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Original Article

Biweekly sunitinib regimen reduces toxicity and retains efficacy in metastatic renal cell carcinoma: A single-center experience with 31 patients

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Abbreviations & Acronyms
CR = complete response
ECOG = Eastern Cooperative Oncology Group
IFN-α = interferon-α
IL-2 = interleukin-2
mRCC = metastatic renal cell carcinoma
MSKCC = Memorial Sloan-Kettering Cancer Center
OR = overall response
OS = overall survival
PDGF = platelet-derived growth factors
PFS = progression-free survival
PR = partial responses
RCC = renal cell carcinoma
TSH = thyroid stimulating hormone
VEGF = vascular endothelial growth factors
WHO = World Health Organization

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Objectives: Sunitinib is the standard care for first-line treatment of metastatic renal cell carcinoma. The aim of this study was to determine whether a sunitinib regimen of 50 mg/day 2-weeks on/1-week off could maintain the same dose-intensity as the standard 4-weeks on/2-weeks off schedule, and provide the same efficacy in terms of objective response, progression-free survival and overall survival, while reducing drug-related toxicity.

Methods: A total of 31 patients with metastatic renal cell carcinoma received sunitinib orally at the dose of 50 mg/day in a 2-weeks on/1-week off regimen until disease progression or intolerable toxicities occurred.

Results: All enrolled patients were assessable in terms of toxicity and response. They received treatment for a median of 16 months (range 2.0–36.0+ months). A total of 13 patients (42%) obtained an objective response; disease stabilization was achieved in 10 patients (32%), whereas eight patients (26%) experienced disease progression. The most important toxicities were anemia, gastrointestinal effects, fatigue and hypertension, but they were all controlled.

Conclusions: Sunitinib 50 mg given orally in a 2-weeks on/1-week off regimen can provide a high response rate and avoid drug-related toxicities, achieving the same dose intensity as the standard schedule, and probably longer disease control.

Key words: metastatic renal cell carcinoma, renal cancer medical treatment, sunitinib, treatment toxicity, tyrosine kinase inhibitors.

Introduction

In the past 10 years, the medical treatment of solid tumors has produced significant results, but there is a paucity of results to date regarding mRCC. There is therefore an urgent need to identify new active agents to combat this carcinoma.[1] Until a few years ago, the 5-year mRCC survival rate was estimated at less than 10%,[2] because mRCC has proved to be highly resistant to conventional chemotherapy, which involves the use of cytotoxic drugs. Thus, only a small group of patients, approximately 20%, has benefited from the use of cytokines, such as INF-α or IL-2, obtaining a mean survival rate of approximately 10–12 months.[3–7] At the same time, recent experimental and clinical studies have shown that RCC is characterized by varying histology. In this way, it has been possible to show how the loss of specific protein functions, typical of von Hippel-Lindau syndrome, but also found in sporadic clear cell RCC, can determine the production of factors linked to hypoxia events[8–10] and consequently induce an overexpression of VEGF and PDGF. These factors have been found to promote angiogenesis that directly contributes to the hypervascularization found in RCC. From these preliminary studies, it can be readily surmised that inhibition of VEGF and PDGF receptors should at least partly control tumor angiogenesis.[11,12] In this context, sunitinib malate (Pfizer, La Jolla, CA, USA) has been found to be the most promising of the targeted molecular drugs proposed for the treatment of mRCC. It is a new orally active

multi-target tyrosine kinase inhibitor, capable of specifically inhibiting the VEGF (types 1–3) and PDGF (α and β) receptors, and also effectively blocking other tyrosine kinases.[13,14]

The present study was undertaken to investigate whether sunitinib, orally administered at the dose of 50 mg/day in 3-week cycles, 2-weeks on/1-week off schedule (2/1-week), can reduce the incidence of the most significant drug-related side effects (WHO criteria) while maintaining the standard planned drug dose intensity.[15] Another goal of the study was to verify the effectiveness of the "2/1-week regimen" in terms of OR (OR = CR + PR) according to the Response Evaluation Criteria in Solid Tumors,[16] PFS and OS compared with the standard regimen.

Methods

Patients

Patients with metastatic RCC were considered eligible for the study.

Eligibility criteria

- Histologically documented metastatic clear cell kidney tumor
- Patient's written informed consent
- Age 18 years or older
- Previous nephrectomy for clear cell renal carcinoma
- Presence of measurable metastatic disease
- Performance status of 0 or 1 according to Eastern Cooperative Oncology Group
- Adequate renal and hepatic function assessed with normal laboratory tests
- Adequate cardiac function
- Must have suspended any previous cytokine treatment for at least 4 weeks.

The study was carried out in accordance with the declaration of Helsinki and Good Clinical practice criteria. All patients gave their informed written consent after being thoroughly informed of the study design, benefits and risks according to the guidelines of Local Ethics Committee.

Exclusion criteria

- Presence of cerebral metastasis
- Ischemic heart disease (with documented evidence for the 12 months preceding the start of the treatment).

Study design and treatment regimen

In the present study, we evaluated a total of 31 patients who received sunitinib 50 mg orally in a 2/1-week schedule. Before the start of the study, 10 patients had received sunitinib 50 mg orally in a 4/2-week regimen that was modified when toxicity of grade ≥2 (WHO) was documented. Then the treatment schedule was modified with the same dose of 50 mg/day of sunitinib, but in a 2/1-week schedule instead of reducing the sunitinib dose to 37.5 mg or 25 mg. At the same time, 21 other patients were enrolled who received sunitinib 50 mg/day in the 2/1-week schedule from the beginning of the study. Alternatively, the dose of sunitinib 50 mg/day was reduced to 37.5 or 25 mg/day, depending on the severity and duration of the toxic effect observed. The treatment was suspended in the event of disease progression, toxicity grade ≥3 or if the patient requested treatment suspension.

Baseline evaluation

At the start of the study and every 3 months thereafter, the patients underwent a full physical examination, diagnostic monitoring of the tumor (brain, chest, abdomen and pelvis scan with computed tomography or magnetic resonance imaging scan, whole body bone scintigraphy and PET when considered necessary, ECOG performance status evaluation; laboratory tests (blood chemistry and coagulation tests, urine tests); electrocardiogram and measurement of the left ventricle ejection fraction by means of echocardiogram. Thyroid function was also evaluated periodically by monitoring the TSH, T3 and T4 values.

Statistical methods

The study was planned as a non-randomized phase II study. The size of the sample was calculated in the expectation of reaching an objective response level varying between 20 and 40%. Thus, according to the Simon two-stage method,[17] if a minimum of objective responses >20% was achieved in the first 15 patients enrolled, enrolment of further patients would have been reasonable. PFS and OS were analyzed according to the Kaplan–Meier method,[18] and plotted with confidence intervals at 95%.[19] The patients who were alive were assessed on the last date of the periodic check-up.

Results

Patients' characteristics

From January 2008 to May 2010, 31 patients with mRCC were enrolled in the study. The final analysis of the data relating to the study was carried out in May 2011. At the time of joining the study, all 31 patients (100%) presented with an ECOG performance status ≤2 and metastatic disease, with 13 patients (42%) presenting with metastatic disease in three or more sites and the lung was the most frequently affected organ. All patients were also classified according to risk classes according to Motzer *et al*.[20] The clinical characteristics of patients are reported in Table 1.

Table 1 Characteristics of the patients at the start of the study

Characteristics	Current study *n* (%)	Motzer' study *n* (%)
Total population involved in the study	31 (100)	106 (100)
Median age (range)	68 years (50–85 years)	56 years (32–79 years)
Sex		
Males	19 (61)	67 (63)
Females	12 (39)	39 (37)
ECOG: performance status		
0	11 (35)	58 (55)
1	20 (64)	48 (45)
No. metastatic sites		
1	10 (32)	13 (12)
2	8 (26)	38 (36)
≥3	13 (42)	55 (52)
Metastatic sites		
Lung	18 (58)	86 (81)
Liver	5 (16)	29 (27)
Bone	8 (26)	27 (26)
Lymph nodes	11 (35)	62 (59)
Soft tissue	9 (29)	–
Contralateral kidney	2 (6)	–
MSKCC: risk factor†		
0	16 (52)	61 (58)
≥1	15 (48)	45 (42)

†Risk factors associated with shorter survival according to MSKCC risk classification.

Sunitinib was given to 21 patients (68%) as first-line treatment, whereas 10 patients (32%) had previously received cytokine treatment. Patients received sunitinib for a median of 16 months (range 2.0–36.0 months). Sunitinib was given orally at a dose of 50 mg/day in 2/1-week regimen. During the study, the daily sunitinib dose had to be reduced to 37.5 mg/day for grade ≥2 (WHO) toxicity in four our of 31 patients (13%).

Efficacy

All 31 patients enrolled in the study were assessable for OR (OR = CR+PR), PFS and OS, which are summarized in Table 2. Three patients (10%) obtained a CR for the metastatic lesions in the lung and lymph gland system; 10 patients (32%) obtained PR with an OR of 42%. Disease stabilization was recorded in 10 patients (32%), whereas the remaining eight patients (26%) presented progression. All the responses were related to target lesions. Skeletal lesions were not included in the response evaluation, as they were

Table 2 Extent of the objective response to treatment with sunitinib

Extent of the response	Patients examined	
	n	%
CR	3	10
PR	10	32
CR + PR (OR)	13	42
Disease stability ≥3 months	10	32
Progression of the disease, stability <3 months or non-assessable	8	26

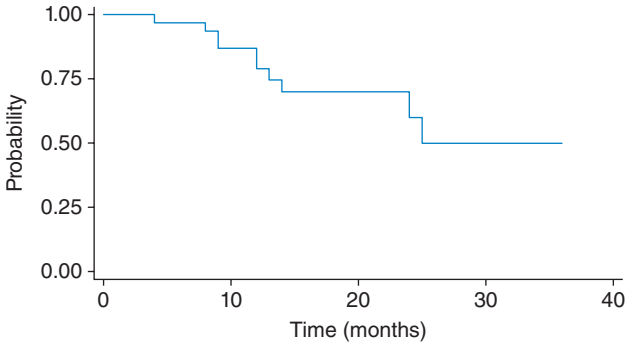

Fig. 1 Kaplan–Meier curve referring to the calculation of PFS in patients with mRCC treated with sunitinib.

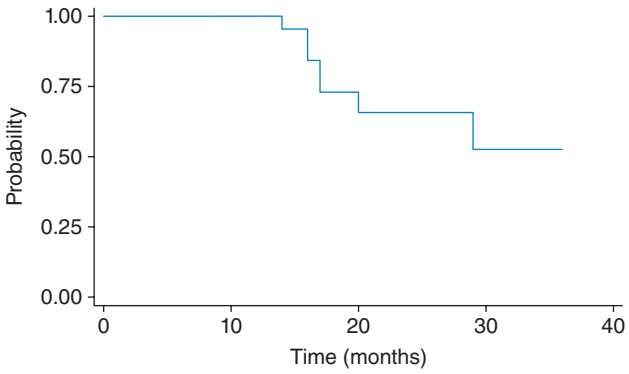

Fig. 2 Kaplan–Meier curve referring to the calculation of OS in patients with mRCC treated with sunitinib.

treated with zoledronic acid (4 mg/month intravenously) and where necessary, with targeted radiation therapy for analgesic purposes. At the time of data analysis, six out of 31 patients (19%; of the eight [26%] recorded with disease progression) died, whereas the other two patients (6%) who had progression, after suspension of the sunitinib treatment, moved to second-line treatment with temsirolimus (Torisel). A total of 24 patients (77%) were still alive after 36 months of treatment. Figures 1 and 2 show the PFS trend, the median value of which is 16.4 months (range 4–36 months,

Table 3 Most common adverse events linked to treatment with sunitinib, identified by grade of severity

Adverse events	Patients ($n = 10$)				Patients ($n = 21$)			
	4/2-Week regimen				2/1-Week regimen			
	Grade 2	Grade 3	Grade 4	Total %	Grade 2	Grade 3	Grade 4	Total %
Anorexia	2	–	–	20	1	–	–	5
Emesis	1	–	–	10	–	–	–	–
Fatigue	1	2	–	30	3	–	–	14
Nausea	1	–	–	10	1	–	–	5
Mucositis – diarrhea	1	1	–	20	3	–	–	14
Bleeding	2	–	–	20	1	–	–	5
Rash	–	1	–	10	2	–	–	10
Hand-foot syndrome	1	–	–	10	1	–	–	5
Hypertension	3	1	–	40	4	–	–	20
Cardiotoxicity	–	–	1	10	–	–	–	–
Blood chemistry changes								
Neutropenia	–	1	–	10	2	–	–	10
Anemia	2	1	–	30	4	–	–	20
Platelet disorder	1	–	–	10	–	–	–	–
↑TSH	3	–	–	30	2	–	–	10

Table 4 Comparison between the most significant data in terms of response and adverse events in Motzer's study and the current study referring to the 21 patients treated with sunitinib 2/1-week regimen

Study	Response			Most significant toxicities (WHO grade ≥2)				Dose reduction cases
	OR	PFS	OS	Anaemia	Fatigue	Mucositis	Hypertension	
	(%)	(months)		(%)				(%)
Motzer'study (regimen 4/2-week)	44	8	26	27	30	13	27	26
Present study† (regimen 2/1-week)	43	13	20	19	13	12	19	9

†The patients characteristics were comparable with those reported in Motzer's study.

95% CI 10.8–22.0), and OS, the median duration of which was 18.1 months (range 6–36 months, 95% CI 15.0–22.2). We believe that the median values of PFS and OS are so close together because the period of follow up was too short.

Safety

Overall, 31 patients were treated with sunitinib for ≥2 months and were included in the safety analysis. The most important sunitinib-related toxic effect was anemia (WHO grade ≥2), which was recorded in seven out of 31 patients (23%), and was easily controlled by administering erythropoietin, following an intravenous iron supplement, when necessary. More frequent was stomatitis/diarrhea in five patients (17%). Another significant side-effect was arterial hypertension, which was recorded in eight patients (26%), but always pharmacologically controllable. Last, a significant increase in TSH values was recorded from cycle II of the treatment in five patients (16%), although it was not accompanied by clinical manifestations of hypothyroidism. After 12 months of sunitinib treatment, we observed cardiac symptoms in one patient, who died of acute heart failure. Table 3 summarizes all the adverse events recorded and their grade during the treatment. Regarding all 31 patients entered in the study: 10 out of 31 patients were treated with the 4/2-weeks regimen and to 21 out of 31 patients were treated with the 2/1-week regimen. We observed a better control of blood pressure (reduced use of antihypertensive drugs) and a reduction of the degree of anaemia – fatigue. In Table 4, the results for response and degrees of toxicity of the 21 patients who from the beginning of the study received sunitinib in a 2/1-week regimen are compared with the results of the study by Motzer *et al*.[21]

Discussion

Metastatic RCC has been considered one of the malignancies that is most difficult to treat with chemotherapy and/or

radiation therapy because of the hyperexpression of the resistance mechanisms to these therapeutic approaches. The histopathological variety most commonly found in RCC is the clear cell form, which presents with highly frequent mutations that are capable of determining neo-angiogenesis and hypervascularization.[8,9] In the past 10 years it has been possible to develop a group of molecules that can control angiogenesis, although not completely, by blocking the tyrosine-kinase receptors, in particular the VEGF and PDGF receptors. In recent times, a number of new drugs and therapeutic regimens have been proposed for the treatment of mRCC. The data in the literature seem to give a prominent role to sunitinib malate, a specific inhibitor of the tyrosine-kinase receptors, VEGFR and PDGFR, as first-line treatment of mRCC. At the same time, as one of the most significant aspects of targeted molecular therapies is the need to continue the treatment until progression of the disease, special attention must be addressed to monitoring any drug-related side-effects, while at the same time understanding the mechanisms that give rise to them and their control in order to maintain adequate dose intensity of the drug given. To date, in mRCC, the pattern of standard treatment involves the administration of sunitinib orally, 50 mg/day in 4/2-week cycles.[21] Furthermore, among related side-effects, the rapidity of onset of arterial hypertension is probably determined by the reduction of the microvascular bed with a consequent increase in peripheral resistance. Yet, it is a common observation that sunitinib-related hypertension tends to spontaneously revert to the normal range during sunitinib suspension. Furthermore, preclinical experiments have shown tumor growth during the sunitinib off-dosing period.[22,23] In light of these observations, more recently a new phase I study[17] was undertaken to investigate sunitinib administration in 3-week courses (2/1-week) to increase the total exposure time by reducing the length of the off-drug period. Other later clinical trials investigated the possibility of guaranteeing equivalent sunitinib activity and efficacy, as well as manageable tolerability in long-term treatment of mRCC, giving sunitinib at the dose of 37.5 mg in a once-daily continuous dosing regimen.[24,25] However, the efficacy and safety profiles in these studies were not superior to those observed when sunitinib was given on 4/2-week schedule. Therefore, we believe that the continuous once-daily dosing of sunitinib might be an alternative only in selected circumstances. Regarding the results reported in the present trial, the primary purpose was to verify if the sunitinib regimen 50 mg/day in a 2/1-week cycle, maintaining the same dose intensity as the standard 4/2-week schedule, can reduce drug-related toxicity while maintaining the same efficacy. Table 4 shows the results of this compared with those of the study by Motzer,[21] which can be considered the reference study for the treatment of mRCC. In terms of response, the results appear to be closely comparable, although we observed fewer objective responses, and higher numbers of patients with disease stabilization, progression free survival and overall survival. However, the most relevant result was the better control of sunitinib-related toxicity, which allowed the continuation of treatment without delays or dose reductions. The present phase II trial confirmed the efficacy of sunitinib treatment in mRCC and showed that the 2/1-week schedule is tolerable, although patients might require minor dose adjustments and/or modifications. In addition, the absence of significant drug accumulation between courses[17] suggests that prolonged sunitinib exposure is feasible over a long period of treatment, allowing us to maintain an adequate sunitinib dose intensity administration. However, we believe these results must be verified in a large series of patients for a longer period.

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Conflict of interest

None declared.

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