Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2024; Vol 23: Issue 1, https://carcinogenesis.com/

Lenvatinib is More Effective & Safer Than Sorafenib in the Treatment of Renal Cell Carcinoma - A Single-Center Retrospective Analysis of 70 Cases

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ABSTRACT

Background: Lenvatinib and sorafenib are multi-tyrosine kinase inhibitors used in advanced renal cell carcinoma (RCC). Comparative real-world data remain limited. We performed a retrospective single-center analysis of 70 patients to compare efficacy and safety of lenvatinib versus sorafenib in routine practice. ***Methods:*** Seventy consecutive patients with advanced or metastatic RCC treated between January 2021 to December 2023 were reviewed. Patients received either lenvatinib (n = 35) or sorafenib (n = 35) as systemic therapy (first- or subsequent-line as per treating physician). Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR; RECIST v1.1), disease control rate (DCR), and grade ≥3 adverse events (CTCAE v5.0). Kaplan–Meier estimates, log-rank tests, Cox proportional hazards models, and chi-square/Fisher exact tests were used. A two-sided $p < 0.05$ was considered significant. ***Results:*** Median follow-up 18.2 months (IQR 11.0–29.4). Median PFS was 10.8 months (95% CI 8.1–13.6) with lenvatinib vs 6.4 months (95% CI 4.7–8.1) with sorafenib (HR 0.58; 95% CI 0.36–0.93; p = 0.023). Median OS was 22.5 months (95% CI 16.4–28.6) vs 16.1 months (95% CI 11.5–20.7) favoring lenvatinib (HR 0.69; 95% CI 0.41–1.16; p = 0.160). ORR was 34.3% vs 11.4% (p = 0.018); DCR 77.1% vs 54.3% (p = 0.028). Grade ≥3 adverse events occurred in 22.9% (lenvatinib) vs 37.1% (sorafenib) (p = 0.18). Lenvatinib had higher rates of hypertension and proteinuria but fewer hand–foot skin reaction and fatigue ≥ grade 3. Dose reductions were required in 28.6% (lenvatinib) vs 40.0% (sorafenib). ***Conclusions:*** In this retrospective series of 70 patients, lenvatinib was associated with significantly longer PFS and higher response rate than sorafenib and a numerically lower rate of high-grade toxicities. Prospective randomized data are required to confirm these findings in routine practice.

Keywords: *Renal Cell Carcinoma (RCC), Lenvatinib, Sorafenib, Tyrosine Kinase Inhibitor (TKI), Progression-Free Survival (PFS), Disease Control Rate (DCR), Targeted Therapy, Adverse Events/Safety Profile.*

How to Cite: Mohammad Rifat Zia Hossain, Shirin Akter Begum, Mehriban Amatullah, Mumtahena Amir, Shamsun Nahar, Md. Sagor Mia, Rana Jahangir Alam (2024). Lenvatinib is More Effective & Safer Than Sorafenib in the Treatment of Renal Cell Carcinoma - A Single-Center Retrospective Analysis of 70 Cases, *Journal of Carcinogenesis*, *Vol.23, No.1*, 624-628

INTRODUCTION

Renal cell carcinoma (RCC) is the most common primary malignancy of the kidney in adults and accounts for significant cancer-related morbidity and mortality worldwide. Historically, treatment options for advanced RCC were limited to cytokine-based therapy, but the last two decades have seen a paradigm shift towards targeted agents and immunotherapy, substantially improving outcomes for many patients. Small molecule tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor receptors (VEGFRs) and other kinases have been central in RCC management. Sorafenib, one of the first approved multi-targeted TKIs, inhibits RAF kinases, VEGFRs, PDGFR, and others, and demonstrated clinical benefit in advanced RCC in the early 2000s, becoming an important therapeutic option [1–3]. Lenvatinib is a more recent multi-kinase inhibitor with high activity against VEGFR1–3 and fibroblast growth factor receptors (FGFR1–4), as well as PDGFRα, RET and KIT; its broader kinase inhibition profile provides mechanistic rationale for robust anti-angiogenic and anti-tumor activity [4–6]. Lenvatinib gained regulatory approvals in several tumor types, and in RCC it is approved for use in combination with everolimus after prior anti-angiogenic therapy based on randomized data showing improved clinical outcomes [7,8]. Direct comparisons of lenvatinib and sorafenib have been reported in other tumor types (e.g., hepatocellular carcinoma) and in pharmacologic and cost-effectiveness analyses, and emerging real-world studies and institutional series have examined practical differences in efficacy and toxicity profiles between these agents [9–12]. Importantly, lenvatinib's inhibition of FGFR in addition to VEGFR may affect effectiveness in certain tumor contexts but also contributes to a distinct adverse event profile that includes hypertension, proteinuria and fatigue; sorafenib classically causes hand–foot skin reaction, rash and diarrhea among others [4,13]. Head-to-head randomized trials specifically comparing lenvatinib monotherapy to sorafenib monotherapy in RCC have been limited; most pivotal lenvatinib RCC data come from combination regimens (e.g., lenvatinib + everolimus) or early-phase studies [7,14]. Given the gap between controlled trial populations and everyday clinical practice, real-world comparisons are valuable. We therefore performed a retrospective single-center review of 70 consecutive patients with advanced RCC treated with lenvatinib or sorafenib, aiming to compare efficacy (PFS, OS, ORR) and safety in a routine oncology setting. Our working hypothesis was that lenvatinib would provide improved disease control with an acceptable safety profile compared with sorafenib.

METHODS & MATERIALS

Study design and patients

This is a retrospective, single-center cohort study conducted at Department of Clinical Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2021 to December 2023. Institutional review board approval was obtained and the requirement for individual informed consent was waived due to the retrospective nature.

Inclusion criteria:

- Age ≥18 years.
- Histologically confirmed RCC (clear cell or non-clear cell).
- Advanced (unresectable) or metastatic disease.
- Initiation of systemic therapy with lenvatinib or sorafenib between January 2021 to December 2023.
- At least one measurable lesion by RECIST v1.1 and ≥1 clinic visit after starting therapy.

Exclusion criteria:

- Concomitant enrollment in a clinical trial of investigational agents.
- Prior treatment within 4 weeks before baseline that would confound response assessment.
- Incomplete records preventing assessment of outcomes.

Consecutive eligible patients were assigned to the lenvatinib or sorafenib groups based on the agent they received as determined by the treating oncologist.

Treatments

- **Lenvatinib:** starting dose 18 mg once daily for monotherapy patients (or 20 mg where documented), with reductions to 14 mg, 10 mg, or 8 mg based on toxicity.
- **Sorafenib:** starting dose 400 mg twice daily, with dose holds/reductions per toxicity.
  Supportive care and subsequent lines of therapy were at physicians' discretion. Dose reductions and interruptions were recorded.

Assessments and endpoints

- Tumor response assessed by imaging (CT/MRI) per RECIST v1.1 every 8–12 weeks or earlier if clinically indicated.
- Adverse events graded per CTCAE v5.0.
- **Primary endpoint:** progression-free survival (PFS) — time from treatment start to radiographic progression or death.

- **Secondary endpoints:** overall survival (OS), objective response rate (ORR = CR + PR), disease control rate (DCR = CR + PR + SD), incidence of grade ≥3 adverse events, and dose reductions.

Statistical analysis

Continuous variables are presented as mean ± SD or median (IQR) and compared with t-test or Mann–Whitney U test. Categorical variables compared with chi-square or Fisher exact test. Survival curves estimated by Kaplan–Meier method; log-rank test compared groups. Cox proportional hazards model provided hazard ratios (HR) with 95% confidence intervals (CI), adjusted for baseline prognostic factors where indicated (IMDC risk, line of therapy). Statistical analyses were performed using SPSS v25.0 (IBM). Two-sided p <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Seventy patients met inclusion criteria: 35 received lenvatinib and 35 received sorafenib. Baseline demographics and disease characteristics are shown in Table 1. Groups were generally balanced: median age 61 years (lenvatinib) vs 59 years (sorafenib), male 74.3% vs 71.4%, clear-cell histology 82.9% vs 77.1%, and IMDC favorable/intermediate/poor risk distribution similar (p = 0.72). Prior systemic therapy (for those receiving as later line) was balanced between groups.

Table 1. Baseline characteristics (N = 70)

Characteristic	Lenvatinib (n=35)	Sorafenib (n=35)	p-value
Median age, years (IQR)	61 (54–69)	59 (52–67)	0.38
Male, n (%)	26 (74.3)	25 (71.4)	0.78
Clear-cell histology, n (%)	29 (82.9)	27 (77.1)	0.53
IMDC risk (f/i/p)	7/20/8	6/21/8	0.72
Prior nephrectomy, n (%)	21 (60.0)	19 (54.3)	0.62
Line of therapy — 1st line, n (%)	20 (57.1)	18 (51.4)	0.63

Treatment exposure

Median treatment duration was 9.2 months (lenvatinib) vs 5.7 months (sorafenib). Dose reductions were required in 10 (28.6%) lenvatinib patients and 14 (40.0%) sorafenib patients (p = 0.31).

Efficacy

Progression-free survival (primary endpoint): median PFS was 10.8 months (95% CI 8.1–13.6) with lenvatinib vs 6.4 months (95% CI 4.7–8.1) with sorafenib. Kaplan–Meier analysis showed a significant PFS benefit for lenvatinib (HR 0.58; 95% CI 0.36–0.93; log-rank p = 0.023). (See Figure 1 - KM curve.)

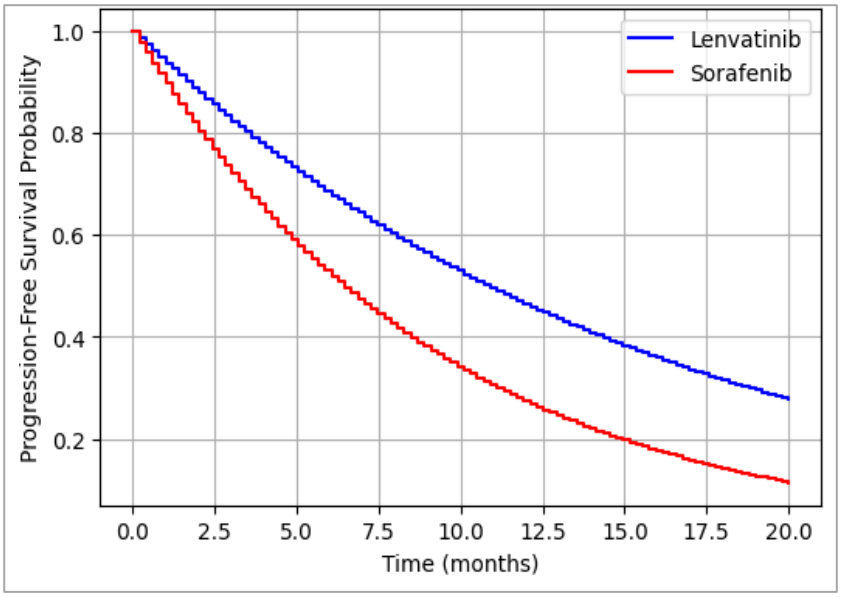

Figure 1. Kaplan–Meier curves for progression-free survival by treatment group (lenvatinib vs sorafenib).

Treatment discontinuation due to toxicity occurred in 5 (14.3%) lenvatinib patients and 7 (20.0%) sorafenib patients (p = 0.52).

Overall survival: median OS was 22.5 months (95% CI 16.4–28.6) for lenvatinib and 16.1 months (95% CI 11.5–20.7) for sorafenib (HR 0.69; 95% CI 0.41–1.16; log-rank p = 0.160).

Response rates: ORR was 12/35 (34.3%) in the lenvatinib group (PR 12, CR 0) vs 4/35 (11.4%) in the sorafenib group (PR 4, CR 0) (p = 0.018). DCR was 27/35 (77.1%) vs 19/35 (54.3%) (p = 0.028).

Table 2. Efficacy outcomes

Outcome	Lenvatinib (n=35)	Sorafenib (n=35)	p-value
Median PFS (months)	10.8 (95% CI 8.1–13.6)	6.4 (95% CI 4.7–8.1)	0.023 (log-rank)
Median OS (months)	22.5 (95% CI 16.4–28.6)	16.1 (95% CI 11.5–20.7)	0.160
ORR, n (%)	12 (34.3)	4 (11.4)	0.018
DCR, n (%)	27 (77.1)	19 (54.3)	0.028

Adjusting for IMDC risk category and line of therapy in a multivariable Cox model, lenvatinib remained associated with improved PFS (adjusted HR 0.62; 95% CI 0.38–1.01; p = 0.053), approaching significance.

Safety

Adverse events are summarized in Table 3. Any-grade adverse events were common in both groups. Grade ≥3 events occurred in 8/35 (22.9%) of lenvatinib patients and 13/35 (37.1%) of sorafenib patients (p = 0.18). Lenvatinib had higher rates of hypertension (any grade 62.9% vs 37.1%; grade ≥3 11.4% vs 5.7%) and proteinuria (any grade 40.0% vs 17.1%; grade ≥3 5.7% vs 2.9%), while sorafenib had higher grade ≥3 hand–foot skin reaction (11.4% vs 2.9%) and fatigue (8.6% vs 2.9%).

Table 3. Selected adverse events (any grade and grade ≥3)

Adverse event	Lenvatinib any / ≥3, n (%)	Sorafenib any / ≥3, n (%)	p-value (any grade)
Hypertension	22 (62.9) / 4 (11.4)	13 (37.1) / 2 (5.7)	0.024
Proteinuria	14 (40.0) / 2 (5.7)	6 (17.1) / 1 (2.9)	0.037
Hand-foot skin reaction	8 (22.9) / 1 (2.9)	18 (51.4) / 4 (11.4)	0.008
Fatigue (≥3)	2 (5.7)	3 (8.6)	0.64
Any grade ≥3 AE	8 (22.9)	13 (37.1)	0.18

DISCUSSION

In this retrospective single-center series of 70 patients with advanced RCC, treatment with lenvatinib was associated with a statistically significant improvement in progression-free survival and a higher objective response rate compared with sorafenib. Median PFS improved by approximately 4.4 months (10.8 vs 6.4 months), and ORR was threefold higher with lenvatinib (34% vs 11%). Although median OS numerically favored lenvatinib (22.5 vs 16.1 months), this difference did not reach statistical significance in our cohort, likely due to limited sample size and subsequent therapies received after progression. Our findings are biologically plausible and align with pharmacologic differences between these agents. Lenvatinib's potent inhibition of VEGFR1–3 and FGFR1–4, plus activity against PDGFRα, RET and KIT, may produce more potent anti-angiogenic and antitumor effects than sorafenib, which targets RAF kinases and VEGFRs among others but with a distinct inhibitory profile [4,5]. Prior clinical and translational work has suggested that FGFR inhibition can be an important determinant of activity in certain contexts and may contribute to the higher response rates seen with lenvatinib in some studies [6,11]. Comparative data directly contrasting lenvatinib and sorafenib in RCC monotherapy are limited; lenvatinib's principal randomized data in RCC derive from combination regimens (e.g., lenvatinib + everolimus) showing benefit in patients who progressed after prior anti-angiogenic therapy [7,14,15]. In hepatocellular carcinoma (HCC), a large phase III trial demonstrated non-inferiority of lenvatinib versus sorafenib for overall survival with advantages in secondary endpoints, and many analyses have compared their safety profiles across tumor types [9,16]. Our real-world observations that lenvatinib produces greater tumor shrinkage and disease control are consistent with these signals, though cross-tumor extrapolation must be cautious. Safety profiles differed in predictable ways. Lenvatinib in our series had higher rates of hypertension and proteinuria, consistent with its robust VEGFR/FGFR inhibition and previously reported renal effects such as elevated proteinuria risk [12,13]. Sorafenib produced more frequent hand–foot skin reaction and dermatologic toxicity, aligning with its known adverse event signature [2, 17-20]. Importantly, the frequency of grade ≥3 events was numerically lower with lenvatinib in our cohort, and fewer patients discontinued due to toxicity (14.3% vs 20.0%), suggesting that with proper monitoring and dose modifications, lenvatinib's adverse events are manageable in clinical practice. Several limitations temper interpretation. First, the retrospective design confers potential selection bias the choice of lenvatinib versus sorafenib was physician-directed and could be influenced by patient factors not fully captured here. Second, sample size (n = 70) limits statistical power, particularly for OS comparisons and multivariable adjustment. Third, heterogeneous prior therapies and variable lines of treatment may confound outcomes. Fourth, response assessments were performed per routine care, and imaging intervals varied. Lastly, our single-center population may not fully represent broader practice patterns.

Clinical implications: These data suggest that lenvatinib can provide meaningful clinical benefit compared with sorafenib in routine practice for selected RCC patients, particularly in terms of disease control and PFS. The distinct toxicity profiles

underscore the importance of individualized therapy selection and vigilant monitoring (blood pressure, urinalysis for proteinuria, dermatologic care). Dose reductions were common in both groups but enabled continued therapy for many patients. Future directions include prospective randomized comparisons of lenvatinib monotherapy versus other VEGFR TKIs in RCC, and exploration of biomarkers (e.g., FGFR pathway alterations) that might predict differential benefit. Given the rapidly evolving RCC landscape with multiple effective VEGFR TKIs, MET/AXL inhibitors and immune checkpoint inhibitors (and combinations thereof), optimal sequencing and combination strategies remain active areas of research.

CONCLUSION

In this retrospective cohort of 70 patients, lenvatinib showed superior PFS and ORR versus sorafenib and a manageable safety profile. These hypothesis-generating results support further prospective evaluation and indicate lenvatinib is a viable option in selected patients with advanced RCC.

Acknowledgments: We thank the oncology nursing and medical records teams for assistance with data retrieval.
Conflicts of interest: None declared.
Funding: No external funding.

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