Kidney Cancer

Third-Line Sorafenib After Sequential Therapy With Sunitinib and mTOR Inhibitors in Metastatic Renal Cell Carcinoma

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Article info

Abstract

Background: Sunitinib and everolimus have been approved for first- and second-line treatment, respectively, in metastatic renal cell carcinoma (mRCC). The role of sorafenib, which is approved for second-line treatment after cytokines failure, is presently to be defined.

Objective: To determine whether third-line sorafenib after sequential use of sunitinib and mammalian target of rapamycin inhibitors (everolimus or temsirolimus) is feasible and effective.

Design, setting, and participants: One hundred fifty medical records of patients with mRCC treated with first-line sunitinib between January 2006 and January 2010 were reviewed at four participating centers. Data regarding patients treated with the sequence sunitinib–everolimus or temsirolimus–sorafenib were extracted. Central analysis of radiographic images was performed using RECIST criteria to determine progression-free survival (PFS) and overall response rate (oRR) to sorafenib treatment.

Measurements: PFS and oRR to sorafenib were the primary end points. Secondary outcomes were safety and overall survival (OS).

Results and limitations: Thirty-four patients were eligible for the study. A median PFS of 4 mo (range: 3–6 mo) and a median OS of 7 mo since sorafenib treatment (range: 6–10 mo) were reported. Of the patients, 23.5% showed response to sorafenib, with an overall disease control rate (complete responses plus partial responses plus stable disease) of 44%. Selection bias, data incompleteness, and absence of study design are inevitable limitations of the study, although central review can strengthen the quality of presented data.

Conclusions: Third-line sorafenib appears to be active and well tolerated in mRCC after first-line sunitinib and second-line everolimus or temsirolimus, with no patients interrupting sorafenib because of toxicity or lack of compliance. Prospective, placebo-controlled trials are completely lacking and are required in this setting.

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1. Introduction

In metastatic renal cell carcinoma (mRCC), the transition to the so-called targeted therapy era has made available an unprecedented variety of effective new agents, such as sunitinib and sorafenib, two vascular endothelial growth factor (VEGF) tyrosine kinase receptor (TKR) inhibitors; bevacizumab (VEGF antibody); and everolimus and temsirolimus, two mammalian target of rapamycin (mTOR) inhibitors. A statistically significant improvement in progression-free survival (PFS) was obtained with these five biological drugs in well-conducted phase 3 trials, in comparison to either interferon alone (in the first-line setting) or placebo (in the second-line setting). Each of these drugs was approved by the Food and Drug Administration (FDA) in the United States and by the European Medicines Agency (EMEA) in Europe and is indicated in specific populations of mRCC patients. As first-line treatment, bevacizumab plus interferon and sunitinib are recommended for good- and intermediate-risk patients, whereas temsirolimus is recommended for poor-risk patients. As second-line treatment, sorafenib is indicated after progression on interferon, and everolimus is recommended after progression on sorafenib or sunitinib [1]. Recently, pazopanib has also been FDA and EMEA approved in locally advanced renal cell carcinoma (RCC) or mRCC on the basis of the results reported by a large, randomized, placebo-controlled trial in patients who were either treatment naive or had been pretreated with interferon [2].

These rapid developments have raised three issues of great clinical importance that have not yet been adequately investigated. First, the optimum sequence of administration of effective agents has not been determined. Second, the effectiveness of combinations of targeted agents (eg, bevacizumab plus everolimus) has yet to be established. Third, several clinical, biochemical, or radiographic markers that are predictive of therapy effectiveness are available but have not been definitively validated [3].

In comparison to everolimus, sorafenib has shown limited activity after failure of first-line sunitinib [4,5]. Cross-resistance between sorafenib and sunitinib can be expected on the basis of their similar mechanisms of action. Nevertheless, based on available preclinical studies, one might speculate that the use of mTOR inhibitors could reverse resistance to VEGF-TKR inhibitors and possibly could enhance sorafenib effectiveness in sunitinib-refractory patients [6]. Very scarce published data, either of a retrospective or prospective nature, are available in the literature on the effectiveness and practicability of third-line sorafenib after first-line sunitinib and second-line everolimus or temsirolimus. In view of the complete lack of information in this setting, we began a multicenter, retrospective study to determine the efficacy and tolerability of third-line sorafenib in this specific population of pretreated mRCC patients.

2. Patients and methods

2.1. Inclusion criteria

One hundred fifty medical records of patients with mRCC treated with first-line sunitinib between January 2006 and January 2010 were reviewed at four participating Italian centers (70 records at University "Federico II" of Naples; 40 at the Regina Elena Cancer Institute of Rome; 20 at the Centro di Riferimento Oncologico of Rionero in Vulture, Potenza; and 20 at the Institute for Cancer Research and Treatment of Candiolo, Turin). Patients with the following criteria were included in this retrospective analysis: (1) histologic diagnosis of mRCC, (2) baseline radiographic assessment and at least one radiographic evaluation of response after at least 1 mo of first-line treatment with sunitinib, (3) baseline radiographic assessment and at least one radiographic evaluation of response after at least 1 mo of second-line treatment with an mTOR inhibitor (either everolimus or temsirolimus), (4) baseline radiographic assessment and at least one radiographic evaluation of response after at least 1 mo of third-line sorafenib treatment, and (5) radiographic images performed during sorafenib therapy for evaluation of response available for central review.

2.2. Retrieved data

Demographic data of eligible patients were retrieved along with clinical and histologic characteristics such as Eastern Cooperative Oncology Group performance status, Memorial Sloan-Kettering Cancer Center (MSKCC) risk group at diagnosis, type of surgical operation, histologic grading, and lymph node status. Data about PFS and best response regarding first and second lines of treatment were collected from reviewed medical records. Best response and PFS of third-line sorafenib treatment were assessed by central review (performed by GDL and VM, according to revised RECIST criteria) [7]. Only grade 3–4 adverse events to sorafenib and sunitinib, as defined according to the National Cancer Institute common toxicity criteria (version 3.0), if applicable, were extracted from reviewed charts.

2.3. Data analysis

Descriptive statistics and frequency counts were used to summarize characteristics of the study population. Median numbers were presented with interquartile ranges. Overall response rate (oRR) to each line of treatment was defined as the percentage of patients who had either a complete response or a partial response as best response at any time during treatment. Overall disease control rate was defined as the percentage of patients who had either a complete response or a partial response or a stable disease as best response at any time during treatment. PFS and overall survival (OS) were calculated using the Kaplan-Meier method. PFS for each line of therapy was calculated from the start of treatment to the time of radiographic progression or death. Only patients who presented a PFS assessed by central review as less than or equal to PFS assessed by "local review" and had been radiographically evaluated at least every 3 mo were included in the final analysis of PFS obtained with sorafenib. Patients lost to follow-up or who were still under treatment as of July 15, 2010, were censored in the analysis. Survival was computed from the start of first-line sunitinib and third-line sorafenib treatment to death. Patients alive as of July 15, 2010, or who were lost at follow-up were censored from the analysis. Univariate analysis with the Fisher exact test was used for testing the hypothesis of a relationship between response to sorafenib an pretreatment variables that included age, sex, performance status, metastatic sites, MSKCC class, response to sunitinib, response to mTOR

inhibitors, dose reduction. A *p* value <0.05 was considered statistically significant.

3. Results

3.1. Study population

Of 150 patients treated with first-line sunitinib, 55 received second-line everolimus or temsirolimus. Of these 55 patients, 37 (67%) received third-line sorafenib. Thirty-four patients (27 men, 7 women; median age: 61 yr; range: 42–69) were finally eligible for this study. Patient characteristics are detailed in Table 1.

3.2. First-line sunitinib and second-line mTOR inhibitors

First-line sunitinib was administered orally at a fixed daily dosage of 50 mg (4 wk on and 2 wk off). Median PFS was

Table 1 – Patient characteristics

No. of patients (%)	34 (100)
Men	27 (79.4)
Women	7 (21.6)
Age, yr	
Median	61
Range	42–69
ECOG PS at first, second, and third line	
ECOG 0	30, 24, 9
ECOG 1	4, 10, 22
ECOG 2	0, 0, 3
Prior nephrectomy, No. (%)	
Yes	33 (97.0)
No	1 (3.0)
Histologic subtypes, No. (%)	
Clear cell	32 (94.1)
Papillary	2 (5.9)
Lymph node involvement at the time of surgery, No. (%)	
Yes	8 (23.5)
No	14 (41.2)
Unknown	12 (35.3)
Systemic therapy for metastatic disease, No. (%)	
First-line sunitinib	34 (100)
Second-line everolimus	24 (70.5)
Second-line temsirolimus	10 (29.5)
Third-line sorafenib	34 (100)
Site of metastases at the time of sorafenib, No.	
Lung	25 (73.5)
Liver	19 (55.8)
Bone	9 (26.4)
Lymph nodes	8 (23.5)
Adrenal	3 (8.8)
Kidney	2 (5.8)
Soft tissue	1 (2.9)
Brain	1 (2.9)
MSKCC risk class at the time of diagnosis, No. (%)	
Good	18 (52.9)
Intermediate	13 (38.2)
Poor	3 (8.8)

ECOG = Eastern Cooperative Oncology Group; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status.

Table 2 – Grade 3–4 toxicity of sorafenib and sunitinib in the population (*n* = 34)

Toxicity	Grade 3–4 events with third-line sorafenib, No. (%)	Grade 3–4 events with first-line sunitinib, No. (%)
Hand-foot syndrome	5 (14.7)	1 (2.9)
Anemia	4 (11.7)	2 (5.8)
Neutropenia	3 (8.8)	5 (14.7)
Fatigue	3 (8.8)	6 (17.6)
Diarrhea	3 (8.8)	3 (8.8)
Hypertension	2 (5.8)	2 (5.8)
Oral mucositis	2 (5.8)	2 (5.8)
Thrombocytopenia	1 (2.9)	2 (5.8)
Nausea/vomiting	1 (2.9)	2 (5.8)

10 mo (range 5.9–12). Grade 3–4 adverse events to sunitinib were uncommon and are reported in Table 2. Seventeen patients (50%) had a partial response, and eight presented stable disease (23%). Median time from sunitinib end to everolimus or temsirolimus start was 2 mo (range: 1–3). As second-line treatment, 10 mg everolimus was administered orally to 25 patients, whereas 9 patients received 25 mg of temsirolimus intravenously weekly. Median PFS was 4 mo (range: 4–6) and 2 mo (range: 1.8–4.9) and oRR was 12.5% and 0% for everolimus and temsirolimus, respectively. Median time from second-line treatment end to sorafenib start was 1 mo (range: 1–1.25).

3.3. Third-line sorafenib

Sorafenib was administered daily at 800 mg. Computed tomography scans were scheduled every two cycles (each cycle: 6 consecutive weeks) and was performed at 3 mo for 32 patients and every 4 mo for 2 patients. Ten patients required dose reduction to 600 mg or 400 mg. There was no toxicity-related death. Grade 3–4 adverse events to sorafenib were uncommon and are reported in Table 2. Local review and central review were concordant for 29 of the 34 patients. Of the remaining five patients, three with "stable disease" by local assessment were judged as having progressive disease by central review, whereas two with "progressive disease" by local assessment were judged as having stable disease by central review. Thirty patients were included in the analysis of PFS. As shown in Figs. 1 and 2, median PFS was 4 mo (range: 3–6) and median OS was 7 mo from sorafenib treatment (range: 6–10). Eight patients showed a partial response assessed by central review, with an overall disease control rate of 44%. Fig. 3 shows best percentage variations in the sum of all measurable lesions. At the time of the analysis, four patients were still alive, and two patients were still receiving sorafenib. No patient has interrupted treatment for reasons other than progression. As shown in Tables 3 and 4, response to first-line sunitinib was the only factor significantly associated with response to third-line sorafenib. In fact, response rate (RR) to sorafenib was 47.0% in patients who had responded to sunitinib, whereas it was 0% in patients who had not responded to

PFS from the start of sorafenib
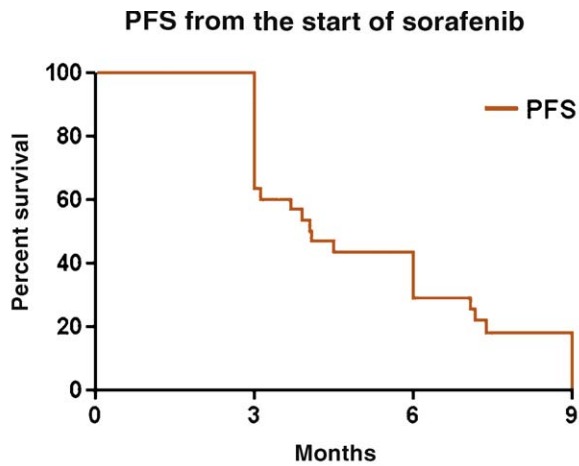
PFS	0	3	6	9
Num of patients at risk	30	30	12	4
Survival fractions %	100	63.3	28.8	0
Total events recorded	0	11	21	28

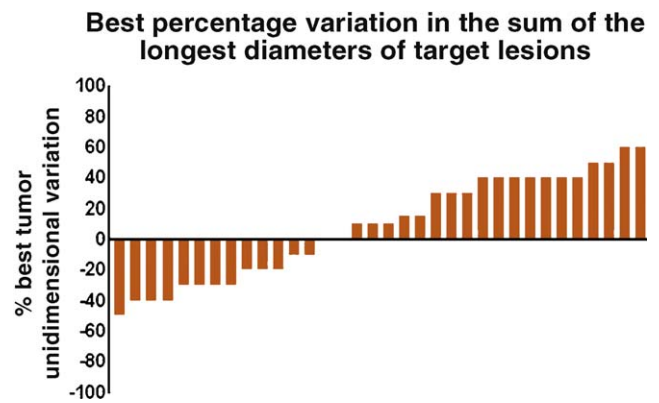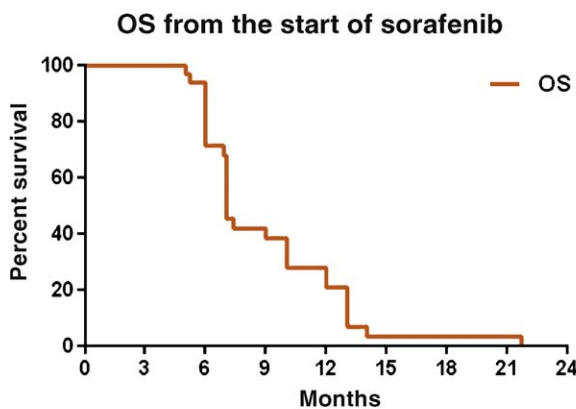Fig. 1 – Progression-free survival (PFS) from the start of sorafenib.

OS from the start of sorafenib

OS	0	3	9	18	24
Num of patients at risk	34	34	12	1	0
Survival fractions %	100	100	38.5	3.5	0
Total events recorded	0	0	19	29	30

Fig. 2 – Overall survival (OS) from the start of sorafenib.

Best percentage variation in the sum of the longest diameters of target lesions

Fig. 3 – Best percentage change from baseline in sum of longest diameters based on central radiology review.

Table 3 – Evaluation of sorafenib responses compared with previous responses to first-line sunitinib[*]

Best response to third-line sorafenib	Patients responding to first-line sunitinib ($n = 17$), No. (%)	Patients not responding to first-line sunitinib ($n = 17$), No. (%)
CR and PR	8 (47.0)	0 (0)
SD	1 (5.8)	6 (35.2)
PD	8 (47.0)	11 (64.7)

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
[*] Response criteria are as given in the materials and methods section.

sunitinib ($p = 0.0027$). OS computed from the start of first-line treatment was 21 mo (range: 18–22.5) in patients with good and intermediate prognosis, whereas the three patients with poor prognosis had a survival of 10, 19.7, and 9.4 mo.

4. Discussion

Data from one large randomized controlled trial demonstrated sorafenib activity in mRCC [8]. Because this study was conducted in a population of patients who had received prior therapy with interferon, which is no longer a standard therapy for mRCC, and no other phase 3 trial has been completed, the exact role of sorafenib in the management of mRCC remains presently to be defined.

Among the several agents approved in mRCC, sunitinib can be considered the drug of choice in patients with good or intermediate prognosis in the first-line setting, with respect to sorafenib or bevacizumab plus interferon, based on the results obtained in two meta-analyses [9,10] but not yet on the basis of comparative phase 3 trials. Sorafenib is a valid first-line option for patients who are intolerant of sunitinib. In the second-line setting, the only FDA-approved drug after progression on VEGF-TKR inhibitors is everolimus, which yielded (1) PFS of 4.9 mo, as assessed by independent central review, and 5.5 mo, as assessed by the investigators, and (2) an OS of 14.8 mo in the experimental arm of a large, placebo-controlled, phase 3 trial [11]. These results seemed to be

Table 4 – Univariable analysis of response to sorafenib[*]

Independent variables		Response rate to sorafenib[**]
Sex	Males vs females	25.9% vs 14.2%, $p = 1$
Age	≤60 y vs > 60 y	40% vs 10.5%, $p = 0.1$
Performance status	ECOG 0 vs ECOG 1–2	11.1% vs 28.0%, $p = 0.4$
Lung metastasis	Presence vs absence	32.0% vs 11.1%, $p = 0.3$
Liver metastasis	Presence vs absence	21.0% vs 26.6%, $p = 1$
Response to sunitinib	Responders vs nonresponders	47% vs 0%, $\boldsymbol{p = 0.0027}$
Response to EVE or TEM	Responders vs nonresponders	66.6% vs 19.3%, $p = 0.1$
Dose reduction of sorafenib	No dose reduction vs dose reduction	20.8% vs 30.0%, $p = 0.6$
MSKCC class	Good vs intermediate/poor	33.3% vs 12.5%, $p = 0.2$

EVE = everolimus; TEM = temsirolimus; ECOG = Eastern Cooperative Oncology Group; MSKCC = Memorial Sloan-Kettering Cancer Center.
[*] Response criteria are as given in the materials and methods section.
[**] Two-sided p values were determined using the Fisher exact test.

superior to those obtained with second-line sorafenib in 52 patients with sunitinib-refractory mRCC by Di Lorenzo et al. [4]. An indirect comparison that performed matching populations of these two studies according to their MSKCC risk class showed that everolimus, with respect to sorafenib, was associated with an improved median PFS (40.8 vs 17.7 wk) and an improved median OS (78 vs. 32 wk) [5]. A recent retrospective study has also shown activity of temsirolimus in a population of mRCC patients, mainly at intermediate or poor risk, pretreated with VEGF inhibitors (median time to progression: 3.9 mo; median OS: 11.2 mo), but prospective trials are lacking in this setting [12].

Preclinical data suggest that concomitant or sequential use of VEGF-TKR inhibitors and mTOR inhibitors might be advantageous in patients with mRCC. In fact, resistance to everolimus and temsirolimus can be mediated by a compensatory increase in hypoxia inducible factor, which could targeted by VEGF blocking agents such as sorafenib, sunitinib, and bevacizumab [6]. Furthermore, if cross-resistance between sunitinib and sorafenib is hypothesized on the grounds of their similar mechanisms of action and the clinical data, it should be considered that sunitinib suspension alone after progression might reverse resistance to sunitinib on its reintroduction [6]. Rini et al rechallenged 23 mRCC patients with third-line sunitinib after first-line sunitinib and different kinds of second-line treatments and obtained a PFS of 7.2 mo and a response rate of 22% on sunitinib rechallenge [13]. In this regard, it must be noted that under the regulations of the Italian drug agency, Agenzia Italiana del Farmaco, sunitinib rechallenge is prohibited in the particular Italian context, whereas administration of third-line sorafenib is allowed.

With all of these considerations taken into account, the third-line setting could be the ideal one in which to exploit the efficacy of sorafenib in mRCC. Data in this setting are almost nonexistent. A PFS of about 5 mo was recently reported in abstract form in a heterogeneous population of 15 everolimus-pretreated mRCC patients treated with third-line therapy, but the variety of agents used, including bevacizumab, sunitinib, or sorafenib, as well as the limited sample size make this result of little value [14]. In contrast, our retrospective study included a quite homogenous population of mRCC patients who had undergone the specific sequence sunitinib–mTOR inhibitor–sorafenib.

Various interesting results were obtained in this study. First, third-line treatment with sorafenib was not associated with unexpected toxicity; the most common grade 3–4 adverse reactions, such as fatigue, diarrhea, hand-foot syndrome, and anemia, were manageable and never responsible for treatment interruption. Second, sorafenib seemed to preserve its activity in the third-line setting with a response rate of 23.5%, a PFS of 4 mo, and an OS of 7 mo. These results compare favorably with those obtained with sorafenib in a phase 3 trial comparing sorafenib to interferon in the first-line setting (median PFS: 5.5 vs. 2.8 mo; median OS: 17.8 vs. 15.2 mo; RR: 10% vs. 2%) [8] and in a single-arm phase 2 trial in the second-line setting after sunitinib (median time to progression, 4 mo; OS, 8 mo; RR: 9.6%) [4]. Third, a sufficiently high proportion (67%) of all patients undergoing second-line treatment with everolimus or temsirolimus were then treated with third-line sorafenib, which might therefore have a considerable impact on the management of mRCC. Fourth, response to first-line sunitinib was associated with response to sorafenib. This finding could help select patients who are most likely to respond to sorafenib and contribute to the growing body of literature regarding markers predictive of therapy effectiveness in mRCC. Stratification for sunitinib response should therefore be considered when designing prospective trials on third-line sorafenib.

The present study is vulnerable to the typical bias of retrospective studies because of possible data incompleteness, absence of study design, and inevitable variability in clinical management among the four participating centers. Assessment of radiographic response every 3 mo is far from being ideal in an experimental setting and can lead to overestimated PFS. Furthermore, owing to the limited sample size, selection bias of patients treated with third-line sorafenib may also affect our results. Nevertheless, it is our belief that central assessment of both PFS and response rate to sorafenib strengthened the quality of presented data because assessment was performed by two well-known investigators in the field by using the RECIST criteria, as specified in the methods section of this paper. Furthermore, treatment with sorafenib and follow-up timing happened to be rather homogenous among the four institutions, with sorafenib being administered at fixed doses ranging from 400 to 800 mg every day of a 6-wk cycle and radiographic

assessments being carried out approximately every two cycles. The inclusion of patients treated with either everolimus or temsirolimus was based on their common mechanisms of action but can also be considered a limitation of our study.

5. Conclusions

The present retrospective study is the first to investigate the effectiveness of third-line sorafenib after sequential therapy with sunitinib and an mTOR inhibitor. Our results indicate that a sufficiently high proportion of patients with mRCC treated with first-line sunitinib and second-line mTOR inhibitor can receive third-line therapy with sorafenib with excellent compliance and tolerability. Sorafenib preserves its activity after sunitinib and everolimus or temsirolimus and seems to be especially effective in the subset of patients who had responded to first-line sunitinib. Prospective, placebo-controlled trials are completely lacking and are required in this setting.

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