

# Negative Effect of Immediate Sunitinib Interruption on Survival in Patients With Metastatic Renal Cell Carcinoma

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**Abstract.** *Background: Treatment modification due to adverse events reduces the dose intensity in cancer treatment. The prognostic impact of sunitinib treatment interruption within the initial period of therapy for metastatic renal cell carcinoma (mRCC) remains unknown. Patients and Methods: We retrospectively evaluated 97 patients with mRCC treated with first-line sunitinib treatment. The patients were classified into two groups according to the presence of treatment interruption (TI) within the initial two cycles. The prognostic impact of TI was analyzed using the Kaplan–Meier method and log-rank test, and multivariate analyses using the Cox proportional hazard model. Results: Thirty-eight patients (39.2%) experienced an immediate TI. The median progression-free (PFS) and overall (OS) survival were significantly shorter in patients with a TI than in those without (PFS= 6.54 vs. 11.3 months,  $p=0.0246$ ; OS=16.9 vs. 30.0 months,  $p=0.0420$ ). Multivariate analyses for PFS and OS showed that TI was an independent factor predicting poorer PFS (hazard ratio(HR)=1.93,  $p=0.0141$ ) and OS (HR=2.09,  $p=0.0102$ ). In addition, the relative dose intensity within the initial two cycles was significantly lower in patients with a TI than in those without (52.7% vs. 75.0%,  $p<0.0001$ ). Conclusion: This study showed the significantly negative effect of immediate TI on survival of patients under sunitinib treatment for mRCC. Therefore, the careful monitoring of patient tolerability is required in order to maintain therapeutic efficacy in the early phase of sunitinib treatment.*

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*Key Words:* RCC, TKI, tyrosine kinase inhibitor, adverse event, toxicity, dose-limiting toxicity.

Treatment modification, including schedule and dosage change, is needed in a subset of patients with drug-induced adverse events (AEs) during cancer treatment. These dose-limiting toxicities (DLTs) reduce the dose intensity, resulting in impaired therapeutic efficacy (1). Therefore, it is important to balance treatment intensity and patient tolerability.

Sunitinib is a molecular-targeted agent commonly used for treatment of metastatic renal cell carcinoma (mRCC) (2, 3); however, an unsolved usage issue is its strong drug-induced toxicity (4, 5). Several studies reported that the reduced dose intensity caused by DLTs in the early phase of sunitinib treatment resulted in poor prognosis (6-9). However, clinical information regarding the prognostic association of treatment modification types, especially treatment interruption (TI) expected to cause a significant decrease in dose intensity, is limited.

Therefore, we retrospectively investigated the effect of treatment interruption developing within the early phase of sunitinib therapy on survival in patients with mRCC.

## Patients and Methods

*Study design.* Between January 2007 and June 2018, 132 patients were treated with first-line sunitinib for mRCC (Figure 1). Of the 132 patients, two patients who had received cytokine therapy before sunitinib treatment were excluded, as were 26 patients whose sunitinib treatment was performed as neoadjuvant or adjuvant therapy. From the 104 remaining patients, seven patients whose data were unavailable owing to loss during follow-up were further excluded. The remaining 97 patients were evaluated in this single-center retrospective study.

The 97 patients were divided into two groups according to the presence of an immediate treatment interruption (TI); 38 and 59 patients were classified into the TI and without TI groups, respectively (Figure 1). We further classified the 59 patients in the no TI group according to the presence of an immediate dose reduction; 22 and 37 patients were classified into the dose reduction and no modification groups, respectively. In this study, patients with at least one interruption, regardless of the presence of dose reduction, were classified into the TI group. Patients categorized

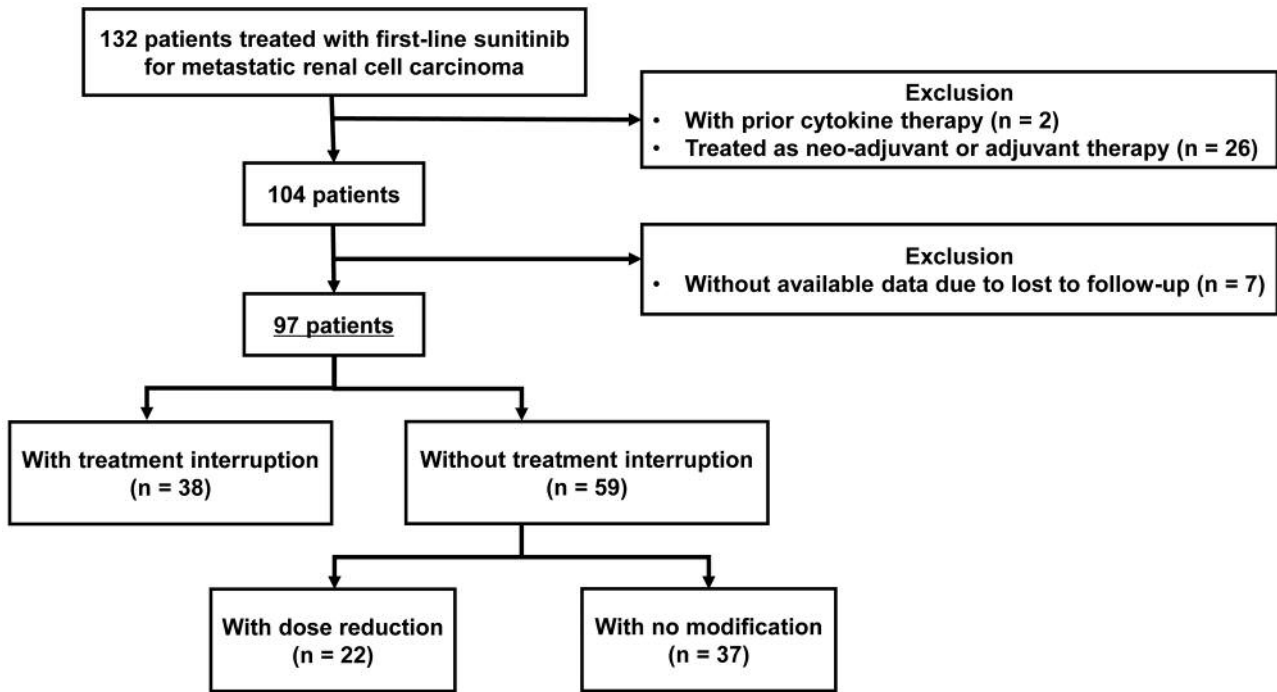


Figure 1. Patient selection and study design.

into the dose reduction group did not experience any TI during sunitinib therapy. All immediate treatment modification was defined as developing within the initial two cycles of sunitinib treatment.

All study procedures were approved by the Institutional Review Board of Tokyo Women’s Medical University and were in accordance with the Declaration of Helsinki (ID: 4551).

**Sunitinib treatment protocol.** The sunitinib treatment protocol adopted at our Department was previously reported (6, 10). Briefly, we administered sunitinib under a 2-weeks-on/1-week-off treatment schedule for most patients based on our previous study (6, 11). The standard initial dose was 50 mg/day. Reduction of the initial dose was considered when patients met the following criteria: (i) Age >65 years, (ii) serum creatinine level >2.0 mg/dl, and (iii) body weight <50 kg. When one of these three factors was present, the initial dose was reduced to 37.5 mg/day. When two or more factors were present, the initial dose was reduced to 25 mg/day. The dose was increased by 12.5 mg/day until we determined the highest dose a patient was able to tolerate, although the dose never exceeded 50 mg/day.

Treatment was continued until disease progression or intolerable AEs were observed.

Post-treatment follow-up scans obtained using plain or contrast-enhanced computed tomography of the chest, abdomen, and pelvis were performed every 2-3 months of treatment according to the patient’s condition, as previously reported (12).

**AE evaluation.** AEs were assessed according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0 (13), and treatment modifications, including reduction or interruption, were subsequently performed as necessary.

When a patient experienced multiple AEs, the highest grade of AE was recorded for each patient. Additionally, when a patient underwent both dose reduction and TI, the interruption was evaluated as a dose modification.

**Statistical analysis.** Continuous variables were analyzed using the Mann–Whitney *U*-test or the Kruskal–Wallis test, and categorical variables were analyzed using the chi-squared or Fisher’s exact test. Progression-free (PFS) and overall (OS) survival were defined as the time from therapy initiation to the date of progression, and to the date of death from any cause, respectively. Survival was calculated using the Kaplan–Meier survival curve method and compared using the log-rank test. Univariate and multivariate analyses using the Cox proportional hazard regression models were used to identify survival factors. The survival risk was expressed as a hazard ratio (HR) and 95% confidence interval (CI). All analyses were performed using JMP software (version 14; SAS Institute Inc., Cary, NC, USA), and values of  $p < 0.05$  were considered statistically significant.

**Results**

**Patient background.** Table I shows the comparison of patient backgrounds according to TI presence. The female patient rate was significantly higher (44.7% vs. 22.0%,  $p=0.0182$ ) and the frequency of patients on the 4-weeks-on/2-weeks-off treatment schedule had a tendency to be higher (42.1% vs. 23.7%,  $p=0.0559$ ) in patients with TI than in those without. In addition, the median RDI during the initial two cycles was significantly lower in patients with TI [52.7% (95% CI=37.5-

Table I. Patient background information.

	Whole cohort (n=97)	With treatment interruption (n=38)	Without treatment interruption (n=59)	<i>p</i> -Value
Age				
Median (range)	64 (59.0-69.5)	67 (61.5-72.5)	63 (56-69)	0.0269
≥65 Years	47 (48.5%)	22 (57.9%)	25 (42.4%)	0.135
Gender				
Male	67 (69.1%)	21 (55.3%)	46 (78.0%)	0.0182
Histopathology				
Clear-cell carcinoma	70 (72.2%)	24 (63.2%)	46 (78.0%)	0.112*
Non-clear cell carcinoma	27 (27.8%)	14 (36.8%)	13 (22.0%)	
Papillary renal cell carcinoma type II	4 (4.12%)	2 (5.26%)	2 (3.39%)	
Clear-cell carcinoma with spindle cells	8 (8.25%)	6 (15.8%)	2 (3.39%)	
Other/unknown	15 (15.5%)	6 (15.8%)	9 (15.3%)	
MSKCC risk group				
Favorable	15 (15.5%)	6 (15.8%)	9 (15.3%)	0.960
Intermediate	68 (70.1%)	27 (71.1%)	41 (69.5%)	
Poor	14 (14.4%)	5 (13.2%)	9 (15.3%)	
Prior nephrectomy				
Yes	85 (87.6%)	32 (84.2%)	53 (89.8%)	0.412
Treatment schedule				
4-weeks-on/2-weeks-off	30 (30.9%)	16 (42.1%)	14 (23.7%)	0.0559
Initial dose				
50 mg	30 (30.9%)	11 (29.0%)	19 (32.2%)	0.927**
37.5 mg	50 (51.6%)	19 (50.0%)	31 (52.5%)	
25 mg	17 (17.5%)	8 (21.1%)	9 (15.3%)	
Site of metastasis				
Multiple	48 (49.5%)	20 (52.6%)	28 (47.5%)	0.619
Liver metastasis				
Yes	13 (13.4%)	7 (18.4%)	6 (10.2%)	0.244
RDI within initial 2 cycles				
Median (95% CI)	68.8 (51.5-76.3)	52.7 (37.5-62.5)	75.0 (65.7-81.3)	<0.0001
Follow-up period				
Median (IQR)	8.84 (3.45-18.6)	12.7 (4.57-25.9)	24.5 (11.0-38.9)	0.0040

CI: Confidence interval; IQR: interquartile range; MSKCC: Memorial Sloan Kettering Cancer Center. \*Clear-cell carcinoma vs. non-clear-cell carcinoma. \*\*≥37.5 vs. <37.5 mg.

62.5%) vs. 75.0% (95% CI=65.7-81.3%),  $p<0.0001$ ] than in those without. There was no significant difference in other factors including age, cancer histopathology, Memorial Sloan Kettering Cancer Center (MSKCC) risk, prior nephrectomy, initial dose, sites of metastases, or presence of liver metastasis (all  $p>0.05$ ). The median follow-up duration was significantly shorter in patients with TI [12.7 (95% CI=4.57-25.9) vs. 24.5 (95% CI=11.0-38.9) months,  $p=0.0040$ ] than in those without.

**Survival according to treatment modification.** Figure 2 shows that median PFS and OS were significantly shorter in patients with TI than those without [PFS=6.54 (95% CI=2.76-10.4) vs. 11.3 (95% CI=8.65-20.7) months,  $p=0.0246$ ; OS=16.9 (95% CI=9.14-39.3) vs. 30.0 (95% CI=20.1-51.7) months,  $p=0.0420$ ].

In addition, we compared PFS and OS according to TI and dose reduction. Twenty-two patients required treatment reduction without interruption, and the patient background is

shown in Table II. When compared to the patients with dose reduction, PFS and OS were shorter in patients with TI, although the statistical difference was not significant (Figure 3). Interestingly, there was no significant difference in PFS or OS between patients with a dose reduction and those without modification [PFS=14.3 (95% CI=6.18-26.2) months,  $p=0.655$ ; OS=30.0 (95% CI=11.0-not reached) months,  $p=0.828$ ].

Furthermore, we evaluated PFS and OS according to whether patients restarted sunitinib treatment after their interruption (Figure 4). Among the 38 patients with TI, sunitinib therapy was restarted in 24. For the other 14 patients, therapy for two was changed to nivolumab and that for the others to supportive care. Median PFS and OS were significantly longer for the patients that restarted sunitinib than for those that discontinued sunitinib [PFS=9.57 (95% CI=6.15-13.9) vs. 2.53 (95% CI=0.79-3.19)  $p<0.0001$ ; OS=26.6 (95% CI=15.0-not reached) vs. 4.54 (95% CI=1.51-20.2),  $p=0.0003$ , respectively].

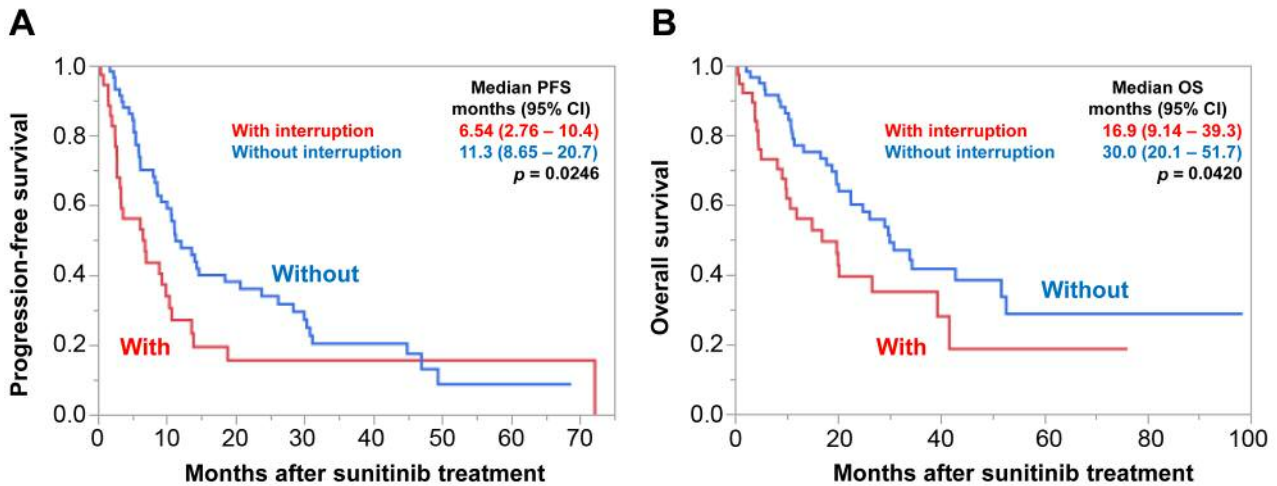


Figure 2. Progression-free (PFS) (A) and overall (OS) (B) survival according to immediate treatment interruption. PFS and OS were significantly shorter for patients with immediate treatment interruption. CI: Confidence interval.

Table II. Patient background (treatment modifications).

	Treatment interruption (n=38)	Dose reduction (n=22)	No modification (n=37)	p-Value
Age				
≥65 Years	22 (57.9%)	10 (45.5%)	15 (40.5%)	0.307
Gender				
Male	21 (55.3%)	17 (77.3%)	29 (78.4%)	0.0613
Histopathology				
Clear-cell carcinoma	24 (63.2%)	15 (68.2%)	31 (83.8%)	0.123*
Non-clear cell carcinoma	14 (36.8%)	7 (31.8%)	6 (16.2%)	
Papillary renal cell carcinoma type II	3 (7.89%)	1 (4.55%)	1 (2.70%)	
Clear-cell carcinoma with spindle cells	6 (15.8%)	1 (4.55%)	1 (2.70%)	
Other/unknown	5 (13.2%)	5 (22.7%)	4 (10.8%)	
MSKCC risk group				
Favorable	6 (15.8%)	2 (9.09%)	7 (18.9%)	0.622
Intermediate	27 (71.1%)	18 (81.8%)	23 (62.2%)	
Poor	5 (13.2%)	2 (9.09%)	7 (18.9%)	
Prior nephrectomy				
Yes	32 (84.2%)	19 (86.4%)	34 (91.9%)	0.588
Treatment schedule				
4-weeks-on/2-weeks-off	16 (42.1%)	5 (22.7%)	9 (24.3%)	0.160
Initial dose				
50 mg	11 (29.0%)	10 (45.5%)	9 (24.3%)	
0.0390**				
37.5 mg	19 (50.0%)	12 (54.6%)	19 (51.4%)	
25 mg	8 (21.1%)	0	9 (24.3%)	
Site of metastasis				
Multiple	20 (52.6%)	12 (54.6%)	16 (43.2%)	0.621
Liver metastasis				
Yes	7 (18.4%)	3 (13.6%)	3 (8.11%)	0.423
RDI within initial 2 cycles				
Median (95% CI)	52.7 (37.5-62.5)	71.9 (61.7-81.3)	75.0 (75.0-93.8)	<0.0001
Follow-up period				
Median (IQR)	12.7 (4.57-25.9)	24.0 (9.55-45.5)	24.5 (12.4-35.3)	0.0160

CI: Confidence interval; IQR: interquartile range; MSKCC: Memorial Sloan Kettering Cancer Center. \*Clear-cell carcinoma vs. non-clear-cell carcinoma. \*\*≥37.5 vs. <37.5 mg.

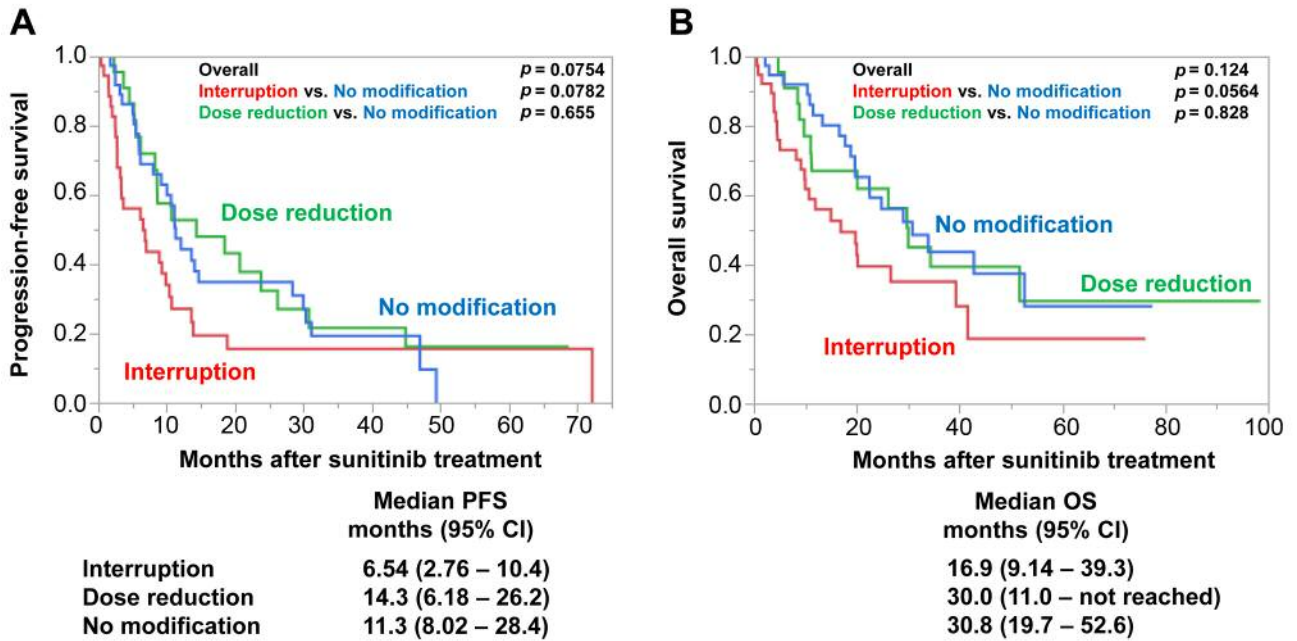


Figure 3. Progression-free (PFS) (A) and overall (OS) (B) survival according to treatment modification. PFS and OS were shorter for patients with immediate treatment interruption compared to those with dose reduction and those without treatment modification, although the statistical difference was not significant. There was no difference in survival between the patients with dose reduction and those without treatment modification. CI: Confidence interval.

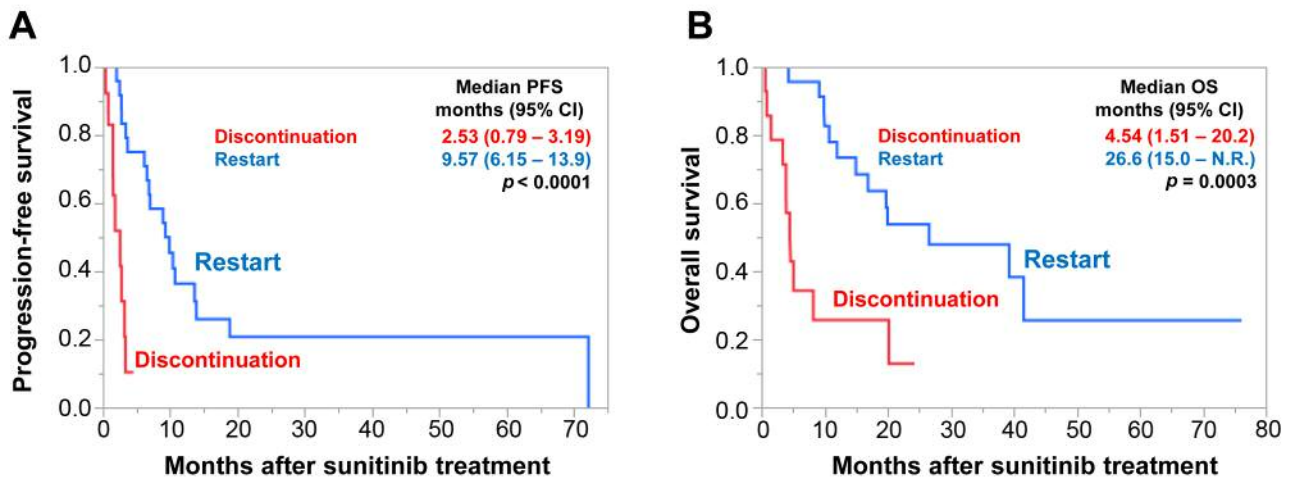


Figure 4. Progression-free (PFS) (A) and overall (OS) (B) survival according to restart of treatment after immediate treatment interruption. PFS and OS were significantly shorter in patients who did not restart treatment. CI: Confidence interval.

**Prognostic factors of PFS and OS.** Univariate analysis of PFS showed that non-clear cell carcinoma histopathology, MSKCC poor-risk group, liver metastasis, and TI were significant factors in poorer overall outcome (all  $p < 0.05$ ; Table III). Multivariate analysis showed that TI was an

independent factor (HR=1.93, 95% CI=1.15-3.22;  $p=0.0141$ ), together with non-clear cell carcinoma histopathology ( $p=0.0097$ ) and the MSKCC poor-risk group ( $p=0.0250$ ). Univariate analysis of OS showed that non-clear cell carcinoma histopathology, MSKCC poor-risk group liver

Table III. Univariate and multivariate analysis for progression-free survival (PFS) and overall survival (OS) according to treatment interruption.

	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age								
≥65 vs. <65 years	0.92 (0.58-1.47)	0.738			1.17 (0.70-1.98)	0.548		
Gender								
Male vs. female	0.69 (0.42-1.16)	0.159			0.63 (0.37-1.10)	0.104		
Histopathology								
Clear-cell carcinoma vs. non-clear cell carcinoma	0.39 (0.23-0.66)	0.0006	0.48 (0.28-0.83)	0.0097	0.40 (0.23-0.71)	0.0025	0.44 (0.25-0.82)	0.0096
MSKCC risk group		0.0013		0.0070		0.0005		0.0013
Favorable vs. intermediate	0.42 (0.19-0.85)	0.0130	0.50 (0.21-1.02)	0.0556	0.43 (0.16-0.95)	0.0364	0.47 (0.17-1.09)	0.0796
Poor vs. intermediate	2.22 (1.12-4.06)	0.0242	2.33 (1.12-4.56)	0.0250	2.98 (1.47-5.62)	0.0034	3.00 (1.45-5.80)	0.0039
Treatment schedule								
4-Weeks-on/2-weeks-off vs. 2-weeks-on/1-week-off	1.12 (0.67-1.81)	0.664			1.10 (0.62-1.89)	0.727		
Initial dose								
≥37.5 vs. <37.5 mg	0.54 (0.30-1.04)	0.0642			0.74 (0.40-1.51)	0.390		
Site of metastasis								
Multiple vs. solitary	1.27 (0.79-2.02)	0.321			1.54 (0.91-2.62)	0.107		
Liver metastasis								
With vs. without	2.40 (1.14-4.56)	0.0229	1.89 (0.88-3.67)	0.0997	3.45 (1.66-6.63)	0.0016	3.11 (1.48-6.04)	0.0039
Treatment interruption								
With vs. without	1.73 (1.05-2.78)	0.0308	1.93 (1.15-3.22)	0.0141	1.72 (1.00-2.91)	0.0486	2.09 (1.20-3.62)	0.0102

CI: Confidence interval; HR: hazard ratio; MSKCC: Memorial Sloan Kettering Cancer Center.

metastasis, and TI were significant factors (all  $p < 0.05$ ). Multivariate analysis showed that TI was an independent factor (HR=2.09, 95% CI=1.20-3.62;  $p=0.0102$ ), together with non-clear cell carcinoma histopathology ( $p=0.0096$ ), MSKCC poor risk group (HR=3.00, 95% CI=1.45-5.80;  $p=0.0039$ ), and liver metastasis (HR=3.11, 95% CI=1.48-6.04;  $p=0.0039$ ) (Table III).

**DLTs and treatment modifications.** Table IV shows the individual AEs inducing treatment interruption. Grade 3 or higher AEs developed in 28 out of the 38 patients (73.7%). The most frequent AE was thrombocytopenia [grade ≥3, 11 patients (28.9%)], followed by leukocytopenia [grade ≥3, six patients (15.8%)].

**Discussion**

This retrospective study showed that PFS and OS were significantly shorter in patients with TI within the initial two cycles after first-line sunitinib treatment for mRCC. Multivariate analyses further showed that TI was an independent factor for shorter PFS and OS. Moreover, rather than dose reduction, TI was likely to be associated with

Table IV. Individual dose-limiting toxicities inducing treatment interruption (n=38).

Adverse event	Grade, n	
	≤2	≥3
Fatigue	0	1
Hand-foot syndrome	1	0
Thrombocytopenia	2	11
Anemia	0	1
Leukocytopenia	1	6
Diarrhea	0	0
Acute kidney injury	0	0
AST/ALT increased	0	2
Fever	2	1
Dysgeusia	1	0
Vomiting	3	0
Nausea	2	0
Anorexia	3	1
Infection	0	2
Hyperkalemia	0	2
Ileal perforation	0	1
Lipase increased	0	2
Total, n (%)	10 (26.3%)	28 (73.7%)

AST/ALT: Aspartate aminotransferase; ALT: alanine aminotransferase.

shorter survival. Furthermore, the most frequent AEs leading to TI were hematotoxicity in our cases.

The RDI may need to be included in the multivariate analysis owing to the possibility of its significance for survival. However, because this is a confounding factor with the presence of TI (Table I), these two factors were not analyzed together in the multivariate analysis. Previous studies indicated that an efficient RDI was needed to maintain therapeutic efficacy in sunitinib treatment (7-9). Porta *et al.* reported that an RDI of less than 70% during the initial three cycles was associated with significantly shorter OS in sunitinib treatment (9). In another study, Kawashima *et al.* suggested that an RDI of 60% or higher within the first month was important for PFS prolongation (7). We also previously reported that an RDI of 60% or higher during the initial cycle was required to maintain therapeutic efficacy (6). However, the number of studies investigating the relationship between modification type (*i.e.*, TI or dose reduction) and survival is limited. In this context, the current study suggested the negative impact of TI, not dose reduction, developed within the initial phase of sunitinib therapy.

Importantly, because sufficient RDI within the initial phase is also required as described above, an excessive initial dose reduction in order to avoid TI is not allowed. That is, our data suggest the importance of careful management so as not to cause TI while maintaining the RDI. In cases with TI development or RDI decrease in the initial phase, a conversion to other targeted agent or therapy with different modes of action, such as immune checkpoint inhibitors, may be an effective option.

The most frequent AE causing TI was hematotoxicity, including thrombocytopenia and leukocytopenia, in our analysis. Indeed, previous studies showed hematotoxicity that developed in the early phase reduced therapeutic efficacy and survival rates (14, 15). Unfortunately, hematotoxicity is generally difficult to treat or prevent by symptomatic treatment. Therefore, careful scheduling or dosage management is required to properly reduce the sunitinib dose to avoid interrupting administration, even in cases with DLT development.

This study had several limitations. Firstly, this study was retrospective in nature, performed at a single center, and had a small sample size. Thus, unavoidable biases exist in any findings. In addition, not all AEs may have been recognized, and the unrecorded AEs might have affected our analyses. Secondly, the majority of patients (69.1%) who followed an alternative 2-weeks-on/1-week-off treatment schedule reported greater comfort and tolerability than those on the standard schedule (11, 16, 17). Thus, this alternative schedule can affect patient tolerability analyses. Finally, not all treatment modification decisions were based on guidelines because of the retrospective nature of this study.

In conclusion, this retrospective study showed that immediate TI resulted in a significantly negative effect on survival of patients under sunitinib treatment for mRCC. Therefore, the careful monitoring of patient tolerability is required in order to maintain therapeutic efficacy in the early phase of sunitinib treatment.

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## Conflicts of Interest

Tsunenori Kondo received honoraria from Pfizer and Ono Pharmaceutical. All other Authors have no conflicts of interest to declare.

## Authors' Contributions

Ryo Ishiyama, Hiroki Ishihara, and Tsunenori Kondo designed the study. Ryo Ishiyama, Hiroki Ishihara, Tsunenori Kondo, and Toshio Takagi interpreted the data and wrote the manuscript. Tsunenori Kondo, Toshio Takagi, Kazuhiko Yoshida, Junpei Iizuka, Hirohito Kobayashi, Masayoshi Okumi, Hideki Ishida, and Kazunari Tanabe collected the data.

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