Alternate sunitinib schedules in patients with metastatic renal cell carcinoma

S. Kalra¹, B. I. Rini² & E. Jonasch¹*

¹Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston; ²Department of Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, USA

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Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor exhibiting antiangiogenic activity. Sunitinib demonstrated improved outcomes in comparison to interferon-α in a large phase III study of treatment naïve patients with metastatic renal cell carcinoma. Maintaining patients on sunitinib treatment is essential for a sustained disease control as higher exposure to sunitinib has been associated with an improved overall response rate, progression-free survival and overall survival. Various studies have compared the outcomes of patients undergoing sunitinib therapy based on modifications from their standard dose and schedule. Several studies have shown that switching to an alternate schedule with more frequent dose interruptions without affecting dose density over a 6-week cycle is associated with improved outcomes and increased tolerability.

Key words: sunitinib, renal cell carcinoma, drug administration schedule, alternate schedule

introduction

The VHL–HIF pathway is pivotal to the pathobiology of clear-cell renal cell carcinoma (RCC), and insights into its dysregulation have been crucial for the development of targeted agents that include vascular endothelial growth factor (VEGF) receptor inhibitors and antibodies to circulating VEGF [1]. Inhibitors of the mammalian target of rapamycin molecule, which is downstream of the phosphoinositide 3-kinase and protein kinase B pathways, have also demonstrated a role in the treatment of metastatic renal cell carcinoma (mRCC). These new agents have dramatically changed the therapeutic landscape of mRCC, and are now considered standard of care for patients with mRCC [2, 3]. Despite their efficacy, these agents continue to be the focus of ongoing investigation, attempting to identify ways to maximize response and minimize toxicity.

Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor exhibiting antiangiogenic activity. Sunitinib demonstrated superior median progression-free survival (PFS) when compared with interferon-α in a large phase III study of patients with mRCC [4]. Sunitinib was FDA approved in 2006, after which it became a standard of care in front-line treatment of mRCC.

Although the therapeutic goal in the treatment of mRCC is prolongation of survival, it is equally important to keep the treatment-related toxicities to a minimum to maximize drug adherence, and overall time on treatment. Maintenance of sunitinib dose intensity can be challenging due to treatment-related adverse events (AEs) such as fatigue, hypertension, hand–foot syndrome (HFS) and diarrhea. In the original phase III trial of sunitinib, 38% and 32% patients in the sunitinib arm underwent dose interruptions and reductions, respectively, because of drug toxicity [4]. In clinical practice, it is often noted that AEs increase throughout each cycle, and tend to be worst in the final 2 weeks of treatment cycle [5]. The impact of treatment-related toxicities on patients can be significant and, for some patients, living longer may not always equate with living better.

Although sunitinib was administered on a continuous daily dose schedule in preclinical studies, the 4-week on followed by 2-week off schedule (4/2 schedule) was designed from the collective results of a few studies. Bone marrow and adrenal toxicities were noted in preclinical studies, but were not frequently observed in phase II clinical trials. In a study assessing the 4/2 schedule with doses of sunitinib between 50 and 100 mg, daily dosing for 28 days led to a 3- to 5.5-fold accumulation of sunitinib and a 7- to 15-fold accumulation of SU-12662, when compared with levels on day 1 of treatment [6, 7]. With a rising concern over drug accumulation, additional studies assessed sunitinib administered every other day and once daily on 2-week on and 2-week off and 4-week on and 2-week off schedules [8]. Pharmacokinetics for these studies were similar to those in the first study: accumulation of sunitinib and SU-12662 was noted after 14 days of continuous dosing, with a decline in the concentration to predose.
levels during the 14-day rest period [8]. Daily dosing with 50 mg was sufficient to produce target plasma concentrations above 50 ng/ml, whereas patients with dose-limiting toxicities exhibited trough concentrations of more than 100 ng/ml [6, 7]. It was also observed that dose-limiting toxicities such as fatigue, asthenia and thrombocytopenia occurred progressively at 75 mg on all schedules, and they worsened in severity during weeks 3 and 4. The results from these studies together led to the recommended phase II dose of 50 mg on discontinuous schedules. In a study by Wong et al., fatigue and diarrhea were the most troublesome toxicities for patients, and patients were willing to forego 4.4 months of PFS to ameliorate their symptoms from severe to mild-to-moderate [9]. Interestingly, with the standard 4-week treatment followed by a 2-week break, a cyclic scoring pattern is observed in patient-reported quality-of-life indicators; with improvement in mean scores after the 2-week treatment break [5].

It is clear from the prospective data of the 4/2 schedule that drug tolerability may be a barrier to maximizing the potential efficacy of sunitinib therapy. We review the available evidence on sunitinib pharmacokinetics and pharmacodynamics and the relationship between these parameters and patient outcome. We also review current data on alternate schedule and dosing schemas to determine whether changes in the way sunitinib is administered may improve overall therapeutic efficacy and patient quality of life.

methods

A literature search was carried out in the Medline database using terms renal cell carcinoma, RCC, sunitinib, pharmacokinetics, pharmacodynamics and endothelial cells between January 2000 and June 2014. The Medline search was supplemented by searches of the published abstracts of major meetings of the American Society of Clinical Oncology and European Society of Medical Oncology. The search was limited to English language articles.

The studies that were included assessed the efficacy of continuous daily dosing (CDD) of sunitinib and administration of sunitinib on alternate schedule. The studies that reported phase I trials and retrospective cohorts with <20 patients were excluded from this review.

results

pharmacokinetics and pharmacodynamics

Sunitinib is a small molecule inhibitor of the tyrosine kinase portion of the receptor for two of the most potent proangiogenic proteins: VEGF type 1–3 and platelet-derived growth factor (PDGF) α and β. Maximum plasma concentration (Cmax) of sunitinib is generally observed between 6 and 12 h following oral administration. Following administration of a single oral dose in healthy volunteers, the terminal half-life of sunitinib and its primary active metabolite range from 62.9 to 101 ng/ml [6]. After repeated daily administration or with repeated cycles in the dosage regimen tested, no significant changes were observed in the pharmacokinetics of sunitinib or SU-12662.

Several lines of evidence lend insight into the concept of maintaining daily sunitinib dose and reducing the length of time off therapy. A pharmacokinetic/pharmacodynamic meta-analysis of six trials by Houk et al. investigated relationships between clinical end points and sunitinib exposure in patients with advanced solid tumors, including patients with advanced solid tumors, gastrointestinal solid tumors and metastatic renal cell carcinoma. The results showed that patients with the highest AUC experienced longer overall survival (OS), longer time to progression and greater tumor size reduction. Tentative relationships were also identified between total drug exposure and the incidence of fatigue, reduction in neutrophil counts and diastolic hypertension [10].

A study by Griffioen et al. revealed that, in primary tumor tissue from patients with mRCC, discontinuation of treatment with tyrosine kinase inhibitors led to proliferation of endothelial cells proportionate to the time off of therapy [11]. Powles et al. observed that, during a 4- to 5-week treatment break for debulking nephrectomy, disease progression occurred in some patients, as measured by follow-up imaging and was associated with an increased risk of death on multivariate analysis (hazard ratio (HR) 5.56; [95% confidence interval (CI) 2.29–13.5]), P < 0.01). Sequential fluorodeoxyglucose positron emission tomography demonstrated a rebound in metabolic activity during the treatment break. They concluded that more rapid progression during planned VEGF TKI treatment interruptions was associated with a poor prognosis [12]. The studies by Powles et al. and Griffioen et al. demonstrated that tumor revascularization and growth during treatment breaks is dynamic, varies from patient to patient, and enhanced rates may be associated with worse clinical outcome. Whether a specific treatment schedule is more effective at controlling disease in patients with more rapid disease rebound during treatment breaks is not known at this time.

continuous dosing regimens

Alternate dose schedules for sunitinib were explored in clinical studies with the goal of improving drug tolerance and dose intensity (Table 1). A study of 107 mRCC patients by Escudier et al. showed that patients who received 37.5 mg of sunitinib on a CDD regimen in the second-line setting had a manageable safety profile. The overall response rate (ORR) was 20% with a median response duration of 7.2 months. In this study, individual investigators were able to dose escalate patients with mild nonhematologic and mild-to-moderate hematologic AEs during the first 8 weeks of study to 50 mg/day. Sixteen patients were discontinued from this study because of AEs, and dosing was reduced to 25 mg/day in 46 patients due to grade 3/4 AEs [13]. Barrios et al. conducted a phase II study testing 37.5 mg CDD in 119 treatment naïve patients. The primary end point was ORR and secondary end points included PFS, safety and pharmacokinetic measurements. The ORR was 35.3% with median response duration of 10.4 months. Median PFS was 9 months (95% CI 5.6–11.1 months) and 1-year survival probability was 67.8%.
Steady-state pharmacokinetics were reached within 3 weeks, with no disproportionate accumulation of sunitinib or its active metabolite throughout the study. The most commonly reported treatment-related AEs were diarrhea (50%) and HFS (43%). The most commonly reported grade 3–4 treatment-related AEs were HFS (13%), neutropenia (11%) and diarrhea (9%) [14]. A recent randomized phase II study comparing a 37.5-mg CDD regimen to the 4/2 schedule (EFFECT trial) demonstrated no differences in drug tolerance or patient-reported symptoms, but showed a trend toward superiority of the 4/2 schedule over CDD in time to tumor progression (9.9 months for 4/2 schedule versus 7.1 months on CDD, HR 0.77, 95% CI 0.57 to 1.04, P = 0.09). No significant difference was observed in the OS (23.1 months for the 4/2 schedule versus 23.5 months for CDD, HR 0.77, 95% CI 0.57–1.04, P = 0.09). No significant difference was observed in the OS (23.1 months for the 4/2 schedule versus 23.5 months for CDD, P = 0.615) [5]. Despite the early thoughts and data that continuous treatment at a reduced dose was going to be better tolerated than the standard regimen, results from various studies that tested lower dose intensity did not show superior tolerability, and based on the EFFECT trial a 4-week on, 2-week off schedule remained the standard of care.

### 2-week on, 1-week off treatment schedules

In another effort to decrease AEs, a 2-week on, 1-week off schedule (2/1 schedule) was evaluated in retrospective analyses and is being assessed in clinical trials (Table 2). The Cleveland Clinic’s retrospective review assessed 30 mRCC patients who were switched from the 4/2 schedule to the 2/1 schedule due to toxicity. While on the 2/1 schedule, there were no grade 4 toxicities observed, and fewer than 30% of patients experienced grade 3 toxicity. In addition, 73% of patients’ worst toxicity on the 2/1 schedule was less severe than on the 4/2 schedule, and no patient’s worst toxicity on the 2/1 schedule was greater than that on the 4/2 schedule (P < 0.0001). Fatigue and HFS, two of the most common toxicities, were significantly less severe on the 2/1 schedule than on the 4/2 schedule (P < 0.0003 for both). Median overall treatment duration of these patients initially on the 4/2 and, subsequently on the 2/1 schedule was 12.6 and 11.9 months, respectively. Median PFS was ∼12.7 months. These data suggest that patients with dose-limiting toxicities on the 4/2 schedule are able to continue sunitinib treatment on a 2/1 schedule with reduced toxicity and preserved efficacy [15]. In addition to the

**Table 1. Summary of studies evaluating the efficacy of sunitinib with alternate dose regimens**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Dosing</th>
<th>Schedule</th>
<th>Primary end point</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motzer et al.</td>
<td>Phase II</td>
<td>292</td>
<td>Group 1: 37.5 mg/day vs Group 2: 50 mg</td>
<td>Group 1: CDD vs Group 2: 4/2 schedule on and 2/2 week off</td>
<td>TTP</td>
<td>Median TTP was on 9.9 months schedule 4/2 and 7.1 months on CDD</td>
<td>No advantage in safety or efficacy for continuous dosing of sunitib with CDD</td>
</tr>
<tr>
<td>Escudier et al.</td>
<td>Phase II</td>
<td>107</td>
<td>37.5 mg</td>
<td>CDD in second-line setting</td>
<td>ORR</td>
<td>ORR was 20% with median response duration of 7.2 months</td>
<td>Manageable safety profile of sunitinib with CDD</td>
</tr>
<tr>
<td>Barrios et al.</td>
<td>Phase II</td>
<td>119</td>
<td>37.5 mg</td>
<td>CDD in front-line setting</td>
<td>ORR</td>
<td>ORR was 35.3% with median response duration of 10.4 months</td>
<td>Manageable safety profile of sunitinib with CDD</td>
</tr>
</tbody>
</table>

CDD, continuous daily dosing; TTP, time to tumor progression; ORR, objective response rate.

**Table 2. Summary of studies evaluating the efficacy of sunitinib with alternate schedule regimens**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Schedule</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkinson et al.</td>
<td>Retrospective</td>
<td>187</td>
<td>Compared TS with AS</td>
<td>Compared with TS, sunitinib on AS had improved OS and PFS and may mitigate toxicities</td>
</tr>
<tr>
<td>Bjarnason et al.</td>
<td>Retrospective</td>
<td>172</td>
<td>All patients were started on TS, and depending on tolerability, were switched to AS</td>
<td>Sunitinib on AS was associated with improved PFS and OS and a manageable toxicity profile. DCE-US in a subset of patients showed decreased TBV from baseline at day 7 and day 14, after which the TBV became stable or increased at day 28.</td>
</tr>
<tr>
<td>Najjar et al.</td>
<td>Retrospective</td>
<td>30</td>
<td>Switched patients from TS to AS and compared the treatment responses</td>
<td>Sunitinib on AS was associated with significantly reduced toxicity in patients who had grade 3 toxicity on TS. Median OTD was 11.9 months on AS and 12.6 months on TS</td>
</tr>
<tr>
<td>Kondo et al.</td>
<td>Retrospective</td>
<td>48</td>
<td>Compared TS with AS</td>
<td>Sunitinib on AS showed a lower incidence of dose interruption and comparable outcomes with the TS group. No difference was seen in the relative dose intensity between two groups.</td>
</tr>
</tbody>
</table>

TS, traditional schedule (4-week on and 2-week off); AS, alternative schedule (2-week on and 1-week off); AE, adverse events; TBV, tumor blood volume; OTD, overall treatment duration.
limitations inherent to a retrospective study, this study had a small sample size and collected AE information from clinic visits, where information on milder AEs could have been missed.

The MD Anderson Cancer Center retrospectively assessed 185 patients treated with front-line sunitinib for clinical outcome and toxicity as a function of treatment schedule. Eighty-seven percent started out receiving sunitinib on a conventional 4/2 schedule. During treatment, 53% of patients continued on a 4/2 treatment schedule and 47% initiated or transitioned to an alternate schedule, which mainly consisted of treatment with a 2/1 schedule. Baseline characteristics were similar between both groups. AEs prompting schedule modification included fatigue (64%), HFS (38%) and diarrhea (32%). Median time to schedule change was 5.6 months. Median OS was 17.7 months (95% CI 10.8–22.2 months) on the 4/2 schedule compared with 33.0 months (95% CI 29.3 to not estimable) on an alternate schedule (P < 0.0001). By multivariate analysis, poor ECOG PS, increased LDH, decreased albumin, unfavorable Heng criteria and conventional schedule were associated with decreased OS (P < 0.05). Comparison of toxicity prevalence before and after schedule adjustment demonstrated a clear reduction in toxicity rates [16]. The prevalence of the more common AEs such as fatigue, HFS and diarrhea at the first follow-up after schedule modification dropped to 29%, 10% and 6%, respectively. Although statistically not significant, the traditional schedule group had a numerically higher number of patients in the poor prognostic category in comparison to the alternative schedule group for the Heng Criteria and the MSKCC model.

Bjarnason et al. conducted a retrospective review of 172 patients using an individualized treatment strategy. All patients were started on sunitinib at 50 mg/day with the intent to continue for 28 days. Dose and schedule modifications (DSM) were considered in patients to keep the toxicity ≤grade 2. Three major groups were compared: Group 1 consisted of patients who received 50 mg of sunitinib on a 4/2 schedule; Group 2 consisted of patients who received 50 mg of sunitinib either a 2/1 schedule or with 7-day on and 7-day off schedule; Group 3 comprised of patients who received 37.5 or 25 mg of sunitinib on 7-day on and 7-day off schedule. At a median follow-up of 22.8 months (95% CI 16.6–26.1), the median PFS for all patients was 8.9 months (95% CI 7.7–11.8). The median PFS in the individualized DSM category was 5.3, 10.9 and 11.9 months for Groups 1, 2 and 3, respectively (P < 0.0001). The median OS in the individualized DSM category was 15.4, 23.4 and 24.5 months for Groups 1, 2 and 3, respectively (Group 2 versus 1; P = 0.03 and Group 3 versus 1; P = 0.003). Moreover, dynamic microbubble ultrasound (DCE-US) in patients receiving sunitinib demonstrated reduction of tumor blood volume at day 7 and day 14, compared with baseline, with no further reduction in blood flow from day 14 to 28 [33]. These findings suggest that the putative antitumor mechanism of sunitinib, i.e. reduction in tumor-associated blood flow, is optimized after 14 days, and dosing of sunitinib from day 15 to 28 may increase toxicity without meaningfully contributing to efficacy [17]. This retrospective study lacked an independent radiological review and had a fairly small number of patients.

Neri et al. prospectively evaluated maintenance of dose intensity and drug tolerance in 31 patients treated with a 2/1 schedule, 10 of whom had previously been on the standard 4/2 schedule. The incidence of grade 3 fatigue and HFS in this study were 16.1% and 0%, respectively. The ORR was 42% and the median time on treatment was 16 months. Only 9% patients on the alternate schedule needed a dose reduction [18]. Although prospective, this study was limited by its small sample size.

In another retrospective evaluation of 48 patients by Kondo et al., all patients initially received sunitinib on 4/2 schedule. After 2011, 26 patients were switched to 2/1 schedule. The starting dose was on the 2/1 schedule was 50 mg for patients who were <65 years old, had a serum creatinine of <2 mg/dl and body weight more than 50 kg. If one of the above factors was present in the patients, then the dose was reduced to 37.5 mg/day and if two or more factors were present, dose was reduced to 25 mg/day. The dose was escalated by 12.5 mg increments until the maximum tolerated dose was reached for the patients. Patients who were on the 2/1 schedule had a lower severity of HFS (P < 0.02) and diarrhea (P < 0.009) compared with those who received sunitinib on the standard 4/2 schedule. Dose interruption due to AEs in the first three cycles was significantly lower in 2/1 schedule patients in comparison to the standard schedule (27% versus 53%, P = 0.04). The median time to progression, although numerically longer for patients on the 2/1 schedule, did not reach statistical significance (18.4 versus 9.1 months, P = 0.13) [19]. This study had a retrospective design, evaluated a small number of patients and had no pharmacokinetic data.

**discussion**

Optimal dosing and scheduling of sunitinib has not been conclusively defined. As is the case for all therapeutic agents undergoing clinical development, limitations in time and resources as well as increased trial complexity prevented an exhaustive evaluation of all potential dose and schedule permutations during the development of sunitinib. Analysis of pharmacokinetic, pharmacodynamic and tissue-based correlative data provides some guidance on optimizing the dose and schedule of sunitinib therapy. There appears to be a relationship between sunitinib dose intensity and improved clinical outcome [8]. Sunitinib steady state is reached after 2 weeks on therapy [7], and optimal suppression of vascular perfusion is achieved after 14 days of therapy [15]. These two sets of observations suggest that if higher overall dose levels can be maintained, alternate scheduling may permit greater daily sunitinib exposure, which may help the individual patient derive greater benefit from sunitinib. Additionally, proliferation of endothelial cells is proportionate to the time off of systemic therapy [9], and unfavorable prognosis is linked to rate of tumor growth while off therapy, generating a hypothesis that shorter breaks are in the patient’s best interest.

In the only randomized prospective study comparing sunitinib treatment schedules, toxicity of the standard 4/2 schedule and a continuous 37.5-mg dosing schema appeared to be quite similar, with a trend toward an efficacy advantage in the 4/2 schedule. The utility of alternate, shorter duration schedules has been largely evaluated in the retrospective setting by various authors. Patients who were either started on or switched to alternate schedules during their course of treatment seem to maintain clinical efficacy as with a standard 4/2 schedule. Although in total, these analyses comprise over 400 patients, a
direct causal relationship between schedule optimization and improved patient outcome is impossible to ascertain until additional prospective data are obtained. To that end, a prospective, multicenter phase II study has been launched to test the hypothesis that a 2/1 schedule would result in a lower rate of grade 3 toxicities, and permit a larger percentage of patients to remain on full-dose sunitinib when compared with published data on standard sunitinib schedules (NCT02060370). Another prospective, multicenter phase II study is being conducted in Canada, which looks at the potential of dose escalation beyond 50 mg/day in patients who are able to tolerate the drug, and schedule adjustment before dose reduction in those who experience treatment-related toxicity (NCT01499121) [17]. In a phase II trial evaluating dose titration of axitinib, the majority of the patients who underwent dose titration received a greater ORR, although no PFS benefit was seen, thereby keeping the question of benefit to dose escalation open at this time [20]. Trials that explore individual dose escalation for patients on sunitinib will yield further insights on maximizing objective response and duration of PFS in mRCC patients. Ideally, randomized studies should be conducted that evaluate the tolerability and efficacy of alternate sunitinib schedules and dosages in comparison to the standard 4-week on, 2-week off regimen. Treatment breaks in the experimental study arm should be triggered by the development of toxicity, with length of treatment breaks shortened commensurate to the duration of treatment. Such a study could also incorporate a dose-escalation step into the experimental arm for patients who experience no toxicity, as is being carried out in the Canadian study described above.

Most other oral agents for RCC are currently administered in a continuous schedule. The data on alternate dosing and scheduling for sunitinib may provide insight into a more broadly applicable paradigm for oral anticancer agents. As a better understanding of the mechanisms of response and resistance to molecularly targeted agents emerges, and representative preclinical and clinical model systems are constructed, the ability to refine dosing and scheduling for all oral anticancer therapies will improve.

disclosure

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references

6. EJ has consulting and research funding from Pfizer.