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著者名	ISHIHARA Hiroki, TAKAGI Toshio, KONDO Tsunenori, IWAMOTO Kana, TACHIBANA Hidekazu, YOSHIDA Kazuhiko, OMAE Kenji, IIZUKA Junpei, KOBAYASHI Hirohito, TANABE Kazunari
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Hiroki Ishihara[1*], Toshio Takagi[1], Tsunenori Kondo[2], Kana Iwamoto[2], Hidekazu Tachibana[2], Kazuhiko Yoshida[1], Kenji Omae[1, 3, 4], Junpei Iizuka[1], Hirohito Kobayashi[1], Kazunari Tanabe[1]

[1]Department of Urology, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan, 162-8666

[2]Department of Urology, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishiogu, Arakawa-ku, Tokyo, Japan, 116-8567

[3]Department of Healthcare Epidemiology, Kyoto University Graduate School of Medicine/ School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto, Japan, 606-8501

[4]Center for Innovative Research for Communities and Clinical Excellence, Fukushima Medical University, 1 Hikarigaoka, Fukushima City, Fukushima, Japan, 960-1295

***Corresponding author:**

Dr. Hiroki Ishihara

Department of Urology, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan, 162-8666

Tel: +81-3-3353-8111

Fax: +81-3-3356-0293

E-mail address: ishihara.hiroki@twmu.ac.jp

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Keywords

renal cancer; targeted therapy; adverse event; tolerability; dose-limiting toxicity

Abstract

Background: Relative dose intensity (RDI) is an indicator of therapeutic efficacy in sunitinib (SU) treatment for metastatic renal cell carcinoma (mRCC). However, the number of studies investigating the influence of decreased RDI during the early phase on oncological outcome is limited.

Methods: A total of 105 patients who received first-line SU treatment for mRCC were evaluated. We assessed the RDI during the initial first cycle (1c-RDI). We found that an optimal threshold of 1c-RDI was associated with progression-free survival (PFS) and overall survival (OS) after the initiation of SU treatment. Additionally, predictive factors for decreased 1c-RDI were analyzed.

Results: The 1c-RDI threshold was determined at 60%. Patients with low 1c-RDI (< 60%, n = 26, [24.8%]) had significantly shorter median PFS (5.79 vs. 14.0 months, p = 0.0014) and OS (13.3 vs. 34.4 months, p = 0.0005) durations than those with high 1c-RDI (≥ 60%, n = 79 [75.2%]). Multivariate analysis showed that the development of dose-limiting toxicity was an independent factor for low 1c-RDI (odds ratio: 3.09, 95% confidence interval: 1.14 – 8.37, p = 0.0266) after adjustment with an initial dose of SU.

Conclusions: More than 60% of 1c-RDI is needed for effective SU treatment. Patient tolerability should be carefully monitored to avoid the development of dose-limiting

toxicity during the early phase of treatment.

Mini Abstract

More than 60% of 1c-RDI is needed for effective sunitinib treatment. Patient tolerability should be carefully monitored to avoid the development of dose-limiting toxicity during the early phase of treatment.

Introduction

Sunitinib (SU) is an anti-cancer drug and a receptor tyrosine kinase inhibitor mainly targeting the vascular endothelial cell growth factor receptors and blocks vascular endothelial cell growth factor signaling. It is approved as a first-line molecular-targeted agent for metastatic renal cell carcinoma (mRCC) [1]. SU is more beneficial to patient survival than conventional cytokine therapy [2,3], and has been broadly applied in current clinical practice. However, its toxicity is a major issue. Frequent and severe adverse events (AEs) induced by SU can result in treatment withdrawal, dose reduction, or treatment interruption, that is, dose-limiting toxicity (DLT) [2,4-9].

In a previous pivotal trial, SU-induced toxicities, mainly gastrointestinal disorder, hypertension, hand-foot syndrome, general fatigue, or hemototoxicity, led to dose reduction and treatment termination in 50% and 19% of the patients, respectively [2]. DLTs can directly decrease relative dose intensity (RDI). Maintaining the RDI, particularly in the early phase of treatment, is essential to efficient and continuous treatment, and is significantly associated with patient survival [10,11]. However, the number of studies investigating the impact of decreased RDI during the early phase of treatment on the oncological outcome is limited, particularly in patients without prior cytokine therapy. Moreover, predicting the decreased RDI before initiation of treatment

or during treatment is difficult. Thus, risk factors for such a possibility should be identified.

In this study, we investigated the influence of decreased RDI during the early phase on the therapeutic efficacy of first-line SU treatment in patients with mRCC without prior cytokine therapy. Additionally, risk factors for decreased RDI were analyzed.

Materials and Methods

Study design

First of all, we nominated patients who received at least one dose of oral SU. In our department between January 2007 and July 2017, 112 patients received first-line SU treatment for mRCC without prior cytokine therapy. Of these, we excluded those who had either undergone a kidney transplantation (n = 1) or whose clinical data was lacking (n = 6). Finally, 105 patients were evaluated in this retrospective single-center analysis. 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).

To determine the influence of decreased RDI during the early phase of treatment on the therapeutic efficacy of first-line SU for mRCC, we calculated the RDI during the initial first cycle (1c-RDI) as RDI in early phase. Patients were classified into the following two groups, low and high 1c-RDI, based on the 1c-RDI threshold associated with oncological outcome, including progression-free survival (PFS) and overall survival (OS), after initiation of treatment. Furthermore, we analyzed the predictive factors for decreased 1c-RDI.

Protocols of first-line sunitinib treatment

We followed the protocol for first-line SU treatment as described elsewhere [12,13]. Briefly, the main agent for first-line molecular-targeted therapy was SU. Patients with mRCC were treated using a 4-week-on/2-week-off or a 2-week-on/1-week-off schedule. SU treatment was initiated at a dosage of 50 mg/day and was modified based on individual patient factors. Three factors were considered for the reduction of the initial dose: (1) age: > 65 years, (2) serum creatinine levels: > 2 mg/dL, and (3) a body weight: < 50 kg. If one of these three factors was observed, the initial dose was reduced to 37.5 mg. If two factors were observed, the initial dose was reduced to 25 mg. We never reduced the initial dose to < 25 mg. The dose was subsequently increased by 12.5 mg until the highest tolerable dose was determined, although the dose never exceeded 50 mg. Toxicity was assessed at each visit (every 1–2 weeks during the first cycle) and then every month according to the patient's condition. AEs were graded using the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0. The dose was reduced or interrupted based on the guidelines for SU therapy.

Statistical analysis

Continuous and categorical variables were analyzed using the Mann-Whitney *U*-test and the χ^2 test or Fischer's extract test, respectively. PFS and OS were defined as the

time from therapy initiation to the date of progression and date of death from any cause, respectively. Survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate logistic regression analyses were used to identify risk factors for low 1c-RDI. Also, univariate and multivariate analyses using Cox proportional hazards regression models were used to identify the prognostic factors for PFS and OS. The risk was expressed as odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs). All analyses were performed using JMP software (version 13; SAS Institute Inc., Cary, NC, USA), and p-values < 0.05 were considered statistically significant.

Results

Patient background

We examined a threshold of 1c-RDI influencing PFS and OS. Consequently, a 1c-RDI threshold of 60% was determined to be strongly associated with PFS and OS after evaluating the p values of various thresholds of 1c-RDI and selecting the threshold with the lowest p values (Table 1). Based on the threshold, 26 patients (24.8%) were classified into the low 1c-RDI group (i.e., < 60%). Female sex ($p = 0.0053$), low initial dose of SU ($p = 0.0345$), and higher incidence of DLT were more frequently observed in the low 1c-RDI group than in the high 1c-RDI group. Other clinicopathological factors, including age, body weight, pathological type, prior nephrectomy status, the Memorial Sloan Kettering Cancer Center risk classification, number of metastatic sites, or treatment schedule did not significantly differ between the two groups (all $p > 0.05$) (Table 2). The follow-up period was significantly shorter in patients with low 1c-RDI than those with high 1c-RDI ($p = 0.0037$).

Survival according to 1c-RDI

In the follow-up period, 73 patients (69.5%) experienced disease progression, and 59 patients (56.2%) died of any cause. Figure 1 shows that the median duration of PFS

and OS were significantly shorter in patients with low 1c-RDI than those with high 1c-RDI (PFS: 5.79 [95% CI: 2.76 – 8.02] vs. 14.0 [95% CI: 10.7 – 20.7] months, p = 0.0014; OS: 13.3 [95% CI: 4.73 – 20.0] vs. 34.4 [95% CI: 26.1 – 52.6] months, p = 0.0005).

Predictors for low 1c-RDI

Table 3 shows the results of univariate and multivariate logistic regression analyses for 1c-RDI < 60%. Univariate analysis showed that female sex, lower initial dose, and DLT development were associated with low 1c-RDI (all, p < 0.05). Multivariate analysis showed that DLT development (OR: 3.09, 95% CI: 1.14 – 8.37, p = 0.0266) and female sex (OR: 3.11, 95% CI: 1.16 – 8.34, p = 0.0240) were independent predictors for low 1c-RDI after adjustment for the initial dose of SU.

Predictors for progression-free survival and overall survival

Supplementary Tables 1 and 2 show the results of univariate and multivariate analyses for PFS and OS, respectively. Multivariate analysis shows that 1c-RDI was an independent predictor (HR: 2.23, 95% CI: 1.27 – 3.79, p = 0.0063), along with sex (HR: 1.74, 95% CI: 1.02 – 2.90, p = 0.0415), histology (HR: 1.97, 95% CI: 1.15 – 3.31, p = 0.0135), MSKCC risk (p = 0.0154), and the number of metastatic sites (HR: 1.77, 95%

CI: 1.10 – 2.88, p = 0.0195) for PFS. For OS, 1c-RDI was an independent predictor (HR: 2.64, 95% CI: 1.45 – 4.68, p = 0.0018), along with histology (HR: 2.07, 95% CI: 1.13 – 3.70, p = 0.0199), MSKCC risk (p = 0.0026), and the number of metastatic sites (HR: 2.65, 95% CI: 1.53 – 4.68, p = 0.0195), according to the multivariate analysis.

Dose-limiting toxicities during the initial first cycle

Table 4 shows the individual AEs that cause DLTs. The most frequent AE was thrombocytopenia (grade 2: n = 16 [30.8%], grade ≥ 3: n = 14 [26.9%]), followed by leukocytopenia (grade 2: n = 3 [5.77%], grade ≥ 3: n = 11 [21.2%]). Among the 52 patients who developed DLT, the dose was reduced and interrupted in 31 (59.6%) and 21 (40.4%) patients, respectively.

Discussion

The present study indicated that more than 60% of RDI during the initial first cycle was needed to maintain the therapeutic efficacy of first-line SU treatment for mRCC. Furthermore, we found that DLT development can decrease the level of sufficient RDI; therefore, patient tolerability should be carefully monitored to avoid the development of DLT during the first cycle.

SU-induced toxicities can disrupt the maintenance of efficient treatment intensity, and this can result in poor prognosis in patients with mRCC. Kawashima et al. reported that continuing treatment for more than one course and ≥ 60% of one-month RDI were important for optimal efficacy of SU treatment [11]. Another study reported that dose intensity below 70% during several landmark periods, including the initial three cycles, was significantly associated with shorter OS in SU treatment [10]. Considering these findings, a threshold of 60% obtained from our analysis was consistent with the findings from previous studies. Notably, a unique point of the present study was that it included patients who had not received prior cytokine therapy. Thus, our findings can be applied on the current treatment strategy for mRCC [14].

As RDI is affected by various factors during treatment, predicting it before treatment initiation or during treatment is difficult. Moreover, despite the need for

predictors for decreased RDI that can be used to prevent it during treatment, only a limited number of clinical researches have focused on such factors. As such, we found that the development of DLT during the initial first cycle should be avoided to maintain the efficient RDI. As the initial dose of SU would be directly associated with 1c-RDI, multivariate analyses were performed to adjust for the confounding factors. The results indicated that DLT development remains a statistical significant factor influencing the RDI.

Treatment discontinuation induced by intolerable AEs was previously reported to negatively affect patient prognosis [10,15]. Treatment was permanently discontinued after interruption during the early phase in eight of the 31 patients (25.8%) in our study. In these eight patients, the median 1c-RDI was 46.5%, and the survival was extremely poor (median PFS and OS: 1.16 and 3.35 months, respectively). Also, in this study, total RDI (i.e., throughout the treatment) in patients with low 1c-RDI was lower than in those with high 1c-RDI (median: 45.6% vs. 64.2%, $p < 0.0001$), suggesting that deterioration of therapeutic efficacy in early period influences entire efficacy, leading to poor survival.

In the current analysis, the most frequent DLTs were hematotoxicities, including thrombocytopenia and leukocytopenia, that could not be treated or prevented via symptomatic treatment. A similar finding was observed in a previous study by

Kawashima et al. who reported that thrombocytopenia and leukocytopenia were the most frequent AEs in SU treatment [11]. Furthermore, a modified treatment schedule was not associated with a maintenance of efficient RDI, although a 2-weeks-on/1-week-off schedule is a common alternative schedule with less toxicity [16-18]. However, the deceased drug efficacy during the early phase of treatment can negate the benefit from the modified schedule. Thus, when severe hematotoxicities occur during the initial cycle, a conversion to other agents, such as pazopanib, which is more tolerable than SU with less hematotoxicity effects [4,5], may be a more effective approach than reduced dosage or schedule modification. The lower frequency of thrombocytopenia and leukocytopenia in pazopanib than that of SU has been demonstrated [4].

Finally, our analysis showed that female patients had a higher risk of decreased RDI than males. This finding was similarly observed in several previous studies. Kawashima et al. reported that women tended to discontinue SU treatment within one course [11]. In their review of SU treatment, Segarra et al. reported that female patients had a higher incidence of AEs than males [19]. Kaymakcalan et al. suggested that further researches should be performed to determine the impact of sex on SU-induced toxicity [20].

This study had several limitations. First, this study was retrospectively performed

in a single-center with a relatively small cohort. Our findings were affected by unavoidable biases in patient or treatment selection. Moreover, several unrecorded AEs might exist. Second, we should note that the safety profile of SU may differ between the Asian and Western populations [21]. Third, an initial dose of SU was modified using a home-based protocol (based on age, body weight, and renal function) according to previous studies showing a high concentration of SU and its active metabolite in plasma with a dosage of 50 mg [22], and higher incidence of AEs in Japanese than Western patients [23]. Indeed, some studies reported the possibility of weak tolerability in elderly patients [24,25]. Moreover, SU can deteriorate renal function [26,27]. In this context, our own protocol can reflect the situation in real world, but we should recognize some possible bias in the protocol.

In conclusion, more than 60% of 1c-RDI was needed to maintain the therapeutic efficacy of first-line SU treatment for mRCC. The development of DLT during the initial first cycle can deteriorate the 1c-RDI regardless of the initial dose or treatment schedule of SU. Patient tolerability should be monitored carefully during the early phase of treatment.

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Figure legends

Figure 1. Progression-free survival and overall survival according to 1c-RDI threshold

Median progression-free survival and overall survival were significantly shorter in patients with low 1c-RDI (progression-free survival: 5.79 vs. 14.0 months, p = 0.0014; overall survival: 13.3 vs. 34.4 months, p = 0.0005).

1c-RDI, relative dose intensity during the initial first cycle

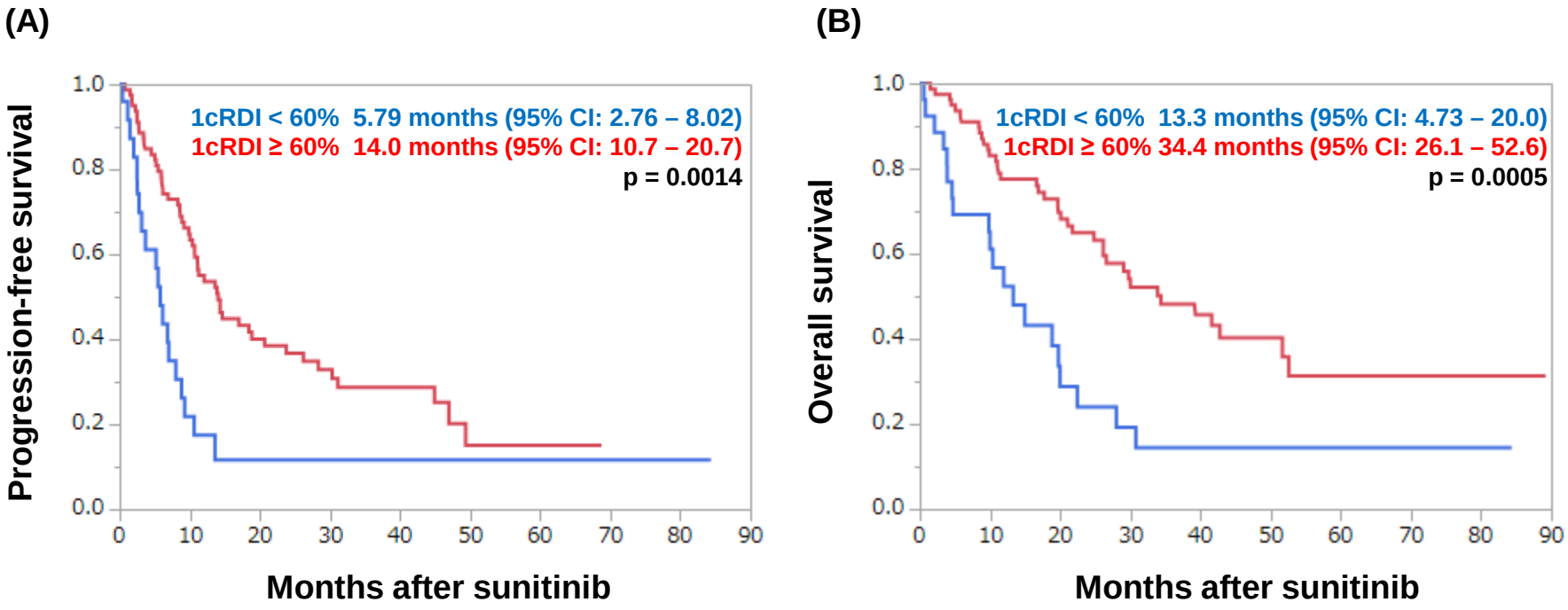
(A)
Progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
80
90
1cRDI < 60% 5.79 months (95% CI: 2.76 – 8.02)
1cRDI ≥ 60% 14.0 months (95% CI: 10.7 – 20.7)
p = 0.0014
Months after sunitinib
(B)
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
80
90
1cRDI < 60% 13.3 months (95% CI: 4.73 – 20.0)
1cRDI ≥ 60% 34.4 months (95% CI: 26.1 – 52.6)
p = 0.0005
Months after sunitinib

Figure 1

Table 1: Determination of the cult-off value of 1c-RDI associated with survival

	n	PFS			OS		
Cut-off value of 1c-RDI	**≥ vs. <**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
55	82 vs. 23	1.95	1.09 – 3.31	0.0256	2.21	1.22 – 3.83	0.0061
60	79 vs. 26	2.31	1.33 – 3.84	0.0035	2.55	1.45 – 4.36	0.0015
65	67 vs. 38	1.59	0.97 – 2.55	0.0664	1.88	1.11 – 3.15	0.0185
70	59 vs. 46	1.58	0.98 – 2.52	0.0582	1.82	1.09 – 3.05	0.0230
75	58 vs. 47	1.65	1.03 – 2.63	0.0373	1.81	1.08 – 3.04	0.0240
80	24 vs. 81	1.09	0.66 – 1.89	0.743	1.13	0.63 – 2.14	0.692

RDI, relative dose intensity; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval

Table 2: Patient background

Variables	**1c-RDI ≥ 60 (n = 79)**	**1c-RDI < 60 (n = 26)**	**p**
Sex			0.0053
Female (ref. male)	17 (21.5%)	13 (50.0%)	
Age, years			0.283
≥ 65 (ref. <65)	36 (45.6%)	15 (57.7%)	
Body weight, kg			0.178
< 50 (ref. ≥50)	12 (15.2%)	7 (26.9%)	
Histology			0.117
Clear-cell carcinoma	61 (77.2%)	16 (61.5%)	
Non-clear-cell carcinoma	18 (22.8%)	10 (38.5%)	
Papillary renal cell carcinoma	4 (5.06%)	2 (7.69%)	
Clear-cell carcinoma with spindle cell	5 (6.33%)	4 (15.4%)	
Others/ unknown	9 (11.4%)	4 (15.4%)	
Prior nephrectomy			0.346
With	72 (91.1%)	22 (84.6%)	
Radical nephrectomy	68 (86.1%)	22 (84.6%)	
Partial nephrectomy	4 (5.06%)	0	
Without	7 (8.86%)	4 (15.4%)	
MSKCC risk			0.830
Favorable	13 (16.5%)	3 (11.5%)	
Intermediate	55 (69.6%)	19 (73.1%)	

Poor	11 (13.9%)	4 (15.4%)	
Number of metastatic sites			0.611
Multiple (ref. single)	41 (51.9%)	12 (46.2%)	
Initial dose, mg			0.0345
50 (ref. ≤37.5)	26 (32.9%)	3 (11.5%)	
Treatment schedule			0.775
4-week-on/ 2-week-off (ref. 2-week-on/ 1-week-off)	22 (27.9%)	8 (30.8%)	
Dose-limiting toxicity			< 0.0001
With	34 (43.0%)	18 (69.2%)	
Dose reduction	20 (25.3%)	1 (3.85%)	
Treatment interruption	14 (17.7%)	17 (65.4%)	
Without	45 (57.0%)	8 (30.8%)	
*Follow-up period, month	23.5 (11.0 – 39.3)	11.2 (4.43 – 20.6)	0.0037

*Median (interquartile)

MSKCC, Memorial Sloan Kettering Cancer Center

Table 3: Univariate and multivariate logistic regression analyses for 1c-RDI < 60%

	Univariate		Multivariate	
Variables	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Sex		0.0068		0.0240
Female (ref. male)	3.65 (1.43 – 9.31)		3.11 (1.16 – 8.34)	
Age, years		0.286		
≥ 65 (ref. < 65)	1.63 (0.67 – 3.99)			
Body weight, kg		0.183		
< 50 (ref. ≥ 50)	2.06 (0.71 – 5.95)			
Histology		0.121		
Non-clear cell carcinoma (ref. clear-cell carcinoma)	2.12 (0.82 – 5.47)			
MSKCC risk		0.822		
Favorable (ref. intermediate)	0.67 (0.17 – 2.60)	0.561		
Poor (ref. intermediate)	1.06 (0.30 – 3.70)	0.936		
Number of metastatic site		0.612		
Multiple (ref. single)	0.79 (0.33 – 1.93)			

Initial dose, mg		0.0444		0.0632
≤ 37.5 (ref. 50)	3.76 (1.03 – 13.7)		3.58 (0.93 – 13.8)	
Treatment schedule		0.775		
4-weeks-on/2-weeks-off (ref. 2-weeks-on/1week-off)	1.15 (0.44 – 3.03)			
Dose-limiting toxicity		0.0235		0.0266
With (ref. without)	2.98 (1.16 – 7.66)		3.09 (1.14 – 8.37)	

OR, odds ratio

Table 4: Individual adverse events inducing dose-limiting toxicities

	N = 52
Grade 2	
Leukocytopenia	3 (5.77%)
Thrombocytopenia	16 (30.8%)
Hand-foot-syndrome	2 (3.85%)
Nausea/vomiting/anorexia	4 (7.69%)
Diarrhea	1 (1.92%)
Fatigue	3 (5.77%)
Fever	4 (7.69%)
Hepatic injury	1 (1.92%)
Interstitial lung disease	1 (1.92%)
Hypertension	1 (1.92%)
Mucotitis	1 (1.92%)
Kidney injury	1 (1.92%)
UTI	1 (1.92%)
Grade 3 or more	
Leukocytopenia	11 (21.2%)
Thrombocytopenia	14 (26.9%)
Hand-foot-syndrome	1 (1.92%)
Fatigue	1 (1.92%)
Hepatic injury	2 (3.85%)
Pancreatic injury	2 (3.85%)

Hyperkalemia	3 (5.77%)
Hepatic abscess	1(1.92%)
Gastrointestinal perforation	1(1.92%)
Components of dose-liming toxicities	
Dose reduction	31 (59.6%)
Treatment interruption	21 (40.4%)

Supplementary Table 1. Univariate and multivariate analyses for progression-free survival

	Univariate		Multivariate	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Sex				
Female (ref. male)	1.78 (1.07 - 2.89)	0.0275	1.74 (1.02 - 2.90)	0.0415
Age				
≧ 65 (ref. < 65)	0.94 (0.59 - 1.49)	0.781		
Body Weight				
< 50 (≧ 50)	1.64 (0.89 - 2.84)	0.107		
Histology				
Non-clear cell carcinoma (ref. clear-cell carcinoma)	2.76 (1.64 - 4.55)	0.0002	1.97 (1.15 - 3.31)	0.0135
MSKCC risk		0.0051		0.0154
Favorable (ref. intermediate)	0.65 (0.30 - 1.26)	0.211	0.63 (0.28 - 1.26)	0.196
Poor (ref. intermediate)	2.52 (1.33 - 4.48)	0.006	2.21 (1.16 - 3.96)	0.0175
Number of metastatic site				
Multiple (ref. single)	1.74 (1.09 - 2.80)	0.0198	1.77 (1.10 - 2.88)	0.0195
1c-RDI				
< 60 (ref. ≧ 60)	2.31 (1.33 - 3.84)	0.0035	2.23 (1.27 - 3.79)	0.0063
Initial dose				
≦ 35 (ref. 50)	1.21 (0.74 - 2.05)	0.461		
Treatment schedule				
4-weeks-on/2-weeks-off (ref. 2-weeks-on/1week-off)	1.28 (0.76 - 2.08)	0.344		
Dose-limiting toxicity				
With (ref.without)	1.35 (0.85 - 2.14)	0.202		

Supplementary Table 2. Univariate and multivariate analyses for overall survival

	Univariate		Multivariate	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Sex				
Female (ref. male)	1.82 (1.05 - 3.07)	0.0344	1.72 (0.96 - 2.99)	0.0677
Age				
≧ 65 (ref. < 65)	1.33 (0.80 - 2.24)	0.273		
Body Weight				
< 50 (≧ 50)	1.82 (0.92 - 3.34)	0.0848		
Histology				
Non-clear cell carcinoma (ref. clear-cell carcinoma)	2.55 (1.42 - 4.43)	0.0022	2.07 (1.13 - 3.70)	0.0199
MSKCC risk		0.0023		0.0026
Favorable (ref. intermediate)	0.59 (0.24 - 1.25)	0.179	0.55 (0.22 - 1.19)	0.137
Poor (ref. intermediate)	3.03 (1.50 - 5.73)	0.003	2.93 (1.44 - 5.61)	0.0042
Number of metastatic site				
Multiple (ref. single)	2.24 (1.33 - 3.87)	0.0025	2.65 (1.53 - 4.68)	0.0004
1c-RDI				
< 60 (ref. ≥ 60)	2.55 (1.45 - 4.36)	0.0015	2.64 (1.45 - 4.68)	0.0018
Initial dose				
≦ 35 (ref. 50)	1.17 (0.67 - 2.14)	0.595		
Treatment schedule				
4-weeks-on/2-weeks-off (ref. 2-weeks-on/1week-off)	1.27 (0.72 - 2.16)	0.406		
Dose-limiting toxicity				
With (ref.without)	1.42 (0.85 - 2.38)	0.179		