Acta Scientific CANCER BIOLOGY (ISSN: 2582-4473)

Volume 9 Issue 3 March 2025

Research Article

Effectiveness of Generic Lenvatinib in Advanced Hepatocellular Carcinoma in Low and Middle-Income Countries

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Received: July 21, 2025

Published: August 19, 2025

Abstract

Objective: This study aims to assess the near equivalence of generic Lenvatinib to the patented Lenvatinib in patients with advanced hepatocellular carcinoma (HCC) in low- and middle-income countries (LMICs), with the goal of enhancing patient access and reducing financial burden, ultimately improving treatment adherence.

Materials and Methods: This is a multi-centric retrospective cohort analysis of 2 cancer centres in Pakistan. Patients who received Lenvatinib between January 2023 and July 2024 for managing advanced HCC were enrolled. Inclusion criteria were radiologically confirmed advanced Hepatocellular Carcinoma, age > 18 years, ECOG status of 0-2, complete medical records. Patients were excluded if they had ECOG status of 3-4, Brain metastasis, pregnant/lactating females, or incomplete records. The primary endpoint was progression-free survival (PFS). The following factors were reviewed: ECOG, performance status, comorbidities, risk factors, etiology of cirrhosis, Child-Pugh score, prior treatment, and socioeconomic status. Tumour assessment was determined by reviewing radiology reports. Progression-free survival was determined by the Kaplan-Meier method. Confidence intervals were calculated where applicable, using SPSS version 26.

Results: The study included 56 patients with a median age of 60 years. Chronic hepatitis C virus infection C (89.2%) was the predominant cause of liver disease, followed by chronic hepatitis B virus infection. 75% patients belonged to Child-Pugh class A at baseline. At baseline, tumor size > 5cm was present in 73.2% of patients, 14.3% had multifocal lesions, 44.6% had angioinvasion, and 23.2% had distant metastasis.

53.6% had received prior therapies, including trans-arterial chemoembolization (TACE) and or Sorafenib. 46.4% had not received any previous treatment. 83.9% received follow-up imaging at 4 months. The median number of cycles given was 5 and mPFS was 11.73 months (comparison is indirect and based on historical data such as the REFLECT trial). The response evaluation according to mRECIST criteria showed that 5.4% of patients achieved a complete response (CR), 19.6% had a partial response (PR), 23.2% experienced stable disease (SD), and 35.7% had progressive disease (PD).

Additionally, 16.1% of patients did not complete their re-evaluation, with 14.3% primarily due to premature discontinuation of the drug due to toxicities such as diarrhea, hand foot syndrome (5.4%) and decompensation of liver disease (3.6%).

Currently, 89.3% of patients are alive, 5.4% died, and the same ratio lost to follow-up

Conclusions: The study demonstrated that generic Lenvatinib is an effective treatment option for advanced HCC in low- and middle-income countries (LMICs) patients, with a median progression-free survival (PFS) of 11.73 months (95% CI = 9.7,13.6), compared to 12.5 months.

Keywords: Generic Lenvatinib; Hepatocellular; Carcinoma

Introduction

Advanced HCC is associated with a high mortality rate. Overall survival is less than 20% at 5 years [1]. over 50% of patients in LMICs present with advanced disease. HCC affects a younger population, negatively impacting quality of life, and has a significant economic impact [11]. HCC is a lethal disease with a poor prognosis [3].

Until recently, very few systemic therapies were available [2]. The treatment landscape has evolved with the advent of tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) [4]. The cost of systemic treatments poses a particular challenge for our patients and healthcare systems in low- and middle-income countries(LMIC). Sorafenib was the first TKI approved for HCC based on the SHARP trial [5,9]. It is one of the most affordable TKIs available for HCC (10); however, it is associated with significant side effects, leading most patients to discontinue the drug within a couple of months [6].

The combination of atezolizumab and bevacizumab demonstrated greater efficacy than sorafenib in terms of response rate (30% versus 11%), progression-free survival (median: 6.8 months versus 4.3 months), and overall survival (median: 19.2 months versus 13.4 months) [8]. The high cost of checkpoint inhibitors limits access to fewer than 1% of patients in low- and middle-income countries who can afford these drugs for treatment. Therefore, TKIs are typically chosen as the first-line systemic therapy for the majority of patients with advanced hepatocellular carcinoma (HCC).

Lenvatinib is a second-generation tyrosine kinase inhibitor (TKI) with activities similar to Sorafenib, but it is significantly more expensive. It is more tolerable and has fewer side effects; it is also less costly than checkpoint inhibitors [7]. Lenvatinib remains a key first-line treatment option for patients with advanced hepatocellular carcinoma (HCC). This is especially true in situations where there are concerns about patients' tolerance, when immunotherapy is contraindicated, or because of financial toxicity.

In low- and middle-income countries, nearly 80% of patients must pay for cancer treatment. Unfortunately, Lenvatinib is costly, and high out-of-pocket expenditures limit its use to a small portion of the population with HCC. Non-compliance and discontinuation due to financial toxicities are common.

To improve access, reduce the financial burden, and enhance patient compliance, we assessed the effectiveness of generic Lenvatinib for patients in LMICs.

Materials and Methods

This is a multi-centric retrospective cohort analysis of 2 cancer centres in Pakistan. Patients who received Lenvatinib between January 2023 and July 2024 for managing advanced HCC were enrolled. Inclusion criteria were radiologically confirmed advanced Hepatocellular Carcinoma, age > 18 years, ECOG status of 0-2, Brain metastasis, pregnant/lactating females, or incomplete records. The primary endpoint was progression-free survival (PFS). The following factors were reviewed: ECOG, performance status, comorbidities, risk factors, etiology of cirrhosis, Child-Pugh score, prior treatment, and socioeconomic status. Tumour assessment was determined by reviewing radiology reports. Progression-free survival was determined by the Kaplan-Meier method. Confidence intervals were calculated where applicable, using SPSS version 26.

Results

The study included **56** patients with a median age of 60 years. Chronic hepatitis C virus infection C (89.2%) was the predominant cause of liver disease, followed by chronic hepatitis B virus infection. 75% patients belonged to Child-Pugh class A at baseline. At baseline, tumor size > 5cm was present in 73.2% of patients, 14.3% had multifocal lesions, 44.6% had angioinvasion, and 23.2% had distant metastasis.

53.6% had received prior therapies, including trans-arterial chemoembolization (TACE) and or Sorafenib. 46.4% had not received any previous treatment. 83.9% received follow-up imaging at 4 months. The median number of cycles given was 5 and mPFS was 11.73 months (comparison is indirect and based on historical data such as the REFLECT trial). The response evaluation according to mRECIST criteria showed that 5.4% of patients achieved a complete response (CR), 19.6% had a partial response (PR), 23.2% experienced stable disease (SD), and 35.7% had progressive disease (PD).

Additionally, 16.1% of patients did not complete their re-evaluation, with 14.3% primarily due to premature discontinuation of the drug due to toxicities such as diarrhea, hand foot syndrome (5.4%) and decompensation of liver disease (3.6%).

Currently, 89.3% of patients are alive, 5.4% died, and the same ratio lost to follow-up.

Generic Lenvatinib (n = 56)			
Variables		**Frequencies**	**Percentages**
Age	Less than 60 years	24	42.8
	More than equal to 60 years	32	57.1
SES	Upper class	0	0
	Middle class	50	89.2
	Lower class	06	10.7
ECOG	0	33	58.9
	1	19	33.9
	2	4	7.1
Risk Factors	Hep b	2	3.5
	Hep c	50	89.2
	Both hep b and c	1	1.7
	Alcoholic liver disease	1	1.7
	Non hep b and c	2	3.5
Generic Lenvatinib (n=56)			
Variables		Frequencies	Percentages
Comorbidities	Htn	13	23.2
	Dm	5	8.9
	Multiple	14	25.0
	None	24	42.8
Ct scan findings	Only cirrhosis (solitary lesion)	10	17.8
	Multifocal	08	14.2
	Angioinvasive	25	44.6
	Distant metastasis	13	23.2
Size of tumor	Less than 3 cm	08	14.2
	3 to 5 cm	07	12.5
	More than 5 cm	41	73.2

Table a

Generic Lenvatinib (N=56)			
Variables		**Frequencies**	**Percentages**
CTP score	A	42	75.0
	B	12	21.4
	C	02	3.5
Previous therapies	TACE	19	33.9%
	Sorafenib	4	7.2%
	Immunotherapy	1	1.8%
	TACE and sorafenib	6	10.7%
	No previous therapy	26	46.4%
Response evaluation	CR	3	5.3
	PR	11	19.6
	SD	13	23.2
	PD	20	35.7

Table b

Generic Lenvatinib (N = 56)			
Ongoing status	Treatment continued	32	57.1
	treatment discontinued	03	5.4
	Change of therapy	10	17.9
	Best supportive care	10	17.9
	Lost to followup	01	1.8
Adverse events according to CTCAE grading system (total 8)	Decompensated liver disease	2	3.6
	Diarrhea grade 3	1	1.8
	Diarrhea grade 4	2	3.6
	Hand foot syndrome	3	5.4
Median number of cycles		5.0	
PFS in months		11.73	

Table c

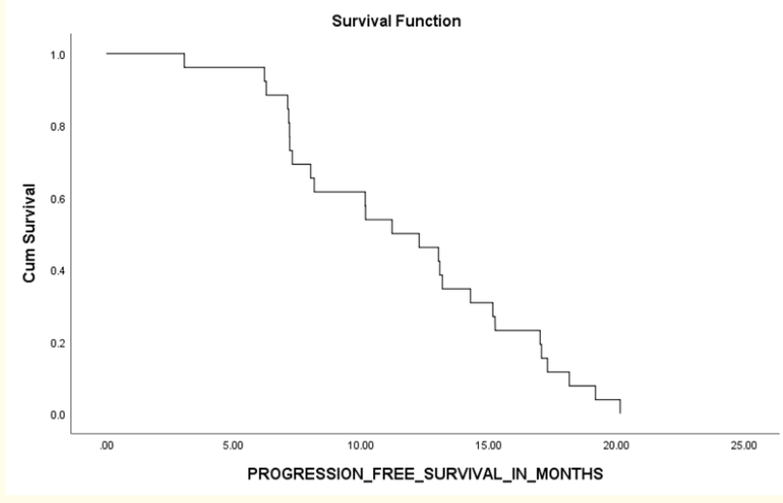

Figure a

Discussion

Pakistan is a low-middle-income country with a high prevalence of Hep C infections, leading to HCC [12]. Over majority of patients must pay for cancer therapy out of their own pockets [13]. The vast majority of patients with HCC belong to marginalized segments, where the prevalence of Hep C is highest. Lenvatinib is extremely expensive, and most patients abandon their treatment due to high out-of-pocket costs. Generic Lenvatinib is three times less expensive, allowing for greater access to our patients and fewer treatment discontinuations.

We aimed to determine the therapeutic efficacy and safety of generic Lenvatinib in patients with advanced hepatocellular carcinoma (HCC).

Our study found that generic Lenvatinib is a viable treatment option for patients with advanced hepatocellular carcinoma (HCC) in low- and middle-income countries (LMICs), yielding a median progression-free survival (PFS) of 11.73 months, compared to 13.6 months in the REFLECT trial. In this trial, the median survival time for Lenvatinib was 13.6 months (95% CI 12-14), which was non-inferior to sorafenib's 12 months (10-13; hazard ratio 0.92, 95% CI 0.79-1.06), meeting the criteria for non-inferiority.

The standard of care in the Western world for patients with advanced HCC is a combination of atezolizumab and bevacizumab, which demonstrated superior efficacy to sorafenib regarding re-

sponse rate (30% versus 11%), progression-free survival (median: 6.8 months versus 4.3 months), and overall survival (median: 19.2 versus 13.4 months).

Sorafenib is the only option for our marginalized patients as it is cheaper but has significant side effects [6], leading to high discontinuation rates or suboptimal, more tolerable doses. Lenvatinib has similar efficacy to Sorafenib but is more manageable due to significantly fewer side effects. However, financial toxicity causes most patients to discontinue Lenvatinib. The cost of generic Lenvatinib is one-third of the original price, making it more affordable, and as a result, more patients are compliant with the therapy. The median PFS is 11.73 months, which is somewhat lower than the 13.6 months reported in the REFLECT trial[6]. However, our patients had more advanced disease and poorer PS.

Conclusion

In LMICs, generic molecules such as Lenvatinib are associated with lower out-of-pocket costs, improved access, reduced utilization of public resources, and increased patient compliance. A significant limitation of our study was that we could not perform pharmacokinetic studies on our patients. The safety, dosage, efficacy, strength, and stability of generic medicines must be ensured. The careful use of generics from reputable companies should be encouraged.

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