Sorafenib as a Second-Line Treatment in Metastatic Renal Cell Carcinoma in Mexico: A Prospective Cohort Study

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Abstract

Background: Sequential inhibition of the vascular endothelial growth factor (VEGF) pathway with sorafenib could be useful for patients with metastatic renal cell carcinoma (RCC). Our aim was to determine the activity and tolerability of sorafenib as a second-line therapy in advanced RCC initially treated with a different VEGF-tyrosine kinase inhibitor (TKI).

Methods: A prospective observational cohort in Mexico (2012–2019). We included 148 subjects with metastatic RCC and who had progression despite treatment with sunitinib (n = 144) or pazopanib (n = 4). The primary end-point was time to disease progression as evaluated every 12–16 weeks.

Results: The mean age of the cohort was 58 years (interquartile range [IQR] 48-68), 104 (70%) were men, and 51 (35%) had a favorable prognosis according to the IMDC (International Metastatic RCC Database Consortium) prognostic model. The median progression-free survival (PFS) and overall-survival after the introduction of sorafenib treatment was 8.5 months (95% confidence interval [CI]: 6.8–10.2) and 40.1 months (95% CI: 35.2–45.0) respectively. The median overall survival from RCC diagnosis to death was 71 months (95% CI: 63.9–79.4). On multivariate analyses, age >65 years was associated with a longer PFS (HR 0.57; 95% CI: 0.35-0.93; p = 0.025). The median PFS in subjects aged >65 years was longer compared to subjects ≤65 years (14.0 [95% CI: 9.2–17.9] *vs*. 7.2 months [95% CI: 5.5–8.9]; p = 0.018). Adverse events grade ≥3 associated with sorafenib occurred in 42 (28%) patients.

Conclusion: Sequential inhibition of VEGF with sorafenib as a second-line treatment may benefit patients with metastatic RCC, especially in subjects >65 years old.

Background

Renal cell carcinoma (RCC) is one of the most common types of cancer and its incidence has been rising by approximately 0.6% each year; however, death rates have been falling by 0.7% each year(1, 2). Patients with advanced RCC develop new metastatic lesions up to 10–30% despite being treated with new drugs, including vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKI) or targeted therapies(3, 4). Additionally, between 20–30% of patients with localized RCC experience relapse in distant sites within 3 years of surgical resection(5–8).

Sorafenib tosylate is a non-selective VEGF-TKI that suppresses multiple isoforms of the intracellular serine/threonine kinase, including the VEGF receptors type 1, 2, and 3 (9, 10). Sorafenib has been tested as a second-line therapy, especially in patients with RCC initially treated with cytokine therapy(11, 12). In patients with advanced RCC treated initially with sunitinib, the sequential use of a second drug with a similar molecular target could raise doubts about its clinical usefulness(13). Nevertheless, there are differences in target specificities among the TKIs demonstrated in pharmacological research(14). Retrospective observational studies have shown a lack of cross resistance between sequential use of TKIs and the distinctive toxicity spectra that occasionally permit tolerance of one TKI over another(15).

The National Comprehensive Cancer Network (NCCN) recommended sorafenib for patients whose disease progressed on a prior therapy as useful only under certain circumstances (category 2A), given the lack of clinical studies with sorafenib as a second-line therapy and the existence of other alternative and effective second-line therapeutic options tested in clinical trials (e.g., cabozantinib, nivolumab, or ipilimumab/nivolumab)(16). Nevertheless, sorafenib remains the main second-line therapy prescribed in many countries like ours because of its availability, relative low-cost, favorable clinical efficacy, and safety. Our aim was to determine the activity and tolerability of sorafenib as a second-line sequential TKI therapy in advanced RCC initially treated with sunitinib or pazopanib.

Methods

This observational cohort study was performed at one tertiary-care center in Mexico City (Centro Médico Nacional Siglo XXI), which belongs to the largest public social security institution in the country. It is a national reference center for specialized treatment of metastatic disease. From July 2012 to July 2019, we included subjects aged ≥ 18 years who had experienced RCC disease progression after treatment with sunitinib or pazopanib. In our center, 2nd line treatments such as cabozantinib, nivolumab, ipilimumab, or axitinib are not available most of the time and sorafenib is the treatment available as second line. The study was approved by the institutional review board (reference number R-2012/2019-3602-007). Patients´ written informed consent was exempted because of the observational nature of the study.

All subjects received sorafenib 400 mg orally twice a day on a continuous dosing schedule until disease progression or intolerable toxicity. Dose reductions, delays, or temporary interruptions of sorafenib were assessed independently by one evaluator. All clinical evaluations were performed every 4 weeks. Evaluation included a clinical interview, a physical examination, and a comprehensive metabolic panel. Imaging with computed tomography or magnetic resonance imaging was performed every 12–16 weeks and was scored per RECIST V.1.1 criteria by an expert radiologist(17). Progression-free survival (PFS) with sorafenib was defined as the time from the start of the sorafenib treatment to disease progression as the primary end-point. Subjects who did not experience progression after treatment suspension for any cause or who were lost during follow-up were censored. Secondary end-points were overall survival (OS) and drug toxicity. Risk factors were classified according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model(18). Strictly regular monitoring of hypothyroidism was performed on a regular basis every 3–6 months. Echocardiography in asymptomatic patients was not included in the active surveillance protocol. We initially calculated a minimal sample size based of 110 patients based on the calculation methods for one sample non-parametric survival test/confidence interval (19) assuming a time at analysis of 12 months, a null survival probability of 0.4, a sorafenib survival probability of 0.55, a follow-up time of 24 months, α value of 0.05, and 1-β of 0.8.

Descriptive quantitative results are presented as mean ± standard deviation for normally distributed data or median (interquartile range [IQR]) for nonnormally distributed data; *t*-test or nonparametric Mann–Whitney *U* test were used to investigate differences. Cross-tabulated data were analyzed with chi-square or Fisher tests. Kaplan–Meier analyses were employed to summarize time-to-event data and statistical

differences were estimated by the log rank test and Cox proportional hazard model. Cox proportional hazard regression models were performed to determined variables that were associated with risk of death. Variables with $p < 0.15$ in the univariate analysis were included in the multivariate models. Logistic regression analysis was performed to assess the risk factors associated with toxicity risk. We compared the agreement between toxicity grade reports related to sunitinib and sorafenib therapies using a concordance test (Kendall's tau-b). All tests of significance were two-tailed and differences were considered statistically significant at a *p*-value < 0.05. All statistical analyses were performed using SPSS software (v. 21.0; IBM SPSS, Armonk, NY, USA) and graphics were analyzed using GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA).

Results

We included 148 subjects with metastatic RCC treated by surgical resection in the majority of cases (n = 141, 95%), and treated with sunitinib (n = 144, 97%) or pazopanib (n = 4, 3%) as the first-line treatment. Their baseline demographic and clinical data are described in Table 1. The mean age of the cohort was 58 (IQR 48–68 years, 104 (70%) were men, 51 (35%) had a favorable prognosis according to the IMDC criteria risk factors, and the most common sites of metastasis were lung (n = 79, 53%) and bone (n = 30, 20%). The majority of patients had undergone nephrectomy, except for 7 (5%) subjects with advanced and metastatic disease who were not candidates for surgical treatment. Histology was a clear cell RCC subtype in 143 (97%) cases. Eighty-eight (59%) subjects were treated initially only with surgical excision and progression was diagnosed after 6 months of active surveillance. The remaining subjects (n = 60, 41%) received TKI as first-line therapy within 3 months of their RCC diagnosis. All subjects received a TKI: i.e., sunitinib (n = 144, 97%, median dose of 37.5 mg/day) or pazopanib (n = 4, 3%). Interferon treatment was employed before TKI treatment in only five cases. The median time between first-line therapy (sunitinib or pazopanib) and second-line therapy (sorafenib) was 15.6 months (IQR, 11–26). A good Karnofsky performance status scale score ≥ 80 was observed in 94 subjects (64%). Fifty-five (38%) subjects had ≥ 2 metastatic sites at the start of their sorafenib treatment. The median follow up of the entire cohort after sorafenib treatment was 7 months (range, 2 to 61 months).

Table 1
Baseline clinical characteristics before sorafenib treatment.

Characteristics **(n = 148)**	**Values**
Age, years	58 (48–68)
Male, n (%)	104 (70)
Age > 60 years, n (%)	65 (44)
Nephrectomy, n (%)	141 (95)
Stage at RCC diagnosis, n (%)	
Unknown	34 (22)
1	4 (3)
2	12 (8)
3	35 (24)
4	63 (43)
Karnofsky performance status scores	
100	1 (1)
90	61 (41)
80	32 (22)
Unknown	54 (36)
High blood pressure, n (%)	48 (32)
Hypothyroidism, n (%)	8 (5)
Site of metastasis	
Lung, n (%)	79 (53)
Bone, n (%)	30 (20)
Liver, n (%)	19 (13)
Lymph node, n (%)	15 (10)
First-line and concomitant treatments	

* Continuous variables are expressed as mean ± SD or as median (25th–75th percentile), categorical variables are expressed as n (%). **Risk status was classified according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC model), in which favorable risk is equivalent to no factors, intermediate risk, 1–2 factors, and high risk, 3–6 factors.(18) LDH = lactate dehydrogenase, Albumin-adj = Albumin-adjusted.

Characteristics (n = 148)	Values
Sunitinib, n (%)	144 (97)
Pazopanib, n (%)	4 (3)
Interferon, n (%)	5 (4)
Radiotherapy, n (%)	30 (20)
Zoledronic acid, n (%)	2 (1)
Risk status, % (n)**	
Favorable risk	51 (34)
Intermediate risk	93 (63)
High risk	4 (3)
Hemoglobin, g/dL	13.7 ± 1.9
Leucocytes, 10^9/L	6.5 (5.3–8.0)
Neutrophils, 10^9/L	3.9 (2.6–5.0)
Platelets, 10^9/L	238 (188–312)
Albumin-adj calcium, g/dL	9.5 (9.1–9.8)
LDH, mg/dL	176 (51–233)

* Continuous variables are expressed as mean ± SD or as median (25th–75th percentile), categorical variables are expressed as n (%). **Risk status was classified according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC model), in which favorable risk is equivalent to no factors, intermediate risk, 1–2 factors, and high risk, 3–6 factors.(18) LDH = lactate dehydrogenase, Albumin-adj = Albumin-adjusted.

The median PFS and survival after the introduction of sorafenib treatment was 8.5 (95% confidence interval [CI]: 6.8–10.2) and 40.1 months (95% CI: 35.2–45.0), respectively (Fig. 1). OS since cancer diagnosis was 71 months (95% CI: 63.9–79.4; Supplementary Fig. 1). The sum of PFS of first-line sunitinib and second-line sorafenib was a median time of 29.8 months (IQR, 25.7–34.0). Progressive disease after sorafenib treatment occurred in 114 (77%) subjects. The common sites of second progression were lung in 30 (20%), bone in 24 (16%), and central nervous system in 11 (11%) subjects. At the end of follow-up, 93 (63%) had died. Complete response, partial response, and stable progression were observed in 3 (2%), 11 (7%), and 18 (12%) subjects respectively. At the time of analysis, 32 (22%) of all patients were still alive and 23 (16%) were lost to follow-up. Third-line treatments for progressors were interferon (27/114, 24%), radiotherapy (26/114, 23%), and nivolumab (1/114, 1%). The median PFS was longer during the first TKI treatment (sunitinib or pazopanib) compared to the second TKI treatment with

sorafenib (15.6 [95% CI: 13.6–17.6] *vs.* 8.5 months [95% CI: 6.8–10.2]; $p < 0.001$; hazard ratio = 1.5; 95% CI: 1.20–1.96; Supplementary Fig. 1).

We performed analyses of several clinical parameters to identify those variables associated with RCC progression. We identified age as the only significant variable differing between subjects who progress on sorafenib treatment versus nonprogressors (Table 2 and Table 3). Median PFS in subjects > 65 years old was longer (14 months, 95% CI: 9.2–17.9) compared to subjects ≤ 65 years old (7.2 months, 95% CI: 5.5–8.9 months; $p = 0.018$; Fig. 2.A). In addition, we found a trend to a longer median OS after the introduction of sorafenib in subjects > 65 years old compared with subjects ≤ 65 years old (43 [95% CI: 37–48] *vs.* 37 months [95% CI: 36–43]; $p = 0.059$). Age > 65 years independently decreased the odds of RCC progression after sorafenib treatment (hazard ratio [HR] = 0.57; 95% CI: 0.35–0.93; $p = 0.025$). Although prognosis according to the IMDC prognostic model was not different between progressors and nonprogressors, the median PFS was higher in metastatic RCC with no IMDC risk factor compared with subjects with ≥ 2 IMDC risk factors (10.3 [95% CI: 6.1–14.6] *vs.* 7.9 months [95% CI: 5.8–9.9], respectively; $p = 0.035$; Fig. 2.B).

Table 2
Characteristics of subjects with advanced RCC with progressors versus nonprogressors on sorafenib treatment.

Baseline characteristics	**Progressors, n = 114 (77%)**	**Nonprogressors, n = 33 (23%)**	***P***
Age, years	57 (47–67)	63 (52–74)	0.007
Age > 65 years, n (%)	20 (17)	13 (39)	0.010
Male, n (%)	80 (70)	23 (70)	0.56
Nephrectomy, n (%)	110 (96)	30 (91)	0.18
Favorable prognosis, n (%)	38 (33)	13 (39)	0.32
1st line with sunitinib	111 (97)	32 (97)	0.64
Radiation therapy, n (%)	22 (19)	8 (24)	0.62
High blood pressure, n (%)	10 (8)	38 (33)	0.84
Karnofsky performance status ≥ 90, n (%)	72 (63)	21 (66)	1.00
≥ 2 metastatic sites, n (%)	44 (39)	11 (33)	0.37
Hemoglobin, g/dL	13.8 ± 2.0	13.4 ± 1.8	0.32
Leucocytes, 10^9/L	6.6 (5.7–8.4)	6.3 (5.2–7.9)	0.37
Neutrophils, 10^9/L	3.7 (2.6–4.8)	4.5 (3.5–5.1)	0.17
Platelets, 10^9/L	237 (188–314)	244 (182–294)	0.62
Albumin-adj calcium, mg/dL	9.5 (9.1–9.9)	9.4 (9.1–9.8)	0.70
LDH, mg/dL	176 (150–234)	176 (161–252)	0.65

* Continuous variables are expressed as mean ± SD or as median (25th − 75th percentile), categorical variables are expressed as n (%). ** Favorable group was classified according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC model), in which favorable risk is equivalent to no factors. TKI = tyrosine kinase inhibitor, LDH = lactate dehydrogenase, Albumin-adj = albumin-adjusted.

Table 3
Multivariate Cox proportional hazard models for the predictors of progression free-survival

Factors	Univariate PFS		Multivariate PFS	
	HR (95% CI)	P	HR (95% CI)	P
Age > 65, yes	0.57 (0.35–0.92)	0.022	0.57 (0.35–0.93)	0.025
Male, yes	1.03 (0.68–1.54)	0.90	0.92 (0.61–1.40)	0.71
Favorable prognosis, yes	1.51 (1.01–2.24)	0.041	1.48 (0.89–2.2)	0.059
1st line with sunitinib	1.35 (0.42–4.29)	0.61	-	-
Karnofsky performance status ≥ 90, n (%)	1.18 (0.80–1.74)	0.41	-	-
≥ 2 metastatic sites, n (%)	1.22 (0.84–1.79)	0.30	-	-
Hemoglobin, g/dL	0.95 (0.85–1.06)	0.32	-	-
Leucocytes, 10^9/L	1.04 (0.93–1.16)	0.48	-	-
Neutrophils, 10^9/L	1.04 (0.92–1.18)	0.55	-	-
Platelets, 10^9/L	1.003 (1.00-1.005)	0.053	-	-
Total calcium, mg/dL	1.074 (0.84–1.37)	0.57	-	-
LDH, mg/dL	0.99 (0.99-1.00)	0.29	-	-

Abbreviations: PFS = progression free-survival, HR = hazard ratio, CI: confidence interval. Favorable group was classified according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC model), in which favorable risk is equivalent to no factors

Adverse events associated with sorafenib occurred in 139 (94%) subjects and included hand-foot syndrome (n = 118, 80%), diarrhea (n = 113, 76%), hypothyroidism (n = 41, 28%), and mucositis (n = 84, 57%) (Table 4). Any adverse events corresponding to a grade > 2 occurred in 42 (28%) patients. In 72 (49%) cases, the sorafenib dose was adjusted at first visit because of toxicity effects. Subjects who developed hypothyroidism related to sorafenib had higher baseline levels of thyroid-stimulating hormone compared to those who did not develop any thyroid disorder (2.9 ± 0.9 *vs.* 2.0 ± 1.2 mU/mL; $p = 0.045$). Development of hypothyroidism during sorafenib therapy was not associated with a favorable response as defined as complete response, partial response, or stable progression (OR = 0.83; 95% CI: 0.3–2.7; $p = 0.76$). Three subjects treated with sorafenib discontinued therapy due to intolerance (hepatotoxicity, ischemic cardiomyopathy, and severe high blood pressure). There was no concordance between the severity of drug toxicity reports related to sunitinib and sorafenib treatments (Kendall's tau-b = 0.018; $p = 0.82$). Likewise, there were no associations for type of adverse events related to sunitinib and sorafenib

therapies, except for nausea, which had a slight concordance between sorafenib and sunitinib use (Kendall's tau-b = 0.18; $p = 0.031$). Twenty-one subjects (51%) with adverse events grade ≥ 3 related to sorafenib did not have any history of previous adverse events grade ≥ 3 during sunitinib therapy. Use of sorafenib in patients with history of adverse events grade ≥ 3 related to sunitinib was not associated with toxicity risk grade ≥ 3 after sorafenib therapy (OR = 1.08; 95% CI: 0.53–2.23; $p = 0.83$).

Table 4
Common adverse events of sequential TKI treatment.

Adverse events related to first-line treatment with sunitinib	Any grade (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%) **
Any adverse event*	146 (98)	23 (15)	62 (42)	59 (40)	2 (1)
Thrombocytopenia	44 (30)	10 (7)	13 (9)	19 (13)	2 (1)
Neutropenia	18 (12)	8 (5)	3 (2)	7 (5)	
HFSR**	117 (80)	59 (40)	41 (28)	17 (12)	
Mucositis	122 (83)	50 (34)	47 (32)	25 (17)	
Diarrhea	101 (68)	58 (39)	30 (20)	13 (9)	
Nausea	28 (19)	23 (16)	5 (3)	0 (0)	
Fatigue	89 (61)	57 (39)	26 (18)	6 (4)	
High blood pressure	41 (28)	25 (17)	12 (8)	4 (3)	0 (0)
Adverse events related to second-line treatment with sorafenib					
Any adverse event	139 (94%)	25 (17)	72 (49)	41 (28)	1 (1)
Hypothyroidism	41 (28)	25 (17)	12 (8)	4 (3)	-
HFSR	118 (80)	62 (42)	33 (22)	23 (16)	
Rash	28 (19)	21 (14)	5 (3)	2 (2)	
Mucositis	79 (53)	50 (34)	21 (14)	8 (5)	
Diarrhea	113 (76)	58 (149)	48 (32)	7 (5)	
Nausea	51 (35)	41 (28)	9 (6)	1 (1)	
Fatigue	121 (82)	68 (46)	43 (29)	10 (7)	
High blood pressure	15 (10)	5 (3)	9 (6)	0 (0)	1 (1)

*Any adverse event for patient, graded as maximum; **HFSR, hand-foot skin reaction; **Grade 4 only in those cases classified according to toxicity grades by the common Terminology Criteria for Adverse Events (CTCAE) classification(37).

Discussion

In this prospective cohort study of 148 Mexican patients with metastatic RCC treated initially with a TKI as first-line therapy, we observed that sequential TKI therapy with sorafenib as second-line therapy is an

acceptable treatment option given the outcomes observed: i.e., a median PFS of almost 9 months and a median survival after the introduction of sorafenib of more than 40 months. In addition, sorafenib administration was safe considering sorafenib-related adverse events.

It is difficult to compare PFS obtained from second-line treatments across observational cohorts and clinical trials, given the variations in the designs, patient characteristics, response criteria, and definitions employed among studies. Nevertheless, some general aspects could be inferred. The median PFS with sorafenib in our cohort seems to be similar to the median PFS obtained in clinical trials for advanced RCC with everolimus (4.4–5.5 months)(20), axitinib (6.7 months)(21), nivolumab (4.6 months)(22), cabozantinib (7.4 months)(23), and nivolumab/ipilimumab (approximately 6 months)(24). Only lenvatinib/everolimus (14.6 months)(25) had shown a median PFS longer than other second-line therapies in randomized clinical trials with a higher rate of related adverse events. According to our results, we propose that sorafenib could be considered as a feasible option for advanced RCC in certain clinical scenarios, considering patient preferences, specific comorbidities(26), tolerability, and availability.

We need to understand the clinical benefits of actual treatments to obtain fair comparisons with new agents for second-line therapies, especially in minority populations and elderly patients(3). NCCN guidelines suggest that for subsequent therapy in metastatic RCC, the simplest approach is to change the mechanism of action related to the second-line therapy, e.g., if a subject was treated with a TKI as first-line treatment, a PD-1 agent should be the second option. Nevertheless, observational data support the use of sequential TKIs following the treatment with an initially different TKI(2, 27). Treatment of metastatic RCC with two TKIs in sequence, both sharing a similar molecular target yet with different clinical effects, could be comparable to newer, more-expensive agents, which are mostly unavailable in developing countries.

In our cohort, it is possible that the majority of patients showed an acceptable PFS time on sorafenib therapy, which is explained by the favorable risk prognosis when the second-line therapy began. Other studies had shown lower PFS with sorafenib. For example, in the AXIS clinical trial, the median PFS with sorafenib as second-line therapy was 4.7 months, where only 28% had a favorable classification according to the Memorial Sloan-Kettering Cancer Center risk(21). Nevertheless, the intermediate-prognosis group in our study had a median progression time of more than 7 months, which seems to be superior to the AXIS trial results. We believe that our patients were highly selected, and our results should not be over-interpreted.

Despite clinically improved outcomes in advanced RCC, it is believed that resistance to VEGF-targeted treatment develops in nearly all patients with RCC(5). In our study, the occurrence of cross-resistance was not observed in all cases during follow-up. Nearly 21% of subjects did not show absolute cross-resistance between the two sequential TKIs (sunitinib or pazopanib and sorafenib). Multiple studies have shown that second-line sorafenib after sunitinib progression is well tolerated and safe over the long term(28, 29). These findings show the urgent need to investigate and understand the acquired resistance to TKIs in patients with RCC.

In a retrospective study with 33 patients who had experienced RCC progression treated with sequential use of either sorafenib or sunitinib, Calvani et al. observed that survival on second-line TKI was longer in the patients who received sorafenib first compared to those treated with sunitinib first (median PFS = 11 *vs*. 3 months). In our results, the increase in median PFS with sunitinib was longer (15 months) than second-line treatment with sorafenib (8.5 months) and the total PFS (the sum of PFS of first-line sunitinib and second-line sorafenib) was longer compared to the referred study (29.8 *vs*. 10 months, respectively) (30).

We found a high rate of sorafenib-related adverse effects (93%), although we did not regularly perform echocardiography in all patients. According to other studies, sorafenib could be associated with almost 100% of adverse effects(31–33). These high rates of toxicity could be attributed to differences in methods to report adverse events. In our study, sorafenib treatment was associated with an astounding number of mucocutaneous side effects, especially hand-foot skin disease compared to reports from other clinical studies(21, 30, 34). In an Asian population, fatigue and hand-foot skin reactions were more common compared to diarrhea, which is the most common adverse effect in non-Asian populations(35). In clinical trials with predominantly non-Asian or non-Latin-American patients, hand-foot skin adverse effects has been observed in between 27–30% of patients(21, 22).

Our study limitations are related to its observational nature, which could be subject to bias, the absence of a comparative treatment, and the inclusion of subjects treated in only one center. We did not verify a clear cell RCC subtype in five (3%) cases; recent studies have shown conflicting results about the effectiveness of TKI in these kinds of cases. Nevertheless, in one study of 53 subjects with kidney cancer with papillary of chromophobe histology, sorafenib or sunitinib treatment showed an acceptable median PFS time of 10.6 months(36).

Conclusion

We observed the acceptable long-term efficacy and safety of sorafenib as a second-line therapy in patients with advanced RCC. Further large clinical trials including sorafenib as a comparator versus new agents are needed.

List Of Abbreviations

Confidence interval: CI.

International Metastatic RCC Database Consortium: IMDC.

Interquartile range: IQR.

National Comprehensive Cancer Network: NCCN.

Overall survival:OS.

Progression-free survival: PFS.

Renal cell carcinoma: RCC.

Tyrosine kinase inhibitor: TKI.

Vascular endothelial growth factor: VEGF

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board (Comité Local de investigación en Salud 3602, COFEPRIS 17CI09015057/ CONBIOÉTICA 09 CEI 022 2017082/ reference number R-2012/2019-3602-007). Patients´ written informed consent was exempted because of the observational nature of the study by the institutional review board.

Consent for publication

Not applicable given that our manuscript does not contain any individual person´s data in any form.

Availability of data and material

The data that support the findings of this study are available on request from the corresponding author, J.C.R.S. Also, the data are publicly available at https://www.researchgate.net/publication/343294988_sorafenib_analysis_2020 with the following identifier: DOI: 10.13140/RG.2.2.28339.04647.

Competing interest

The authors of this paper declare that the paper is original, is not plagiarized, is submitted for first publication in this journal and has not been published or submitted for publication elsewhere, and that there is no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript that may affect the reporting of the article submitted. No pharmaceutical or biotechnology company, foundation, or any other source participated in the design, monitoring, data collection, and analysis.

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Authors' contributions

All authors conceived and designed the study. M.A.A.E. and N.H.L.N., performed the inclusion of subjects, and follow-up. M.A.A.E., N.H.L.N, and R.S.J.C., analyzed the data, reviewed the results, and wrote the article. All authors have read and approved the manuscript.

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Consent for publication

The authors of this paper declare that the paper is original, is not plagiarized, is submitted for first publication in this journal and has not been published or submitted for publication elsewhere, and that there is no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript that may affect the reporting of the article submitted. We warrant that we have the rights in the work and can supply all necessary permissions for the reproduction of any copyright works not owned by you.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

Dr. Ana Elena Martin Aguilar had the following relationships with companies: Bayer Mexico (speakers´ Bureau), Pfizer Mexico (speakers´ Bureau and travels to academic congress), Bristol-Myers Squibb Mexico (speakers´ Bureau), and Ipsen (speakers' bureau). Dr. Haidé Nayeli Nuñez Lopez has received funding for travels to academic meetings from Bristol-Myers Squibb Mexico. Dr. Juan Carlos Ramírez Sandoval had the following relationship with companies: Takeda Mexico (speakers' bureau), Roche Mexico (speakers' bureau), Amgen Mexico (speakers' bureau), Valdecasas Mexico (research funding), and Mercurio S.A. de C.V (English manuscript writing).

References

1. Kidney and Renal Pelvis Cancer - Cancer Stat Facts [Internet]. [cited 2020 May 5]. Available from: https://seer.cancer.gov/statfacts/html/kidrp.html
2. Motzer R, Jonasch E, Michaelson M, Nandagopal L, Gore J, George S, et al. NCCN Guidelines Insights: Kidney Cancer, Version 2.2020. J Natl Compr Canc Netw. 2019;17:1278–85.
3. Tannir N, Pal S, Atkins M. Second-Line Treatment Landscape for Renal Cell Carcinoma: A Comprehensive Review. Oncologist. 2018;23:540–55.
4. Chen C, Fang H, Jiao Y, Zhou Y, Guo Q, Lv Z. Clinical Efficacy and Complication Rate of Sunitinib 2/1 Versus 4/2 Schedule for the Treatment of Metastatic Renal Cell Cancer: A Systematic Review and Meta-Analysis. Clin Genitourin Cancer. 2019;17:319–31.

5. Schmidt A, Azad A, Goh J, Harris C, Joshua A, Weickhardt A, et al. Treatment selection for first-line metastatic renal cell carcinoma in Australia: Impact of new therapy options. Asia Pac J Clin Oncol. 2019;15 Suppl 10:3-10.
6. Eggener S, Yossepowitch O, Pettus J, Snyder M, Motzer R, Russo P. Renal cell carcinoma recurrence after nephrectomy for localized disease: Predicting survival from time of recurrence. J Clin Oncol. 2006;24:3101–6.
7. Tafreshi A, Thientosapol E, Liew M, Guo Y, Quaggioto M, Boyer M, et al. Efficacy of sorafenib in advanced renal cell carcinoma independent of prior treatment, histology or prognostic group. Asia Pac J Clin Oncol. 2014;10:60-65.
8. Jhavar S, Swanson G, Pruszynski J. Risk factors for locoregional relapse after radical nephrectomy. *A*sia Pac J Clin Oncol. 2018;14:192-197.
9. Roskoski R. Vascular endothelial growth factor (VEGF) and VEGF receptor inhibitors in the treatment of renal cell carcinomas. Pharmacol Res. 2017;120:116–32.
10. Fogli S, Porta C, Del Re M, Crucitta S, Gianfilippo G, Danesi R, et al. Optimizing treatment of renal cell carcinoma with VEGFR-TKIs: a comparison of clinical pharmacology and drug-drug interactions of anti-angiogenic drugs. Cancer Treat Rev. 2020;84:101966.
11. Escudier B, Eisen T, Stadler W, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009;27:3312–8.
12. Bellmunt J, Maroto-Rey P, Trigo J, Carles J, Guillem V, López-Martín J, et al. A phase II trial of first-line sorafenib in patients with metastatic renal cell carcinoma unwilling to receive or with early intolerance to immunotherapy: SOGUG Study 06-01. Clin Transl Oncol. 2010;12:503–8.
13. Dudek AZ, Zolnierek J, Dham A, Lindgren B, Szczylik C. Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. Cancer. 2009;115:61–7.
14. Hartmann J, Haap M, Kopp H, Lipp H. Tyrosine Kinase Inhibitors – A Review on Pharmacology, Metabolism and Side Effects. Curr Drug Metab. 2009;10:470–81.
15. Sneed G, Lee S, Brown J, Hammond J. The Role of Pazopanib in Non-Clear Cell Renal Cell Carcinoma: A Systematic Review. Clin Genitourin Cancer. 2019;17:419–24.
16. Motzer R, Jonasch E, Agarwal N, Bhayani S, Bro W, Chang S, et al. Kidney Cancer, Version 2.2017: Clinical practice guidelines in oncology. JNCCN J Natl Compr Cancer Netw. 2017;15:804–34.
17. Eisenhauer E, Therasse P, Bogaerts J, Schwartz L, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
18. Heng D, Xie W, Regan M, Warren M, Golshayan A, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. J Clin Oncol. 2009;27:5794–9.
19. Borgan Ø, Liestøl K. A note on confidence intervals and bands for the survival function based on transformations. Scandinavian Journal of Statistics 1990; 17(1): 35–41

20. Motzer R, Escudier B, Oudard S, Hutson T, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372:449–56.
21. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson T, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomised phase 3 trial. Lancet. 2011;378:1931–9.
22. Motzer R, Escudier B, McDermott D, George S, Hammers H, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1803–13.
23. Choueiri T, Escudier B, Powles T, Mainwaring P, Rini B, Donskov F, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1814–23.
24. Hammers H, Plimack E, Infante J, Rini B, McDermott D, Lewis L, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: The checkmate 016 study. J Clin Oncol. 2017;35:3851–8.
25. Motzer R, Hutson T, Glen H, Michaelson M, Molina A, Eisen T, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: A randomised, phase 2, open-label, multicentre trial. Lancet Oncol. 2015;16:1473–82.
26. Leonetti A, Bersanelli M, Castagneto B, Masini C, Di Meglio G, Pellegrino B, et al. Outcome and Safety of Sorafenib in Metastatic Renal Cell Carcinoma Dialysis Patients: A Systematic Review. Clin Genitourin Cancer. 2016;14:277–83.
27. Miyake H, Kusuda Y, Harada KI, Sakai I, Fujisawa M. Third-line sunitinib following sequential use of cytokine therapy and sorafenib in Japanese patients with metastatic renal cell carcinoma. Int J Clin Oncol. 2013;18:81–6.
28. Kontovinis L, Laschos K, Karadimou A, Andreadis C, Bamias A, Paraskevopoulos P, et al. Sequential treatment with sorafenib and sunitinib in metastatic renal cell carcinoma: Clinical outcomes from a retrospective clinical study. Med Oncol. 2012;29:750–4.
29. Di Lorenzo G, Cartenì G, Autorino R, Bruni G, Tudini M, Rizzo M, et al. Phase II study of sorafenib in patients with sunitinib-refractory metastatic renal cell cancer. J Clin Oncol. 2009;27:4469–74.
30. Calvani N, Morelli F, Leo S, Orlando L, Lombardi L, Gnoni A, et al. Sequential use of sorafenib and sunitinib in advanced renal cell carcinoma: Does the order of sequencing matter? Med Oncol. 2012;29:1908–13.
31. Bandini M, Smith A, Marchioni M, Pompe R, Martel T, Cindolo L, et al. Adjuvant Therapies in Nonmetastatic Renal-Cell Carcinoma: A Review of the Literature. Clin Genitourin Cancer. 2018;16:176–83.
32. Oh W, Mcdermott D, Porta C, Levy A, Elaidi R, Scotte F, et al. Angiogenesis inhibitor therapies for advanced renal cell carcinoma: Toxicity and treatment patterns in clinical practice from a global medical chart review. Int J Oncol. 2014 Jan;44:5–16.
33. Ibrahim E, Kazkaz G, Abouelkhair K, Bayer A, Elmasri O. Sunitinib adverse events in metastatic renal cell carcinoma: A meta-analysis. Int J Clin Oncol. 2013;18:1060–9.

34. Afonso F, Anido U, Fernández-Calvo O, Vázquez-Estévez S, León L, Lázaro M, et al. Comprehensive overview of the efficacy and safety of sorafenib in advanced or metastatic renal cell carcinoma after a first tyrosine kinase inhibitor. Clin Transl Oncol. 2013;15:425–33.
35. Mir M, Changal K, Aziz S, Bhat G, Lone A. Sunitinib in metastatic renal cell carcinoma (mRCC): a developing country experience. Do our patients behave differently than the Western patients? Int Urol Nephrol. 2016;48:1811–6.
36. Fernández-Pello S, Hofmann F, Tahbaz R, Marconi L, Lam T, Albiges L, et al. A Systematic Review and Meta-analysis Comparing the Effectiveness and Adverse Effects of Different Systemic Treatments for Non-clear Cell Renal Cell Carcinoma. Eur Urol. 2017;71:426–36.
37. National Institute of Cancer. Common Terminology Criteria for Adverse Events (CTCAE). NIH Publ [Internet]. 2010;0–71. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

Figures

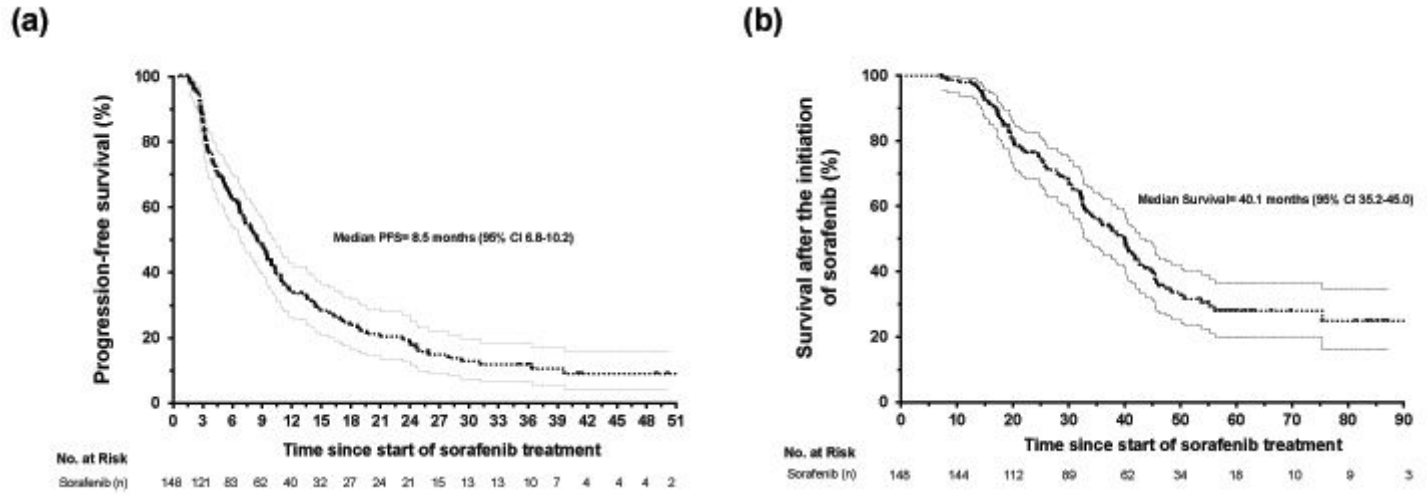

Figure 1

Progression-free survival (a) and survival (b) after the introduction of sorafenib treatment

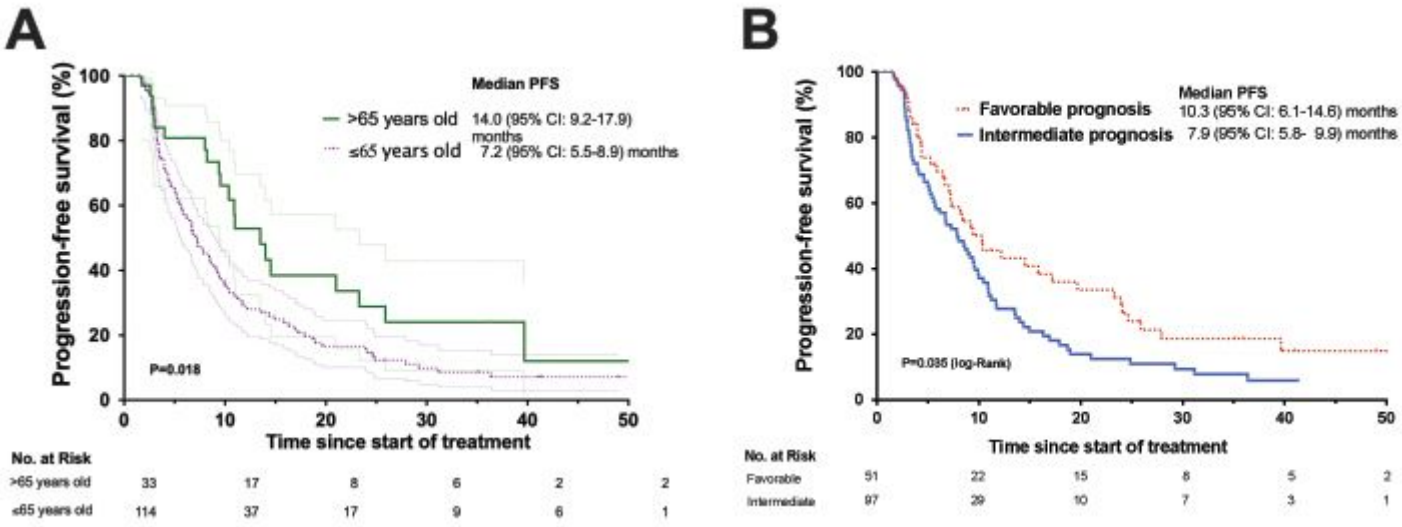

Figure 2

Progression-free survival on sorafenib in subjects >65 and ≤65 years old (panel A) and progression-free survival on sorafenib in subjects with no risk factors (favorable prognosis) and ≥1 risk factors (intermediate prognosis) (panel B)

Supplementary Files

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