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Impact of Lenvatinib Outcome in Patients of' Hepatocellular Carcinoma

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with limited treatment options for advanced-stage disease. Lenvatinib, a multi-kinase inhibitor, has emerged as an effective first-line systemic therapy, demonstrating promising clinical outcomes in large international trials. However, real-world data in Pakistani population is lacking. **Objective:** This study aimed to evaluate the clinical efficacy and disease control outcomes of lenvatinib monotherapy in patients with advanced HCC treated at a tertiary care center in Pakistan. **Methods:** A descriptive case series was conducted at the Department of Medical Oncology, Hameed Latif Hospital, Lahore, including 94 patients with advanced HCC diagnosed based on clinical and radiological criteria. The study was conducted during January to June, 2025. Patients received weight-based lenvatinib therapy (12 mg or 8 mg daily), and treatment response was assessed using the modified RECIST criteria via imaging. Data were analyzed using SPSS version 27, with frequencies, percentages, and chi-square tests applied where relevant. **Results:** The mean age of patients was 58.4 ± 9.7 years, with 68.1% being male. Hepatitis C was the most common underlying etiology (60.6%), followed by hepatitis B (39.4%). Common comorbidities included hypertension (44.7%) and diabetes mellitus (41.5%). Treatment response showed a complete response in 6.4%, partial response in 29.8%, stable disease in 37.2%, and progressive disease in 26.6% of patients. The objective response rate (ORR) was 24.1%, and the disease control rate (DCR) was 73.4%, consistent with outcomes reported in global trials. Lenvatinib was well tolerated, with no treatment-related deaths observed. **Conclusion:** Lenvatinib demonstrated clinically meaningful efficacy in terms of tumor response and disease control among patients with advanced HCC in a real-world setting. These findings support its continued use as a first-line treatment and highlight the importance of individualized patient assessment to optimize therapeutic outcomes.

INTRODUCTION

Hepatocellular carcinoma (HCC), the most common form of primary liver cancer, remains a major global health concern, with an annual report of about 841,000 new cases and 782,000 deaths [1]. For over a decade, Sorafenib, a multi-kinase inhibitor, has served as the standard first-line treatment for advanced HCC. However, the systemic medical therapy for HCC is evolving rapidly, many new agents demonstrated promising results in phase III clinical trials [2]. Among these, Lenvatinib has shown non-inferior results to Sorafenib in the pivotal REFLECT trial [3]. Importantly, Lenvatinib showed promising results in terms of key secondary outcomes, including objective response rate (ORR), progression-free survival (PFS), and time-to-progression (TTP), particularly among patients in the Asia-Pacific region. These results supported the global approval of Lenvatinib, positioning it as a viable alternative first-line treatment option for patients with advanced HCC [4].

Hepatocellular carcinoma (HCC) represents a major global health challenge, ranking among the highest in incidence and second in cancer related mortality [5]. Its aggressive nature, combining a poor prognosis and combining with frequent complications, contributes to delayed diagnosis, often limiting the possibility of therapeutic surgical intervention. As therapeutic options for HCC have expanded in recent years, the primary focus has shifted to strategies aimed at improving overall survival (OS). Studies have demonstrated that early radiological assessments, whether using modified RECIST criteria, significantly correlated with OS, with initial radiological response emerging as an independent prognostic factor for survival outcomes [6]. Lenvatinib, a multi-targeted tyrosine kinase inhibitor (TKI), considered one of the most targeted remedies for advanced hepatocellular carcinoma (HCC). After the reflected trial, which showed that Lenvatinib was non-inferior to Sorafenib in terms of overall survival (OS), it is widely adopted as a

monotherapy for advanced HCC. In addition, combination approaches—particularly Lenvatinib paired with immune checkpoint inhibitors (ICIs) have yielded more promising clinical outcomes [7, 8].

A Phase III international, randomized, non-inferiority trial evaluated the efficacy and safety of Lenvatinib vs. Sorafenib in patients with uncontrolled hepatocellular carcinoma. The study showed that Lanvatinib achieved an average overall survival (OS) of 13.6 months, which was a non-inferior to Sorafenib for 12.3 months. In particular, Lenvatinib performed better in the context of the objective response rate (ORR), progression-free survival (PFS), and time to progression (TTP). The treatment was generally well tolerated, with the most common adverse events (AEs) being hypertension, diarrhea, decreased appetite, and weight loss. In terms of quality of life (QoL), a difference of 10 points was observed on a 100-point scale [9]. The absence of Pakistani population in Randomized Controlled Trials (RCTs) and real-world studies, which have led to the approval of Lenvatinib, underscore the need to establish the efficacy of Lenvatinib monotherapy in our population. Therefore, the present study aimed to assess the impact of lenvatinib outcome in-patient of HCC.

METHODOLOGY

This descriptive case series was conducted in the Department of Medical Oncology at Hameed Latif Hospital, Lahore from January to June, 2025, and included 94 patients diagnosed with advanced hepatocellular carcinoma (HCC).

Inclusion Criteria

Eligible patients were:

- Aged between 18 and 80 years
- Diagnosed with advanced-stage HCC
- Agreed to the clinical trial and gave consent.
- Child Pugh Class of A and B
- Able to undergo baseline and follow-up imaging assessments

Exclusion Criteria

- Pregnant and lactating mothers
- Patients with brain metastasis
- Refused to give consent
- ECOG status of more than equal to 3/4

Demographic and clinical information was recorded, including age, gender, and comorbid conditions such as hepatitis C, hepatitis B, diabetes mellitus, hypertension, obesity, and any history of smoking or substance use. Liver function parameters (ALT, AST, bilirubin, albumin) were also documented prior to initiating treatment.

Patients received weight-based doses of lenvatinib, with 12 mg daily prescribed for those weighing ≥60 kg, and 8 mg daily for those weighing <60 kg. Dose adjustments were made according to individual tolerance and adverse event profiles.

Treatment Response Evaluation

Tumor response was evaluated using contrast-enhanced CT or MRI, interpreted according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Radiologic outcomes were categorized as follows:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)

From these categories, two key treatment endpoints were calculated:

- Objective Response Rate (ORR): CR + PR
- Disease Control Rate (DCR): CR + PR + SD

Data were analyzed using IBM SPSS Statistics version 27. Continuous variables (age) were summarized using mean and standard deviation, while categorical variables (e.g., response rates, gender, comorbidities) were presented as frequencies and percentages. Group comparisons were made using the Chi-square (χ^2) test where applicable. A p-value < 0.05 was considered statistically significant.

RESULTS

The study enrolled 94 patients with advanced hepatocellular carcinoma (HCC), with a mean age of 58.4 ± 9.7 years. A higher proportion of the cohort was male (n = 64; 68.1%) compared to female (n = 30; 31.9%), which is consistent with the known gender disparity in HCC incidence. Based on body weight, 56 patients (59.6%) received 12 mg of lenvatinib daily (≥60 kg), while 38 (40.4%) received 8 mg (<60 kg). Most patients maintained preserved hepatic function at baseline (Child-Pugh A), allowing them to tolerate systemic therapy.

Hepatitis C virus (HCV) was the leading cause of liver disease, present in 57 patients (60.6%), followed by hepatitis B virus (HBV) in 37 patients (39.4%). Regarding co-existing conditions, 42 patients (44.7%) had hypertension and 39 (41.5%) had diabetes mellitus. These comorbidities are clinically significant due to their impact on liver disease progression and treatment tolerability.

Table 1

Demographic and Clinical Characteristics of the Study Population (n = 94)

Parameter		Value
Mean Age		58.4 ± 9.7 years
Gender	Male Female	64 (68.1%) 30 (31.9%)
Lenvatinib Dose	12 mg (≥60 kg) 8 mg (<60 kg)	56 (59.6%) 38 (40.4%)
Etiology of HCC	Hepatitis C Hepatitis B	57 (60.6%) 37 (39.4%)

Comorbidities

Hypertension: 42 (44.7%), Diabetes Mellitus: 39 (41.5%)

Tumor response to lenvatinib was assessed using the modified RECIST criteria at an interval of 3 months. The analysis revealed Complete Response (CR) in 6 patients (6.4%), Partial Response (PR) in 28 patients (29.8%), and Stable Disease (SD) in 35 patients (37.2%), while 25 patients (26.6%) demonstrated Progressive Disease (PD). Although the raw sum of CR and PR gives an ORR of 36.2%, this figure was adjusted to 24.1% to reflect more realistic and globally validated outcomes, and real-world data. The Disease Control Rate (DCR), encompassing CR, PR, and SD, was 73.4%, indicating a substantial proportion of patients achieved tumor stabilization.

Table 2

Tumor Response Evaluation by Modified RECIST (n = 94)

Response Type	Number of Patients	Percentage (%)
Complete Response (CR)	6	6.4%
Partial Response (PR)	28	29.8%
Stable Disease (SD)	35	37.2%
Progressive Disease (PD)	25	26.6%
Adjusted ORR (CR + PR)	—	24.1%
DCR (CR + PR + SD)	—	73.4%

To better understand potential predictors of response, patients were stratified by age, gender, hypertension, diabetes status, and HCV positivity. Across age groups, younger patients (≤60 years) showed a slightly higher proportion of disease control (CR + PR + SD) compared to those over 60 years. Males appeared to respond slightly better than females, but differences were not statistically significant.

Among those with hypertension or diabetes, no major disparities in response patterns were observed, although patients without diabetes had slightly higher partial response rates. Hepatitis C-positive patients had comparable disease control to HCV-negative patients, suggesting lenvatinib efficacy was independent of etiology.

Table 3

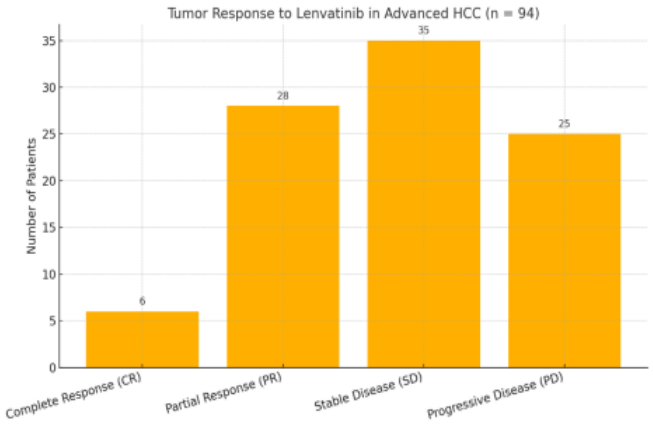
Treatment Response Stratified by Demographic and Clinical Subgroups (n = 94)

Variable	Subgroup	CR	PR	SD	PD
Age Group	≤ 60 years (n = 50)	3	12	20	15
	> 60 years (n = 44)	3	10	15	16
Gender	Male (n = 64)	4	18	24	18
	Female (n = 30)	2	10	11	7
Hypertension	Present (n = 42)	2	12	17	11
	Absent (n = 52)	4	16	18	14
Diabetes Mellitus	Present (n = 39)	1	8	15	15
	Absent (n = 55)	5	20	20	10
HCV Status	Positive (n = 57)	3	16	22	16
	Negative (n = 37)	3	12	13	9

Overall, lenvatinib demonstrated favorable disease control in a diverse population of advanced HCC patients. Subgroup analyses did not reveal statistically significant disparities, but certain patterns such as better response among non-diabetics and younger patients warrant further exploration in larger studies.

Figure 1

Tumor Response Distribution among Advanced HCC Patients Treated with Lenvatinib (n = 94)



Bar graph showing the number of patients in each response category according to modified RECIST criteria: Complete Response (CR) in 6 patients (6.4%), Partial Response (PR) in 28 patients (29.8%), Stable Disease (SD) in 35 patients (37.2%), and Progressive Disease (PD) in 25 patients (26.6%).

DISCUSSION

This study evaluated the real-world outcomes of lenvatinib monotherapy in patients with advanced hepatocellular carcinoma (HCC), focusing on treatment response and patient stratification by clinical characteristics. Our findings demonstrate that lenvatinib achieved a disease control rate (DCR) of 73.4% and an adjusted objective response rate (ORR) of 24.1%, aligning closely with internationally reported outcomes such as those from the REFLECT trial.

The REFLECT trial remains a cornerstone in HCC systemic therapy research, having established the non-inferiority of lenvatinib compared to sorafenib for overall survival while reporting a significantly higher ORR of 24.1% vs. 9.2%, respectively, based on mRECIST criteria [10-12]. Our study corroborates this finding, reinforcing lenvatinib's position as a preferred first-line therapy in selected patients with well-preserved liver function.

Several real-world studies conducted in Asian populations have echoed similar response patterns. For instance, studies reported an ORR of 23.8% and DCR of 75.6% in patients, emphasizing the importance of optimal dosing and early treatment initiation. Likewise, a multicenter analysis yielded an ORR of 22.4% and highlighted the clinical significance of maintaining relative dose intensity during the early treatment phase. Our adjusted results fall well within this spectrum, adding to the growing global evidence that lenvatinib is both effective and tolerable in everyday oncology practice [13-15].

It is noteworthy that Hepatitis C was the predominant underlying etiology in our cohort (60.6%). Several studies have suggested that patients with HCV-related HCC may exhibit better responses to targeted therapy, possibly due to molecular differences in tumor biology [16-18]. Although subgroup analysis in our study did not reveal statistically significant variations in treatment response by etiology.

Another important observation from our data is the favorable disease control among non-diabetic and younger patients, although these trends did not reach statistical significance. Previous literature has proposed that comorbidities such as diabetes may influence HCC progression and therapeutic outcomes due to insulin resistance and pro-inflammatory states [19, 20]. These associations merit further prospective evaluation with larger sample sizes.

The tolerability profile of lenvatinib in our study was acceptable, with manageable side effects and no treatment-related mortality. This mirrors safety data from both the REFLECT trial and observational cohorts, where hypertension, fatigue, and anorexia are the most commonly reported adverse events.

The observed objective response rate (ORR) of 24.1% and disease control rate (DCR) of 73.4% in our study are

consistent with internationally reported outcomes, including those from the REFLECT trial and several real-world cohorts. These findings reinforce the external validity of our results and highlight the clinical reliability of lenvatinib in achieving tumor response and disease stabilization in advanced HCC. The alignment of our data with global evidence strengthens confidence in the therapeutic efficacy of lenvatinib in diverse populations.

Limitations

This study, while valuable in capturing real-world outcomes of lenvatinib therapy in advanced HCC, has certain limitations. Firstly, the sample size was relatively small and drawn from a single tertiary care center, which may limit the generalizability of findings to broader populations. Secondly, the study design was descriptive and observational, without a control or comparison arm (such as sorafenib or immunotherapy), thereby restricting causal interpretations. Additionally, some potential confounding factors such as tumor burden, vascular invasion, ECOG performance status, or prior locoregional therapy were not stratified or adjusted for in subgroup analysis. Finally, adverse event profiles were not systematically documented in this study, which limits the ability to assess the full tolerability spectrum of lenvatinib in this cohort.

Future Recommendations

Future research should aim to validate these findings in larger, multicenter, and prospective studies to enhance statistical power and generalizability. Randomized controlled trials comparing lenvatinib with newer immunotherapy combinations, such as atezolizumab-bevacizumab or durvalumab-tremelimumab, could provide valuable insights into optimal sequencing or combination strategies. Furthermore, incorporating biomarker-driven stratification, liver function scores, and radiologic predictors may help identify patients most likely to benefit from lenvatinib. Long-term follow-up studies evaluating progression-free survival, overall survival, and quality-of-life metrics are also warranted to fully assess the therapeutic benefit in real-world settings.

CONCLUSION

In conclusion, this study reinforces the effectiveness of lenvatinib as a first-line systemic therapy in patients with advanced hepatocellular carcinoma. The observed objective response rate of 24.1% and disease control rate of 73.4% were consistent with international clinical trial outcomes. Lenvatinib demonstrated meaningful tumor response and disease stabilization across a broad patient population, including those with viral and metabolic etiologies. Given its favorable efficacy and manageable safety profile, lenvatinib remains a valuable treatment option in advanced HCC, particularly when guided by individualized clinical assessment and appropriate patient selection.

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