https://doi.org/10.5301/tj.5000342.
13. Nagyiványi K, Budai B, Bíró K, Gyergyay F, Noszek L, Küronya Z, Németh H, Nagy P, Géczi L. Synergistic survival: a new phenomenon connected to adverse events of first-line sunitinib treatment in advanced renal cell carcinoma. Clin Genitourin Cancer. 2016;14(4):314–22. https://doi.org/10.1016/j.clgc.2015.11.016.
14. Huh CG, Factor VM, Sánchez A, Uchida K, Conner EA, Thorgeirsson SS. Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. Proc Natl Acad Sci USA. 2004;101(13):4477–82.
15. Giebeler A, Boekschoten MV, Klein C. et al. c-Met confers protection against chronic liver tissue damage and fibrosis progression after bile duct ligation in mice. Gastroenterology. 2009;137(1):297–308.
16. Marquardt JU, Seo D, Gómez-Quiroz LE. et al. Loss of c-Met accelerates development of liver fibrosis in response to CCl(4) exposure through deregulation of multiple molecular pathways. Biochim Biophys Acta. 2012;1822(6):942–51.