Original article

Sunitinib dosing schedule 2/1 improves tolerability, efficacy, and health-related quality of life in Chinese patients with metastatic renal cell carcinoma

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Received 8 February 2015; received in revised form 6 March 2015; accepted 7 March 2015

Abstract

Purpose: To assess the efficacy and tolerability of sunitinib dosing schedule of 2 weeks on and 1 week off (schedule 2/1) vs. the traditional schedule of 4 weeks on and 2 week off (schedule 4/2) and its influence on health-related quality of life (HRQoL) in Chinese patients with metastatic renal cell carcinoma (mRCC).

Materials and methods: A retrospective analysis of 108 patients with mRCC who were treated with sunitinib regimens (50 mg daily) between January 2009 and July 2013 was undertaken. Overall, 3 groups of patients were studied according to the dosing schedule they received: schedule 4/2 (n = 50), transitional schedule 2/1 (T2/1; patients switched from schedule 4/2 to 2/1; n = 26), and initial schedule 2/1 (I2/1; n = 32). The tumor response, progression-free survival (PFS) time, adverse events, and HRQoL were assessed and compared among the groups.

Results: The incidences of diarrhea, fatigue, hand-foot syndrome, and neutropenia induced by the treatment of sunitinib were all significantly less common with schedule I2/1 and T2/1 than with schedule 4/2 (P < 0.05). Although there was no statistically significant difference in the tumor response among the 3 groups, the median PFS time was significantly longer with schedule I2/1 than with schedules T2/1 and 4/2 (11.2 vs. 9.4 and 9.5 mo, respectively, P = 0.030), and HRQoL (as determined by 19-item Functional Assessment of Cancer Therapy Kidney Symptom Index scores) was better.

Conclusions: Treatment with sunitinib 50 mg daily using a 2/1 dosing schedule can provide better tolerability and a longer PFS with better HRQoL in Chinese patients with mRCC than the traditional schedule 4/2. © 2015 Elsevier Inc. All rights reserved.

Keywords: Metastatic renal cell carcinoma; Sunitinib; Dosing schedules; Adverse events; Tumor response; Quality-of-life

Financial support: This work was supported by grants from Shanghai Municipal Education Commission for Innovative Research Project, China (no. 14yz084), Military Health Care Special Subject, China (no. 13BJZ29), The National Natural Science Foundation of China, China (nos. 30973006 and 81170637), and Shanghai Municipal Committee of Science and Technology General Program for Medicine, China (no. 11JC1402302). Editing assistance was provided by Shicui Liu of China Oncology Medical Affairs of Pfizer Investment Company Ltd. and Content Ed Net, Shanghai Co. Ltd.

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http://dx.doi.org/10.1016/j.UROLONC.2015.03.008
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1. Introduction

According to current cancer incidence statistics, there were 63,920 new cases of kidney cancer and 13,860 deaths owing to these cancers (including renal cell and renal pelvis carcinomas) in the United States in 2014 [1], and they were the second leading cause of cancer-related death among urinary system diseases. It is generally acknowledged that renal cell carcinoma (RCC) is the most common pathological type of kidney tumor. In clinical practice, a clear diagnosis of RCC is increasingly being achieved with the use of conventional abdominal imaging technologies [2]. The European Association of Urology Guidelines for RCC recommend nephron-sparing surgery as a treatment option for RCC in the early stages [3]; however, the treatment of metastatic RCC (mRCC) remains a thorny issue in urological practice.

With the advent of targeted therapy approaches, use of the oral multitargeted tyrosine kinase inhibitor sunitinib as a first-line agent has been widely adopted for the treatment of advanced and mRCC. Sunitinib is an inhibitor of vascular endothelial growth factor receptors 1 to 3, fibroblast growth factor receptor, FMS-like tyrosine kinase 3 (a class III receptor tyrosine kinase (RTK) structurally related to the receptors for platelet derived growth factor (PDGF)), platelet-derived growth factor receptor, and stem cell factor receptor [4–7]. A phase III clinical trial of sunitinib in patients with mRCC reported that the median progression-free survival (PFS) time was significantly increased by more than 6 months in comparison with interferon alpha treatment [8]. Currently, sunitinib 50 mg daily for 4 weeks followed by 2-weeks-off therapy (schedule 4/2) is recommended as the standard dosing schedule globally [9]. However, adverse events (AEs) associated with sunitinib should be strictly monitored including hypertension, hand-foot syndrome (HFS), proteinuria, cardiac toxicity, bone marrow suppression, fatigue, diarrhea, hypothyroidism, and hepatotoxicity [10], as they result in poor tolerance of the drug and a relatively diminished health-related quality of life (HRQoL). Consequently, a sunitinib dosing schedule of 2 weeks on and 1 week off (schedule 2/1) is increasingly being used as an alternative regimen for reducing the incidence of AEs while achieving a comparable oncological outcome to the traditional schedule 4/2 [11–13].

In this study, we retrospectively compared the efficacy and tolerability of the sunitinib 2/1 dosing schedule with the traditional 4/2 dosing schedule in the treatment of Chinese patients with mRCC. In addition, we also evaluated the influence of the 2/1 dosing schedule on HRQoL.

2. Materials and methods

2.1. Patient populations

Clinical data on 120 patients with mRCC who received sunitinib as first-line therapy at Changzheng hospital and Shanghai hospital between January 2009 and July 2013 were retrospectively summarized and evaluated. Among these patients, 108 who were diagnosed pathologically as having mRCC receiving 1 cycle (6 wk) of treatment at least but were without other organ dysfunction and were not receiving other systemic therapy were considered eligible for inclusion in the study. A whole-body computed tomography scan was routinely performed in all patients to locate and assess the metastases before treatment was started. This study was approved by the Institutional Review Board of Changzheng Hospital of Second Military Medical University, and all patients provided informed consent.

2.2. Treatment regimens

Patients were divided into 3 treatment groups according to the sunitinib dosing schedule they received: a schedule 4/2 group, a transitional schedule 2/1 (T2/1) group, and an initial schedule 2/1 (I2/1) group. The schedule 4/2 group received sunitinib 50 mg daily on a 4-weeks-on/2-weeks-off basis throughout the study. The transitional schedule 2/1 group received sunitinib 50 mg daily on a 2-weeks-on/1-week-off basis. This group included patients who were switched to the schedule 2/1 from the traditional schedule 4/2. These patients were switched to the schedule 2/1 as they were unable to tolerate the severe AEs experienced with the 4/2 dosing schedule. At present, sunitinib should be withdrawn in such patients, and the dosing regimen should only be changed to the schedule 2/1 after the AEs have subsided. The initial schedule 2/1 group received sunitinib 50 mg daily on a 2-weeks-on/1-week-off basis from the beginning of treatment. All eligible patients were fully informed of the performance of the standard schedule 4/2 and the initial schedule 2/1. Most of the patients opted for the schedule 2/1.

2.3. Outcomes assessment

Patients were evaluated in an outpatient clinic at an average of 6-weekly intervals, usually at the end of the 28th day of sunitinib dosing on schedule 4/2 and at the end of the 14th day of dosing on schedule 2/1. During these visits, the following data were collected: initial dose and dose schedule of sunitinib, laboratory abnormalities, and AEs, which were graded according to the National Cancer Institute’s Common Terminology Criteria for AEs, version 4.0. The Memorial Sloan-Kettering Cancer Center risk classification [14] was applied for stratifying the prognostic risks.

HRQoL was assessed via the responses of patients to 2 accepted instruments—the 13-item Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), which scores fatigue from 0 to 52 (a higher score for which indicates less fatigue), and the 19-item Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-19), which scores kidney symptoms from 0 to 76 (a higher score for which indicates fewer symptoms). The 2 QoL questionnaires were administered by the same physician and
an assistant at the beginning of treatment (baseline value) and at the first and the last day of each treatment cycle.

The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [15] was adopted to assess the tumor response. For the survival analysis, PFS data were determined.

2.4. Statistical analysis

The patients’ characteristics were summarized as medians and ranges for continuous variables, whereas categorical variables were arranged by frequency counts and percentages. All statistical tests were 2 sided, and \( P < 0.05 \) was considered statistically significant. To compare various patient factors among the groups, the Wilcoxon rank sum test was performed for continuous variables, and a chi-square test or Fisher exact test was used for categorical variables.

PFS was defined as the time from the date of initiation of sunitinib therapy to tumor progression as assessed by RECIST or the occurrence of death from all causes. PFS was calculated using the Kaplan-Meier method, and a log rank test was performed for evaluation of differences among the 3 treatment groups. SPSS version 19 (IBM Corporation, USA) was used for all statistical calculations.

3. Results

3.1. Patient characteristics

A total of 108 patients met the inclusion criteria and were enrolled in the study. Their baseline demographic and clinical characteristics are shown in Table 1. The median age of the patients at diagnosis was 62 years (range: 40–80 years). Overall, 50 patients (46.3%) with a median age of 62 years (range: 41–76 years) were maintained on schedule 4/2 throughout the study, 26 (24.1%) with a median age of 64 years (range: 40–74 years) were switched from the schedule 4/2 to the schedule 2/1 before treatment was discontinued, and 32 patients (29.6%) with a median age of 66 years (range: 45–80 years) were initiated on the sunitinib schedule 2/1. The subset of the patients who were started on schedule 2/1 or transitioned to schedule 2/1 had similar baseline characteristics equivalent to those of the schedule 4/2 group. There were no statistically significant differences in the sex ratio and histology findings among the groups (\( P = 0.911 \) and \( P = 0.830 \), respectively). Although 92 patients (85.5%) underwent nephrectomy before sunitinib treatment, none were receiving other systemic therapy. As shown in Table 1, the lung was the most common site of tumor metastasis (73/108; 67.6%). Based on
3.2. Treatment schedules

In all 3 treatment groups, the starting dosage of sunitinib was 50 mg daily. Patients switched to sunitinib schedule 2/1 (T2/1 group) received schedule 4/2 for an average of 3.6 months (range: 1.2–6.0 mo). The decision to switch patients to schedule 2/1 was made at the discretion of the physician based on the patients' subjective and objective toxicity. A total of 26 patients were switched to the alternative treatment schedule because of poor tolerability on sunitinib; 10 of these patients (38.5%) had grade 3 HFS, 4 (15.4%) had grade 3 neutropenia, 4 (15.4%) had grade 3 cardiotoxicity, 3 (11.5%) had grade 3 diarrhea, 2 (7.7%) had grade 3 fatigue, 2 (7.7%) had grade 3 thrombocytopenia, and 1 (3.8%) had grade 3 flulike symptoms.

3.3. AEs and tolerability of sunitinib

The common AEs occurring during a year of treatment, including all grades of AEs and grades 3 to 4 AEs, are shown in Table 2. The most frequently encountered AEs were HFS, fatigue, diarrhea, and bone marrow suppression such as neutropenia. These AEs were significantly less common in the schedule 2/1 and schedule T2/1 groups than in the schedule 4/2 group ($P = 0.002, P = 0.002, P = 0.014$, and $P = 0.000$, respectively). No patient died of drug-related AEs.

Addtionally, grades 3 to 4 toxic reactions rarely occurred in any of the 3 groups. The collective incidences of all grades 3 to 4 neutropenia, thrombocytopenia, diarrhea, and HFS in the patients of the 3 groups were 13.9%, 13.9%, 11.1%, and 8.3%, respectively, and there were no significant differences among the 3 treatment groups. It was noteworthy that the incidence of all AEs in the transitional 2/1 group decreased by 28% at an average of 2.6 months after switching from the previous schedule 4/2 (data not shown).

In total, 5 patients (15.6%) in the schedule 12/1 group required modification of the sunitinib dose or interruption of treatment owing to drug toxicity, as did 8 patients in the schedule T2/1 group (30.8%) and 18 in the schedule 4/2 group (36.0%), but there were no significant differences among the groups ($P = 0.448$). The most common toxic reactions requiring dose reduction or treatment interruption were grade 3 HFS, grade 3 diarrhea, grade 3 thrombocytopenia, grade 3 neutropenia, and grade 3 cardiotoxicity.

3.4. HRQoL score assessment

HRQoL scores during each treatment cycle were quantified by use of the FACIT-F and FKSI-19 instruments. An average of the scores in 2 consecutive schedule 2/1 cycles was used for comparison with the scores in 1 schedule 4/2 cycle. As shown in Fig. 1A, there was a sharp decline in FACIT-F scores from the baseline in all 3 treatment groups during the first treatment cycle, but thereafter the scores gradually increased during subsequent cycles. However, there were no significant differences in FACIT-F scores among the 3 groups in each cycle of treatment (cycles 1–9: $P = 0.248, P = 0.736, P = 0.213, P = 0.675, P = 0.861, P = 0.824, P = 0.675, P = 0.465$, and $P = 0.197$). Fig. 1B shows that there were no significant

<table>
<thead>
<tr>
<th>Adverse events (AEs)</th>
<th>Sunitinib dosing schedule</th>
<th>P-values$^*$</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>4/2 ($n = 50$)</td>
<td>Transitional 2/1 ($n = 26$)</td>
</tr>
<tr>
<td></td>
<td>All grades</td>
<td>Grades 3–4</td>
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<td>Hematological AEs</td>
<td>Neutropenia</td>
<td>33 (66.0%)</td>
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<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>18 (36.0%)</td>
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<td></td>
<td>Anemia</td>
<td>15 (30.0%)</td>
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<td>Other AEs</td>
<td>Fatigue</td>
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<td>Hand-foot syndrome</td>
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<td></td>
<td>Diarrhea</td>
<td>32 (64.0%)</td>
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<td></td>
<td>Taste alteration or mucositis or both (oral)</td>
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<td>Cardiotoxicity</td>
<td>15 (30.0%)</td>
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<tr>
<td></td>
<td>Flulike symptoms</td>
<td>10 (20.0%)</td>
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</tbody>
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*Pearson chi-square test or Fisher exact test. Adverse events on schedule 4/2, transitional 2/1 vs. initial 2/1.
differences among the 3 groups in FKSI-19 scores during the first 2 treatment cycles (cycle 1: $P = 0.541$; cycle 2: $P = 0.175$). However, in subsequent treatment cycles (3–9), the HRQoL scores were significantly less decreased in the schedule I2/1 group than in the schedule 4/2 and T2/1 groups (cycles 3–9: $P = 0.043, P = 0.011, P = 0.005, P = 0.0001, P = 0.0001, P = 0.0001, P = 0.0001$).

3.5. Therapeutic efficacy

Best tumor responses after 1 year of treatment with sunitinib in the 3 groups are shown in Table 3. The median follow-up duration was 1.7 years (range: 1.0–2.7 y). No significant differences in tumor responses were evident among the 3 groups ($P = 0.787$). In the schedule I2/1 group, 2 patients (6.3%) had a complete response and 3 (9.4%) had a partial response, and findings in the other 2 groups were similar. Although more patients in the schedule 4/2 and T2/1 groups had progressive disease than in the schedule I2/1 group (58.0% and 53.8% vs. 50.0%, respectively), the differences were not statistically significant ($P = 0.774$). However, as shown in Fig. 2, the PFS of patients in the schedule I2/1 group was significantly longer than that of patients in the schedule 4/2 or T2/1 groups (median PFS: 11.2 vs. 9.4 and 9.5 mo, respectively, $P = 0.030$).

4. Discussion

Sunitinib has been recommended as a first-line therapeutic option for patients with mRCC in the clinical setting.
and has demonstrated both efficacy and comparable or even superior tolerance to most other chemotherapeutic agents [8,16–19]. The most commonly used sunitinib treatment schedule is 50 mg daily for 4 weeks followed by a 2-week interval off treatment (schedule 4/2). Although previous reports have suggested that a maximal dose and area under the serum concentration-time curve may intensify the therapeutic response [20,21], a phase III clinical trial showed that more than 50% of patients required modification of the sunitinib dosage or interruption of treatment owing to drug toxicity [8]. The larger the dosage, the better the effect, but also the greater the toxicity.

The pivotal challenge for clinicians is to determine an optimal balance between the toxicity and efficacy of sunitinib. In clinical practice, we have noted that the incidence of AEs during each treatment cycle is greater with the schedule 4/2 and tends to be worst in the first 2 weeks of the cycle, which was also demonstrated in a randomized, phase II clinical trial of sunitinib [20]. In addition, mean HRQoL scores tend to be worst in the last 2 weeks of each treatment cycle but typically increase after each 2-week interval off treatment [20]. Patients who are unable to tolerate severe AEs on the schedule 4/2 (either at the standard or a modified dosage) are generally switched to an alternative dosing schedule. In recent years, there has been increasing evidence that the schedule 2/1 is associated with a lower frequency of dose reductions or treatment interruptions and has a comparable or even better oncological outcome than the traditional schedule 4/2, especially in Asian patients [11–13,22].

Our clinical experience has been that all patients who initially received sunitinib 50 mg daily in the traditional schedule 4/2 develop AEs, and 24.1% were subsequently switched to the schedule 2/1 because of severe toxicity within a short period (median 3.6 mo). Data from the present study indicate that the most common and troublesome toxicities, neutropenia, were significantly less severe in the schedule T2/1 group than in the schedule 4/2 group, which allowed a dose reduction or treatment interruption to be implemented such that a good survival outcome was achieved. Based on these primary results and the favorable outcomes achieved with the modified intermittent treatment schedule in other studies [23–25], we have been using a 2-weeks-on/1-week-off sunitinib treatment schedule (with a starting dose of 50 mg daily) as a control arm for patients with mRCC since 2011. After that, all eligible patients were fully informed with the performance of the standard schedule 4/2 and the initial schedule 2/1; however, most of the patients opted for the schedule 2/1.

In the present study, the 2 most common AEs were fatigue (76/108; 70.4%) and HFS (73/108, 67.6%). HFS has previously been reported to be more common in Asians than in Western patients [10]. Although the incidence of grades 3 to 4 AEs showed no significant differences among the 3 treatment groups, the total incidences of HFS, fatigue, neutropenia, and diarrhea were significantly lower in the schedule I2/1 and T2/1 groups than in the schedule 4/2.

Regarding HRQoL, our data showed that the FACIT-F scores of patients in the 3 treatment groups initially showed a sharp decrease, but then gradually increased during following cycles, as has been reported previously [26]. It was notable that almost all of the AEs occurred during the first treatment cycle, when patients might be expected to be experiencing both physical and mental distress despite detailed education regarding potential adverse effects before the initiation of therapy. With positive interventions regarding some AEs, including fatigue, HFS, diarrhea, and hypertension, and comforting advice from the treating physician, patients are able to progressively adapt to the hypodynamic state. Interestingly, although patients in the schedule I2/1 group had a lower incidence of fatigue and higher FACIT-F scores, the scores in the 3 groups did not differ significantly during each treatment cycle, which could be partially ascribed to the limited sample size. However, with the FKSI-19 score, the mean change from baseline and the actual score were both significantly superior to those in the schedule I2/1 group from the third cycle until the end of the observation period. Because the FFSI-19 instrument covers a wide spectrum of disease-related symptoms, it can more comprehensively evaluate the HRQoL of patients with mRCC. Thus, if the results of the FACIT-F and FFSI-19 assessments are combined, the HRQoL of patients in the schedule I2/1 group was better than that of patients in the schedule 4/2 and T2/1 groups. Consequently, the 2-weeks-on/1-week-off dosing schedule provided better tolerability than the traditional schedule 4/2.

As with previous reports [12,13], the median PFS in our study was longer in the schedule I2/1 group than in the schedule 4/2 group (11.2 vs. 9.5 mo), which might partially reflect a relatively lower frequency of dose reductions or treatment interruptions. Interestingly, the incidences of some other common AEs that might be the predictive biomarkers of favorable outcomes in a clinical setting, including hypertension and hypothyroidism, were similar among the treatment groups in our patient population [27,28]. Because these AEs are closely correlated with therapeutic efficacy, some reports have suggested that a higher grade of toxicity is required for enhanced efficacy. Although the data in our study do raise the possibility that toxicity might be a biomarker of drug response, maintaining a higher level of AEs did not appear necessary for improved clinical benefits. Despite the inherent limitations of this study’s retrospective design and its small sample size, our findings showed that a modified dosing schedule with a shorter period off treatment was a useful approach for minimizing drug toxicity and maximizing the HRQoL of patients without compromising efficacy.

5. Conclusions

The findings of this study indicate that a 2/1 sunitinib dosing schedule is a better-tolerated and more effective
therapeutic option than the traditional schedule 4/2. The schedule 2/1 provided better HRQoL for Chinese patients with mRCC owing to significantly decreased toxicity and a superior PFS outcome.

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