Evaluation of relative dose intensity during the early phase of first-line sunitinib treatment using a 2-week-on/1-week-off regimen for metastatic renal cell carcinoma

Evaluation of relative dose intensity during the early phase of first-line sunitinib treatment using a 2-week-on/1-week-off regimen for metastatic renal cell carcinoma

Kana Iwamoto[1,2], Hiroki Ishihara[1*], Toshio Takagi[1], Tsunenori Kondo[2], Kazuhiko Yoshida[1], Junpei Iizuka[1], Kazunari Tanabe[1]

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

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

***Corresponding author:**

Hiroki Ishihara

Department of Urology, Tokyo Woman's Medical University

Tel.: +81- 3-3810-1111

Fax: +81- 3-3894-0282

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

Abstract

Purpose: Sunitinib treatment with a 2-week-on/1-week-off schedule (Schedule 2/1) is a common alternative regimen with high relative dose intensity (RDI) and superior tolerability for patients with metastatic renal cell carcinoma (mRCC). The prognostic impact of RDI is reported only in 4-week-on/2-week-off or mixed regimens. Herein, we evaluated the prognostic impact of RDI during early-phase sunitinib treatment using Schedule 2/1.

Methods: Seventy-four patients who received first-line sunitinib treatment using Schedule 2/1 were evaluated. Endpoints were progression-free survival (PFS) and overall survival (OS). We assessed RDI within the initial 2 cycles (2c-RDI), and its prognostic impact. Predictive factors for 2c-RDI deterioration were also evaluated.

Results: The cut-off value of 2c-RDI was set at 65%. Based on this cut-off, 31 patients (42.0%) were classified into the low 2c-RDI group (<65%). PFS and OS were significantly shorter in the low-2c-RDI patients, compared with the high 2c-RDI patients (median PFS: 6.15 vs. 18.4 months, p=0.0005; OS: 11.0 vs. 39.3 months, p=0.0002). Furthermore, multivariate analyses showed that the development of dose-limiting toxicities (DLTs) within the initial two cycles, as well as low initial dose, were independent factors for low 2c-RDI (DLTs: OR, 18.6, 95% CI: 3.27–105.30, p=0.0010; initial dose: OR, 9.26, 95% CI: 1.42–60.40, p=0.020). The most common adverse event was thrombocytopenia (any grade: 24.3%; grade ≥3: 8.1%).

Conclusions: More than 65% of 2c-RDI should be maintained for optimal therapeutic effect of sunitinib treatment using Schedule 2/1. To achieve the appropriate 2c-RDI, careful follow-up for patient tolerability is needed to avoid early DLT development.

Keywords

Targeted therapy; Renal cancer; Kidney cancer; Dose-limiting toxicity; Tolerability; Adverse events

Introduction

Sunitinib is an orally administered, multi-targeted tyrosine kinase inhibitor that exhibits antitumor and antiangiogenic activity [1, 2] and is a preferential option for first-line, molecular-targeted therapy of patients with metastatic renal cell carcinoma (mRCC) [3, 4]. The standard dosing schedule of sunitinib is 4-week-on/2-week-off (Schedule 4/2) [5]. However, the frequent development of dose limiting toxicities (DLTs) induced by Schedule 4/2 is a serious issue for many patients. To overcome these DLTs, several studies have indicated that an alternative 2-week-on/1-week-off schedule (Schedule 2/1) can decrease the incidence of adverse events (AEs) and maintain a high relative dose intensity (RDI), while providing an equivalent therapeutic effect as Schedule 4/2 [6-11]. Therefore, the Schedule 2/1 regimen is broadly applied in real-world clinical practice.

The prognostic impact of RDI during early-phase sunitinib treatment has been reported [12–14]. However, in these previous studies RDI was calculated in patients who received Schedule 4/2, or mixed Schedule 4/2 and 2/1, regimens. Moreover, cytokine therapy prior to sunitinib treatment has been performed in previous studies [12,14], although the current treatment strategy for mRCC does not preferentially recommend cytokine therapy [4,15]. Furthermore, the number of studies which have investigated predictive factors for RDI remains limited since it is difficult to predict RDI before or during treatment; predictive factors for RDI are necessary for physicians to modulate dosage regimens in patients with mRCC.

Collectively, the aim of this study was to evaluate the prognostic impact and predictive factors of RDI during early-phase sunitinib treatment using Schedule 2/1 in patients with mRCC who have not received prior cytokine therapy.

Material and Methods

Patient selection

Between January 2007 and March 2017, a total of 118 patients received first-line sunitinib treatment for mRCC at our department. We excluded patients who received sunitinib treatment with Schedule 4/2 (n = 35), received kidney transplantation (n = 1), or received prior cytokine therapy (n = 2). In addition, patients who received sunitinib treatment for a short duration (n = 1), or whose detailed data were missing (n=5), were excluded from this study. Finally, 74 patients were evaluated in this study (Fig. 1).

Ethical approval

All the procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Protocol of sunitinib treatment

In our department, the main agent administered for first-line molecular-targeted therapy of mRCC is sunitinib. Recently, we have administered sunitinib with Schedule 2/1, based on our previous study [6].

Our protocol for sunitinib treatment has been previously reported [16, 17]. Briefly, the standard initial dose of sunitinib is 50 mg/day. However, we considered dose reduction if patients had the following criteria: (1) age >65 years, (2) serum creatinine >2 mg/dL, and (3) body weight <50 kg. If one of these factors was present, the starting dose was reduced to 37.5 mg/day. If two of these factors were present, we then reduced the dose to

25 mg/day. The dose of sunitinib was increased by 12.5 mg/day and until we found the highest dose a given patient could tolerate; however, the dose never exceeded 50 mg/day.

Follow-up schedule of sunitinib treatment

Before starting sunitinib, all patients underwent computed tomography imaging to evaluate metastasis. During the first course of sunitinib, we followed-up patients on a weekly basis at our outpatient clinic, and then every 3 or 6 weeks thereafter. At every visit, we assessed patient adverse events and laboratory data. In addition, a CT scan was conducted every 12 weeks to evaluate therapeutic effect. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [18]. AEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, version 4.0 [19]. Dose reduction and interruption was conducted according to guidelines for sunitinib therapy. In these regimens, the drugs were administered until disease progression was observed or intolerable adverse events developed.

Relative Dose Intensity

The RDI was determined as the ratio of the cumulative dose that was received during the cycle to 1,400 mg. In this study, we calculated the RDI during the initial 2 cycles (2c-RDI) of sunitinib therapy as an evaluation of early-phase RDI.

Statistical analysis

Continuous variables were analyzed using the Mann-Whitey *U* test, and categorical variables were analyzed using the χ^2 test or Fisher's exact test. We assessed progression-

free survival (PFS) and overall survival (OS) after initiating sunitinib treatment as study endpoints. PFS was defined as the time from sunitinib treatment initiation to the date of disease progression. OS was defined as the time from sunitinib treatment initiation to death from any cause. We determined a cut-off value for 2c-RDI and divided patients into 2 groups according to the cut-off value (i.e., high 2c-RDI and low 2c-RDI group). PFS and OS was calculated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate logistic regression analyses were used to identify predictive factors of 2c-RDI deterioration. Risk was expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

The patients' clinicopathological characteristics are shown in Table 1. The median age was 64.0 years-old, and 55 patients (74.3%) were male. Sixty-six patients (89.2%) underwent prior nephrectomy. Based on the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification, 17 (23.0%), 45 (60.8%), and 12 (16.2%) patients were classified as favorable, intermediate, and poor risk, respectively. The initial dose of sunitinib was 50.0 mg, 37.5 mg, and 25.0 mg/day in 20 (27.0%), 38 (51.4%), and 16 (21.6%) patients, respectively. The median 1c-RDI and 2c-RDI were 75.0% and 71.9%, respectively. The median follow-up period was 25.9 months.

Cut-off value of 2c-RDI

We examined cut-off values of 2c-RDI at 5.0% intervals from an initial cut-off value of 80% and conducted a univariate analysis of treatment results at PFS and OS. Consequently, a cut-off value of 65% was found to be a strongly associated value after evaluating the p-values of various 2c-RDI cut-off values, by selecting the cut-off value with the lowest p-value (Table 2). Based on this cut-off value, 31 (41.9%) and 43 patients (58.1%) were classified into low (<65%) and high (≥65%) 2c-RDI groups, respectively. According to the 65% cut-off value, PFS was significantly shorter in patients with low-2c-RDI compared to those with high 2c-RDI (median PFS: 6.15 months [95% CI: 3.68–8.84] vs. 18.4 months [95% CI: 11.1–47.0], p = 0.0005). Moreover, OS was also shorter in patients with low 2c-RDI (median OS: 11.0 months [95% CI: 8.42–21.80] vs. 39.3 months [95% CI: 26.6–not reached], p = 0.0002) (Fig. 2). Furthermore, as for differences in patient characteristics based on the 65% 2c-RDI cut-off value, older age, female gender,

lower initial dose, and higher frequency of DLTs were associated with the low 2c-RDI group (all variables, $p < 0.05$) (Supplementary Table 1).

Predictive factors for 2c-RDI

Univariate and multivariate logistic regression analyses showed that DLT development within the initial 2 cycles of sunitinib and low initial dose were independent factors for low 2c-RDI (initial dose: OR, 9.26, 95% CI: 1.42–60.40, $p = 0.020$; DLTs: OR, 18.6, 95% CI: 3.27–105.30, $p = 0.0010$) after adjustment for other factors including sex, age, body weight, MSKCC risk factor, and serum creatinine levels (Table 3).

Adverse events induced by dose limiting toxicities during the initial two cycles

Table 5 shows the individual DLTs requiring dose reduction or treatment interruption during the initial 2 cycles of sunitinib. Twenty patients (27.0%) and 23 patients (31.1%) experienced dose reduction and treatment interruption due to DLTs, respectively. For any grade, thrombocytopenia was the most common AE observed in 18 patients (24.3%), followed by hand-foot syndrome (n = 10, 13.5%) and leukocytopenia (n = 9, 12.2%). For grade ≥3, thrombocytopenia and leukocytopenia were the most common AEs (both, n = 6, 8.1%), followed by anorexia and hepatic dysfunction (n = 2, 2.7%).

Discussion

In this study, we examined the RDI and DLT profiles using a Schedule 2/1 in patients receiving sunitinib treatment for mRCC. Patients with at least 65% of 2c-RDI had a significantly longer PFS and OS compared to those with less than 65% of 2c-RDI. In addition, early DLT development and low initial dose were independent factors for low 2c-RDI. Furthermore, hematotoxic AEs, such as thrombocytopenia and leukopenia, comprised of most DLTs in this study. To the best of our knowledge, this is the first study to indicate the prognostic impact and predictive factors for RDI during early-phase sunitinib treatment using Schedule 2/1 without receiving prior cytokine therapy.

The prognostic impact of RDI during early-phase sunitinib treatment using Schedule 4/2 was previously reported [12-14]. Kawashima et al. showed that 60% of the one-month RDI was an important indicator for survival, and Porta et al. showed that patients below 70% of the RDI had shorter OS. Considering these findings, the threshold of 65% adopted in our analysis was consistent with previous findings.

We found that two factors, early DLT development and initial dose, were predictive of 2c-RDI deterioration. As expected, the initial dose was directly associated with 2c-RDI. Therefore, when the initial dose was $\leq$25.0 mg/day due to patient factors (as shown in Materials and Methods), administration of another targeted agent other than sunitinib, can be an optimal treatment choice. More importantly, DLT development significantly affected 2c-RDI after adjustment of the initial dose. Therefore, to maintain the therapeutic efficacy of sunitinib, particular attention should be paid for patient tolerability to avoid early DLT development.

Several studies reported favorable tolerability and feasibility of sunitinib treatment with Schedule 2/1, compared to that with the standard Schedule 4/2 [6-11]. We previously

reported that AE incidence rates did not differ between Schedule 2/1 and Schedule 4/2, and treatment interruption was less frequently observed in Schedule 2/1 [6]. Miyake et al. showed that the incidence rates of ≥grade 3 AEs were significantly low, and a favorable health-related quality of life was observed for Schedule 2/1 [9]. In the present study, 31.1% of patients experienced treatment interruption. Since 60% of patients experienced treatment interruption with Schedule 4/2 according to previous data from a large Japanese population-based study [20], this study supports the idea that the alternative Schedule 2/1 regimen has superior tolerability.

We also found that hematotoxicity majorly composed of DLTs. These types of AEs are difficult to monitor using patient symptoms. As previously discussed, early DLT development and initial dose can deteriorate 2c-RDI. Therefore, for the patients with severe hematotoxic AEs, switching the therapeutic agent to another drug (e.g., pazopanib) can be an effective option. Initiating treatment with pazopanib may be advantageous for patients who are less susceptible to RDI, such as elderly female patients. Indeed, pazopanib was demonstrated to be more tolerable and had less hematotoxicity risk, when compared to sunitinib [21, 22].

This study had several limitations. First, this was a retrospective study performed at a single center with a small cohort size. Therefore, unavoidable biases for patient or treatment selection may exist. Moreover, due to the retrospective nature, all AEs may not have been recognized and any unrecorded AEs could affect our analyses. Second, our findings were obtained from results collected in the clinical setting. Therefore, all treatment modifications, such as dose reduction and treatment interruption, were not conducted based on treatment guidelines. Third, several studies reported the differences in AE profiles between Asian and Western populations [23–26]. Taken together, our

findings should be confirmed by a further prospective study performed on a large population, including Western patients.

In conclusion, this study showed that more than 65% of 2c-RDI was necessary to maintain therapeutic efficacy for sunitinib treatment using a 2-week-on/1-week-off schedule. Furthermore, DLT development and initial dose were predictive factors for 2c-RDI deterioration. Therefore, careful monitoring of patient tolerability for this treatment regimen is needed.

Acknowledgments

The authors thank Editage for English language editing and Nobuko Hata for secretarial work.

Compliance with ethical standards

Conflicts of interest

Tsunenori Kondo received honoraria from Pfizer, Bayer, and Novartis. All other authors have no conflicts of interest to declare.

References

1. Abrams TJ, Lee LB, Murray LJ, et al (2003) SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. Mol Cancer Ther 2:471–8
2. Mendel DB, Laird AD, Xin X, et al (2003) In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 9:327–37
3. Motzer RJ, Rini BI, Bukowski RM, et al (2006) Sunitinib in Patients With Metastatic Renal Cell Carcinoma. JAMA 295:2516–2524 . doi: 10.1001/jama.295.21.2516
4. Motzer RJ, Hutson TE, Tomczak P, et al (2009) Overall Survival and Updated Results for Sunitinib Compared With Interferon Alfa in Patients With Metastatic Renal Cell Carcinoma. J Clin Oncol 27:3584–3590 . doi: 10.1200/JCO.2008.20.1293
5. Faivre S, Delbaldo C, Vera K, et al (2006) Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol 24:25–35 . doi: 10.1200/JCO.2005.02.2194
6. Kondo T, Takagi T, Kobayashi H, et al (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. Jpn J Clin Oncol 44:270–277 . doi: 10.1093/jjco/hyt232
7. Najjar YG, Mittal K, Elson P, et al (2014) A 2 weeks on and 1 week off schedule

of sunitinib is associated with decreased toxicity in metastatic renal cell carcinoma. Eur J Cancer 50:1084–9 . doi: 10.1016/j.ejca.2014.01.025

8. Atkinson BJ, Kalra S, Wang X, et al (2014) Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules. J Urol 191:611–8 . doi: 10.1016/j.juro.2013.08.090
9. Miyake H, Harada K, Miyazaki A, Fujisawa M (2015) Improved health-related quality of life of patients with metastatic renal cell carcinoma treated with a 2 weeks on and 1 week off schedule of sunitinib. Med Oncol 32:78 . doi: 10.1007/s12032-015-0528-8
10. Bracarda S, Iacovelli R, Boni L, et al (2015) Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: the RAINBOW analysis. Ann Oncol 26:2107–2113 . doi: 10.1093/annonc/mdv315
11. Crumbaker M, Guminski A, Gurney H, et al (2017) Real-world experience of the feasibility and tolerability of the 2/1 dosing schedule with sunitinib in the treatment of patients with advanced renal cell carcinoma in Australia. Asia Pac J Clin Oncol. doi: 10.1111/ajco.12686
12. Kawashima A, Tsujimura A, Takayama H, et al (2012) Importance of continuing therapy and maintaining one-month relative dose intensity in sunitinib therapy for metastatic renal cell carcinoma. Med Oncol 29:3298–3305 . doi: 10.1007/s12032-012-0236-6
13. Porta C, Levy A, Hawkins R, et al (2014) Impact of adverse events, treatment modifications, and dose intensity on survival among patients with advanced renal cell carcinoma treated with first-line sunitinib: a medical chart review across ten centers in five European countries. Cancer Med 3:1517–1526 . doi:

10.1002/cam4.302

14. Arakawa-Todo M, Yoshizawa T, Zennami K, et al (2013) Management of adverse events in patients with metastatic renal cell carcinoma treated with sunitinib and clinical outcomes. Anticancer Res 33:5043–50
15. Motzer RJ, Hutson TE, Tomczak P, et al (2007) Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma. N Engl J Med 356:115–124 . doi: 10.1056/NEJMoa065044
16. Ishihara H, Kondo T, Omae K, et al (2016) Sarcopenia and the Modified Glasgow Prognostic Score are Significant Predictors of Survival Among Patients with Metastatic Renal Cell Carcinoma Who are Receiving First-Line Sunitinib Treatment. Target Oncol 11:605–617 . doi: 10.1007/s11523-016-0430-0
17. Ishihara H, Kondo T, Yoshida K, et al (2017) Time to progression after first-line tyrosine kinase inhibitor predicts survival in patients with metastatic renal cell carcinoma receiving second-line molecular-targeted therapy. Urol Oncol 35:542.e1-542.e9 . doi: 10.1016/j.urolonc.2017.05.014
18. Eisenhauer EA, Therasse P, Bogaerts J, et al New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). doi: 10.1016/j.ejca.2008.10.026
19. Cancer Institute N (2009) Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events v4.0 (CTCAE)
20. Akaza H, Naito S, Ueno N, et al (2015) Real-world use of sunitinib in Japanese patients with advanced renal cell carcinoma: efficacy, safety and biomarker analyses in 1689 consecutive patients. Jpn J Clin Oncol 45:576–83 . doi: 10.1093/jjco/hyv045

21. Motzer RJ, Hutson TE, Cella D, et al (2013) Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. N Engl J Med 369:722–731 . doi: 10.1056/NEJMoa1303989

22. Escudier B, Porta C, Bono P, et al (2014) Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. J Clin Oncol 32:1412–8 . doi: 10.1200/JCO.2013.50.8267

23. Uemura H, Shinohara N, Yuasa T, et al (2010) 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 . doi: 10.1093/jjco/hyp146

24. Lee S-H, Bang Y-J, Mainwaring P, et al (2014) Sunitinib in metastatic renal cell carcinoma: An ethnic Asian subpopulation analysis for safety and efficacy. Asia Pac J Clin Oncol 10:237–245 . doi: 10.1111/ajco.12163

25. Tomita Y, Shinohara N, Yuasa T, et al (2010) 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 . doi: 10.1093/jjco/hyq146

26. Kim HS, Hong MH, Kim K, et al (2011) Sunitinib for Asian patients with advanced renal cell carcinoma: a comparable efficacy with different toxicity profiles. Oncology 80:395–405 . doi: 10.1159/000330361

Figure legends

Fig. 1: Study design.

Fig. 2: Progression-free and overall survivals according to 65% of relative dose intensity during the initial two cycles.

Patients with <65% of relative dose intensity during the initial two cycles (n = 31) had significantly shorter progression-free survival (median: 6.15 months [95% CI: 3.68–8.84] vs. 18.4 months [95% CI: 11.1–47.0], p = 0.0005) and overall survival (median: 6.84 months [95% CI: 4.57–14.3] vs. 28.4 months [95% CI: 14.7–not reached], p = 0.0002), as compared to those with ≥65% of relative dose intensity (n = 43).

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

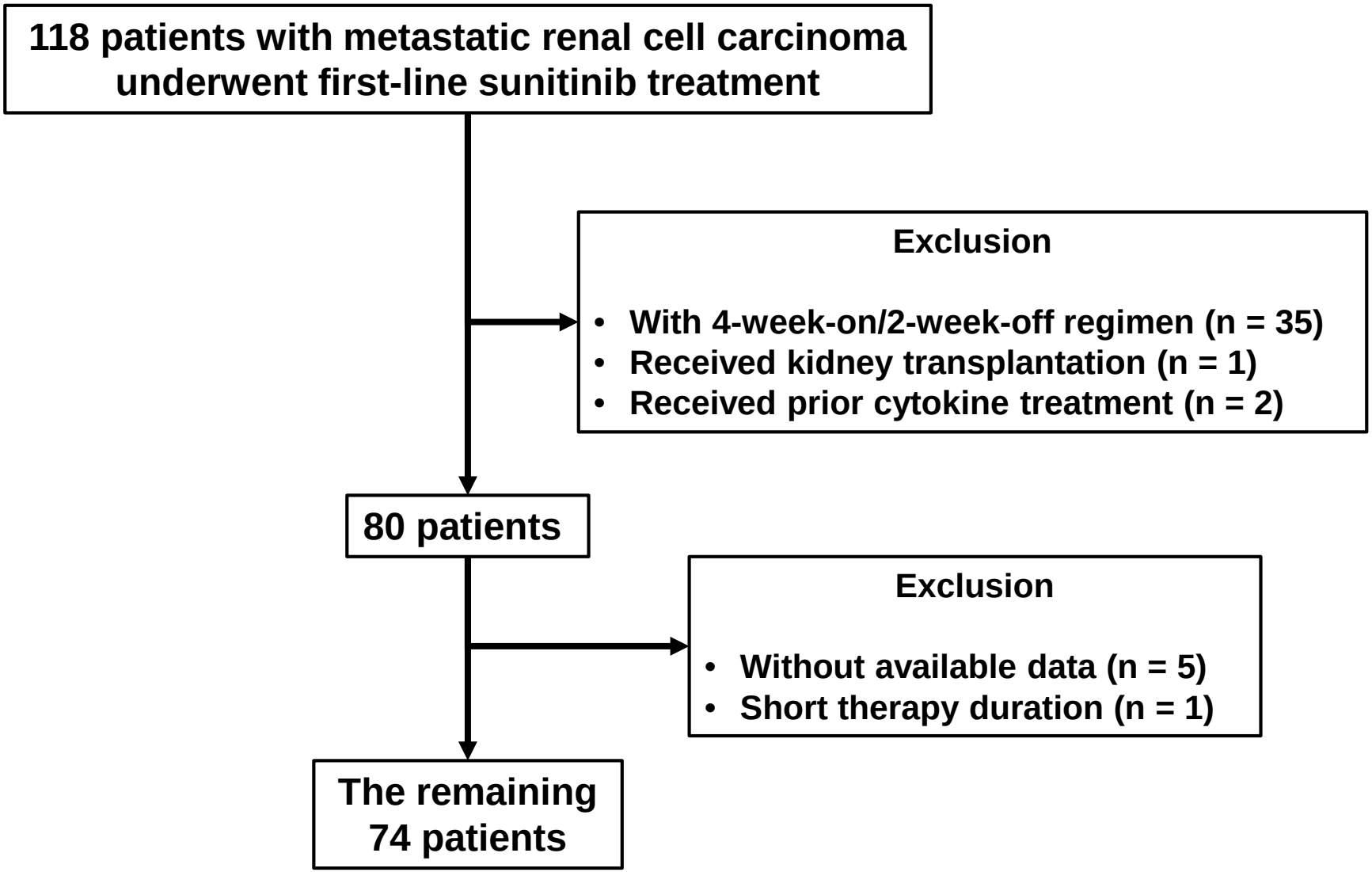
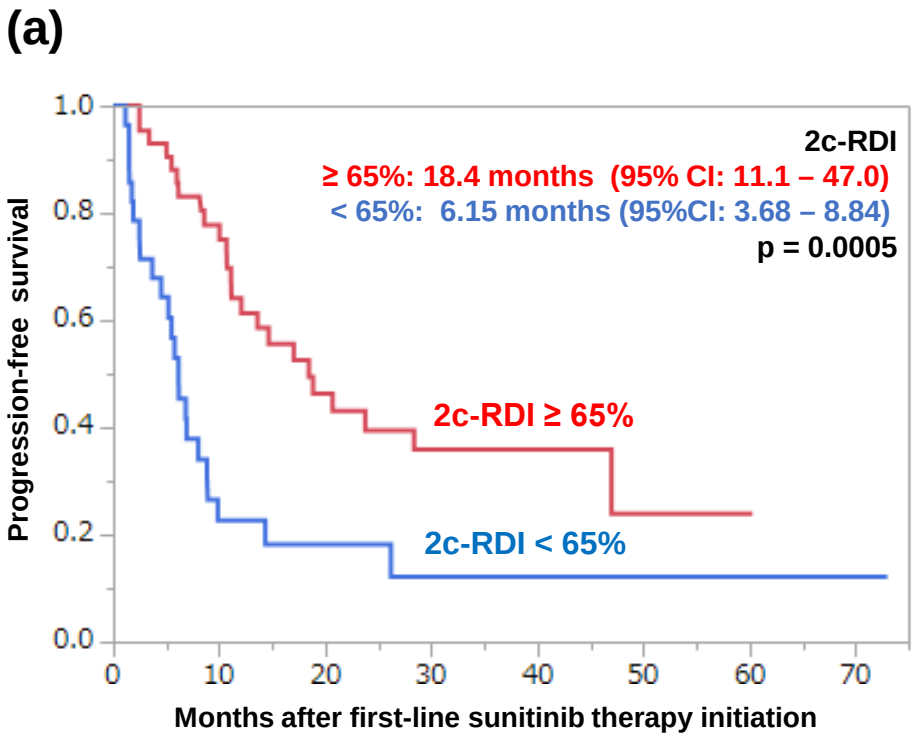

118 patients with metastatic renal cell carcinoma underwent first-line sunitinib treatment
Exclusion
• With 4-week-on/2-week-off regimen (n = 35)
• Received kidney transplantation (n = 1)
• Received prior cytokine treatment (n = 2)
80 patients
Exclusion
• Without available data (n = 5)
• Short therapy duration (n = 1)
The remaining 74 patients

Figure 1


(a)
Progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
Months after first-line sunitinib therapy initiation
2c-RDI
≥ 65%: 18.4 months (95% CI: 11.1 – 47.0)
< 65%: 6.15 months (95%CI: 3.68 – 8.84)
p = 0.0005
2c-RDI ≥ 65%
2c-RDI < 65%

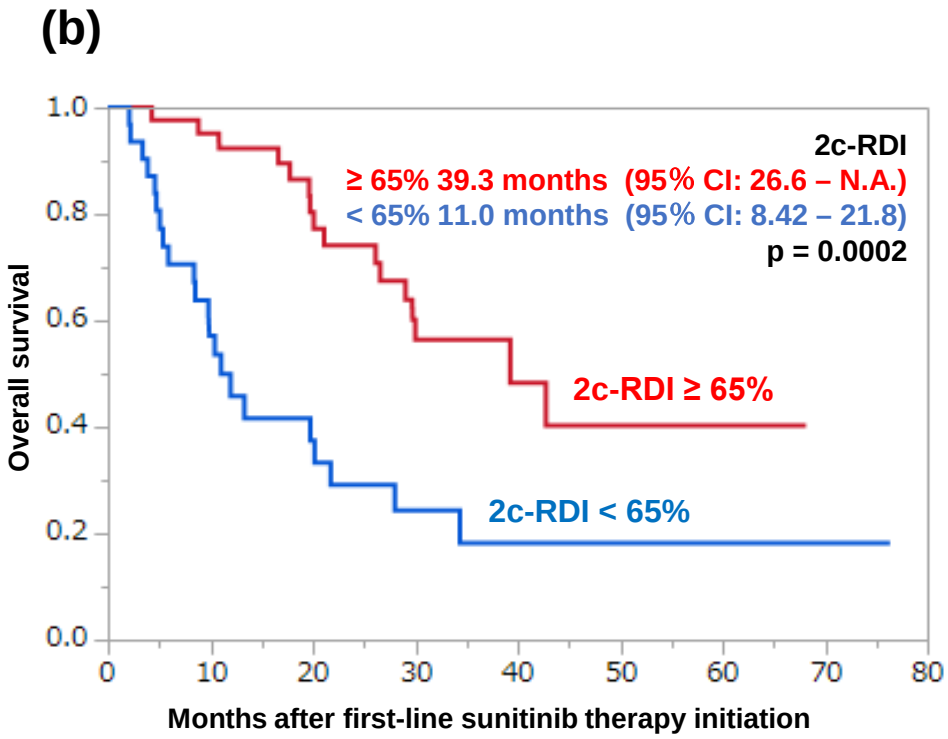

(b)
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
80
Months after first-line sunitinib therapy initiation
2c-RDI
≥ 65% 39.3 months (95% CI: 26.6 – N.A.)
< 65% 11.0 months (95% CI: 8.42 – 21.8)
p = 0.0002
2c-RDI ≥ 65%
2c-RDI < 65%

Figure 2

Table 1. Patient characteristics

		n = 74
* Age (year-old)		64.0 (59.8–69.3)
Sex	Male	55 (74.3%)
	Female	19 (25.7%)
*BMI (kg/m^2)		23.1(20.9–24.9)
Prior nephrectomy	With	66 (89.2%)
	Radical	63 (85.1%)
	Partial	3 (4.1%)
	Without	8 (10.8%)
Metastatic sites	Lung	44 (59.5%)
	Liver	10 (13.5%)
	Bone	18 (24.3%)
	Lymph nodes	29 (39.2%)
Pathology	Clear cell carcinoma	55 (74.3%)
	Non- clear cell carcinoma	19 (25.7%)
	Papillary renal cell carcinoma II	4 (5.4%)
	Clear cell carcinoma with spindle cell	5 (6.8%)
	Others/Unknown	10 (13.5%)
MSKCC risk	Favorable	17 (23.0%)
	Intermediate	45 (60.8%)
	Poor	12 (16.2%)
*Serum creatinine level (mg/dL)		1.27 (1.00–1.84)

*Serum CRP level (mg/dL)		0.50 (0.23–4.20)
Initial dose (mg)	50 mg	20 (27.0%)
	37.5 mg	38 (51.4%)
	25 mg	16 (21.6%)
*Follow-up periods (months)		25.9 (10.7–45.2)
*1 cycle-RDI (%)		75.0 (61.8–84.8)
*2 cycle-RDI (%)		71.9 (55.5–77.4)
DLTs	With	43 (58.1%)
	Without	31 (41.9%)

* Median (interquartile range)

MSKCC, Memorial Sloan-Kettering Cancer Center; CRP, C-reactive protein; BMI, Body Mass Index; RDI, relative dose intensity; DLTs, dose limiting toxicities

Table 2. Comparisons of survivals after sunitinib treatment according to cut-off values of relative dose intensity during initial two cycles

Cut-off value, %	n	PFS HR	95% CI	p-value	OS HR	95% CI	p-value
< 80 vs. ≥ 80	57 vs. 17	1.26	0.65–2.67	0.513	1.51	0.70–3.73	0.308
75	38 vs. 36	2.36	1.32–4.32	0.0038	2.50	1.30–5.06	0.0057
70	36 vs. 38	2.22	1.24–4.01	0.0071	2.70	1.41–5.36	0.0027
65	31 vs. 43	2.69	1.49–4.83	0.0011	3.22	1.69–6.28	0.0004
60	26 vs. 48	2.36	1.28–4.24	0.0062	2.44	1.27–4.63	0.0078

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival

Table 3. Univariate and multivariate analyses for the factors influencing 2c-RDI

	Univariate		Multivariate	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Sex Female (vs. male)	4.45 (1.45–13.6)	0.0138	4.09 (0.85–19.6)	0.078
Age ≥ 65 years-old (vs. < 65 years-old)	3.07 (1.17–8.02)	0.0333	2.89 (0.78–10.7)	0.111
Body weight < 50 kg (vs. ≥ 50 kg)	3.89 (0.92–16.5)	0.0834	5.15 (0.57–46.5)	0.144
MSKCC risk Poor (vs. favorable/intermediate)	0.95(0.29–3.09)	1.00	1.09 (0.21–5.51)	0.920
Serum creatinine level > 2.0 mg/dL (vs. ≤ 2.0 mg/dL)	0.65 (0.18–2.38)	0.750	1.62 (0.25–10.3)	0.610
Initial dose < 37.5 mg (vs. ≥ 37.5 mg)	6.16 (1.75–21.7)	0.0037	9.26 (1.42–60.4)	0.020
DLTs within 2cycle with (vs. without)	7.95 (2.55–24.8)	0.0001	18.6 (3.27–105.3)	0.0010

RDI, relative dose intensity; OR, odds ratio; MSKCC, Memorial Sloan-Kettering Cancer Center; DLTs, dose limiting toxicities

Table 4. Dose limiting toxicities during initial two cycles of sunitinib treatment

	Any grade	Grade ≥ 3
Dose reduction	20 (27.0%)	5 (6.6%)
Treatment interruption	23 (31.1%)	13 (17.6%)
Adverse events requiring in dose reduction or interruption		
Thrombocytopenia	18 (24.3%)	6 (8.1%)
Hand-foot syndrome	10 (13.5%)	0
Leukopenia	9 (12.2%)	6 (8.1%)
Anorexia	8 (10.8%)	2 (2.7%)
Diarrhea	7 (9.5%)	0
Hepatic dysfunction	6 (8.1%)	2 (2.7%)
Fatigue	6 (8.1%)	0
Renal dysfunction	4 (5.4%)	0
Fever	3 (4.1%)	0
Stomatitis	2 (2.7%)	0
Hyperkalemia	1 (1.4%)	1 (1.4%)
Nausea	1 (1.4%)	0
Hematuria	1 (1.4%)	0
Interstitial pneumonia	1 (1.4%)	0
Amylase increased	1 (1.4%)	0

Supplementary Table 1. Patient characteristics

		Low 2c-RDI (n = 31)	High 2c-RDI (n = 43)	P value
* Age (year-old)		68.0 (63–72)	63 (56–67)	0.001
Sex	Male	18 (58.1%)	37 (86.0%)	0.0138
	Female	13 (41.9%)	6 (14.0%)	
*BMI (kg/m^2)		23.1 (20.5–24.3)	23.5 (21.4–25.3)	0.906
Prior nephrectomy	With	26 (83.9%)	40 (93.0%)	
	Radical	26 (83.9%)	37 (86.0%)	0.674
	Partial	0	3 (7.0%)	
	Without	5 (16.1%)	3 (7.0%)	
Metastatic sites	Lung	19 (61.3%)	25 (58.1%)	0.815
	Liver	6 (19.4%)	4 (9.3%)	0.304
	Bone	9 (29.0%)	9 (20.9%)	0.584
	Lymph nodes	15 (48.4%)	14 (32.6%)	0.228
Pathology	Clear cell carcinoma	20 (64.5%)	35 (81.4%)	
	Non- clear cell carcinoma	11 (35.5%)	8 (18.6%)	
	Papillary renal cell carcinoma II	3 (9.7%)	1 (2.3%)	0.115
	Clear cell carcinoma with spindle cell	4 (12.9%)	1 (2.3%)	
	Others/Unknown	4 (12.9%)	6 (14.0%)	
MSKCC risk	Favorable	4 (12.9%)	16 (37.2%)	
	Intermediate	21 (67.7%)	19 (44.2%)	0.057
	Poor	6 (19.4%)	8 (18.6%)	

*Serum creatinine level (mg/dL)		1.12 (0.82–1.61)	1.38 (1.02–1.97)	0.27
*Serum CRP level (mg/dL)		0.66 (0.31–4.62)	0.39 (0.21–3.37)	0.64
Initial dose (mg)	50 mg	3 (9.7%)	17 (39.5%)	
	37.5 mg	16 (51.6%)	22 (51.2%)	0.0001
	25 mg	12 (38.7%)	4 (9.3%)	
*Follow-up periods (months)		11.8 (6.74–34.4)	31.2 (21.1–50.6)	0.0036
*1 cycle-RDI (%)		51.7 (50–68.8)	75.0 (75.0–87.5)	< 0.0001
*2 cycle-RDI (%)		50.9 (37.5–59.0)	75.0 (75.0–84.4)	< 0.0001
DLTs	With	26 (83.9%)	17 (39.5%)	0.0001
	Without	5 (16.1%)	26 (60.5%)	

* Median (interquartile range)

MSKCC, Memorial Sloan-Kettering Cancer Center; CRP, C-reactive protein; BMI, Body Mass Index; RDI, relative dose intensity; DLTs, dose limiting toxicities