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Efficacy and Safety of Axitinib as First-Line Therapy in Japanese Patients with Metastatic Renal Cell Carcinoma

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Abstract

Previous study reported that patients treated with axitinib as second-line therapy had longer median progression-free survival than those treated with sorafenib for metastatic renal cell carcinoma (mRCC). In this study, we reviewed our experience of axitinib as a first-line therapy for mRCC in Japanese patients, focusing on its efficacy and safety. We retrospectively assessed 26 patients treated with axitinib as a first-line therapy for mRCC from July 2010 to July 2014 at Chiba Cancer Center and Kinki University Hospital. Observation period was 24.6 ± 18.3 months. The objective response rate was 50.0%, and the median progression-free survival was 27.5 months. Overall survival was not estimable. Common grade 3 adverse events were hypertension in 19 patients and proteinuria in 5 patients. Axitinib demonstrated significant efficacy as a first-line therapy in Japanese patients with mRCC. Careful monitoring and management of the adverse effects may help to control its toxicities.

Keywords

Axitinib, Renal Cell Carcinoma, First Line

1. Introduction

Renal cell carcinoma (RCC) is highly resistant to chemotherapy. Cytokine therapies, including interferon-α and

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interleukin-2, were, until recently, the only treatments available for metastatic RCC (mRCC), but cytokine therapies have limited roles in the treatment of mRCC [1].

The development of antiangiogenic drugs that target vascular endothelial growth factor (VEGF) receptors was based on extensive investigations into the molecular mechanisms underlying RCC. These drugs with proven benefits in the treatment of mRCC have been approved, and they include sunitinib, sorafenib, pazopanib, and axitinib [2]-[4].

Axitinib is a potent, selective second-generation inhibitor of VEGF receptors that has shown efficacy in phase II and III clinical trials in patients with mRCC who had been treated previously [4]-[7].

A subgroup analysis of the phase III AXIS trial showed a longer median progression-free survival (PFS) and a higher objective response rate (ORR) for axitinib-treated Japanese patients compared with the overall population [8]. On the other hand, in a randomized phase III trial that compared axitinib with sorafenib as a first-line therapy for mRCC, the median PFS was numerically longer in patients treated with axitinib, but the difference was not significant [9].

To the best of our knowledge, this is the first report that examined efficacy and safety of axitinib as a first-line therapy for the treatment of mRCC in Japanese patients.

2. Methods

2.1. Patients and Treatment

We retrospectively assessed 26 patients who had been treated with axitinib as a first-line therapy for the treatment of mRCC between July 2010 and July 2014 at Chiba Cancer Center (CCC) and Kinki University Hospital (KUH). 14 of the patients had enrolled in a phase II trial that assessed the efficacy and safety of axitinib dose titration (NCT00835978) [7]. Therefore, 14 patients were treated according to the phase II clinical trial protocol, and, of these, three patients were assigned to the dose-titration group. We also adopt evaluation based on the phase II trial for the 12 patients who were not registered to the clinical trial.

We undertook clinical assessments, which included the patients' medical histories, physical examinations, their vital signs, clinical laboratory results, their Eastern Cooperative Oncology Group performance statuses (ECOG PS), and their Memorial Sloan Kettering Cancer Center (MSKCC) risk classifications at baseline [11].

We assessed the tumors, which included computed tomography and/or magnetic resonance imaging scans at baseline, and every 6 - 8 weeks thereafter, and the responses were defined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 [12]. We did not examine the responses of three patients who had bone metastases only in accordance with the RECIST criteria. Safety was assessed throughout the study, with adverse events (AEs) graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [13].

Ethical approval for the study was obtained from the Chiba Cancer Center's Institutional Review Board (Approval no. CCCIRB-1231).

2.2. Statistical Analysis

The PFS and overall survival (OS) rates were calculated using the Kaplan-Meier method, and a log-rank test was used to compare the results from the groups of patients with and without proteinuria. A Cox proportional-hazards model that considered the onset of proteinuria as a time-dependent covariate was used to estimate the hazard ratios (HRs) for PFS and OS.

All statistical analyses were performed using JMP®, version 11.0 (SAS Institute Inc., Cary, NC, USA). Probability (p) values < 0.05 were considered statistically significant, and confidence intervals (CIs) were set at the 95% level.

3. Results

The median duration of the observation period for this study was 15.6 months (range 4.5 - 52.9 months). **Table 1** summarizes the characteristics of the 21 patients who were included in this study. One patient, who did not undergo a radical nephrectomy, underwent needle biopsies of the primary tumor to determine its histological subtype. Initially, 5 mg of axitinib was administered twice daily to all these patients. Nineteen patients (73.1%) had their doses of axitinib reduced because of AEs. The axitinib dose was increased to more than 5 mg twice

Table 1. Patient demographic and baseline characteristics.

	All patients	CCC	KUH	*p* value
Number of patients	26	21	5	
Age (years)	63 (41 - 78)	63 (41 - 78)	66 (53 - 81)	0.379
Sex				
Male	15 (57.7)	13 (61.9)	2 (40.0)	0.376
Female	11 (42.3)	8 (38.1)	3 (60.0)	
ECOG PS				
0	21 (80.8)	16 (76.2)	5 (100.0)	0.121
1	5 (19.2)	5 (23.8)	0	
Previous nephrectomy				
Yes	25 (96.2)	20 (95.2)	5 (100.0)	0.509
No	1 (3.8)	1 (4.8)	0	
Histology of primary tumor				
Clear cell RCC	23 (88.5)	19 (90.5)	4 (80.0)	0.536
Non-clear cell RCC	3 (11.5)	2 (9.5)	1 (20.0)	
MSKCC risk group				
Favorable	6 (23.1)	5 (23.8)	1 (20.0)	0.947
Intermediate	16 (61.5)	13 (61.9)	3 (60.0)	
Poor	4 (15.4)	3 (14.3)	1 (20.0)	
Site of metastasis				
Lung	18 (69.2)	15 (71.4)	3 (60.0)	0.549
Lymph node	12 (46.2)	9 (42.9)	3 (60.0)	0.490
Bone	7 (26.9)	7 (33.3)	0	0.059
Liver	2 (7.7)	2 (9.5)	0	0.345

Data are median (range) or n (%). CCC = Chiba Cancer Center. KUH = Kinki University Hospital. ECOG PS = Eastern Cooperative Oncology Group performance status. MSKCC = Memorial Sloan-Kettering Cancer Center.

daily in 7 patients (26.9%). Among the 26 patients, 17 (65.4%) stopped receiving axitinib because of disease progression 11 patients (42.3%) or intolerable AEs in 6 patients (23.1%).

Figure 1 presents the maximum reductions in the target tumors from baseline for 23 patients. We did not examine the responses of three patients who had bone metastases only in accordance with the RECIST criteria. **Table 2** summarizes the patients' responses to axitinib. The ORR was 50.0% (95% CI 32.1 - 67.9). There is no significant difference in the ORR between CCC and KUH.

PFS and OS were determined for all the patients who were included in this study; as shown in **Figure 2**, the meian PFS was 27.5 months and the OS was not estimable (NE) for this patient series. Although difference was not significant ($p = 0.53$), the median PFS for the patients with proteinuria (38.8 months) was longer than without proteinuria (27.5 months) (**Figure 3**).

Table 3 summarizes the AEs associated with axitinib. All the patients experienced AEs, and the common AEs that corresponded to grade 3 in the CTCAE were hypertension in 19 patients (73.1%) and proteinuria in five patients (19.2%). There was no evidence of treatment-related death in this patient series.

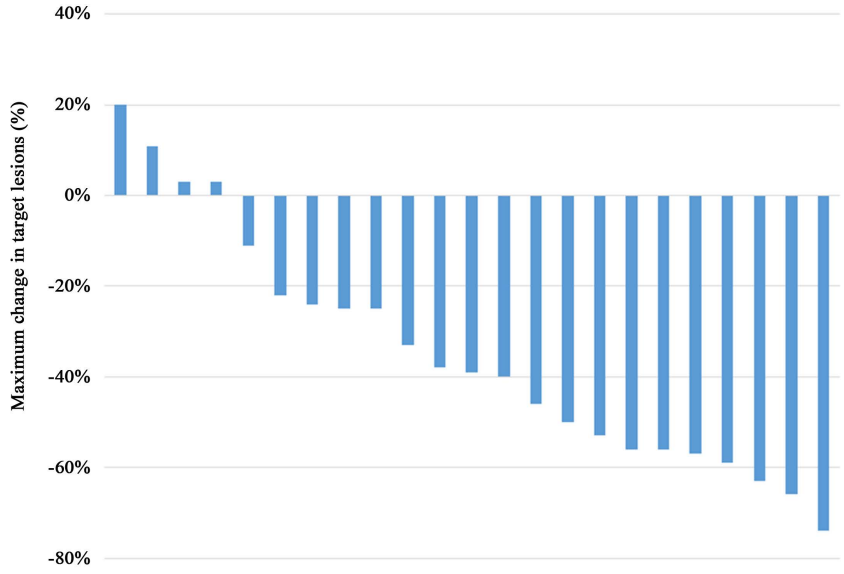

Figure 1. Maximum percent change in target lesions from baseline.

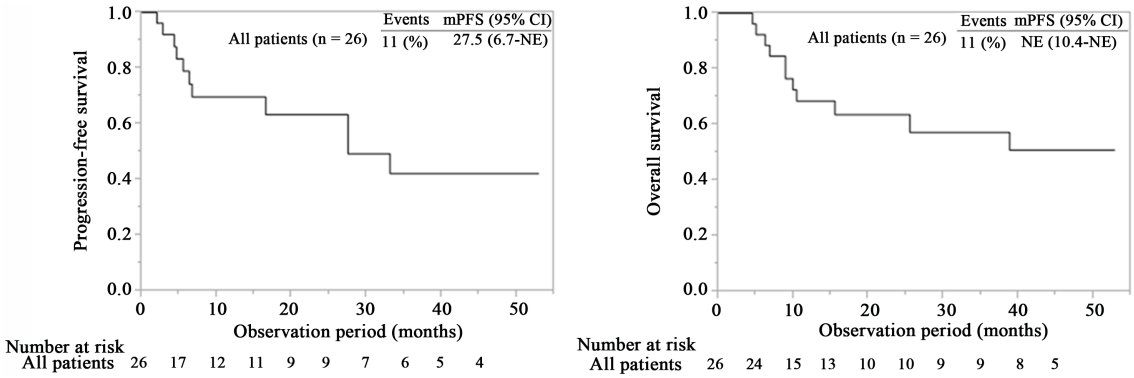

Figure 2. Kaplan-Meier estimates of (a) progression-free survival and (b) overall survival. mPFS denotes median progression-free survival, mOS denotes median overall survival, CI denotes confidence interval, NE denotes not estimable.

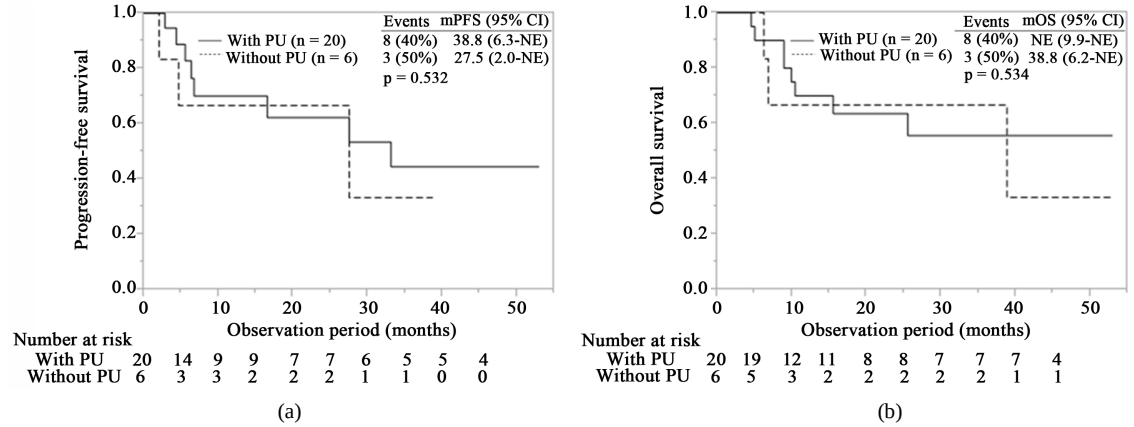

Figure 3. Kaplan-Meier estimates of (a) progression-free survival and (b) overall survival based on the presence or absence of proteinuria. PU denotes proteinuria, mPFS denotes median progression-free survival, mOS denotes median overall survival, CI denotes confidence interval, NE denotes not estimable, HR denotes hazard ratio. *p* values are based on one-sided log-rank tests.

Table 2. Objective tumor response.

	All patients	CCC	KUH	*p* value
Number of patients	26	21	5	
Best observed RECIST response				
Complete response	0	0	0	
Partial response	13 (50.0)	10 (47.6)	3 (60.0)	
Stable disease	10 (38.5)	8 (38.1)	2 (40.0)	
Progressive disease	3 (11.5)	3 (14.3)	0	
Objective response rate	13 (50.0)	10 (47.6)	3 (60.0)	0.618
95% CI	32.1 - 67.9	28.3 - 67.6	23.0 - 88.2	

Data are median (range) or n (%). CCC = Chiba Cancer Center. KUH = Kinki University Hospital. CI = confidence interval.

Table 3. Summary of common all-causality adverse events and laboratory abnormalities.

	All grade	Grade ≥ 3
Hypertension	22 (84.6)	19 (73.1)
Fatigue	19 (73.1)	1 (3.8)
Hand-foot syndrome	16 (61.5)	3 (11.5)
Hypothyroidism	16 (61.5)	0
Dysphonia	15 (57.7)	0
Diarrhea	12 (46.2)	0
Decreased appetite	8 (30.8)	2 (7.7)
Stomatitis	8 (30.8)	0
Rash	6 (23.1)	1 (3.8)
Dysgeusia	5 (19.2)	0
Nausea	4 (15.4)	2 (7.7)
Vomiting	4 (15.4)	0
Constipation	4 (15.4)	0
Laboratory abnormalities		
Proteinurea	20 (76.9)	5 (19.2)
Blood uric acid increased	11 (42.3)	0
Blood creatinine increased	8 (30.8)	0
ALT increased	8 (30.8)	0
Thrombocytopenia	8 (30.8)	0
Anemia	5 (19.2)	1 (3.8)
AST increased	5 (19.2)	0

Data are n (%). ALT = alanine aminotransferase. AST = aspartate aminotransferase.

4. Discussion

The results of phase II and III clinical trials have led to the approval of axitinib for the treatment of mRCC in Japan in 2012 [8] [14]. Presently, axitinib is listed as a first-line therapy for mRCC in the National Comprehen-

sive Cancer Network (NCCN) guidelines, and it is recommended as a second-line therapy for mRCC in the NCCN guidelines and in the European Association of Urology guidelines [15] [16].

In a phase II study of axitinib treatment in Japanese patients with cytokine-refractory mRCC, the ORR was 50.0% and the median PFS was 11.0 months [14]. Thus, the ORR was higher but the PFS was shorter compared with the ORR (44.2%) and the PFS (15.7 months) reported from a similar study conducted in a western country [6]. As a first line therapy, the median PFS was numerically longer in patients treated with axitinib (10.1 months) than with sorafenib (6.5 months), but the difference was not significant in a randomized phase III trial [9].

On the other hand, sunitinib is currently regarded as a new reference standard of care for the first-line treatment of mRCC [15] [16]. In a Japanese phase II trial of sunitinib as a first-line therapy, Tomita et al. reported that the PFS was 12.2 months [17]. Recently, an alteration in the dosing schedule to 2 weeks on treatment followed by 1 week off treatment was reported to increase patient tolerability, and patient survival was longer because the treatment duration was prolonged [18] [19]. Kondo *et al*. reported that the median PFS was 18.4 months and the ORR was 50% in Japanese patients who participated in a 2 weeks on treatment and 1 week off treatment schedule [20].

To the best of our knowledge, there have been no investigations into axitinib as a first-line therapy for the treatment of mRCC in Japanese patients. We retrospectively investigated the clinical outcomes in 26 Japanese patients who received axitinib as first-line therapy for mRCC. In this study, the median PFS was 27.5 months and the ORR was 50.0%, and these results are superior compared with any previously reported results. A retrospective study reported that the PFS is an important prognostic parameter in patients with mRCC who are treated with first-line VEGF-targeted therapy [21]. Indeed, treatment with axitinib as a first-line therapy for mRCC might contribute to improving OS in Japanese patients.

In this study, 14 of 26 patients were phase II clinical trial participants [10]. In the phase II dose-titration study, the nonrandomized group of patients who were ineligible for dose titration had a higher proportion of Japanese patients than the randomized group [10]. In this study, 11 of 14 patients were allocated to the nonrandomized group, which suggests that Japanese patients are likely to develop axitinib-related toxic effects, including hypertension.

Hypertension was the most commonly reported treatment-related AEs and it affected 85% of the patients in the current study, but this was manageable with antihypertensive medications. The incidence of hypertension was similar to that reported from other Japanese studies (64% - 84%) [8] [14], but it was higher than that reported from studies carried out in western countries (35% - 57%) [4] [6] [7] [9] [10].

With regard to sunitinib, which is a VEGF inhibitor that is similar to axitinib, previous studies have reported that sunitinib-induced hypertension is an efficacy biomarker in mRCC patients. Indeed, the median PFS and OS were more than four-fold longer for patients with hypertension than for patients without hypertension [22] [23]. Rini *et al*. hypothesized that the susceptibility of normal blood vessels to VEGF blockade, which would lead to hypertension, is linked to the susceptibility of the tumor vessels to VEGF blockade, resulting in a more robust antiangiogenic effect in response to sunitinib treatment, and hence, enhanced clinical outcomes [22].

Given the small number of cases without axitinib-induced hypertension, we were unable to compare the PFS and OS between groups of patients with and without hypertension; however, we suspect that the high frequency of axitinib-induced hypertension in Japanese patients is a key factor that is associated with the long PFS.

Similarly, the frequency of proteinuria (77%) in this study was higher than that reported for studies carried out in western countries (8% - 28%) [6] [10]. Proteinuria is a widely reported side effect that occurs after VEGF signaling is inhibited, and it may reflect severe glomerular damage [24]. The pathogenesis of proteinuria in patients receiving anti-VEGF therapy likely relates to multiple pathways, including post-exercise proteinuria-like syndrome [25], the perturbation of podocyte-endothelial VEGF axis signaling [26] [27], podocyte protein junction downregulation [28], and subacute glomerular thrombotic microangiopathy [24]. On the other hand, no major differences were found between Asian and Caucasian people in relation to axitinib plasma pharmacokinetics during the phase I pharmacokinetic studies [29] [30]. Thus, the reasons underlying the high frequency of proteinuria among Japanese patients treated with axitinib remain unclear.

Although the differences were not significant, the median PFS tended to be longer in patients with axitinib-induced proteinuria (38.8 months) than in those without proteinuria (27.5 months). We consider that careful monitoring of proteinuria and management to control proteinuria might lead to longer PFS and OS.

Hand-foot syndrome and hypothyroidism were also commonly reported AEs in this study, but they were effectively managed with axitinib dose reductions or interruptions and thyroid medications.

The limitations of this study include its retrospective nature and the small number of patients. Furthermore, the duration of the observation period was insufficient to draw definitive conclusions in relation to the prognostic issues.

5. Conclusion

Axitinib as a first-line therapy demonstrated significant efficacy in the treatment of mRCC in Japanese patients. However, the incidence rates of some AEs, including proteinuria and hypertension, were higher in Japanese patients than the patients from western countries. Thus, careful monitoring and management to control these toxicities are important to improve patients' prognoses.

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References

[1] Rini, B.I. (2009) Metastatic Renal Cell Carcinoma: Many Treatment Options, One Patient. *Journal of Clinical Oncology*, **27**, 3225-3234. http://dx.doi.org/10.1200/JCO.2008.19.9836

[2] Motzer, R.J., Hutson, T.E., Tomczak, P., Michaelson, M.D., Bukowski, R.M., Rixe, O., Oudard, S., Negrier, S., Szczylik, C., Kim, S.T., Chen, I., Bycott, P.W., Baum, C.M. and Figlin, R.A. (2007) Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma. *New England Journal of Medicine*, **356**, 115-124. http://dx.doi.org/10.1056/NEJMoa065044

[3] Escudier, B., Eisen, T., Stadler, W.M., Szczylik, C., Oudard, S., Siebels, M., Negrier, S., Chevreau, C., Solska, E., Desai, A.A., Rolland, F., Demkow, T., Hutson, T.E., Gore, M., Freeman, S., Schwartz, B., Shan, M., Simantov, R. and Bukowski, R.M. (2007) Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma. *New England Journal of Medicine*, **356**, 125-134. http://dx.doi.org/10.1056/NEJMoa060655

[4] Rini, B.I., Escudier, B., Tomczak, P., Kaprin, A., Szczylik, C., Hutson, T.E., Michaelson, M.D., Gorbunova, V.A., Gore, M.E., Rusakov, I.G., Negrier, S., Ou, Y.-C., Castellano, D., Lim, H.Y., Uemura, H., Tarazi, J., Cella, D., Chen, C., Rosbrook, B., Kim, S. and Motzer, R.J. (2011) Comparative Effectiveness of Axitinib versus Sorafenib in Advanced Renal Cell Carcinoma (AXIS): A Randomised Phase 3 Trial. *The Lancet*, **37**, 1931-1939. http://dx.doi.org/10.1016/S0140-6736(11)61613-9

[5] Hu-Lowe, D.D., Zou, H.Y., Grazzini, M.L., Hallin, M.E., Wickman, G.R., Amundson, K., Chen, J.H., Rewolinski, D.A., Yamazaki, S., Wu, E.Y., McTigue, M.A., Murray, B.W., Kania, R.S., O'Connor, P., Shalinsky, D.R. and Bender, S.L. (2008) Nonclinical Antiangiogenesis and Antitumor Activities of Axitinib (AG-013736), an Oral, Potent, and Selective Inhibitor of Vascular Endothelial Growth Factor Receptor Tyrosine Kinases 1, 2, 3. *Clinical Cancer Research*, **14**, 7272-7283. http://dx.doi.org/10.1158/1078-0432.CCR-08-0652

[6] Rixe, O., Bukowski, R.M., Michaelson, M.D., Wilding, G., Hudes, G.R., Bolte, O., Motzer, R.J., Bycott, P., Liau, K.F., Freddo, J., Trask, P.C., Kim, S. and Rini, B.I. (2007) Axitinib Treatment in Patients with Cytokine-Refractory Metastatic Renal-Cell Cancer: A Phase II Study. *Lancet Oncology*, **8**, 975-984. http://dx.doi.org/10.1016/S1470-2045(07)70285-1

[7] Rini, B.I., Wilding, G., Hudes, G., Stadler, W.M., Kim, S., Tarazi, J., Rosbrook, B., Trask, P.C., Wood, L. and Dutcher, J.P. (2009) Phase II Study of Axitinib in Sorafenib-Refractory Metastatic Renal Cell Carcinoma. *Journal of Clinical Oncology*, **27**, 4462-4468. http://dx.doi.org/10.1200/JCO.2008.21.7034

[8] Ueda, T., Uemura, H., Tomita, Y., Tsukamoto, T., Kanayama, H., Shinohara, N., Tarazi, J., Chen, C., Kim, S., Ozono, S., Naito, S. and Akaza, H. (2013) Efficacy and Safety of Axitinib versus Sorafenib in Metastatic Renal Cell Carcinoma: Subgroup Analysis of Japanese Patients from the Global Randomized Phase 3 AXIS Trial. *Japanese Journal of Clinical Oncology*, **43**, 616-628. http://dx.doi.org/10.1093/jjco/hyt054

[9] Hutson, T.E., Lesovoy, V., Al-Shukri, S., Stus, V.P., Lipatov, O.N., Bair, A.H., Rosbrook, B., Chen, C., Kim, S. and Vogelzang, N.J. (2013) Axitinib versus Sorafenib as First-Line Therapy in Patients with Metastatic Renal-Cell Carcinoma: A Randomised Open-Label Phase 3 Trial. *Lancet Oncology*, **14**, 1287-1294. http://dx.doi.org/10.1016/S1470-2045(13)70465-0

[10] Rini, B.I., Melichar, B., Ueda, T., Grünwald, V., Fishman, M.N., Arranz, J.A., Bair, A.H., Pithavala, Y.K., Andrews, G.I., Pavlov, D., Kim, S. and Jonasch, E. (2013) Axitinib with or without Dose Titration for First-Line Metastatic Renal-Cell Carcinoma: A Randomised Double-Blind Phase 2 Trial. *Lancet Oncology*, **14**, 1233-1242.

http://dx.doi.org/10.1016/S1470-2045(13)70464-9

[11] Motzer, R.J., Bacik, J., Murphy, B.A., Russo, P. and Mazumdar, M. (2002) Interferon-Alfa as a Comparative Treatment for Clinical Trials of New Therapies against Advanced Renal Cell Carcinoma. *Journal of Clinical Oncology*, **20**, 289-296. http://dx.doi.org/10.1200/JCO.20.1.289

[12] Therasse, P., Arbuck, S.G., Eisenhauer, E.A., Wanders, J., Kaplan, R.S., Rubinstein, L., Verweij, J., Van Glabbeke, M., van Oosterom, A.T., Christian, M.C. and Gwyther, S.G. (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors. *The Journal of the National Cancer Institute*, **92**, 205-216. http://dx.doi.org/10.1093/jnci/92.3.205

[13] National Cancer Institute (2009) Common Terminology Criteria for Adverse Events (Version 4). National Cancer Institute.

[14] Tomita, Y., Uemura, H., Fujimoto, H., Kanayama, H.O., Shinohara, N., Nakazawa, H., Imai, K., Umeyama, Y., Ozono, S., Naito, S. and Akaza, H., Japan Axitinib Phase II Study Group (2011) Key Predictive Factors of Axitinib (AG-013736)-Induced Proteinuria and Efficacy: A Phase II Study in Japanese Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma. *European Journal of Cancer*, **47**, 2592-2602. http://dx.doi.org/10.1016/j.ejca.2011.07.014

[15] National Comprehensive Cancer Network (2015) NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer. National Comprehensive Cancer Network.

[16] Ljungberg, B., Bensalah, K., Bex, A., Canfield, S., Dabestani, S., Hofmann, F., Hora, M., Kuczyk, M.A., Lam, T., Marconi, L., Merseburger, A.S., Mulders, P.F.A., Staehler, M. and Volpe, A. (2013) Guidelines on Renal Cell Carcinoma. European Association of Urology.

[17] Tomita, Y., Shinohara, N., Yuasa, T., Fujimoto, H., Niwakawa, M., Mugiya, S., Miki, T., Uemura, H., Nonomura, N., Takahashi, M., Hasegawa, Y., Agata, N., Houk, B., Naito, S. and Akaza, H. (2010) Overall Survival and Updated Results from a Phase II Study of Sunitinib in Japanese Patients with Metastatic Renal Cell Carcinoma. *Japanese Journal of Clinical Oncology*, **40**, 1166-1172. http://dx.doi.org/10.1093/jjco/hyq146

[18] Atkinson, B.J., Kalra, S., Wang, X., Bathala, T., Corn, P., Tannir, N.M. and Jonasch, E. (2014) Clinical Outcomes for Patients with Metastatic Renal Cell Carcinoma Treated with Alternative Sunitinib Schedules. *The Journal of Urology*, **191**, 611-618. http://dx.doi.org/10.1016/j.juro.2013.08.090

[19] Ohzeki, T., Fukasawa, S., Komaru, A., Namekawa, T., Sato, Y., Takagi, K., Kobayashi, M., Uemura, H., Ichikawa, T. and Ueda, T. (2014) Efficacy of Traditional and Alternative Sunitinib Treatment Schedules in Japanese Patients with Metastatic Renal Cell Carcinoma. *International Journal of Urology*, **21**, 1065-1068. http://dx.doi.org/10.1111/iju.12504

[20] Kondo, T., Takagi, T., Kobayashi, H., Iizuka, J., Nozaki, T., Hashimoto, Y., Ikezawa, E., Yoshida, K., Omae, K. and Tanabe, K. (2014) Superior Tolerability of Altered Dosing Schedule of Sunitinib with 2-Weeks-On and 1-Week-Off in Patients with Metastatic Renal Cell Carcinoma—Comparison to Standard Dosing Schedule of 4-Weeks-On and 2-Weeks-Off. *Japanese Journal of Clinical Oncology*, **44**, 270-277. http://dx.doi.org/10.1093/jjco/hyt232

[21] Seidel, C., Busch, J., Weikert, S., Steffens, S., Fenner, M., Ganser, A., Grunwald, V. (2012) Progression Free Survival of First Line Vascular Endothelial Growth Factor-Targeted Therapy Is an Important Prognostic Parameter in Patients with Metastatic Renal Cell Carcinoma. *European Journal of Cancer*, **48**, 1023-1030. http://dx.doi.org/10.1016/j.ejca.2012.02.048

[22] Rini, B.I., Cohen, D.P., Lu, D.R., Chen, I., Hariharan, S., Gore, M.E., Figlin, R.A., Baum, M.S. and Motzer, R.J. (2011) Hypertension as a Biomarker of Efficacy in Patients with Metastatic Renal Cell Carcinoma Treated with Sunitinib. *Journal of the National Cancer Institute*, **103**, 763-773. http://dx.doi.org/10.1093/jnci/djr128

[23] Rautiola, J., Donskov, F., Peltola, K., Joensuu, H. and Bono, P. (2014) Sunitinib-Induced Hypertension, Neutropenia and Thrombocytopenia as Predictors of Good Prognosis in Metastatic Renal Cell Carcinoma Patients. *BJU International*. (Epub ahead of print)

[24] Izzedine, H., Massard, C., Spano, J.P., Goldwasser, F., Khayat, D. and Soria, J.C. (2010) VEGF Signalling Inhibition-Induced Proteinuria: Mechanisms, Significance and Management. *European Journal of Cancer*, **46**, 439-448. http://dx.doi.org/10.1016/j.ejca.2009.11.001

[25] Gunduz, F., Kuru, O. and Senturk, U.K. (2003) Effect of Nitric Oxide on Exercise-Induced Proteinuria in Rats. *Journal of Applied Physiology*, **95**, 1867-1872. http://dx.doi.org/10.1152/japplphysiol.00599.2003

[26] Schrijvers, B.F., Flyvbjerg, A. and De Vriese, A.S. (2004) The Role of Vascular Endothelial Growth Factor (VEGF) in Renal Pathophysiology. *Kidney International*, **65**, 2003-2017. http://dx.doi.org/10.1111/j.1523-1755.2004.00621.x

[27] Kamba, T., Tam, B.Y., Hashizume, H., Haskell, A., Sennino, B., Mancuso, M.R., Norberg, S.M., O'Brien, S.M., Davis, R.B., Gowen, L.C., Anderson, K.D., Thurston, G., Joho, S., Springer, M.L., Kuo, C.J. and McDonald, D.M. (2006) VEGF-Dependent Plasticity of Fenestrated Capillaries in the Normal Adult Microvasculature. *American Journal of Physiology Heart and Circulatory Physiology*, **290**, H560-H576. http://dx.doi.org/10.1152/ajpheart.00133.2005

[28] Garovic, V.D., Wagner, S.J., Petrovic, L.M., Gray, C.E., Hall, P., Sugimoto, H., Kalluri, R. and Grande, J.P. (2007) Glomerular Expression of Nephrin and Synaptopodin, but Not Podocin, Is Decreased in Kidney Sections from Women with Preeclampsia. *Nephrology, Dialysis, Transplantation*, **22**, 1136-1143. http://dx.doi.org/10.1093/ndt/gfl711

[29] Pithavala, Y.K., Tortorici, M., Toh, M., Garrett, M., Hee, B., Kuruganti, U., Ni, G. and Klamerus, K.J. (2010) Effect of Rifampin on the Pharmacokinetics of Axitinib (AG-013736) in Japanese and Caucasian Healthy Volunteers. *Cancer Chemotherapy and Pharmacology*, **65**, 563-570. http://dx.doi.org/10.1007/s00280-009-1065-y

[30] Fujiwara, Y., Kiyota, N., Chayahara, N., Suzuki, A., Umeyama, Y., Mukohara, T. and Minami, H. (2012) Management of Axitinib (AG-013736)-Induced Fatigue and Thyroid Dysfunction, and Predictive Biomarkers of Axitinib Exposure: Results from Phase I Studies in Japanese Patients. *Investigational New Drugs*, **30**, 1055-1064. http://dx.doi.org/10.1007/s10637-011-9637-1