Med Oncol (2015) 32:78
DOI 10.1007/s12032-015-0528-8

ORIGINAL PAPER

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

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Received: 20 January 2015 / Accepted: 13 February 2015 / Published online: 20 February 2015

Abstract The objective of this study was to investigate the significance of changes from the standard dosing schedule of sunitinib, which is 4 weeks of treatment and 2 weeks off (schedule 4/2), to an alternative schedule with 2 weeks of treatment and 1 week off (schedule 2/1), after encountering dose-limiting toxicity in 45 consecutive Japanese patients with metastatic renal cell carcinoma (mRCC). Despite a definitively improved relative dose intensity of sunitinib by changing from schedule 4/2 to 2/1, this difference was not significant. Adverse events (AEs) occurred in all patients on both schedules 4/2 and 2/1; however, the proportion of patients experiencing AEs $\geq$ grade 3 on schedule 2/1 was significantly lower than that on schedule 4/2. Quality of life (QOL) analysis using SF-36 revealed that all eight scores during schedule 2/1 were more favorable than those during schedule 4/2, and there were significant differences in 2 of the 8 scores between these two schedules. Furthermore, multivariate analyses, which were performed to evaluate the contribution of several AEs on schedule 2/1 to the improvement of each score in SF-36, revealed that fatigue had independent impacts on two scores, despite the lack of an independent association between any scores and the remaining AEs examined. These findings suggest that schedule 2/1 is the optimal dosing schedule of sunitinib against mRCC that balances efficacy and toxicity, since treatment on schedule 2/1 resulted in a markedly improved QOL compared with that on schedule 4/2 by relieving the profile of sunitinib-related AEs.

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Keywords Metastatic renal cell carcinoma · Sunitinib · Alternative dosing schedule · Quality of life

Introduction

In recent years, several types of novel molecular-targeted agent against renal cell carcinoma (RCC) have been developed based on intensive investigation of the molecular mechanism involved in the progression of RCC, and the introduction of these agents into clinical practice has resulted in a paradigm shift in the therapeutic strategy for metastatic RCC (mRCC) [1]. Of these new drugs, sunitinib, an orally available receptor inhibitor of multiple tyrosine kinases, such as vascular endothelial growth factor receptors and platelet-derived growth factor receptors, is widely regarded as a current standard of care for patients with untreated mRCC [2]. In experimental studies, sunitinib was shown to have powerful inhibitory effects on tumor cell proliferation as well as angiogenesis [3], while in a clinical setting as well, sunitinib was demonstrated to have a significantly superior efficacy to interferon-α (IFN-α) as first-line therapy for mRCC, with a median progression-free survival (PFS) of 11 and 5 months in the sunitinib and IFN-α arms, respectively [4].

The current standard dosing schedule of sunitinib is 50 mg daily for 4 weeks, followed by 2 weeks off (schedule 4/2), which was determined according to preclinical pharmacokinetic and pharmacodynamic data on this drug to maintain its optimal plasma level. In addition, despite being planned to provide continuous administration, an interval of 2 weeks off was recommended to allow patients to recover from the toxicities associated with bone marrow and adrenal functions observed in animal studies [5]. Based on these findings, several subsequent clinical

trials examined schedule 4/2, and this regimen was approved due to its excellent antitumor activity and manageable safety profile [4, 6].

In real world clinical practice, maintenance of the dose intensity of sunitinib is frequently challenging as a result of treatment-related adverse events (AEs), such as fatigue, hypertension, hand-foot syndrome (HFS) and thrombocytopenia, resulting in the necessity of dose reduction or interruption in a large proportion of patients receiving sunitinib [7], whereas Houk et al. [8] analyzed pharmacologic data from six clinical trials, and reported that patients with high-level drug exposure showed longer overall survival, prolonged time to progression and increased reduction of the tumor burden. Therefore, alternative schedules of sunitinib for mRCC patients have been explored in order to improve its tolerability and maintain an effective dose intensity, and favorable outcomes with them have been reported [9–12]; however, it remains unclear whether the use of an alternative dosing schedule of sunitinib for patients with mRCC has a significant impact on their quality of life (QOL), which has been shown to be significantly affected by the administration of sunitinib [13–16]. Considering the above, we retrospectively reviewed the findings on changing from schedule 4/2 to an alternative schedule with 2 weeks of treatment and 1 week off (schedule 2/1) after encountering dose-limiting toxicity in a total of 45 consecutive Japanese patients with mRCC focusing on its impact on the health-related QOL (HRQOL).

Patients and methods

This was conducted as a retrospective study, reviewing clinicopathological data from a total of 45 consecutive Japanese patients with mRCC who started treatment with sunitinib using schedule 4/2 between January 2012 and September 2014, but switched to schedule 2/1 due to dose-limiting toxicity. Of these 45 patients, there were 2 who did not receive radical nephrectomy and underwent needle biopsies of the primary tumor to determine the histological subtype; thus, all 45 were pathologically diagnosed with primary RCC. In this series, sunitinib was initially administered to all patients based on the standard schedule of 4/2 reported by Motzer et al. [4]. In cases with severe treatment-related AEs, the treating physician determined whether to switch to the alternative schedule 2/1 reported by Najjar et al. [9] or attempt dose reduction based on the patient's subjective as well as objective toxicity, considering the type and timing for each patient.

As baseline assessments, risk classification was conducted based on the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification [17], and all patients were examined by computed tomography (CT) of the brain, chest and abdomen, and radionuclide bone scan. As a rule, after the introduction of sunitinib, patients were seen in the clinic every 6 weeks at the end of the 4 weeks of dosing on schedule 4/2 and at the end of the second 2 weeks of dosing on schedule 2/1. At each visit, AEs associated with sunitinib were evaluated by the treating physician based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Tumor measurements were generally performed by CT every 12 weeks after the initiation of treatment with sunitinib, and responses were assessed according to the Response Evaluation Criteria in Solid Tumors 1.0.

A HRQOL survey was carried out using the Medical Outcomes Study 36-Item Short Form (SF-36) Japanese version 2.0 [18] every other clinic visit. This questionnaire consists of 36 self-administered questions for quantifying the HRQOL with eight multi-item scales for the health status covering the mental as well as physical aspects, which includes the physical function (PF), role limitations because of physical health problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social function (SF), role limitations because of emotional problems (RE) and mental health (MH). Each domain is scored on a scale between 0 and 100, with higher scores indicating a superior status. We standardized these scores using Japanese population norms to yield mean scores of 50 and standard deviations (SDs) of 10 [18, 19].

All statistical analyses were performed using Statview 5.0 software (Abacus Concepts, Inc., Berkeley, CA, USA), and probability (P) values less than 0.05 were considered significant. Differences between the two dosing schedules were analyzed using the Chi squared test or unpaired t–test. Forward stepwise logistic regression analysis was used to determine the association between several parameters and scale scores calculated based on the SF-36 surveys.

Results

The characteristics of the 45 patients included in this study are summarized in Table 1. The median intervals of treatment with sunitinib on schedule 4/2 and schedule 2/1 in these 45 patients were 3.4 months (range 1.3–19.7 months) and 8.9 months (range 2.3–21.4 months), respectively. Median relative dose intensities (RDIs) of sunitinib during treatment on schedules 4/2 and 2/1 were 60.1 % (range 45.7–90.7 %) and 66.5 % (range 40.5–88.9 %), respectively; however, there was no significant difference in the RDI between the two dosing schedules.

Table 2 shows the profiles of AEs related to treatment with sunitinib according to the dosing schedule. All patients experienced AEs on both schedules 4/2 and 2/1; therefore, there was no significant difference in the overall

incidence of AEs between these two dosing schedules. However, the proportion of patients experiencing AEs ≥ grade 3 on schedule 2/1 was significantly lower than that on schedule 4/2. Furthermore, there were significant differences between these two groups in the incidences of AEs, including diarrhea, HFS, hypertension and fatigue, all of which favored schedule 2/1 compared with schedule 4/2, while the incidence of thrombocytopenia corresponding to ≥ grade 3 on schedule 2/1 was significantly lower than that on schedule 4/2.

The HRQOL of the 45 mRCC patients was analyzed using the SF-36 survey (Fig. 1). All eight scores during schedule 2/1 were more favorable than those during schedule 4/2, and there were significant differences in 2 (GH and MH) of the 8 scores between these two dosing schedules. As shown in Table 3, the contribution of several AEs on schedule 2/1 to the improvement of each scale score in the SF-36 survey by switching from schedule 4/2 to 2/1 was then evaluated by uni- and multivariate logistic regression analyses. Univariate analysis revealed that hypothyroidism, diarrhea, HFS, hypertension and fatigue were associated with 2 (PF and GH), 2 (VT and MH), 2 (PF, GH), 1 (PF) and 4 (PF, GH, SF, MH) scale scores, respectively. However, only fatigue appeared to have independent impacts on 2 (GH and SF) scale scores on multivariate analysis.

Table 1 Patient characteristics

Median age (years, range)	61.5 (41–80)
Gender (%)	
Male	36 (80.0)
Female	9 (20.0)
Nephrectomy (%)	
Yes	43 (95.6)
No	2 (4.4)
Histology of primary tumor (%)	
Clear cell cancer	41 (91.1)
Non-clear cell cancer	4 (8.9)
Major metastatic organs (%)	
Lung	29 (64.4)
Lymph node	14 (31.1)
Bone	13 (28.9)
Liver	6 (13.3)
Brain	4 (8.9)
MSKCC risk group (%)	
Favorable	12 (26.7)
Intermediate	24 (53.3)
Poor	9 (20.0)

MSKCC Memorial Sloan-Kettering Cancer Center

Discussion

As a result of the pivotal randomized phase III clinical trial [4], sunitinib is currently regarded as a novel reference standard of care for the first-line treatment of mRCC patients. Several studies have also confirmed the efficacy of sunitinib against mRCC in routine clinical settings [20, 21]. However, it has been well documented that significant AEs occur in a large proportion of mRCC patients treated with sunitinib [7], resulting in possible interference with its therapeutic activity [8]. Accordingly, it would be necessary to develop an alternative schedule for sunitinib that can maximize the dosing intensity of this agent. Such a point of view seems to be particularly true of Japanese patients with

Table 2 Major adverse events according to dosing schedule of sunitinib

	Schedule 4/2		Schedule 2/1		*P* value	
	All grades (%)	Grade > 3 (%)	All grades (%)	Grade > 3 (%)	All grades (%)	Grade > 3 (%)
All adverse events	45 (100)	36 (80.0)	45 (100)	22 (48.9)	–	0.0020
Thrombocytopenia	44 (97.8)	23 (51.1)	41 (91.1)	13 (28.8)	0.17	0.031
Leukopenia	36 (80.0)	8 (17.8)	33 (73.3)	3 (6.7)	0.45	0.11
Anemia	28 (62.2)	4 (8.9)	26 (53.6)	3 (6.7)	0.67	0.16
Hypothyroidism	28 (62.2)	1 (2.2)	20 (44.4)	0 (0)	0.091	0.31
Diarrhea	27 (60.0)	1 (2.2)	16 (50.0)	0 (0)	0.020	0.31
Skin discoloration	26 (57.8)	0 (0)	19 (42.2)	0 (0)	0.14	–
Hand-foot syndrome	25 (55.6)	5 (11.1)	15 (33.3)	1 (2.2)	0.019	0.091
Hypertension	25 (55.6)	5 (11.1)	16 (35.6)	1 (2.2)	0.034	0.091
Fatigue	23 (51.1)	8 (17.82)	13 (28.9)	4 (8.9)	0.031	0.21
Stomatitis	13 (28.9)	0 (0)	11 (24.4)	0 (0)	0.63	–
Dysgeusia	13 (28.9)	0 (0)	10 (22.2)	0 (0)	0.47	–

mRCC, since they have been shown to exhibit a more sensitive toxicity profile of sunitinib than Western populations [4, 20–22]. Furthermore, although there have been several studies showing promising outcomes of alternative dosing schedules of sunitinib in mRCC patients, it has not been investigated whether the introduction of an alternative schedule affects the QOL of these patients. Taken together, in this study, we retrospectively reviewed findings on changing from the standard dosing schedule of sunitinib (schedule 4/2) to an alternative schedule (schedule 2/1) after encountering dose-limiting toxicity in a total of 45 consecutive Japanese mRCC patients, focusing on its effect on the HRQOL.

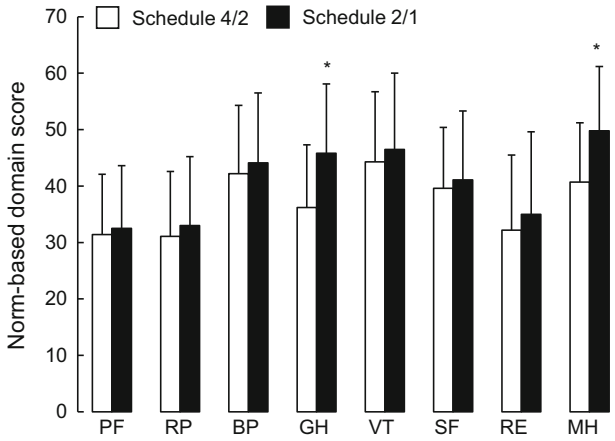

Fig. 1 Comparison of scale scores using the medical outcomes study 36-Item Short Form survey between schedules 4/2 and 2/1 in 45 patients with metastatic renal cell carcinoma who received sunitinib. *PF* physical function, *RP* role limitations because of physical health problems, *BP* bodily pain, *GH* general health perception, *VT* vitality, *SF* social function, *RE* role limitations because of emotional problems, *MH* mental health. *Significantly different from values on schedule 4/2 ($P < 0.01$)

Although there has been heterogeneity in practice patterns of previously reported alternative dosing schedules of sunitinib [12], schedule 2/1 was selected in this series due to the following reasons: a randomized study comparing a 37.5 mg continuous daily dose regimen of sunitinib with schedule 4/2 showed no difference in the tolerability between these two regimens, but demonstrated a superiority of schedule 4/2 in time to tumor progression, suggesting the advantage of higher intermittent dosing over the continuous administration of a lower dose [23], while in clinical practice, it is frequently recognized that AEs associated with the use of sunitinib increase throughout each cycle, and tend to be worse in the final 2 weeks during schedule 4/2. In fact, switching from schedule 4/2 to schedule 2/1 resulted in the reduction of sunitinib-induced

Table 3 Uni- and multivariate analyses of the association between several adverse events and scale scores in the SF-36 survey

Univariate analysis (*P* value)	PF	RP	BP	GH	VT	SF	RE	MH
Thrombocytopenia	0.60	0.44	0.12	0.63	0.20	0.24	0.28	0.38
Leukopenia	0.40	0.16	0.32	0.55	0.36	0.87	0.64	0.49
Anemia	0.61	0.51	0.88	0.47	0.77	0.32	0.18	0.53
Hypothyroidism	0.047	0.31	0.65	0.036	0.57	0.67	0.39	0.58
Diarrhea	0.38	0.70	0.34	0.32	0.044	0.11	0.44	0.039
Skin discoloration	0.44	0.55	0.38	0.29	0.44	0.56	0.45	0.90
Hand-foot syndrome	0.037	0.15	0.41	0.033	0.30	0.39	0.27	0.19
Hypertension	0.045	0.28	0.44	0.19	0.63	0.52	0.33	0.77
Fatigue	0.034	0.11	0.57	0.011	0.084	0.019	0.15	0.041
Stomatitis	0.31	0.54	0.38	0.29	0.37	0.40	0.52	0.61
Dysgeusia	0.38	0.38	0.47	0.74	0.42	0.89	0.29	0.37
Multivariate analysis (*P* value)	PF	RP	BP	GH	VT	SF	RE	MH
Thrombocytopenia	0.65	0.45	0.31	0.49	0.38	0.47	0.49	0.41
Leukopenia	0.49	0.37	0.52	0.63	0.38	0.90	0.54	0.54
Anemia	0.71	0.56	0.89	0.40	0.67	0.52	0.34	0.61
Hypothyroidism	0.18	0.33	0.55	0.16	0.69	0.57	0.44	0.62
Diarrhea	0.48	0.77	0.44	0.39	0.087	0.31	0.55	0.12
Skin discoloration	0.54	0.40	0.59	0.26	0.61	0.57	0.62	0.78
Hand-foot syndrome	0.14	0.45	0.46	0.27	0.41	0.54	0.39	0.44
Hypertension	0.11	0.31	0.52	0.34	0.42	0.66	0.44	0.65
Fatigue	0.090	0.23	0.60	0.040	0.23	0.038	0.36	0.19
Stomatitis	0.42	0.61	0.54	0.77	0.39	0.52	0.47	0.66
Dysgeusia	0.45	0.47	0.60	0.39	0.46	0.85	0.35	0.47

SF-36 Short Form-36 survey, *PF* physical function, *RP* role limitations because of physical health problems, *BP* bodily pain, *GH* general health perception, *VT* vitality, *SF* social function, *RE* role limitations because of emotional problems, *MH* mental health

toxicity in terms of the incidence as well as severity in this series, which was shown to be marked for common and problematic AEs, including diarrhea, HFS, hypertension, fatigue and thrombocytopenia. In addition, despite the lack of significance, the RDI was also definitively improved from 60.1 to 66.5 % by introducing schedule 2/1. Collectively, these findings clearly showed that even if dose-limiting toxicity occurred on schedule 4/2, sunitinib could be continued by the introduction of schedule 2/1 for an additional median of 8.9 months, maintaining an acceptable RDI.

Consideration of the QOL status is particularly important in patients who are usually incurable and characterized by reduced life-expectancy, like those with mRCC, since maintenance of the physical function by relieving disease-associated symptoms is one of the primary objectives of medical intervention for such patients [24]. Therefore, it is of interest to assess the impact of the alternative dosing schedule of sunitinib on the HRQOL of patients with mRCC. In this series, the SF-36 survey in patients with mRCC revealed the improvement of all eight scale scores by switching from schedule 4/2 to 2/1, including 2 scores (GH and MH) showing significant differences between these two schedules. In several previous studies, no significant change in the QOL status of patients with mRCC was noted after the introduction of sunitinib [14, 25]. For example, Cella et al. showed that there were no significant decreases in either the overall health status scores or cancer-specific HRQOL of patients with mRCC after treatment with sunitinib compared with their baseline scores prior to treatment. Considering these findings, the potential effects of schedule 2/1 on the alleviation of sunitinib-associated toxicities compared with those of schedule 4/2 may result in the marked improvement of the HRQOL.

Another point of interest is to identify AEs potentially influencing the HRQOL of mRCC patients receiving sunitinib. In this series, the significance of major AEs observed during schedule 2/1 were evaluated as possible factors having an impact on the improved HRQOL after changing schedule 4/2 to 2/1. Of these, hypothyroidism, diarrhea, HFS, hypertension and fatigue were shown to be significantly correlated with the outcomes of one or more scores on univariate analysis, while only fatigue, but none of the other four significant AEs, appeared to have independent impacts on 2 scores (GH and SF) on multivariate analysis. The HRQOL of cancer patients has been reported to be affected by a wide variety of parameters [24, 26]; however, these findings suggest that excessive fatigue due to treatment with sunitinib could be a significant obstacle to improving the HRQOL by the introduction of schedule 2/1. Although fatigue is a complex and cumulative condition of mRCC patients undergoing multiple treatments, there have been several studies on the impact of fatigue on the QOL of patients receiving sunitinib, similar to that in this study [27, 28]. For example, Cella et al. [27] reported that the relationship between most HRQOL scores and fatigue in mRCC patients treated with sunitinib was close to linear, with unfavorable HRQOL scores corresponding to a higher fatigue grade.

Here, we would like to describe several limitations of this study. Firstly, this was conducted as a retrospective study including a small number of patients. Secondly, despite there being multiple survey systems, only the SF-36 was used to assess HRQOL in this study. Thirdly, this study included Japanese patients alone, who are generally regarded as having strong concerns over illness itself rather than the QOL compared with Western populations [29]; therefore, it may be difficult to apply the findings of this study to all cohorts receiving sunitinib. Fourthly, the present survey of the HRQOL of each patient was performed at the baseline and 3 months after the introduction of TKIs using only the SF-36; however, more useful findings might be expected by addressing changes in the time-dependent QOL status using multiple survey systems. Finally, the decision to switch from schedule 4/2 to 2/1 rather than reduce the dosage was made by the treating physician without the use of objective guidelines, which may affect the current outcomes.

In conclusion, switching from the standard dosing schedule 4/2 to alternative schedule 2/1 could significantly improve the profile of AEs in patients with mRCC who were treated with sunitinib. Furthermore, relief from AEs, particularly fatigue, by the introduction of schedule 2/1 resulted in the achievement of a markedly favorable HRQOL in these patients. Although further examinations in a prospective randomized setting are required to draw a definitive conclusion on the utility of schedule 2/1, this alternative dosing schedule may become a future standard regime of sunitinib for mRCC patients.

Conflict of interest H. Miyake, KI. Harada and M. Fujisawa have received lecture fees from Pfizer, while A. Miyazaki declares no conflict of interest.

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