Original article

A new modified schedule of Sunitinib for metastatic renal cell carcinoma: a retrospective analysis

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Abstract. *Background and aim of the work:* Sunitinib 50 mg/day given for 4 weeks followed by 2 weeks off treatment (4+2 schedule) is a standard treatment for metastatic renal cell carcinoma, but several patients are forced to reduce the doses and/or had to discontinue therapy permanently due to toxicity. Recent data showed that increased exposure to sunitinib is associated with improved clinical outcome underlining the key role of dose-intensity in the efficacy/toxicity balance. We investigated the tolerability and efficacy of a modified schedule. *Patients and methods:* This is a retrospective analysis which assessed consecutive non-progressive metastatic renal cell carcinoma patients admitted to our hospital who had at least a grade 2 toxicity during sunitinib therapy, and then switched to a modified schedule maintaining the same dose-intensity of 4+2 schedule: starting on Monday, 1 tablet/day for 5 consecutive days a week (days 6 and 7 off therapy) for 5 weeks and 1 tablet/day on days 1, 3 and 5 in the sixth week (days 2, 4, 6 and 7 off therapy) until disease progression. Primary end points were toxicity changes assessment and schedule feasibility. *Results:* Complete data from eight nephrectomized patients were collected: 6 males; median age 61; 3 pretreated patient. Median time from start therapy to switch was 7.4 months. After switch, treatment delays and dose reductions decreased from 50% to 25% and from 37% to 12% of patients respectively. Toxicity was reduced. *Conclusions:* Even though no conclusions can be drawn about the actual effectiveness and toxicity of our schedule compared to the standard dosing schedule, it seems to be well tolerated and able to maintain a high adherence to therapy, resulting in maintenance of antitumour activity. This new modified schedule requires and deserves further studies.(www.actabiomedica.it)

Key words: Sunitinib, modified, schedule, renal cell carcinoma, dose intensity

Introduction

Clinical data

Sunitinib (sunitinib malate; SU11248; SUTENT; Pfizer Inc, New York, NY; USA) is an oral multitargeted tyrosine kinase inhibitor with antitumor and antiangiogenic activities, that has been approved for the treatment of advanced renal cell carcinoma (RCC) and for gastrointestinal stromal tumor (GIST) after disease progression or intolerance to imatinib mesylate therapy (1). In addition, clinical studies confirm that this drug shows activity in several other solid tumor types (2-5).

For the treatment of metastatic renal cell carcinoma Sunitinib is administered at 50 mg daily given for 4 weeks followed by 2 weeks off treatment (4+2 schedule) (Fig. 1A), comprising a 6-week cycle. Treatment with sunitinib is not free from toxicity (its more frequent side effects include hypothyroidism, hypertension, fatigue, hand-foot syndrome, diarrhea, nausea, mucositis/stomatitis, neutropenia etc) (6, 7): that's why it's not always possible to treat the patients without any reduction or dose delay, even at the expense of its effectiveness. Indeed about 20% of patients had to discontinue treatment permanently and about 50% of patients are forced to reduce the doses due to adverse

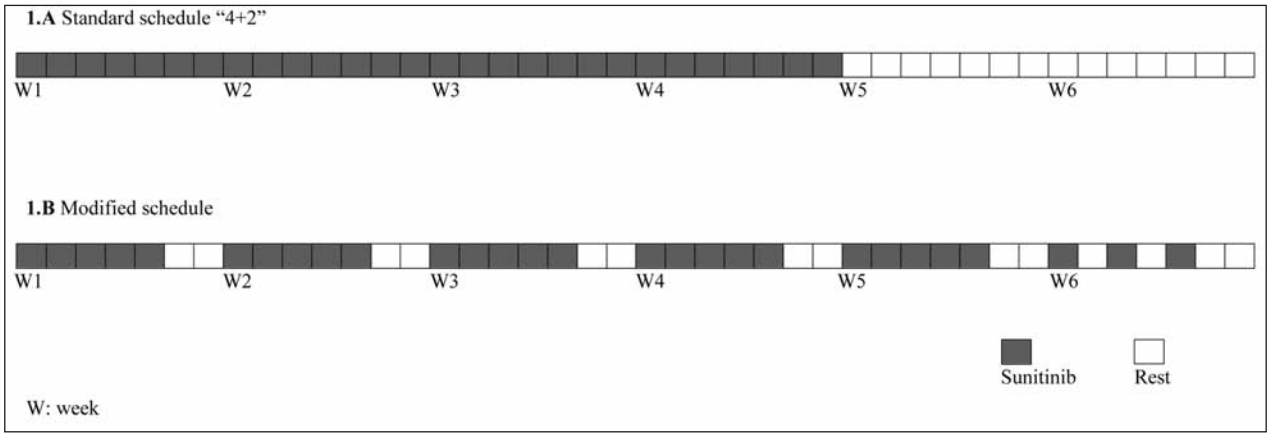

Figure 1. Classic 4+2 schedule and modified schedule

events (7). A meta-analysis published in 2010 by Houk et al. showed that increased exposure to sunitinib is associated with improved clinical outcome: longer time to progression (TTP), longer overall survival (OS), greater chance of antitumor response (8). It was also reported that a longer duration of treatment with sunitinib may increase the objective response rate, so currently it is recommended to keep the patient on treatment with the drug until it is clear a clinical benefit for the patient (6, 7, 9, 10).

Pharmacokinetic data

Sunitinib and its active equipotent **metabolite SU12662 have a half-life of 40-60 and 80-110 hours respectively** (8). Steady state concentrations are achieved within 10-14 days and maximum tolerated dose (MTD) is 50 mg/die (8). Pharmacokinetic is significantly influenced by gender, age and weight, but the magnitude of the predicted change exposure minimizes the necessity for dose adjustments (11). Sunitinib exhibited dose- and time-dependent antitumor activity in mice. Data from animal and acute myeloid leukemia patients studies showed that target plasma concentration of total drug capable of inhibiting platelet-derived growth factor-β and **Vascular Endothelial Growth Factor receptor-2** phosphorylation were established in the range of 50 to 100 ng/mL (8, 12). Doses of sunitinib sufficient to produce plasma concentrations of 50-100 ng/ml for at least 12 h of a 24-h dosing interval would lead to inhibition of the target receptors sufficient to result in antiangiogenic activity, and it is not necessary to maintain continuous inhibition of the target receptors to achieve efficacy in the murine models (12). The occurrence of dose limiting toxicities was associated with sunitinib plasma levels more than 100 ng/mL and doses of 50 mg/die led to plasma concentration ranging from 50 to 100 ng/mL (1).

The schedule

Although initial studies were planned to provide continuous administration, the 4+2 schedule was selected at the request of the health authorities to allow patients to recover from potential bone marrow and adrenal toxicity observed in animal models (1). A recent phase II study with sunitinib 50 mg administered as 4+2 standard schedule to mRCC patients showed that median trough plasma concentrations of total drug reached therapeutic levels (> 50 ng/ml) on day 14 of cycle 1, and that levels were sustained throughout treatment during the dosing periods; it also showed that median trough plasma concentrations of total drug on days 14 and 28 of cycle 1 were comparable to those observed on day 28 of cycles 2 and 3, but the plasma drug levels were not detectable on day 1 of cycle 2, suggesting a complete washout of the drug in the two-week break (13). The direct consequence of the latter observation may result in the phenomenon of tumor regrowth during the two week break, a phenomenon described both in clinical practice and in pre-clinical setting (14, 15).

So the 4+2 schedule mainly involves two problems: a) it is quite toxic, resulting in greater likelihood of reducing patient exposure to the drug and potential resultant lower efficacy, b) tumor regrowth with major symptoms can occur in the two week break. To overcome these difficulties only one randomized phase II multicenter study has recently investigated the safety and efficacy of an alternative continuous daily dosing schedule (37.5 mg/dose) versus 4+2 schedule (50 mg/dose) as first-line therapy in 292 patients with mRCC showing a trend toward inferior TTP with continuous dosing while overall response rate (ORR), OS, and toxicity profile were similar for the approved 4+2 schedule versus continuous dosing (16).

Purpose

In light of these considerations, at our center, we thought reasonable the administration of a possibly better tolerated modified schedule, that while maintaining the same dose-intensity of classical schedule (28 tablets in 6 weeks) could both allow the patient to be treated for longer time, with fewer dose reductions, and limit the symptomatic tumor regrowth.

Methods

Patients and treatment

This retrospective analysis considered 50 consecutive mRCC patients seen in our institution (Oncology Division, Azienda Istituti Ospitaleri di Cremona, Italy) between December 2006 and August 2010, of whom 20 (from June 2008) were treated with a modified schedule during sunitinib treatment. We obtained patient informed consents and ethical approval for the study.

In our institution, the patients without progression of disease (PD) who had at least a grade 2 toxicity (graded by the National Cancer Institute Common Terminology Criteria for AEs version 3.0 [NCI-CTCAEv.3]) with 4+2 schedule, could switch to a modified schedule, maintaining the same dose-intensity: starting on Monday, 1 tablet a day (50, 37.5 or 25 mg on the basis of any previous dose reduction) for five consecutive days a week for five weeks and 1 tablet per day on days 1, 3 and 5 in the sixth week (28 tablets in 6 weeks), every 42 days until disease progression (Fig. 1B). Such decision was to discretion of the referring oncologist also considering the desire of the informed patients to be still treated with sunitinib without (sometimes further) dose reduction or delay. Since for any oral therapy it exists the possibility of error or misunderstanding by the patients, they were instructed in how and when to take the drug even with the help of a diary and of a clear illustrated memo on a brochure paper.

The analysis considered consecutive patients aged over 18 years with histologically confirmed mRCC and evidence of measurable disease, based on Response Evaluation Criteria in Solid Tumors (RECIST) (17), admitted to our hospital where they started treatment with sunitinib administered with 4+2 schedule. Additional eligibility criteria included: completeness of toxicity and response data; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; adequate hematologic, hepatic, and renal function; informed written consent. Patients were excluded if they had known brain metastasis untreated by surgery or radiotherapy or any second malignancy within the previous three years other than adequately treated basal cell carcinoma, squamous cell skin cancer, or in situ carcinoma. Additional exclusion criteria included a history of or clinically significant cardiovascular disease, cardiac dysrhythmias, prolongation of the QTc interval, or uncontrolled hypertension.

The titration of dosage down to 25 mg/day was allowed on an individual basis depending on tolerability. Patients who experienced sunitinib-related, grade 3 or 4 toxicities stopped treatment until the severity decreased (to grade 1 for non hematologic or grade 2 for hematologic adverse events), and then resumed treatment at either the same or a lesser dose, as per the investigator's discretion. Patients requiring further dose reduction below 25 mg/day, or longer than 6 weeks of dose interruption, were discontinued from the sunitinib therapy. Treatment was otherwise continued until disease progression.

Procedures, baseline and during treatment evaluations

Main purpose of this small retrospective analysis was hypothesis generating; therefore the primary end points were toxicity changes assessment after the

switch from 4+2 schedule to modified schedule and the feasibility of the latter (with measurement of administered drug, dose reduction and dose delay rates). Secondary end point was overall progression free survival (PFS) that was summarized using Kaplan–Meier method; this end point was defined from the date of enrollment to the date of documented PD assessed by RECIST. Analyses of safety results were summarized for all patients receiving at least one cycle of sunitinib.

Baseline assessment: history, ECOG PS evaluation, physical examination, arterial blood measurement, 12-lead electrocardiography, cells blood count and blood chemistry tests (including also thyrotrophic stimulating hormone, tetraiodothyronine and phosphatemia), urinalysis, pregnancy test (if appropriate), total-body computed axial tomography or magnetic resonance imaging; bone scan; any other examination suitable for measuring target lesions.

During treatment assessment every two week (only for first cycle of 4+2 and first cycle of modified schedule): evaluation of toxicity (graded by the NCI-CTCAEv.3) with history, physical examination, blood and urine tests, any other examination needed for toxicity assessment.

Every six to eight weeks during treatment and *long-term follow-up assessment:* history, physical examination and blood and urinalysis, electrocardiography, disease evaluation with the same baseline instrumental examinations as assessed by the investigators using RECIST.

Results

From June 2008 to August 2010 were enrolled eight eligible patients. Among these, at the time of the occurrence of at least grade 2 toxicity during therapy with 4+2 schedule, three patients had preferred to reduce the tablet doses and four had the need to delay treatment, before switching to the modified schedule. The Table 1 shows the characteristics of the patients. No selection of the patients was made according to the line of therapy or to the number of previous therapies, to more reflect our clinical practice: one patient was poor risk according to the Memorial Sloan Kettering Cancer Center (MSKCC) score (18) and was pretreated with chemotherapy (gemcitabine and 5-fluorouracil), two patients were pretreated with chemo-immunotherapy plus bevacizumab as part of a research protocol (19), one low MSKCC risk patient was pretreated with only immunotherapy (interferon-α and interleukin-2).

Seven patients discontinued treatment with sunitinib because of PD: an elderly patient (age 82 years) has discontinued the sunitinib treatment for his own will, in the absence of clear PD or significant toxicity, as a consequence of cytoreductive nephrectomy, performed after seven cycles (one with 4+2 and six with modified schedule).

Six patients received a subsequent line of therapy (three everolimus, two sorafenib, one chemotherapy) of whom two still ongoing at collection data time (may 2011), and two patients received a further line of therapy (one everolimus and one sorafenib) of whom one still ongoing.

Table 1. Baseline patients characteristics

Characteristic	Sunitinib (N = 8)	
	No.	%
Age, years		
Median	61,5	
Range	51-82	
Sex		
Male	6	75
Female	2	25
ECOG performance status		
0	5	62.5
1	2	25
> 1	1	12.5
Histology		
Clear cell	6	75
Papillary	1	12.5
Undifferentiated	1	12.5
No. of metastatic sites		
1	2	25
2	3	37.5
≥ 3	3	37.5
Prior Therapy		
Nephrectomy	7	87.5
IT + Bev + CT *	2	25
CT	1	12.5
IT	1	12.5
MSKCC risk factors		
0 (good)	3	37.5
1-2 (intermediate)	4	50
≥ 3 (poor)	1	12.5

MIT: immunotherapy with low doses interleukin-2 and interferon-α; Bev: Bevacizumab; CT: chemotherapy; MSKCC Memorial Sloan Kettering Cancer Center; ECOG Eastern Cooperative Oncology Group.

* regimen in the context of a previous clinical trial

Median time from start therapy to switch was 7.4 months (range 1.4-16.1). Overall a median of 10.5 cycles (range 5-20) were administered. Delivered treatment, dose reductions and delays are shown in Table 2: after the switch to modified schedule there was a decrease in dose reduction from 37.5% (3) to 12.5% (1) of patients and in treatment delays from 50% (4) to 25% (2) of patients. The Table 3 shows the toxicity changes: there were no new toxicities. Overall median PFS was 16.3 months (CI 95% 5.6-23.4) and Fig. 2 shows the obtained PFS for each patient with the two schedules. Median OS was 28.5 months [CI 95% 11.9-45.0] with 70% of patient alive at two years.

Discussion

For the first time, in this very small retrospective analysis we explored the toxicity and feasibility of a new modified schedule of sunitinib in non progressive mRCC patient that switched from the standard 4+2 schedule, maintaining the same dose intensity. The wide time range of data collection, from June 2008 until August 2010, and the small number of patient were due to the fact that we considered for the analysis only patients with completeness of the data. Even though this modified schedule seems to be well tolerated and able to maintain a high adherence to therapy, supposedly resulting in maintenance of antitumour activity, it is not possible to draw definitive conclusions nor to state that this schedule is better than the standard schedule on the bases of only these data. Moreover, the modified schedule seems to provide the advantage of preventing tumour regrowth during the off-treatment period, that has been observed in some cases. Although no published specific data exist, the "tumor regrowth" is a phenomenon described both in animals and in clinical practice (14, 15, 20, 21).

With this modified schedule each cycle of therapy is "smeared" over six weeks and the maximum time interval between tablet intake and the other is 72 hours: given the pharmacokinetic data described above, theoretically this should not allow the drug to lower at ineffective (or too low) blood levels.

Two open label phase II trials investigated the continuous once-daily sunitinib at a dose of 37.5 mg in treatment-naïve and cytokine-refractory patients, suggesting, with the significant limitations of cross-trial comparison, similar efficacy outcomes and comparable toxicity between the continuous and 4+2 schedule (22): but the most definitive comparison of these regimens is

Table 2. Delivered treatment, dose reductions and delays

	Sunitinib 4 + 2 schedule	Sunitinib modified schedule
Median time from start to switch	7.4 (1.4-16.1)	-
Median duration of treatment after switch, months (range)	- (2.2-20.4)	6.7
Mean actual daily dose intensity, mg (range)	40.9 (20.4-50.0)	41.9 (22.7-50.0)
Mean relative dose intensity, % (range)	88.9 (54-100)	98.9 (91-100)
Median cycles, number (range)	4.5 (1-11)	5 (2-13)
Median total cycles, number (range)	10.5 (5-20)	
Patient with a dose reduction, number (%)	3 (37.5)	1 (12.5)
Patient with a dose interruption, number (%)	4 (50)	2 (25)
Patient still on treatment, number (%)	0 0	

Table 3. Toxicities

Adverse event	Grade 1-2		Grade 3		% of patients with G1-3 toxicity during 4+2 schedule	% of patients with G1-3 toxicity after switch to modified schedule	% of patients that obtained at least 1 grade toxicity reduction after switch to modified schedule
	4+2 schedule	Modified schedule	4+2 schedule	Modified schedule			
Neutropenia	2	3	3	1	62.5	50.0	60.0
Thrombocytopenia	5	3	1	0	75.0	37.5	66.7
Anemia	5	5	0	0	62.5	62.5	20.0
Asthenia	7	7	1	0	100.0	87.5	75.0
Stomatitis	3	2	1	0	62.5	25.0	80.0
Loss of appetite	7	2	0	0	87.5	25.0	71.4
Cutaneous toxicity	2	3	1	0	37.5	37.5	100.0
Diarrhea	3	3	0	0	50.0	37.5	25.0
Bleeding	3	1	0	0	50.0	12.5	75.0
Arterial hypertension	2	1	1	0	50.0	12.5	75.0
Hypophosphatemia	2	1	0	1	50.0	25.0	50.0
Hypothyroidism	3	0	0	0	37.5	0.0	66.7
Pause symptoms	4	2	0	0	50.0	12.5	100.0
Other	3	5	0	0	75.0	62.5	33.3

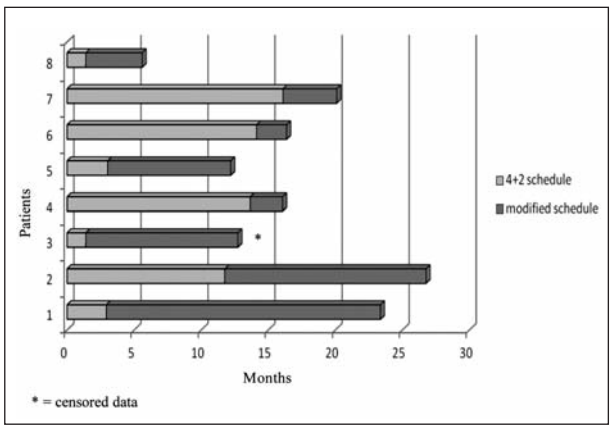

Figure 2. Overall progression free survival for each patient

offered by the EFFECT trial mentioned above, in which 292 first-line mRCC patients were randomized to receive sunitinib either at 50 mg using 4+2 schedule or 37.5 mg using continuous dosing (16). Of note, the theoretical total dose in six weeks of continuous daily dosing schedule was 1575 mg (37.5 mg x 42 days), while in 4+2 schedule was 1400 mg (50 mg x 28 days). This study revealed superior clinical outcomes and higher steady-state sunitinib plasma concentrations for 4+2 schedule, inferior dose intensity and more dose reductions for continuous once-daily sunitinib, without significant different toxicity (16). Pharmacokinetic analyses and the outcome of clinical trials have suggested that treating patients at a lower dose intensity may result in reduced efficacy. The data also indicate that maintaining daily dose intensity is more important than giving a minimal dose each day (22-23).

Since toxicity and drug administration data presented above are only for descriptive purposes, no statistical tests were performed to compare the two schedules: indeed, to perform these tests it would be necessary *ad hoc* hypothesis study with appropriate statistical design. The present analysis has the following limitations: it is retrospective, the number of patients is small, the pharmacokinetics has not been evaluated and quality of life has not been measured. Patients could reduce the dose during therapy with 4 +2 schedule, but in our opinion this did not alter the results of the analysis because the schedule change was done without changing the dose for each patient at the time of the switch.

Altogether, this work shows that sunitinib schedule can be changed in different ways, it stays effective maintaining a certain dose intensity, and some side effects in individual patients might be reduced. However, no conclusions can be drawn about its actual effectiveness and toxicity compared to the standard dosing schedule.

Despite these limitations, considering that the main purpose of this small retrospective analysis was hypothesis generating, we believe that this modified schedule deserves to be studied in future *ad hoc* trials.

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