Leukopenia as a Biomarker of Sunitinib Outcome in Advanced Renal Cell Carcinoma

TETSUO FUJITA, YOJI WAKATABE, KAZUMASA MATSUMOTO, KEN-ICHI TABATA, KAZUNARI YOSHIDA and MASATSUGU IWAMURA

Department of Urology, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan

Abstract. *Background: Sunitinib is known to cause a variety of adverse events. The aim of the present study was to investigate the prognostic significance of leukopenia for patients with advanced renal cell carcinoma (RCC) treated with sunitinib. Patients and Methods: Between December 2008 and January 2012, 44 consecutive patients with advanced RCC were treated with sunitinib. Adverse events that occurred during the study were identified. Cox proportional hazards regression analysis estimated the relative importance of the predictive factors for progression-free survival (PFS). Results: On multivariate analysis, leukopenia was a significant predictor of PFS (p=0.0185). The cohort with leukopenia comprised of 36 patients (81.8%) and the cohort without leukopenia of 8 patients (18.2%). Patients with leukopenia had a significantly higher response rate (p=0.0062) and significantly longer PFS (p<0.0001) compared to patients without leukopenia. Conclusion: Leukopenia is an independent, significant prognostic indicator for patients with advanced RCC treated with sunitinib.*

Sunitinib malate (Sutent, Pfizer Inc., New York, NY, USA) is an orally-administered, multi-target inhibitor of tyrosine kinases, including vascular endothelial growth factor receptor, platelet-derived growth factor receptor, phosphorylation of stem cell factor receptor, Fms-like tyrosine kinase-3, colony-stimulation factor-1 receptor, and RET. Sunitinib is approved worldwide for the treatment of advanced renal cell carcinoma (RCC). In a randomized, multi-center, phase III trial, 750 patients with previously-untreated metastatic RCC were enrolled to receive either sunitinib or interferon-alpha (IFN-α). Sunitinib was found to be superior to IFN-α with respect to objective response rate (47% *vs*. 12%), progression-free survival (PFS) (median 11.0 *vs*. 5.0 months), and overall survival (OS) (median 26.4 *vs*. 21.8 months) (1, 2). Despite its superior efficacy, sunitinib has been also associated with more frequent treatment-related adverse events compared to IFN-α (1, 2). Key clinical adverse events of sunitinib were diarrhea (61%), fatigue (54%), hypertension (30%), stomatitis (30%), hand-foot syndrome (29%), and asthenia (20%) (2). Abnormal laboratory findings for patients treated with sunitinib included leukopenia (78%), anemia (79%), increased creatinine (70%), and thrombocytopenia (68%) (2).

The need to identify molecular and clinical markers predicting the efficacy sunitinib is urgent. Several authors have recently shown that the treatment-related adverse events hypertension and hypothyroidism were significantly associated with outcomes of sunitinib treatment (3-6). The correlation between selected treatment-related adverse event and efficacy of sunitinib will be informative. Sunitinib has been related to a variety of adverse events. To investigate the biomarker from these treatment-related adverse events will be important, as well as adverse event monitoring and management. Therefore, we herein evaluated the prognostic relevance of selected treatment-related adverse events using multivariate analysis, and identified an independent biomarker of efficacy in patients with advanced RCC treated with sunitinib.

Patients and Methods

Patients and treatment. Forty-four consecutive patients with advanced RCC treated with sunitinib between December 2008 and January 2012 were enrolled in the present study. Eligible patients had measurable tumors, metastatic or primary. All patients underwent surgical treatment or biopsy of the primary lesion and had histologically proven RCC. The sample comprised of 32 men and 12 women with a median age of 63.5 years (range=36-80 years) at the time of sunitinib initiation. In general, 50 mg sunitinib were administered orally once daily in a 6-week cycle consisting of 4 weeks of treatment followed by 2 weeks without treatment. Response and progression were assessed by the treating physician

Correspondence to: Tetsuo Fujita, MD, Ph.D., Department of Urology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan. Tel: +81 427789091, Fax: +81 427789374, e-mail: tfujita@cd5.so-net.ne.jp

Key Words: Renal cell carcinoma, sunitinib, leukopenia, survival.

based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, with computed tomography or magnetic resonance imaging performed every 4 to 10 weeks. Adverse events were evaluated by means of physical examination and laboratory assessments such as hematological and serum chemistry every 2 to 4 weeks during treatment with sunitinib and according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

Prognostic relevance of selected adverse events. Patients' charts were retrospectively reviewed. Adverse events that occurred during the study were identified; hypertension, hand-foot syndrome, stomatitis, diarrhea, fatigue, altered taste, edema, nausea, fever, cholecystitis, enteritis, nasal bleeding, leukopenia, anemia, thrombocytopenia, increased creatinine, liver dysfunction, increased alkaline phosphatase, increased lipase, hypothyroidism, and proteinuria. Univariate and multivariate Cox proportional hazards regression analysis estimated the relative importance of the predictive factors for PFS.

Assessment of prognostic significance of leukopenia. Cases of leukopenia that occurred as a treatment-related adverse event during the study period were identified. PFS was analyzed for patients who developed leukopenia as well as for those who did not.

Statistical analysis. The groups were analyzed using the *t*-test for differences of means between groups. The Chi-square test was used to evaluate differences for categorical variables. Non-parametric estimates of survival were performed using Kaplan-Meier curves. Survival curves were generated on the basis of PFS. Log-rank tests were used for statistical comparisons. Effects on survival were assessed with univariate and multivariate regression using the Cox proportional hazards model. All analyses were carried out with StatView, version 5.0 (SAS Institute, Cary, NC, USA), and $p<0.05$ was considered statistically significant.

Results

Patients' characteristics. The clinical characteristics of all patients treated with sunitinib are summarized in Table I. The median follow-up period was 7.5 months (range=1–38 months). Of the 44 patients, 42 (95.5%) had clear-cell RCC and 2 (4.5%) had papillary RCC. Thirty-five patients (79.5%) had previously undergone nephrectomy and the remaining 9 patients (20.5%) received sunitinib as pre-surgical or neoadjuvant treatment. Twenty-three patients (52.3%) had received prior immunotherapy, and 15 (34.1%) had received sorafenib tosilate (Nexavar, Bayer Pharmaceuticals Corporation, West Haven, CT, USA). Nineteen patients (43.2%) received first-line treatment, 12 (27.3%) second-line, and 13 (29.5%) third-line. The median relative dose intensity (RDI) of sunitinib was 62.2% (range=25-100%).

Efficacy of sunitinib. Overall, 11 patients (25.0%) demonstrated a partial response (PR) to treatment and 13 patients (29.5%) had stable disease (SD), according to the RECIST criteria. Median PFS was 12.0 months.

Table I. *Patients' characteristics*.

Characteristic	N	Frequency, %
Gender		
Male	32	72.7
Female	12	27.3
Age, years		
Median	63.5	
Range	36-80	
ECOG PS		
0	31	70.5
≥1	13	29.5
MSKCC risk classification		
Favorable	8	18.2
Intermediate	25	56.8
Poor	11	25.0
Histological classification		
Clear-cell	42	95.5
Papillary	2	4.5
Prior nephrectomy		
Yes	35	79.5
No	9	20.5
Prior immunotherapy		
IFN-α	14	31.8
IL-2 and IFN-α	9	20.5
Prior targeted-therapy		
Sorafenib	15	34.1
Metastatic sites		
Lung	34	77.3
Bone	15	34.1
Lymph nodes	10	22.7
Brain	4	9.1
Pancreas	4	9.1
Adrenal	4	9.1
Skin	3	6.8
Liver	3	6.8
Kidney	2	4.5
Local	2	4.5
Prostate	1	2.3
No of metastatic sites		
1	17	38.6
≥2	26	59.1
Treatment		
First-line	19	43.2
Second-line	12	27.3
Third-line	13	29.5
RDI, %		
Median	62.2	
Range	25-100	

ECOG, Eastern Cooperative Oncology Group; PS, performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; IFN-α, interferon-alpha; IL-2, interleukin-2; RDI, relative dose intensity.

Adverse events. Selected treatment-related adverse events that occurred during the study are summarized in Table II. The most frequent adverse event was thrombocytopenia (93.2%). The NCI CTCAE grade 3 adverse events that occurred were hypertension, hand-foot syndrome, stomatitis,

Table II. *Selected treatment-related adverse events.*

	Total		Maximum NCI CTCAE Grade					
			Grade 1		Grade 2		Grade 3	
Adverse event	N	%	N	%	N	%	N	%
Hypertension	22	50.0	4	9.1	16	36.4	2	4.5
Hand-foot syndrome	21	47.7	6	13.6	9	20.5	6	13.6
Stomatitis	20	45.5	7	15.9	11	25.0	2	4.5
Fatigue	17	38.6	7	15.9	7	15.9	3	6.8
Diarrhea	16	36.4	10	22.7	6	13.6	–	–
Altered taste	16	36.4	12	27.3	4	9.1	–	–
Edema	11	25.0	4	9.1	6	13.6	1	2.3
Nausea	6	13.6	1	2.3	1	2.3	4	9.1
Fever	3	6.8	3	6.8	–	–	–	–
Cholecystitis	3	6.8	–	–	–	–	3	6.8
Enteritis	1	2.3	–	–	–	–	1	2.3
Nasal bleeding	1	2.3	–	–	–	–	1	2.3
Laboratory abnormalities								
Leukopenia	36	81.8	7	15.9	17	38.6	12	27.3
Anemia	34	77.3	14	31.8	16	36.4	4	9.1
Thrombocytopenia	41	93.2	12	27.3	12	27.3	17	38.6
Increased creatinine	19	43.2	10	22.7	8	18.2	1	2.3
Increased alanine transaminase	2	4.5	–	–	2	4.5	–	–
Increased alkaline phosphatase	2	4.5	–	–	1	2.3	1	2.3
Increased lipase	1	2.3	–	–	1	2.3	–	–
Hypothyroidism	25	56.8	4	9.1	21	47.7	–	–
Proteinuria	29	65.9	14	31.8	11	25.0	4	9.1

NCI CTCAE, National Cancer Institute Commn Terminology Criteria for Adverse Events.

fatigue, edema, nausea, cholecystitis, enteritis, nasal bleeding, leukopenia, anemia, thrombocytopenia, increased creatinine, increased alkaline phosphatase, and proteinuria.

Prognostic relevance of selected adverse events. To assess the prognostic relevance of selected adverse events, univariate and multivariate Cox proportional hazards regression analysis was performed (Table III). On univariate analyses, significantly longer PFS was predicted by hypertension (hazard ratio [HR]=0.368; 95% confidence interval [CI]=0.171-0.792; p=0.0105), hand-foot syndrome (HR=0.373; 95%CI=0.174-0.796; p=0.0108), altered taste (HR=0.460; 95%CI=0.213-0.994; p=0.0483), leukopenia (HR=0.171; 95%CI=0.065-0.451; p=0.0004), increased creatinine (HR=0.4; 95%CI=0.184-0.870; p=0.0208), and hypothyroidism (HR=0.414; 95%CI=0.194-0.882; p=0.0223).

Variables in the multivariate analysis included hypertension, hand-foot syndrome, altered taste, leukopenia, increased creatinine, and hypothyroidism (Table III). After adjustment for differences in these variables, leukopenia was a significant predictor of PFS (HR=0.280; 95%CI=0.097-0.807; p=0.0185) (Table III).

Prognostic significance of leukopenia. According to the significant result from prognostic relevance of selected adverse events by multivariate Cox proportional hazards regression analysis, patients were grouped into two cohorts: those with leukopenia and those without leukopenia. Various grades of leukopenia occurred in 36 (81.8%) of the 44 patients: grade 1 in 7 (15.9%) patients, grade 2 in 17 (38.6%) patients, and grade 3 in 12 (27.3%) patients (Table II). The cohort with leukopenia comprised of 28 men and 8 women with a median age of 63.5 years (range=46-80 years). The cohort without leukopenia comprised of 4 men and 4 women with a median age of 63 years (range=36-71 years). The cohort with leukopenia demonstrated significantly higher rates of Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 and Memorial Sloan-Kettering Cancer Center (MSKCC) non-poor risk patients (p=0.0018 and 0.0191, respectively) (Table IV). The response rate was 63.9% for the cohort with leukopenia and 12.5% for the cohort without leukopenia; this was a statistically significant difference (p=0.0062) (Table IV).

Non-parametric estimates of PFS were analyzed with Kaplan-Meier curves for both cohorts. The median PFS for the

Table III. *Univariate and multivariate analyses with Cox proportional hazards model of selected adverse events for predicting progression-free survival.*

	Univariate		Multivariate	
Variable	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Hypertension	0.368 (0.171-0.792)	0.0105	0.446 (0.179-1.110)	0.0825
Hand-foot syndrome	0.373 (0.174-0.796)	0.0108	0.558 (0.215-1.445)	0.2292
Stomatitis	0.593 (0.283-1.243)	0.1665		
Fatigue	0.663 (0.313-1.404)	0.2834		
Diarrhea	0.789 (0.381-1.635)	0.5245		
Altered taste	0.460 (0.213–0.994)	0.0483	0.787 (0.314-1.976)	0.6107
Edema	0.669 (0.287-1.563)	0.3533		
Nausea	0.879 (0.302-2.553)	0.8123		
Fever	1.084 (0.254-4.636)	0.9130		
Cholecystitis	1.299 (0.390-4.329)	0.6705		
Enteritis	0.787 (0.106-5.859)	0.8149		
Nasal bleeding	1.387 (0.185-10.378)	0.7497		
Abnormal laboratory findings				
Leukopenia	0.171 (0.065-0.451)	0.0004	0.280 (0.097-0.807)	0.0185
Anemia	1.356 (0.551-3.339)	0.5078		
Thrombocytopenia	0.293 (0.062-1.378)	0.1201		
Increased creatinine	0.400 (0.184-0.870)	0.0208	0.491 (0.210-1.147)	0.1004
Increased alanine transaminase	1.782 (0.233-13.645)	0.5782		
Increased alkaline phosphatase	1.565 (0.367-6.676)	0.5451		
Increased lipase	0.413 (0.052-3.317)	0.4057		
Hypothyroidism	0.414 (0.194-0.882)	0.0223	1.211 (0.450-3.260)	0.7041
Proteinuria	1.000 (0.466-2.145)	0.9997		

HR, Hazard ratio; CI, confidence interval.

cohort without leukopenia was 1.0 months. In contrast, the median PFS for the cohort with leukopenia was significantly longer at 18.0 months (log-rank $p<0.0001$) (Figure 1).

To assess the prognostic significance of selected variables, univariate and multivariate Cox proportional hazards regression analysis was performed (Table V). On univariate analyses, significantly longer PFS was predicted by ECOG PS 0 (HR=0.286; 95%CI=0.133-0.616; $p=0.0014$) and leukopenia (HR=0.171; 95%CI=0.065-0.451; $p=0.0004$). After adjustment for differences in these variables, leukopenia was an independent, significant predictor of PFS (HR=0.281; 95%CI=0.094-0.841; $p=0.0232$).

Discussion

Biomarkers predictive for efficacy of sunitinib in patients with advanced RCC are a subject of investigation. Selected severe treatment-related adverse events are among the candidates with potential prognostic value. If adverse events depend on the degree of systemic exposure to sunitinib, on which clinical efficacy also depends, adverse events might predict efficacy of sunitinib (7). Associations have been reported between clinical response to sunitinib and hypertension or hypothyroidism (3-6).

Rini *et al.* (3) demonstrated that sunitinib-related hypertension is associated with improved clinical outcomes. This analysis included pooled data from four clinical trials of 4,915 patients with metastatic RCC who were treated with sunitinib. Patients with sunitinib-induced hypertension defined as maximum systolic blood pressure ≥140 mmHg had significantly better outcomes than those without treatment-induced hypertension, with regard to objective response rate (54.8% *vs.* 8.7%), median PFS (12.5 *vs.* 2.5 months), and median OS (30.9 *vs.* 7.2 months) ($p<0.001$ for all) (3). Bono *et al.* reported that sunitinib-induced hypertension, defined as persistent blood pressure >150/100 mmHg was associated with frequent tumor response ($p=0.001$), significantly longer disease progression ($p=0.0003$), and significantly longer OS ($p=0.001$) (4). On multivariate analysis including the variables of pre-treatment hemoglobin, pretreatment calcium level, PS, time from diagnosis to onset of metastasis, and treatment-related hypertension, hypertension was an independent predictor of PFS (HR=0.21; 95%CI=0.076-0.59; $p=0.0030$) (4). Szmit *et al.* reported that patients who developed hypertension related to sunitinib treatment experienced significantly longer PFS and OS compared to those who did not develop hypertension ($p<0.00001$) (5). Patients treated with at least three anti-

Table IV. *Patients' characteristics grouped by leukopenia as treatment-related adverse event.*

	With leukopenia	Without leukopenia	*p*-Value
N (%)	36 (81.8)	8 (18.2)	
Gender, N (%)			0.1106
Male	28 (77.8)	4 (50.0)	
Female	8 (22.2)	4 (50.0)	
Age, years			0.2167
Median	63.5	63	
Range	46-80	36-71	
Mean±standard deviation	64.3±8.1	60.0±11.8	
ECOG PS, N (%)			0.0018
0	29 (80.6)	2 (25.0)	
≥1	7 (19.4)	6 (75.0)	
MSKCC risk classification, N (%)			0.0191
Favorable	8 (22.2)	0 (0)	
Intermediate	22 (61.1)	3 (37.5)	
Poor	6 (16.7)	5 (62.5)	
Prior nephrectomy, N (%)			0.1864
Yes	30 (83.3)	5 (62.5)	
No	6 (16.7)	3 (37.5)	
T stage, N (%)			0.0635
T1 or T2	22 (61.1)	2 (25.0)	
≥T3	14 (38.9)	6 (75.0)	
Grade, N (%)			0.4947
1 or 2	10 (27.8)	1 (12.5)	
3	23 (63.9)	5 (62.5)	
Prior immunotherapy, N			0.8869
IFN-α	13	1	
IL-2 and IFN-α	6	3	
Prior targeted therapy, N			0.5487
Sorafenib	13	2	
Metastatic sites, N			
Lung	27	7	
Bone	11	4	
Lymph nodes	9	1	
Brain	3	1	
Pancreas	4	–	
Adrenal	3	1	
Skin	1	2	
Liver	2	1	
Kidney	2	–	
Local	2	–	
Prostate	1	–	
No. of metastatic sites, N (%)			0.3116
1	16 (44.4)	2 (25.0)	
≥2	20 (55.6)	6 (75.0)	
Treatment, N (%)			0.9084
First-line	15 (41.6)	4 (50.0)	
Second-line	10 (27.8)	2 (25.0)	
Third-line	11 (30.6)	2 (25.0)	
Response, N (%)			0.0062
PR+SD	23 (63.9)	1 (12.5)	
RDI, %			0.2699
Median	63.3	54.2	
Range	27.1–100	25–75	
Mean±standard deviation	63.2±19.6	54.7±19.3	

ECOG, Eastern Cooperative Oncology Group; PS, performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; IFN-α, interferon-alpha; IL-2, interleukin-2; PR, partial response; SD, stable disease; RDI, relative dose intensity.

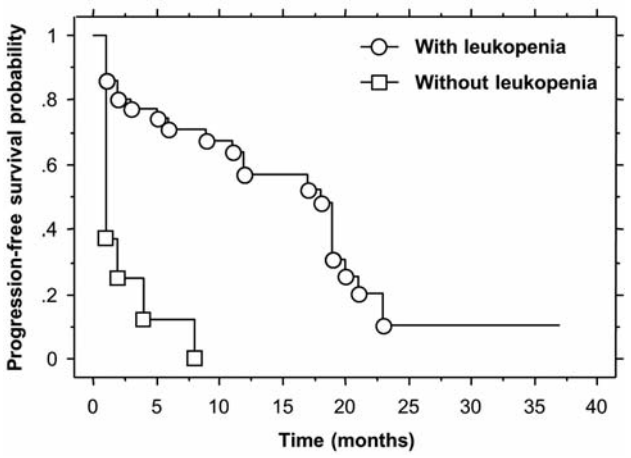

Figure 1. *Kaplan-Meier estimate of progression-free survival (PFS). The cohort with leukopenia had significantly longer PFS than the cohort without leukopenia (median 18.0 vs. 1.0 months, log-rank p<0.0001).*

hypertensive drugs experienced significantly longer PFS (p=0.00002) and OS (p=0.00001) compared to patients who received one or two medications or patients who received no medications (5).

Treatment-related hypothyroidism has also been reported to be a useful predictor of PFS for metastatic RCC patients undergoing treatment with sunitinib (6). Out of the 52 patients with metastatic RCC treated with sunitinib, 13 (25.0%) developed hypothyroidism during treatment. Hypothyroidism was associated with longer PFS (p=0.032) (6).

Although leukopenia is one of the major abnormal laboratory findings indicative of a treatment-related adverse event in patients treated with sunitinib, no previous study has addressed the prognostic value of leukopenia in these patients. In the present study, 81.8% of patients developed leukopenia as a treatment-related adverse event. However, a significantly higher response rate and longer PFS were observed in the cohort with leukopenia (p=0.0062 and p<0.0001, respectively). A univariate Cox proportional hazards model revealed that treatment-related hypertension, hand-foot syndrome, altered taste, leukopenia, increased creatinine, and hypothyroidism were significantly associated with longer PFS (p=0.0105, 0.0108, 0.0483, 0.0004, 0.0208, and 0.0223, respectively). These hypertension and hypothyroidism results support previous reports. Multivariate analysis demonstrated that leukopenia was a significant predictor of PFS (HR=0.280; 95%CI=0.097-0.807; p=0.0185). This association between survival outcome of sunitinib treatment and a treatment-related adverse event is a novel finding. There were no significant differences between neutropenia or lymphopenia and PFS in sub-group analyses (p=0.1819 or 0.8319,

Table V. *Univariate and multivariate analyses with Cox proportional hazards model for predicting progression-free survival.*

	Univariate		Multivariate	
Variable	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
ECOG PS 0	0.286 (0.133-0.616)	0.0014	0.430 (0.174-1.063)	0.0676
MSKCC non-poor	0.485 (0.229-1.029)	0.0595		
Leukopenia	0.171 (0.065-0.451)	0.0004	0.281 (0.094-0.841)	0.0232

HR, Hazard ratio; CI, confidence interval. ECOG, Eastern Cooperative Oncology Group; PS, performance status; MSKCC, Memorial Sloan-Kettering Cancer Center.

respectively). Furthermore, no significant association was found between RDI and leukopenia (p=0.2699). Interestingly, 91.7% of patients developed leukopenia in the first cycle of sunitinib treatment. This fact suggests that if leukopenia occurs, it will be an early biomarker of sunitinib effectiveness.

Previously, Rixe *et al*. retrospectively analyzed the putative correlation between sunitinib response and adverse events in 32 patients with metastatic RCC treated with sunitinib (8). The pattern of toxicity was compared among responders and non-responders. In univariate analysis, a higher response rate was found in patients with stomatitis (p=0.0015), fatigue (p=0.0019), hypertension (p=0.02), testicular erythema (p=0.04), or hair depigmentation (p=0.042). Using multivariate analysis with logistic regression, they found that the onset or worsening of hypertension was the single independent predictor of improved clinical response (HR=2.33; 95%CI=1.69–3.22; p=0.009) (8). Although this is the first report to use multivariate analysis to evaluate the correlation between sunitinib response and treatment-related adverse events, the end-point was either responder or non-responder. Therefore, we believe that ours is the first report of a significant association between PFS and selected treatment-related adverse events based on multivariate analysis.

ECOG PS and MSKCC risk classification are well-known as major prognostic or predictive factors in patients with advanced RCC. In the present study, the cohort without leukopenia had significant worse characteristics such as ECOG PS≥1 and MSKCC poor risk (p=0.0018 and 0.0191, respectively). However, a univariate Cox proportional hazards model revealed that ECOG PS 0 and leukopenia were significantly associated with longer PFS (p=0.0014 and 0.0004, respectively). And multivariate analysis demonstrated that leukopenia was an independent, significant predictor of PFS (HR=0.281; 95%CI=0.094–0.841; p=0.0232). Based on these significant results of multivariate analyses, we concluded that leukopenia is an independent biomarker of efficacy in patients with advanced RCC treated with sunitinib.

Racial differences associated with treatment-related adverse events should be considered. A Japanese phase II study showed that Japanese patients had a higher incidence of hematological adverse events than Western patients (9, 10). Leukopenia of any grade was reported in 22 patients (88.0%) in the 25 first-line patients and 22 patients (84.6%) of the 26 pre-treated patients (10). A higher incidence of leukopenia was observed in Japanese patients (86%) (10) than in Western patients (78%) (2).

The mechanism by which sunitinib induced leukopenia and the reason for the significant association with longer PFS require further elucidation. Genomic mechanisms of myelosuppression induced by sunitinib have been reported (11, 12). And the relationship between polymorphisms and the development of sunitinib toxicity, including leukopenia, has been reported (13). However, based on these reports it is difficult to explain why leukopenia is a significant predictor. Further investigation is necessary to identify the mechanisms responsible for the significant association between therapeutic efficacy of sunitinib and not only leukopenia but also other treatment-related adverse events in patients with advanced RCC.

In conclusion, leukopenia as a treatment-related adverse event is an independent, significant prognostic indicator for patients with advanced RCC treated with sunitinib. If leukopenia occurred during sunitinib treatment, PFS was significantly better. Leukopenia is a potential biomarker to predict sunitinib efficacy.

References

1 Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM and Figlin RA: Sunitinib *versus* interferon alfa in metastatic renal-cell carcinoma. N Engl J Med *356*: 115-124, 2007.

2 Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA, Garcia-del-Muro X, Sosman JA, Solska E, Wilding G, Thompson JA, Kim ST, Chen I, Huang X and Figlin RA: Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol *27*: 3584-3590, 2009.

3 Rini BI, Cohen DP, Lu DR, Chen I, Hariharan S, Gore ME, Figlin RA, Baum MS and Motzer RJ: Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst *103*: 763-773, 2011.
4 Bono P, Rautiola J, Utriainen T and Joensuu H: Hypertension as predictor of sunitinib treatment outcome in metastatic renal cell carcinoma. Acta Oncologica *50*: 569-573, 2011.
5 Szmit S, Langiewicz P, Żołnierek J, Nurzyński P, Zaborowska M, Filipiak KJ, Opolski G and Szczylik C: Hypertension as a predictive factor for survival outcomes in patients with metastatic renal cell carcinoma treated with sunitinib after progression on cytokines. Kidney Blood Press Res *35*: 18-25, 2012.
6 Riesenbeck LM, Bierer S, Hoffmeister I, Köpke T, Papavassilis P, Hertle L, Thielen B and Herrmann E: Hypothyroidism correlates with a better prognosis in metastatic renal cancer patients treated with sorafenib or sunitinib. World J Urol *29*: 807-813, 2011.
7 Yuasa T, Takahashi S, Hatake K, Yonese J and Fukui I: Biomarkers to predict response to sunitinib therapy and prognosis in metastatic renal cell cancer. Cancer Sci *102*: 1949-1957, 2011.
8 Rixe O, Billemont B and Izzedine H: Hypertension as a predictive factor of sunitinib activity. Ann Oncol *18*: 1117, 2007.
9 Uemura H, Shinohara N, Yuasa T, Tomita Y, Fujimoto H, Niwakawa M, Mugiya S, Miki T, Nonomura N, Takahashi M, Hasegawa Y, Agata N, Houk B, Naito S and Akaza H: A phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma: insights into the treatment, efficacy and safety. Jpn J Clin Oncol *40*: 194-202, 2010.
10 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: Overall survival and updated results from a phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma. Jpn J Clin Oncol *40*: 1166-1172, 2010.
11 Kumar R, Crouthamel MC, Rominger DH, Gontarek RR, Tummino PJ, Levin RA and King AG: Myelosuppression and kinase selectivity of multikinase angiogenesis inhibitors. Br J Cancer *101*: 1717-1723, 2009.
12 van Erp NP, Mathijssen RH, van der Veldt AA, Haanen JB, Reyners AK, Eechoute K, Boven E, Wessels JA, Guchelaar HJ and Gelderblom H: Myelosuppression by sunitinib is flt-3 genotype dependent. Br J Cancer *103*: 757-758, 2010.
13 van Erp NP, Eechoute K, van der Veldt AA, Haanen JB, Reyners AK, Mathijssen RH, Boven E, van der Straaten T, Baak-Pablo RF, Wessels JA, Guchelaar HJ and Gelderblom H: Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. J Clin Oncol *27*: 4406-4412, 2009.

Received March 22, 2014
Revised May 26, 2014
Accepted May 27, 2014