# EFFICACY OF LENVATINIB TREATMENT IN ADVANCED HEPATOCELLULAR CARCINOMA

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**ABSTRACT**

***Background:*** *Lenvatinib - a multi-target oral multi-kinase inhibitor with activity against multiple carcinogenesis pathways - was approved in 2018 as a first-line treatment for patients with unresectable hepatocellular carcinoma (HCC). This study aimed to assess efficacy and the safety profile of lenvatinib therapy for patients with advanced HCC in real-world settings.*

***Objective:*** *Evaluate the overall survival (OS), progression-free survival (PFS), disease control rate (DCR), and toxicity of lenvatinib in advanced HCC.*

***Patients and method:*** *Retrospective descriptive study from 32 patients with advanced HCC to receive lenvatinib at Military Hospital 175 from January 2022 to July 2024.*

***Results****: Median OS was 10.5 months [95% CI: 7 months- NA]. Median PFS was 8 months [95% CI: 6 months - NA], DCR was 71.9%. The most common toxicity was elevated aspartate aminotransferase (40.6%), of which grade 3-4 accounted for 3.1%.*

***Conclusion:*** *Lenvatinib in the treatment of advanced HCC prolongs PFS and OS, has a favorable disease control rate and common toxicities were grade 1-2.*

***Keywords:*** *Lenvatinib, hepatocellular carcinoma, HCC, advanced stage.*

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## 1. STATEMENT OF THE PROBLEM

Hepatocellular carcinoma (HCC) is a malignant disease with a high mortality rate and an increasing number of new cases every year, especially in developing countries. In Vietnam, HCC ranks 2nd in incidence and first in terms of mortality, with 24,502 new cases and 23,333 deaths, respectively [1]. HCC often develops in patients with chronic liver disease, especially in patients with cirrhosis, and this can lead to limitations in treatment options as well as a reserved prognosis at all stages of the disease [2]. The principle of HCC treatment should be a combination of tumor treatment and treatment of underlying diseases of the liver. However, at the advanced stage of the disease, the disease has a poor prognosis, a short survival time, and chemotherapy has been shown to be of no benefit to the patient [2],[3].

In 2017, Lenvatinib was launched, which is a vascular endothelial growth factor receptor (VEGFR) inhibitor, fibroblast growth factor receptor, platelet-derived growth factor receptor (PDGFR), and other signaling kinases, providing HCC patients with a breakthrough treatment option which efficacy was proven through research REFLECT study phase 3, multinational, randomized, achieving the primary target with a PFS of 7.2 months and an OS of 13.6 months[4].

In order to summarize real-life data on the effectiveness of lenvatinib treatment, we conducted this study : "**Efficacy of lenvatinib treatment in advanced hepatocellular carcinoma"** at Military Hospital 175 with 2 objectives:

1. Determination of total survival and advanced disease-free survival of lenvatinib therapy in the treatment of advanced hepatocellular carcinoma.

2. Evaluation of disease control rates and some toxicity of lenvatinib therapy in the study subjects.

## 2. SUBJECTS - RESEARCH METHODS

### 2.1 Objects of study

Patient was diagnosed with advanced HCC and treated with lenvatinib at Military Hospital 175 from January 2022 to July 2024.

**Selection Criteria**

-18 years of age or older.

-The expected survival is at least 12 weeks.

-The histopathological diagnosis is HCC.

-Clinically confirmatory diagnosis of HCC according to AASLD criteria.

-Stage C, D (according to the Barcelona Clinic Liver Cancer classification system), or recurrent disease.

Measurable lesions according to the RECIST standard.

The ECOG overall status index is from 0 – 2.

Child-Pugh A, Child-Pugh B score 7

**Exclusion Criteria**

- secondary cancer.
- Renal failure requires dialysis.
- History of heart disease.
- Clinically having a serious infection.
- History of infection with human immunodeficiency virus (HIV).
- The patient had gastrointestinal bleeding within 30 days.

**1.2. Research Methodology**

Descriptive retrospective study.

**1.3. Sample Scale and Sampling**

Convenient sample size.

**1.4. Research Process**

Step 1: Select patient accordimg to research criteria

From the list of patients with HCC diagnosis from 01/2022 to 06/2024 of Military Hospital 175, we selected patients who met the research criteria. Record the following information:

History and medical history

Evaluation of viral hepatitis, alcoholism.

Tests: blood count, blood biochemistry (albumin, total bilirubin, INR, AST, ALT, GGT), AFP. Total urine analysis.

Anatomy of the disease.

Diagnostic imaging: CT scan of the chest and abdomen, MRI of the abdomen, bone scans,...

Step 2: lenvatinib treatment

Lenvatinib 12 mg/day (for patients weighing ≥ 60 kg) or 8 mg/day (for patients weighing < 60 kg), 28-day cycle, dose reduction based on toxicity with reduced doses of 8 mg/day or 4 mg/day. Treatment until disease progression or intolerance to therapeutic toxicity.

Step 3: Evaluation of treatment results

**Total survival assessment:** the time from the start of treatment to death from any cause.

**Progressiom-free survival assessment:** the time from the start of treatment to the progression of the disease or death from any cause.

**Response assessment:** including diagnostic imaging tests every 6 weeks of treatment or when patient has abnormal clinical symptoms. The assessment method meets the RECIST standard. Disease control rates include complete response, partial response, and stable disease that lasts at least 28 days.

**Toxicity assessment:** toxicity is noted after each course of treatment or when clinical signs appear. Toxicity assessment standards according to CTCAE version 5.0.

Management of side effects and dose adjustment during treatment:

- Toxicity grade 0-1: Continue treatment with initial dose

- Grade 2-3 toxicity: Reduce the therapeutic dose by 8 mg/day or 4 mg/day (1st time), reduce the therapeutic dose by 4 mg/day (2nd time), discontinue treatment (3rd time for patients < 60 kg)

- Grade 4 toxicity: Discontinuation of treatment

- Discontinuation criteria: Grade 2-3 toxicity appears up to the 3rd time (for patients < 60 kg) or grade 4 toxicity

### 1.5. Statistical methods

The collected data are encoded and processed using statistical software R 4.4.1. Use conventional medical statistical methods in processing and analyzing results.

### 1.6. Medical Ethics considerations

This study is a descriptive study, does not interfere with the diagnosis or treatment process, so it does not violate research ethics.

## 2. RESULT

### 1.1. Characteristics of the study object

Our study collected 32 patients with the characteristics shown in Table 1.

**Table 1. Patient characteristics**

| Characteristics | | Number of patients (n=32) | Rate (%) |
|---|---|---|---|
| Gender | : Male | 30 | 93.7 |
| | Female | 2 | 6.3 |
| Median Age (Age Range) | | 64 (31 – 89 years old | |
| ECOG | 1 | 28 | 87.5 |
| | 2 | 4 | 12.5 |
| BCLC | Phase B | 10 | 31.3 |
| | Stage C | 21 | 65.6 |
| | Phase D | 1 | 3.1 |
| Extrahepatic metastases | : Yes | 9 | 28.1 |
| | None | 23 | 71.9 |

| | | |
|---|---|---|
| Location of metastases Lung | 5 | 15.6 |
| Lymph nodes | 5 | 15.6 |
| Others | 2 | 6.3 |
| Vascular invasion Yes | 14 | 43.8 |
| None | 18 | 56.2 |
| Child-Pugh A | 26 | 81.3 |
| B | 6 | 18.7 |
| Causes of the disease | | |
| HBV | 19 | 59.4 |
| HCV | 5 | 15.6 |
| Alcohol | 6 | 18.7 |
| Others | 2 | 6.3 |
| Previous treatment* | | |
| TACE | 14 | 43.8 |
| Surgery | 2 | 6.3 |
| RFA | 1 | 3.1 |
| MWA | 2 | 6.3 |
| Radiation therapy | 1 | 3.1 |
| Immunotherapy | 1 | 3.1 |
| Target therapy | 3 | 8.4 |
| None | 16 | 50 |
| Weight ≤60 kg | 23 | 71.9 |
| > 60 kg | 9 | 28.1 |

A patient may receive more than 1 previous treatment.

**1.2. Total Survival - OS**

Our study had a median overall survival time of 10.5 months [95% CI: 7.0 months – NA].

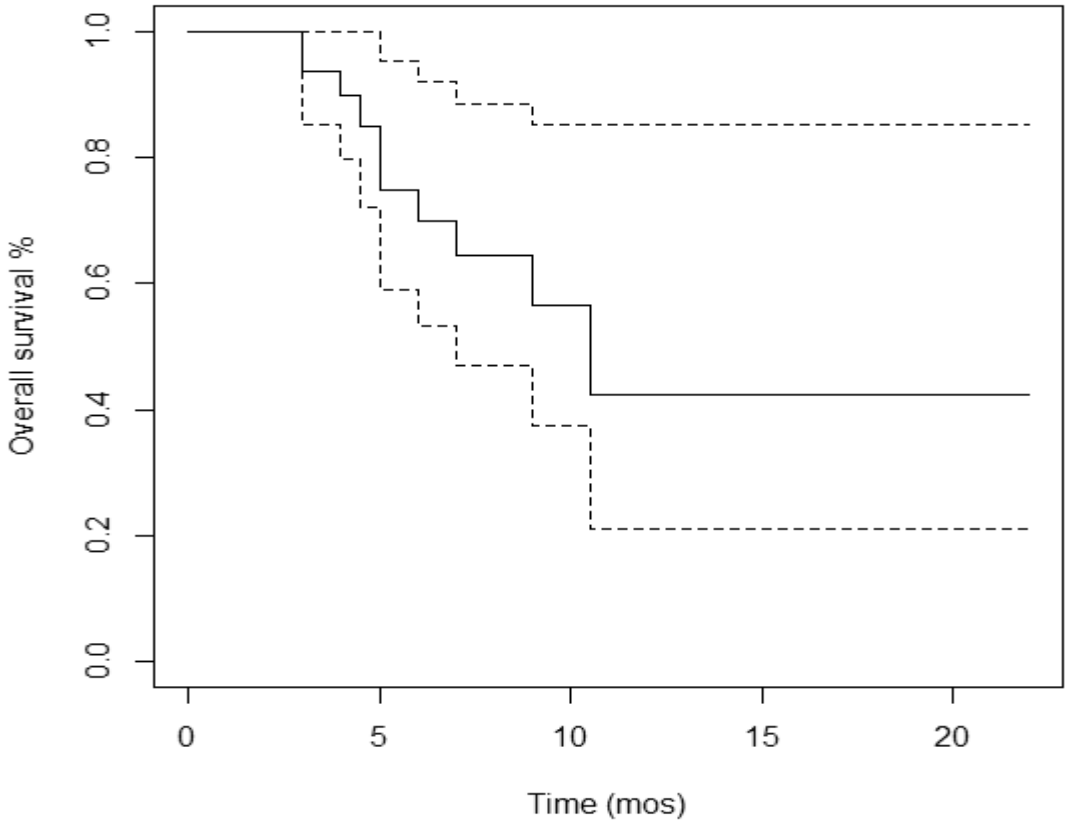


**Figure 1. Total survival on population study**

*Log-rank verification*

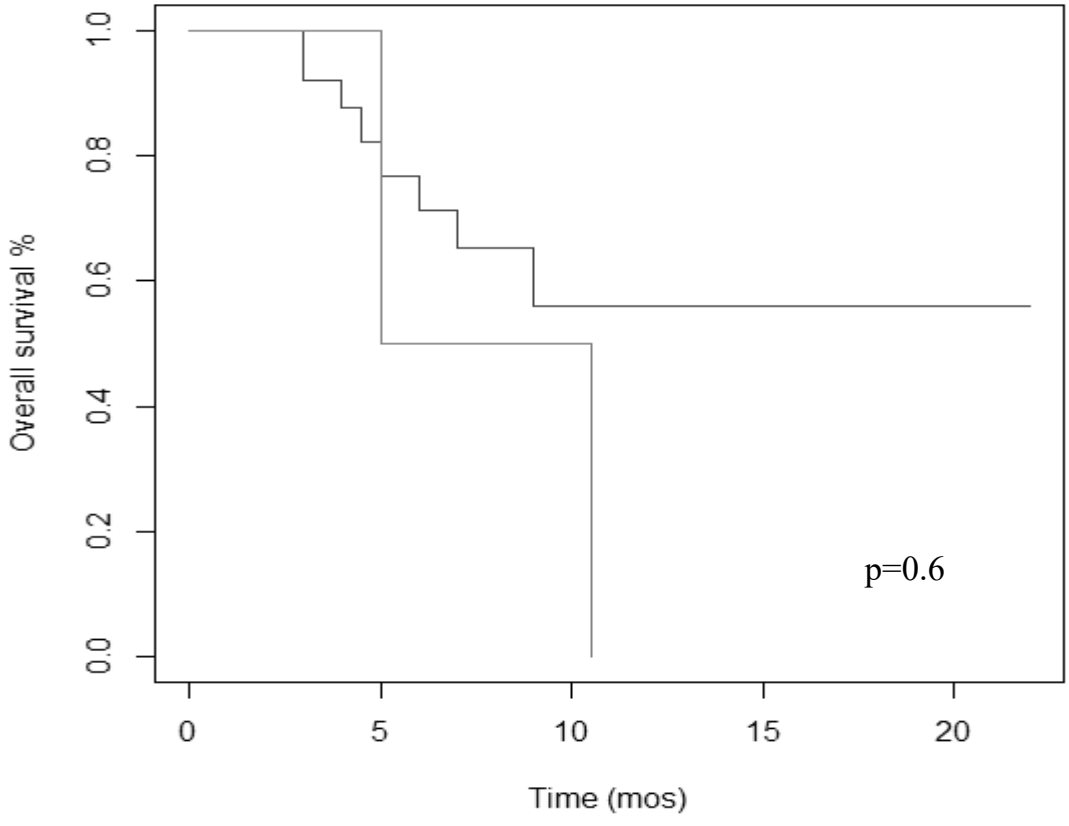


**Figure 2. Total survival on the Child-Pugh A and Child-Pugh B subtypes**

The Child-Pugh A group has not yet assessed the median OS, the Child-Pugh B group has a median OS of 7.75 months [95% CI: 5.0 months - NA]. A total survival analysis of the Child-Pugh subgroup noted no OS difference between the Child-Pugh A and Child-Pugh B groups with p=0.6.

### 1.3. Survival without advanced disease - PFS

Our study had a median progression-free survival time of 8.00 months [95% CI: 7.0 months - NA].

*Estimates in Kaplan-Meier*

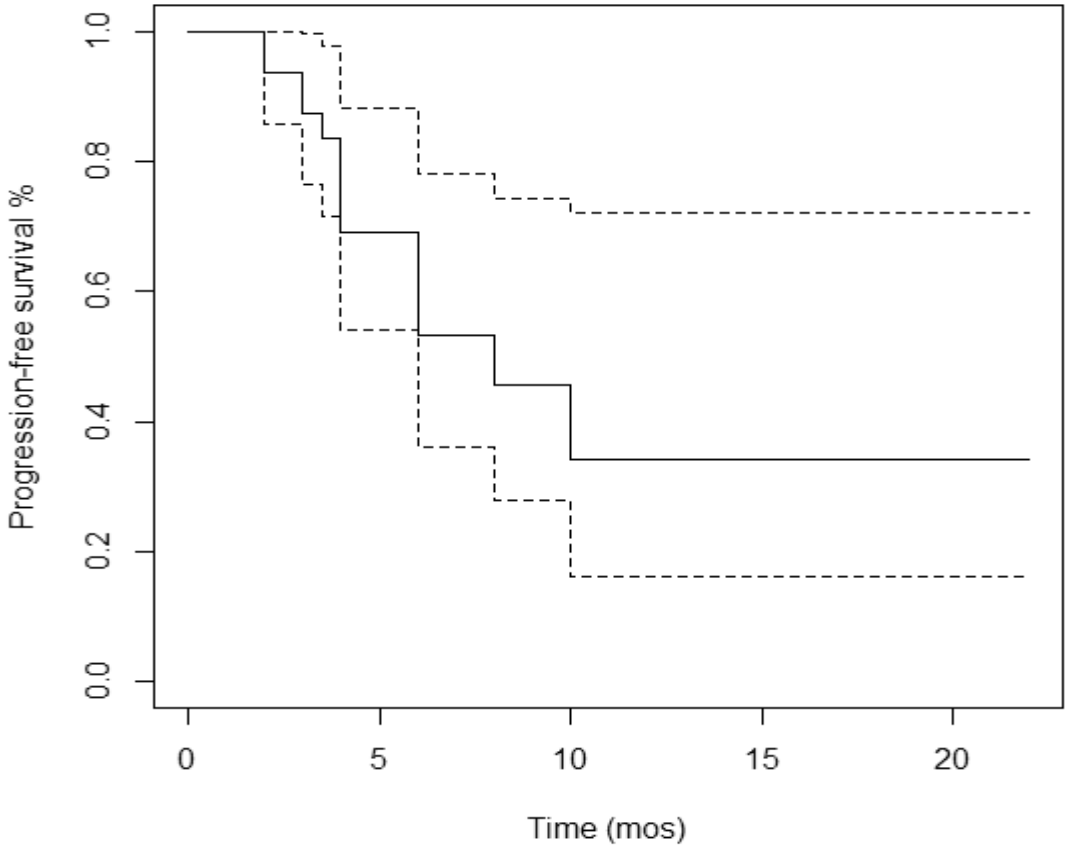


**Figure 3. Progressive disease-free survival on study population**

### 1.4. Disease Control Rate - DCR

| Table 2. Response Rate | Number of patient (n=32) | Rate (%) |
|---|---|---|
| **Complete response** | 0 | 0 |
| **Partial Response** | 5 | 15.6 |
| **Stable disease** | 18 | 56.3 |
| **Disease progression** | 9 | 28.1 |

**Comment:**

DCR in our study there was 71.9%.

### 1.5. Therapeutic Toxicity:

**Table 3. Toxicity**

| Toxicity | Number of patient | | Grade 3 - 4 | |
|---|---|---|---|---|
| | n | % | n | % |
| **Increase AST/ALT** | 13 | 40.6 | 1 | 3.1 |
| **Thrombocytopenia** | 5 | 15.6 | 2 | 6.3 |
| **Vomiting** | 3 | 8.4 | 0 | 0.0 |
| **Hand-foot syndrome** | 3 | 8.4 | 0 | 0.0 |
| **Skin rash** | 1 | 3.1 | 0 | 0.0 |

The most common toxicity was increased liver enzymes, accounting for 40.6%, followed by thrombocytopenia by 15.6%, vomiting and hand-foot syndrome at 8.4%. Grade 3-4 toxicity is most common thrombocytopenia with 6.3%.

## 3. DISCUSSION

### 3.3. Overall survival rate

The median OS in our study was 10.5 months. The results of the REFLECT study by Kudo M in 2018 on 478 patients with advanced HCC had a median OS of 13.6 months [5]. The results of the post hoc analysis conducted by Alsina A et al. in 2020 showed a median OS of 11.5 months in the group that did not receive anticancer therapy after lenvatinib treatment [6]. The retrospective study conducted in Korea in 2021 by Goh M.J. et al. had a median OS of 10.5 months [7]. The median OS of our study was lower than that of the REFLECT study, which can be explained by differences in sample size and selection criteria. Kudo M et al. limited patients with Child-Pugh A hepatic function as well as PS 0-1 overall status to the study. Because it is thought that poorer liver function or poor overall condition will skew the results. Our study has quite similar results to the results of Alsina A and especially the retrospective study in Korea by Goh M.J. This is understandable because the patient characteristics of these 2 studies are similar to our study.

### 3.4. Progression-free survival

The median PFS result of our study was 8 months, which is quite similar to the

median PFS in the REFLECT study of 7.4 months [5] and higher than the Korean study of 6.2 months [7].

### 3.5. Disease control rate

The Disease Control Rate (DCR) in the REFLECT study was 75%, while it was 75.7% in a retrospective study conducted in Korea. Our study reported a DCR of 71.9%, which is comparable to the results of these two reference studies.

### 3.6. Therapeutic toxicity

Our study recorded that the most common toxicity was elevated liver enzymes, accounting for 40.6%, grade 3-4 was 3.1%, followed by thrombocytopenia accounting for 15.6%, and grade 3-4 was 6.3%. The REFLECT study had elevated liver enzyme toxicity of 14%, grade 3-4 was 5%, thrombocytopenia accounted for 18%, and grade 3-4 was 5% [5]. The study in Korea had an elevated toxicity of liver enzymes of 2.8%, and a grade 3-4 of 1.4% [7]. Overall, our study did not detect any new toxicity, the toxicity rate at levels 3-4 is comparable to that of the reference studies.

## 4. CONCLUSION

Treatment of lenvatinib in advanced HCC is effective in prolonging overall survival and survival without progressive disease, with a positive disease control rate and common toxicity at level 1-2, which is the first-line regimen of choice in clinical practice at Military Hospital 175.

## REFERENCES

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