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One-month relative dose intensity of not less than 50% predicts favourable progression-free survival in sorafenib therapy for advanced renal cell carcinoma in Japanese patients

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ABSTRACT

Background: Sorafenib is a multikinase inhibitor used as a second-line treatment for metastatic renal cell carcinoma (mRCC). However, it is very difficult to estimate sorafenib dosage because it is difficult to maintain stable administration and dosage intervals due to several side-effects. We examined the correlation between relative dose intensity (RDI) and clinical outcome of sorafenib therapy in a multi-institutional study.

Methods: A study population of 70 first-line therapy-refractory patients with pathologically confirmed RCC was eligible for this investigation. Clinical outcomes were evaluated according to clinicopathological features and RDI for 1 month (1M-RDI).

Results: There was significant difference in progression-free survival (PFS) time but not overall survival (OS) time when the 1M-RDI cut-off value was $\geqslant$50%. In 15 patients (21.4%) with 1M-RDI of <50%, median PFS time was 4.1 months (95% I collagen (95% CI): 2.0–6.2), whereas it was 10.5 months (95% CI: 7.6–13.4) in the patients with 1M-RDI of $\geqslant$50% ($P = 0.022$). Multivariate analysis showed 1M-RDI status to be significantly associated with PFS (HR: 3.838, 95% CI: 1.658–8.883, $P = 0.002$) but not OS ($P = 0.328$).

Conclusion: Although this study was retrospective, a 1M-RDI cut-off value of $\geqslant$50% for sorafenib may be the first factor to predict PFS but not OS in cytokine pretreated mRCC patients. The data indicate that a dose of 400 mg/day of sorafenib administered succes-

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sively for the first one month was necessary to prolong disease stabilisation and could be tolerated by Japanese patients.

1. Introduction

Renal cell carcinoma (RCC) is the most common tumour arising in the kidney.[1] The outlook for patients with distant metastases is poor; the 5-year survival rate for patients presenting with stage IV RCC is <10%. Several treatment modalities have been used to treat metastatic RCC (mRCC), including immunotherapy.[2] The first therapeutic breakthrough in the treatment of advanced RCC was the development of multi-targeted tyrosine kinase inhibitors (TKIs), including sorafenib, sunitinib and pazopanib. In the phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), sorafenib doubled progression-free survival (PFS) time, showed a significant benefit in overall survival (OS) compared with placebo and had a manageable safety profile.[3] Akaza et al. reported that the clinical outcome of a phase II study to investigate sorafenib therapy in Japanese patients was better than that of TARGET, and sorafenib is generally well tolerated in Japanese patients.[4] Since approval in 2008 in Japan, sorafenib has been an effective treatment to prolong PFS time, but its toxicity in Japanese patients tends to be more severe than that in patients of other countries. Recently, Ueda et al. reported that maintenance with 800 mg was difficult and recommended dose reduction in Japanese patients.[5] However, no reports have addressed appropriate doses of sorafenib.

Estimation of sorafenib dosage is very challenging because TKI dosage and dosage intervals are difficult to maintain due to several side-effects such as hand-foot skin reaction, diarrhoea and hypertension.[5] Relative dose intensity (RDI) is a very useful tool for evaluation of the total delivered dose of a chemotherapy drug per unit of time expressed as a percentage of the target dose.[6,7] There are no reports on the correlation between the RDI of sorafenib and clinical outcome in RCC. Therefore, we calculated the RDI of sorafenib and examined the relation between the RDI of sorafenib and prognosis in a multi-institutional study of cytokine-refractory mRCC patients.

2. Material and methods

2.1. Patients

We used a database comprising 98 patients treated from April 2005 to July 2010 with sorafenib for first-line therapy-refractory mRCC at Osaka University Graduate School of Medicine and its affiliated hospitals listed in the acknowledgements. Patients without pathologically confirmed RCC from their primary or metastatic sites and those with incomplete data were excluded. Thus, 70 patients were eligible for this study. Patients were evaluated for this study at the time of sorafenib administration according to Memorial Sloan-Kettering Cancer Center (MSKCC) risk groups,[8] and their initially diagnosed tumours were staged according to the AJCC (2002) cancer staging classification.[9] Most of the patients received continuous treatment with oral sorafenib at a dose of 400 mg twice daily. Doses were delayed or reduced if patients experienced clinically significant haematologic or other adverse events that were considered to be related to sorafenib. Dose intensity (DI) was defined as the cumulative dose received divided by the duration of the study therapy in weeks. RDI was defined as DI divided by the dose prescribed for the duration of the study therapy (800 mg × the number of days the patient received treatment).

Clinical features evaluated were age, sex, number of organs involved in metastasis, tumour pathology, initial TNM stage, MSKCC risk groups, initial sorafenib dose and RDI. The study was approved by an institutional review board with Osaka University providing the necessary institutional data-sharing agreements before initiation of the study.

2.2. Follow-up regimen

Patient follow-up generally consisted of a history, physical examination, routine blood work, abdominopelvic computed tomography (CT) and chest radiography. Elective bone scan and chest CT were performed when clinically indicated by several urologists. Tumour response was evaluated by the treating urologist every 1–3 months according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Adverse events related to sorafenib therapy were recorded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0. OS time was calculated from the date of initiation of sorafenib treatment until death or the date of the patient's last follow-up visit. PFS time was measured from the date of initiation of sorafenib treatment until documented disease progression, death from disease progression or the date of the patient's last follow-up visit. Both OS and PFS rates were calculated by the Kaplan–Meier method.

2.3. Statistical analysis

The primary aim was to determine whether the 1-month RDI (1M-RDI) of sorafenib could become a predictive marker of OS and PFS for mRCC patients. Cohorts were defined by sex (male or female), age (<70 years old or ⩾70 years old), number of organs involved in metastasis (single or multiple), pathological histology (clear cell carcinoma only or other histology), initial TNM stage (stage I, II, and III or stage IV), MSKCC risk categories (favourable or intermediate and poor), initial sorafenib dose (800 mg/day or <800 mg/day) and 1M-RDI (<50% or ⩾50%). Associations between 1M-RDI status and clinicopathological features were evaluated with Fisher's exact test and Pearson's chi-square test. In the univariate analysis, survival rates were compared by log rank test according to the clinicopathological features mentioned. We used the Cox regression model to calculate the hazard ratio (HR) for univariate and multivariate analyses. Prognostic factors related to PFS and CSS were analysed with Cox regression analysis using a

step-wise forward selection with $P < 0.05$ as the criterion for model entry or stay for multivariate analysis. Statistical significance was set as $P < 0.05$. Statistical analysis was performed with the Statistical Package for the Social Sciences software, version 16.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

The clinical and pathological characteristics of the 70 patients with mRCC in this study are shown in Table 1. Median age was 71 years (range, 52–92 years) and the majority of the patients were male (85.7%). Most patients had an Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) score of 0 (45 patients) or 1 (22 patients) and were in the intermediate MSKCC risk group (74.3%). All patients had undergone radical nephrectomy, and their primary histology was clear cell carcinoma (90%). Sixty-eight (97.1%) patients had been treated previously with interferon-alpha, and 30 (42.9%) and 5 (7.1%) patients had been treated with interleukin-2 and other TKIs, respectively. The most common sites of metastasis were lung (80%), bone (24.3%) and liver (20%). The initially administered doses of sorafenib were 800 mg in 61 patients, 400 mg in 7 patients, and 200 mg in 2 patients. In 20 patients (28.5%), continued administration seemed intolerable due to adverse events (AE) (intolerant group). The median period of sorafenib administration was 42.5 days (range 4–504 days) in the intolerant group. 1M-RDI was 100% in 33 patients, and median and average 1M-RDIs were 95% and 77%, respectively (range 7–100%). Radiologically confirmed complete response (CR), partial response (PR) and stable disease (SD) for 3 months as the best objective responses were observed in 1 (1.4%), 16 (22.9%) and 26 (37.1%) patients, respectively, and the disease control rate was 61.4% (Table 2). No patients discontinued treatment within 1 month because of disease progression. Median follow-up time was 5.8 months (range, 0.8–24.0 months).

Table 1 – Clinical and pathologic characteristics of 70 patients.

Characteristic	1M-RDI ⩾50% $n = 55$	1M-RDI <50% $n = 15$	P-value
Age (median)	52–92 (68)	58–84 (75)	0.227
Sex			
Male	49	11	0.122
Female	6	4	
Clinical T stage			
I, II, III	24	7	0.834
IV	31	8	
MSKCC risk group			
Favourable	10	3	0.872
Intermediate + poor	45	12	
Metastatic site			
Single	23	7	0.737
Multiple	32	8	
Histology			
Clear cell carcinoma only	44	11	0.577
Others	11	4	
Initial sorafenib dose			
800 mg/day	50	11	0.071
Less than 800 mg/day	5	4	

1M-RDI: 1-month relative dose intensity; MSKCC: Memorial Sloan-Kettering Cancer Center.

3.2. Relation between 1M-RDI and treatment results

We established cut-off values of 1M-RDI in this study at 10% intervals from a cut-off value of 90% and conducted univariate analysis of treatment results at individual points (Table 3). There was a significant difference in PFS when the 1M-RDI cut-off values were ⩾50% and no significant difference in OS at any 1M-RDI cut-off value. Moreover, there was no significant difference in any 1M-RDI cut-off value to predict tumour control (CR, PR, or SD) with sorafenib treatment. In this study, we used a 1M-RDI of 50% as the cut-off value. Patient characteristics according to the 1M-RDI cut-off values of ⩾50% and <50% are shown in Table 1. Associations between these two groups and clinicopathologic factors as analysed by Pearson's chi-square test showed no significant difference between the two groups.

3.3. Univariate analysis of predictive factors for PFS and OS

Median PFS time and OS time were 9.0 months and 24.6 months, respectively (Fig. 1a, b). Median PFS time was 4.1 months (95% I collagen (95% CI): 2.0–6.2) in the patients with 1M-RDI <50% and 10.5 months (95% CI: 7.6–13.4) ($P = 0.022$) in the patients with 1M-RDI ⩾50% (Fig. 2a). The difference in OS between these two patient groups was not statistically significant ($P = 0.313$). MSKCC risk group was significantly associated with an increase in PFS time but not OS time ($P = 0.034$, 0.101, respectively). Median PFS time was not reached at the time of this analysis for patients in the favourable risk group, but it was 8.0 months (95% CI: 5.2–10.8) for patients in the intermediate and poor risk group (Fig. 2b). Sex, age, initial clinical stage, number of organs involved in metastasis, initial sorafenib dose, and tumour histology did not confer significant differences in PFS and OS (Table 4 and data not shown).

3.4. Multivariate analysis of predictive factors for PFS and OS

Multivariate analysis showed 1M-RDI status to be significantly associated with PFS (HR: 3.838, 95% C: 1.658–8.883, $P = 0.002$) but not with OS ($P = 0.328$) (Table 4 and data not shown).

Table 2 – Clinical responses to sorafenib therapy.

Clinical response	Number of patients
CR	1 (1.4%)
PR	16 (22.9%)
SD	26 (37.1%)
Disease stabilisation	43 (61.4%)

CR: complete response; PR: partial response; SD: stable disease.

Table 3 – Comparison of treatment results according to 1M-RDI cut-off value.

1M-RDI cut-off point (%)	Patient number	PFS			OS		
	N	Exp	95% CI	P	Exp	95% CI	P
<90 versus ⩾90	33/37	1.647	0.841–3.223	0.145	1.060	0.339–2.817	0.908
<80 versus ⩾80	29/41	1.429	0.722–2.826	0.305	0.906	0.310–2.645	0.857
<70 versus ⩾70	23/47	1.418	0.675–2.981	0.357	0.974	0.310–3.064	0.964
<60 versus ⩾60	24/46	1.330	0.649–2.725	0.435	0.681	0.189–2.457	0.558
<50 versus ⩾50	15/55	2.370	1.100–5.108	**0.028**	0.370	0.049–2.882	0.347

1M-RDI: 1-month relative dose intensity; PFS: progression-free survival; OS: overall survival; CI: confidence interval.

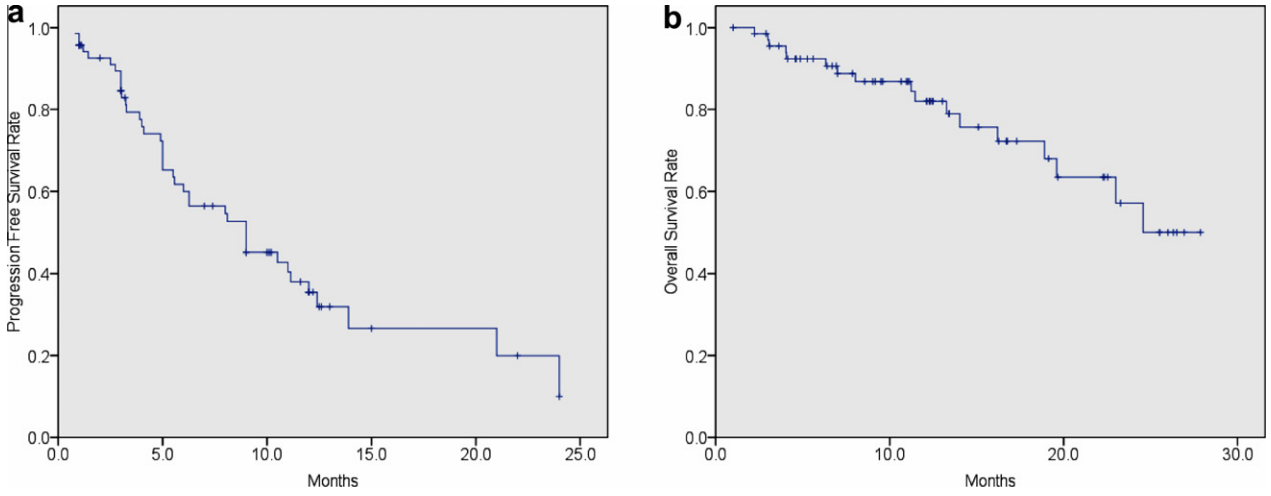

Fig. 1 – Probability estimates of progressive-free survival rate (a) and overall survival rate (b) in 70 patients receiving sorafenib therapy.

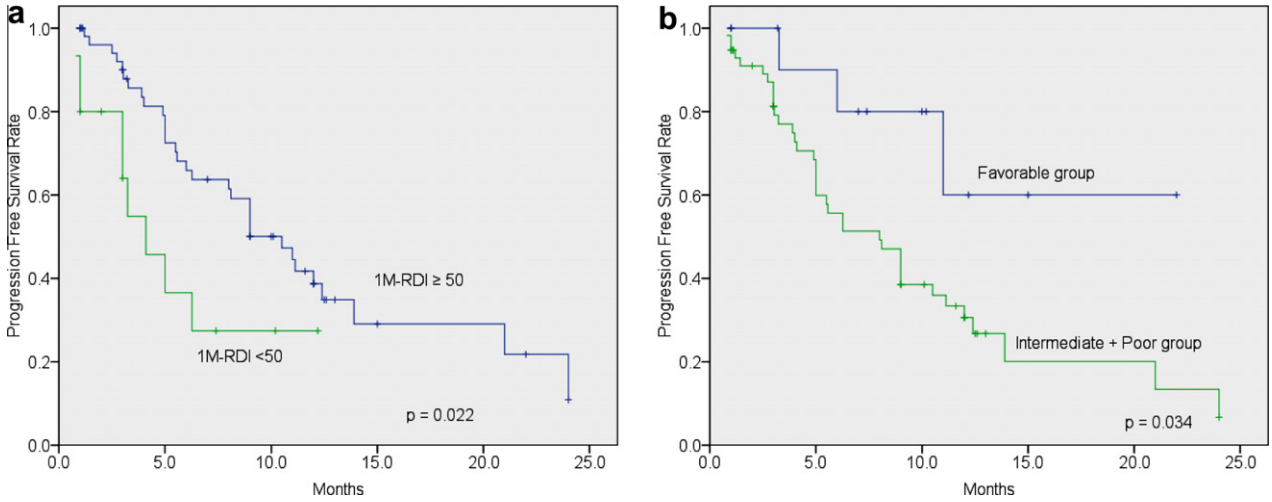

Fig. 2 – Probability estimates of progressive-free survival rate in 70 patients into two groups based on 1-month relative dose intensity of 50% as a cut-off value (a) and Memorial Sloan-Kettering Cancer Center (MSKCC) risk groups (b).

MSKCC risk group was significantly associated with PFS (HR: 5.029, 95% CI: 1.466–17.252, $P = 0.010$). Other factors were not significantly associated with PFS and OS by multivariate analysis (Table 4 and data not shown).

4. Discussion

Sorafenib is a multikinase inhibitor with proven efficacy as a second-line treatment in mRCC. We retrospectively analysed

Table 4 – Univariate and multivariate analysis of predictive factors for PFS.

Prognostic factor	Univariate	Multivariate		
	P	Exp	95% CI	*P*
Sex (female versus male)	0.292	–	–	–
Clinical stage (I, II, III versus IV)	0.944	–	–	–
MSKCC risk category (Favourable versus intermediate + poor)	**0.034**	5.029	1.466–17.252	**0.010**
Metastatic site (Single versus multiple)	0.640	–	–	–
Age (years) (<70 versus ⩾70)	0.853	–	–	–
Histology (clear cell only versus others)	0.294	–	–	–
Initial sorafenib dose (800 mg/day versus less than 800mg/day)	0.954	–	–	–
1M-RDI (%) (<50 versus ⩾50)	**0.022**	3.838	1.658–8.883	**0.002**

multi-centre data of Japanese patients who received sorafenib for first-line therapy-refractory mRCC. We also investigated the correlation between clinical features and clinical outcome. In the present study, a 1M-RDI ⩾50% and MSKCC favourable group were found to be a statistically significant factor predictive of favourable PFS but not OS.

Akaza et al. reported data from a phase II study of sorafenib in Japan showing median PFS and OS in 129 patients of 7.9 months and 25.3 months, respectively, and 86.8% of patients attained disease stabilisation.[4] In a retrospective study of 50 patients, Ueda et al. reported median PFS and OS of 7.3 months and 11.9 months, respectively, and 68% of patients attained disease stabilisation.[5] These clinical outcome data were similar to our data, although our study contained 5 patients (7.1%) in the MSKCC poor risk group. Median PFS time of Japanese patients was better than that of the TARGET data. We believe this is due to epidemiological and genetic differences between Japanese and US/European populations. In the Japanese phase II study, 10 patients (7.6%) discontinued treatment due to AE, and sorafenib was reported to be generally well tolerated in Japanese patients.[4] However, Ueda et al. reported in their retrospective study that 28 of 50 patients (56.0%) discontinued treatment as a result of AE and noted that reduced doses were thought to be more preferable for Japanese patients.[5] Although the rate of discontinuance was lower in our study (28.5%), maintenance with an 800-mg dose was very difficult for our Japanese patients to tolerate. Determining the appropriate dose of sorafenib is challenging because of difficulties in maintaining stable dosing and dosage interval due to AE.

There is a correlation between the dose of an antitumour agent and its therapeutic effects.[7,10,11] Although previous studies reported that an increased DI improved treatment results for other malignancies, survival may be shortened even when more potent therapeutic effects are achieved because of treatment-associated toxicity from the higher doses of the antitumour agent. To our knowledge, no reports have discussed a correlation between RDI and sorafenib. Recently, Hutson et al. reported that in long-term follow-up of patients from TARGET, AEs of any severity tended to develop early during treatment with sorafenib, and 14 of 17 (82.4%) patients suffered AEs in the first treatment cycle, a frequency higher than in any other cycle thereafter.[12] In the present study, the median period of sorafenib administration was 42.5 days (range 4–504 days) in the intolerant patients. Therefore, we retrospectively analysed the correlation between 1M-RDI and clinical outcome to determine the necessary minimum dose of sorafenib. The results showed that a 1M-RDI of not less than 50% was significantly related to favourable PFS but not to OS in both univariate and multivariate analyses. We observed a non-significant tendency in which an increase in 1M-RDI improved PFS and OS (data not shown). It is important to maintain disease stabilisation when TKIs are administered to mRCC patients because it is difficult to attain a complete response with TKIs. A 1M-RDI of 50% is equal to administration of 400 mg/day of sorafenib for 1 month. Although an initial sorafenib dose of 800 mg/day was used in 61 patients (87.1%), that dose could be maintained in only 32 patients (45.7%). It was difficult to determine the appropriate initial sorafenib dose. However, our data indicate that at a minimum, administration of 400 mg/day of sorafenib successively for 1 month was necessary to attain disease stabilisation, and such a dose could be tolerated in most Japanese patients because almost 80% patients could achieve a 1M-RDI of not less than 50%.

With regard to other clinicopathological factors, compared with the intermediate and poor MSKCC risk classification, the favourable risk classification was a good predictive factor for PFS but not OS in both the univariate and multivariate analyses. The relation of survival to treatment programme was studied in the development of the MSKCC model. Motzer et al. suggested that patients with favourable prognostic features according to the model may derive therapeutic benefit from cytokine therapy.[8] In the TKI era, Escudier et al. examined the potential biomarkers of disease prognosis and drug benefit from the phase III placebo-controlled TARGET results. ECOG PS score, MSKCC classification and VEGF level were independent predictive factors for OS but not for PFS.[13] Recently, Peña et al. additionally reported that TIMP-1 was a predictive marker for OS by multivariate analysis that also included ECOG PS score, MSKCC classification and other biomarkers, and no biomarkers predicted the outcome for PFS by multivariate analysis.[14] Jonasch et al. also reported no predictive markers, which included treatment arm (sorafenib vs sorafenib and IFN), ECOG PS, and anaemia, for PFS and OS by multivariate analysis.[15] With regard to tumour control, Zhang et al. found by multivariate analysis that favourable pretreatment ECOG PS score, presence of lymph node metastasis and the use of nephrectomy were statistically significant predictive factors.[16] In our study, however, no factors predicted tumour control with sorafenib treatment. Thus, to

our knowledge, the present study might be the first in the English literature to report multivariate analysis showing that a 1M-RDI of not less than 50% for sorafenib in the treatment of mRCC might be a predictive factor of favourable PFS but not of favourable OS.

We could not investigate factors necessary for maintaining the 1M-RDI at $\geqslant$50% in the present study. Maintaining the 1M-RDI at $\geqslant$60% was difficult in female patients ($P = 0.010$), and maintaining the 1M-RDI at $\geqslant$70% was difficult in both female patients ($P = 0.007$) and patients >70 years of age ($P = 0.050$). There was no difference between initial doses of sorafenib of 800 mg/day and <800 mg/day. Although we could not clarify the reason for the lower 1M-RDI in female and elderly patients, they were not necessary factors for maintaining the 1M-RDI at $\geqslant$50% ($P = 0.122$ and $P = 0.227$, respectively). Sorafenib should be administered carefully, especially to female and elderly patients, to maintain a 1M-RDI of $\geqslant$50%, regardless of whether the initial dose of sorafenib is 800 mg/day or <800 mg/day.

In conclusion, a 1M-RDI of not less than 50% for sorafenib is, to our knowledge, the first factor found to be predictive of superior PFS but not OS in first-line therapy-refractory mRCC patients. To prolong disease stabilisation, administration of 400 mg/day of sorafenib successively for the first 1 month was necessary, and such a dose could be tolerated in most Japanese patients. A larger study will be necessary to determine the appropriate doses of sorafenib.

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Conflict of interest statement

None declared.

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