Comparative Efficacy of Sunitinib versus Sorafenib as First-Line Treatment for Patients with Metastatic Renal Cell Carcinoma

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Key Words

First-line therapy · Renal cell carcinoma · Sorafenib · Sunitinib

Abstract

Background: This study investigated the efficacy and toxicity of sorafenib and sunitinib as primary treatment for patients with metastatic renal cell carcinoma (mRCC). **Methods:** We identified 49 and 220 patients treated with sorafenib and sunitinib, respectively, as first-line therapy in the Asan Medical Centre from April 2005 to March 2011. **Results:** Disease control rates of 71 and 74% were achieved with sorafenib and sunitinib, respectively ($p = 0.687$). After a median follow-up of 27.6 months, progression-free survival (PFS) and overall survival (OS) were not significantly different between the sorafenib and the sunitinib group (PFS 8.6 vs. 9.9 months, respectively, $p = 0.948$, and OS 25.7 vs. 22.6 months, $p = 0.774$). Patients treated with sorafenib required dose reduction due to toxicities less frequently than those treated with sunitinib (37 vs. 54%, $p = 0.034$). Haematological toxicity of grade 3 or 4 was more common in the sunitinib group than in the sorafenib group (45 vs. 4%, $p < 0.001$). Multivariate analysis showed old age, Heng's risk group, and bone and liver metastases, but not the type of vascular endothelial growth factor tyrosine kinase inhib-

itor, were independent prognostic factors affecting OS. **Conclusion:** The results of this study indicate that sorafenib has comparable efficacy to sunitinib in the treatment of mRCC patients and fewer and less severe toxicities, but the number of patients included in the study was small.

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Introduction

Treatment strategies for metastatic renal cell carcinoma (mRCC) have evolved greatly over the last decade. In the past, cytokine regimens with interferon (IFN) α -2a and interleukin-2 have been the primary treatment for mRCC. However, newly developed targeted agents have recently replaced the cytokine regimen in the initial treatment for advanced RCC [1, 2]. Currently, six targeted agents have been approved for the treatment of mRCC, all of which showed efficacy and tolerable safety in large phase III clinical trials. With an ever-increasing number of treatment options, selecting the first-line regimen for a particular patient has become a hard decision for clinicians. The 2011 guidelines of the National Comprehensive Cancer Network recommended several targeted agents for first-line treatment of advanced RCC and mRCC as category 1. Among

them, the vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) sunitinib has been a preferred choice for mRCC patients with favourable and intermediate risk based on the risk criteria of the Memorial Sloan-Kettering Cancer Centre, because it was the only agent that showed statistically and clinically significant prolongation of progression-free survival (PFS) compared with IFN- α in phase III clinical trials [3]. However, there are no published clinical data that directly compare the efficacy of targeted agents in the first-line setting.

Sorafenib is an oral multi-kinase inhibitor that targets tumour proliferation and angiogenesis and has demonstrated anti-tumour activity in various tumour types including mRCC [4, 5]. The phase III TARGET (Treatment Approach in Renal Cell Global Evaluation Trial) demonstrated that sorafenib improved PFS twofold compared with placebo in 903 patients with clear cell mRCC that was refractory to prior cytokine therapy [1]. However, in a randomised phase II trial of first-line sorafenib versus IFN- α , sorafenib resulted in a similar PFS to that of IFN- α although sorafenib-treated patients showed greater tumour size reduction and better quality of life [6]. Therefore, evidence-based medicine suggested sorafenib as the second-line treatment after cytokine therapy (category 1) and its use as the first-line agent only in selected patients (category 2A) [7].

However, the randomised phase II trial did not have enough power to confirm superiority or inferiority of PFS, and the PFS data reported in previous studies were variable for both sorafenib and sunitinib. In addition, retrospective data reported in North American cancer centres that showed similar overall survival (OS) among patients treated with different first-line drugs suggest that OS, the ultimate endpoint, is not dependent on the first-line agent [8]. Therefore, at present it is difficult to compare the efficacy of first-line treatment with sorafenib and sunitinib because each previous study has different limitations with different prognostic or predictive factors. Furthermore, prospective clinical studies directly comparing the efficacy of these agents are lacking.

Therefore, we retrospectively compared the efficacy of sorafenib and sunitinib administered as first-line targeted agents in our patients with mRCC.

Patients and Methods

Patients

We retrospectively reviewed the medical records of all consecutive patients with mRCC who had been treated with VEGF

TKIs at the Asan Medical Centre from April 2005 to March 2011. Among them, patients who were treated initially with sorafenib or sunitinib were analysed in this study. Patients who were treated with adjuvant TKI after complete resection of both the primary and the metastatic tumour were excluded from the analysis. Patients who received prior immunotherapy or chemotherapy prior to VEGF TKI treatment were also reviewed as previous studies showed no statistically significant differences in the efficacy of sunitinib or sorafenib between patients with or without prior immunotherapy or chemotherapy [9–11].

Treatment and Data Collection

Sorafenib (400 mg) was administered orally twice daily. Sunitinib (50 mg) was administered orally once a day for 4 weeks followed by a 2-week resting period (4/2 schedule). When necessary, the dose of sunitinib was reduced to 37.5 or 25 mg depending on the type and severity of adverse events. Patients who were initially intolerant to sunitinib using the 4/2 schedule, even after dose reductions, were given the reduced dose for 2 consecutive weeks followed by a 1-week rest period every 3 weeks (2/1 schedule) [12], which seemed to improve tolerability and compliance. The subsequent dosing schedule depended on the treating physicians' discretion.

Comprehensive clinical, laboratory and pathological data were collected and reviewed to optimise accuracy and completeness. Number and site(s) of organ metastases as well as the presence of lymph node metastases were determined based on radiographic imaging at the time of treatment initiation. The most recent laboratory values before initiation of treatment were used. Information on the presence or absence of adverse events and their severity was collected from the electronic medical records and laboratory values, and toxicity was graded according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 4.0. Response was reassessed according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 [13]. This study was approved by the Institutional Review Board of the Asan Medical Centre, which waived requirement for informed consent due to the retrospective design.

Statistical Analyses

All data were analysed using the Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, Ill., USA) and S-plus 2000 (Mathsoft Inc., Seattle, Wash., USA). PFS was calculated from the start of first-line TKI treatment to the date of disease progression or death. Time to treatment failure was defined as the time from first-line TKI treatment to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference or death. OS was calculated from the start of first-line TKI treatment to death from any cause. Disease control rate (DCR) was defined as the proportion of responders who showed complete or partial response, or stable disease. PFS and OS were analysed by the Kaplan-Meier method and compared by the log-rank test. To identify clinical factors prognostic for PFS, we performed univariate and multivariate analyses using stepwise Cox proportional hazard regression. All potential prognostic factors with a value of $p \leq 0.2$ on univariate analyses were entered into the multivariate Cox models. All statistical analyses were two sided with $p < 0.05$ considered significant.

Results

Patient Characteristics

From April 2005 to March 2011, we identified 304 consecutive patients who received VEGF TKIs for mRCC. Of the 304 patients, 49 and 220 patients who were treated with sorafenib and sunitinib, respectively, as first-line therapy were included in this study. The baseline characteristics of these 269 patients are presented in table 1. Most of the patients (82%) had clear cell carcinoma. Seventy-seven per cent of the patients received nephrectomy before starting the TKI treatment and 26% received metastasectomy.

The baseline characteristics were relatively well balanced between both groups, but the patients in the sorafenib group were older than those in the sunitinib group (median age 62.0 vs. 56.5 years, respectively) and had a trend to a better performance status as indicated by a higher Karnofsky performance status score.

Efficacy of Sorafenib and Sunitinib

In the sorafenib group, 11 patients (24%) achieved a partial response and 21 (47%) had stable disease. Response was not evaluable in 4 patients because of absence of measurable lesions. Five patients discontinued treatment before response assessment, because of toxicities in 2 patients and patient refusal in 3 patients, and 1 patient was lost to follow-up before assessment. In the sunitinib group, 3 patients (2%) achieved a complete response, 61 (29%) had a partial response, and 90 (43%) had stable disease. Response was not evaluable in 11 patients because of the absence of measurable lesions, and 4 patients discontinued treatment because of toxicities, 16 patients were lost to follow-up, and 2 patients died before response assessment. Therefore, DCR was 71 and 74% in the sorafenib and the sunitinib group, respectively ($p = 0.687$; table 2).

Over a median follow-up duration of 27.6 months (95% confidence interval, CI, 24.1–31.0 months), the median PFS for the sorafenib and the sunitinib group was 8.6 (95% CI, 1.4–15.9) and 9.9 months (95% CI, 7.0–12.9), respectively ($p = 0.948$); the median time to treatment failure was 6.6 (95% CI, 3.9–9.2) and 7.2 months (95% CI, 6.5–7.9), respectively ($p = 0.665$), and the median OS was 25.7 (95% CI, 15.3–36.1) and 22.6 months (95% CI, 17.9–27.2), respectively ($p = 0.774$; figure 1).

Adverse Events and Safety

Of the 49 patients who were treated with sorafenib as first-line therapy, dose reduction was required in 18 (37%), a significantly lower rate than the 115 patients

Table 1. Patient and disease characteristics

	Sorafenib (n = 49)	Sunitinib (n = 220)	p value
Median age (range), years	62.0 (26–85)	56.5 (17–86)	0.019
Gender			
Male	35 (71%)	161 (73%)	0.803
Female	14 (29%)	59 (27%)	
Pathology			
Clear cell	43 (88%)	177 (81%)	0.320
No clear cell	6 (12%)	43 (19%)	
Prior nephrectomy			
Yes	42 (86%)	164 (75%)	0.095
No	7 (14%)	56 (25%)	
Prior metastasectomy			
Yes	16 (33%)	55 (25%)	0.280
No	33 (67%)	165 (75%)	
Prior immunotherapy			
Yes	14 (29%)	41 (19%)	0.119
No	35 (71%)	179 (81%)	
Karnofsky performance score			
<80	3 (6%)	35 (16%)	0.075
≥80	46 (94%)	185 (84%)	
Heng's risk group			
Favourable risk	13 (28%)	35 (17%)	0.203
Intermediate risk	25 (53%)	134 (64%)	
Poor risk	9 (19%)	41 (20%)	

Numbers are shown (unless indicated otherwise).

Heng's criteria: low Karnofsky performance status (<80%), low haemoglobin (<lower limit of normal), high corrected serum calcium (>ULN), high platelet count (>ULN), high neutrophil count (>ULN); favourable = 0, intermediate = 1–2, poor = 3–6 risk factors.

Table 2. Response to first-line VEGF TKIs

	Sorafenib, n (%)	Sunitinib, n (%)
Total	49	220
Measurable disease	45	209
Complete response	0	3 (2)
Partial response	11 (24)	61 (29)
Stable disease	21 (47)	90 (43)
Progressive disease	7 (16)	33 (16)
Not available	6 (13)	22 (10)
No measurable disease	4	11

(54%) who required dose reduction among those treated with sunitinib ($p = 0.034$). The patient distribution with respect to grade 3 or 4 toxicity is summarised in table 3. The most common grade 3/4 toxicity was hand-foot syndrome (HFS) for sorafenib treatment and haematological toxicity for sunitinib treatment. Haematological toxicity

Fig. 1. PFS (a) and OS (b) according to sorafenib (—) and sunitinib (.....).

ties were more common in the sunitinib group than in the sorafenib group (45 vs. 4%, $p < 0.001$) and hypertension also tended to occur more frequently in the sunitinib group (14 vs. 4%, $p = 0.066$). The incidence of HFS was similar in the two groups.

Prognostic Factors

Univariate analysis revealed that neutrophil count (exceeding the upper limit of normal, $>ULN$), platelet count ($>ULN$), bone metastases, Heng's risk group (intermediate and poor risk) and the absence of nephrectomy were statistically associated with poor OS (table 4). In multivariate analysis, age (≥ 60 years), Heng's risk group, and bone and liver metastases were independent prognostic factors of OS, whereas the type of VEGF TKI (sorafenib vs. sunitinib) was not significant (table 5).

Table 3. VEGF-TKI-related adverse events [n (%)]

Category	Sorafenib (n = 49)		Sunitinib (n = 220)		p value
	G3	G4	G3	G4	
Haematologic toxicity	2 (4)	0	78 (38)	17 (8)	<0.001
Anaemia	0	0	24 (11)	3 (1)	0.007
Leukopaenia	0	0	13 (6)	1 (1)	0.08
Neutropaenia	1 (2)	0	52 (24)	2 (1)	<0.001
Thrombocytopaenia	2 (4)	0	38 (17)	12 (5)	0.002
AST elevation	1 (2)	1 (2)	4 (2)	1 (1)	0.616
ALT elevation	1 (2)	1 (2)	5 (2)	1 (1)	0.645
Bilirubin elevation	1 (2)	0	2 (1)	0	0.465
Bleeding	0	0	5 (2)	2 (1)	0.354
Fatigue	2 (4)	0	5 (2)	0	0.613
Abdominal pain	0	0	2 (1)	0	1.0
Nausea	0	0	3 (1)	0	1.0
Vomiting	0	0	1 (1)	0	1.0
Stomatitis	0	0	12 (5)	0	0.131
Diarrhoea	2 (4)	0	7 (3)	0	0.672
HFS	9 (18)	1 (2)	35 (16)	1 (1)	0.552
Hypertension	2 (4)	0	29 (14)	0	0.066
Rash	2 (4)	0	4 (2)	0	0.301

Grade 3 (G3) and 4 (G4) toxicity was combined in p value calculation.

Table 4. Univariate associations with OS

Characteristics	Hazard ratio (95% CI)	log-rank p
Age (≥ 60 vs. <60 years)	1.20 (0.87–1.66)	0.275
Heng's risk group		
Favourable risk	1	
Intermediate risk	2.32 (1.34–4.03)	0.003
Poor risk	6.50 (3.56–11.87)	<0.001
Neutrophil count ($>ULN$ vs. $\leq ULN$)	2.38 (1.48–3.82)	0.001
Platelet count ($>ULN$ vs. $\leq ULN$)	2.27 (1.46–3.53)	0.001
Liver metastasis (yes vs. no)	1.40 (0.90–2.17)	0.133
Bone metastasis (yes vs. no)	2.08 (1.47–2.96)	0.001
Lymph node metastasis (yes vs. no)	1.38 (0.97–1.97)	0.077
Nephrectomy (no vs. yes)	2.43 (1.71–3.45)	0.001
Prior immunotherapy (no vs. yes)	1.27 (0.86–1.89)	0.228
Type of VEGF TKIs (sorafenib vs. sunitinib)	0.94 (0.60–1.47)	0.774

Discussion

In the current study, the results suggested that the efficacy of sorafenib is comparable to that of sunitinib in VEGF-TKI-naïve patients with mRCC (PFS of 8.6 vs. 9.9 months and OS of 25.7 vs. 22.6 months, respectively).

Table 5. Patient and disease characteristics and OS: multivariate analysis

Parameter	Hazard ratio	95% CI	p value
Age (≥60 vs. <60 years)	1.46	1.02–2.08	0.037
Prior nephrectomy (no vs. yes)	1.21	0.81–1.82	0.356
Heng's risk group			
Favourable risk	1		
Intermediate risk	2.27	1.29–4.01	0.005
Poor risk	4.71	2.26–9.81	<0.001
Neutrophil count (>ULN vs. ≤ULN)	1.53	0.90–2.59	0.117
Platelet count (>ULN vs. ≤ULN)	1.31	0.77–2.24	0.322
Bone metastases (yes vs. no)	1.84	1.27–2.65	0.001
Liver metastases (yes vs. no)	1.67	1.04–2.69	0.033
Type of VEGF TKIs (sorafenib vs. sunitinib)	0.83	0.52–1.34	0.453

Moreover, adverse effects were significantly less frequent in the patients treated with sorafenib.

Although sorafenib has shown efficacy as first-line VEGF TKI treatment against mRCC in several studies, there were no direct comparisons with other targeted agents. In a retrospective study from China, median PFS was 60 weeks (95% CI, 41–79 weeks) with a 1-year PFS rate of 58.4% in 98 patients with mRCC [14]. A Japanese phase II trial of sorafenib in patients with mRCC who did not respond to cytokine treatment also demonstrated the efficacy of sorafenib with a DCR of 87.8%, a response rate of 14.7% and PFS of 32 weeks (95% CI, 25–40 weeks) [15]. In a randomised phase II trial of sorafenib with AMG-386 or placebo in treatment-naïve patients with mRCC in which the addition of AMG-386 to sorafenib did not significantly improve PFS, the patients in the sorafenib-alone arm achieved PFS of 9 months with a DCR of 85% [16]. In addition, in the NA-ARCCS (North American Advanced Renal Cell Carcinoma Sorafenib) trial including 246 patients with mRCC, PFS was 36 weeks (95% CI, 33–45 weeks) and DCR 83% [17]. However, in a randomised phase II trial of sorafenib versus IFN- α as the first-line agent in patients with advanced clear-cell-type RCC, PFS with sorafenib was 5.7 months, which was not significantly different from that with IFN- α [6].

The reason for the discrepancy among these studies is that the patient populations enrolled in each study differ in many aspects that are related to prognosis. In the randomised phase II trial comparing sorafenib with IFN- α , Escudier et al. [6] reported that the patient population had features associated with a less favourable prognosis concerning the number of metastases compared with

those in the TARGET study [1]. Another possible reason is differences associated with ethnicity. In a pooled safety and efficacy analysis of phase I trials of sorafenib in solid tumours including RCC, the severity of skin reactions and diarrhoea was associated with prolonged time to disease progression [18] and, in addition, body mass index and diminished muscle mass was reported to be a significant predictor of toxicity in mRCC patients treated with sorafenib [19]. Therefore, the lower body mass index of patients with Asian ethnicity compared with Caucasians might be related to the relatively higher dose and better clinical outcome of sorafenib in Asian mRCC patients. Actually, the sorafenib dose is closely related to its efficacy, as observed in previous studies by Escudier et al. [6] and Amato [20] that showed possible clinical benefits of sorafenib dose escalation after disease progression.

Similar variation in the reported PFS is observed in studies with sunitinib. Although PFS was 11 months in a randomised phase III trial comparing sunitinib with IFN- α , this result was not reproduced in other studies [3]. Recently, Motzer et al. [21] presented the results of a phase II trial comparing two different dose schedules of sunitinib, which showed PFS of 8.5 and 7.0 months for a sunitinib 50-mg 4/2 (4 weeks on and 2 weeks off) schedule and a 37.5-mg daily schedule, respectively.

Although studies have reported variable PFS for first-line VEGF TKI treatment in patients with mRCC, in a retrospective study of more than 600 patients treated with sorafenib, sunitinib or bevacizumab as the first-line targeted therapy, OS was not significantly different between patients who received sunitinib or sorafenib [8]. As several agents showed efficacy in the treatment of mRCC, not only the first-line treatment, but also subsequent therapies are important. Porta et al. [22] reported limited cross-resistance between sorafenib and sunitinib, and showed that sorafenib treatment followed by sunitinib may result in longer combined PFS than sunitinib treatment followed by sorafenib in 189 patients with mRCC. In addition, in an observational study of 145 mRCC patients that showed considerable side effects of VEGF TKIs, only 17.6% of the patients treated with sunitinib as first-line treatment could receive a second-line treatment, whereas 38.3% of the patients treated first with sorafenib could receive second-line treatment [23].

In selecting the first-line agent in mRCC patients, the toxicity profile is one of the most important factors along with efficacy. In the current study, sorafenib was well tolerated by patients with mRCC, consistent with previous reports [1, 24, 25]. Although HFS was the most common grade 3/4 toxicity with sorafenib treatment, the incidence

of HFS was not significantly different between sorafenib and sunitinib treatment. With sunitinib treatment, haematological toxicity was not only the most common grade 3/4 toxicity, its occurrence was also more frequent than with sorafenib treatment. HFS and haematological toxicities were relatively high in Asian patients treated with sunitinib compared with Caucasians [26]. Therefore, sorafenib seemed to have fewer and less severe adverse events than sunitinib, although this should be confirmed by further studies.

The current study has several limitations. It is a retrospective review of a limited number of patients with inhomogeneous clinicopathologic characteristics. Consequently, the total number of patients enrolled in each group was different, and the median age and performance status were significantly different between both study groups. Especially due to the limited number of patients included in the sorafenib group, the group comparison might be statistically underpowered. These consequences reflect the beliefs of the participating physicians that sunitinib is considered the standard first-line treatment in

mRCC patients, whereas sorafenib has favourable tolerability even in older patients, as shown in previous studies [27]. Therefore, these factors might add substantial selection bias; however, we analysed efficacy after adjusting for these variables and used multivariate analysis to overcome this limitation.

In conclusion, the present study has suggested that sorafenib was both effective as a first-line treatment and well tolerated in patients with mRCC. Although limited, our findings warrant further confirmation by a randomised clinical study comparing VEGF TKIs as the first-line treatment of mRCC patients with better balanced and well-characterised prognostic factors.

Acknowledgement

This study was supported by grants from the Korea Healthcare Technology R & D Project, Ministry of Health, Welfare & Family Affairs, Republic of Korea (grant Nos. A070001 and A102059) and a grant from the Foundation for Industry Cooperation, University of Ulsan (grant No. 2010-1312).

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