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# Clinical Outcome of Lenvatinib Versus Sorafenib in the Management of Advanced Hepatocellular Carcinoma: a Comparative Study in Dhaka, Bangladesh

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**Key words:**
Clinical parameters, hepatocellular carcinoma, Lenvatinib, Sorafenib

## Abstract

***Background:*** *Hepatocellular carcinoma, 2nd leading cause of cancer death, is a global threat around the world due to its high incidence rate. If we analysis about the last 5 to 8 years of clinical studies of different countries, the incidence of hepatocellular carcinoma (HCC) is increasing in an alarming rate. Clinical parameters play an important role in early diagnosis and overall prognosis of Hepatocelullar Carcinoma. This study aims to assess and compare the outcome of clinical parameters of Lenvatinib versus Sorafenib in the management of Hepatitis B virus related Hepatocellular Carcinoma.* ***Methods:*** *This comparative study was conducted in the department of Hepatology, Sir Salimullah Medical College Mitford Hospital from March'2022 to September'2022 from the date of randomization to next 6 months or till death whichever one was earlier. A total of 24 patients diagnosed as advanced Hepatocellular Carcinoma by imaging, inclusion and exclusion criteria were enrolled by randomization and divided into two arms.* ***Results:*** *Majority of the patients were from 51-60 years of age group. 28% of respondents had no exposure to schooling or illiterate. According to BCLC staging, 16.6% patients were at stage B. On the other hand, 45.8% patients were in Stage A according to Child Pugh Score using Lenvatinib. Aspartate aminotransferase (AST) level is reduced comparing with baseline to 3months. Moreover, Sorafenib reduced Alanine transaminase (ALP) from 214.9 U/L to 98.3 U/L within 3 months. More clinical studies should be expected to be done in future for better outcome.* ***Conclusion:*** *Lenvatinib positively changes the clinical outcome in HCC patients especially in tumor size reduction.*

## Introduction:

Hepatocellular carcinoma, 2nd leading cause of cancer death, is a global threat around the world due to its high incidence rate. If we analysis about the last 5 to 8 years of clinical studies of different countries, the incidence of hepatocellular carcinoma (HCC) is increasing in an alarming rate[1]. Within 2025, the incidence rate of HCC is assumed >1 million. In case of risk factors, hepatitis B and hepatitis C are the major risk factors that can cause HCC. Moreover, cirrhotic patients are more prone to HCC[1].

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Being the 5th most frequent carcinoma, the prevention is a must, however, unsuccessful early diagnosis and providing unfeasible primary treatment may deteriorate the ultimate health condition of the patient. It is a matter of disappointment that there is no vaccine invented for HCV. However, public health awareness should be raised to diminish the factors that can exaggerate this condition for example of excessive alcohol intake and smoking.[3]

In the last few decades, the diagnosis and treatment of hepatocellular carcinoma (HCC) are dramatically changed. Treatment depends on the severity of underlying liver disease, tumor bulk, and associated co-morbidities as well as medical facilities like availability and expertise in surgical resection, transplantation, and ablative therapies.[4]

It is a common scenario that half of the of HCC patients come with advanced level of disease due to delay diagnosis. However, the survival and the prognosis depend on early diagnosis of the patients.[5]

In Bangladeshi scenario, like other countries, the cases of HCC is increasing in an alarming rate, for our country, Hepatitis B is the major reason of HCC. However, it is a matter of hope that, after including the HBV vaccine in expanded program on immunization (EPI), prevalence of HBV is significantly decreasing.[6]

At present, physicians are widely using Sorafenib and Lenvatinib as a first-line systemic treatment for advanced HCC. Sorafenib is a multikinase inhibitor that inhibits serine/threonine kinases such as Raf-1 and B-Raf, vascular endothelial growth factor (VEGF) receptors 1, 2, and 3, and platelet-derived growth factor receptor b. On the other hand, Lenvatinib inhibits multiple receptor tyrosine kinases such as VEGF receptors 1, 2, and 3, fibroblast growth factor receptors 1, 2, 3, and 4, platelet-derived growth factor receptor â, and RET and KIT oncogenes.[7]

This study aims to assess and compare the outcome of clinical parameters of Lenvatinib versus Sorafenib in the management of Hepatitis B virus related Hepatocellular Carcinoma.

**Methods:**

This comparative study had conducted from March' 2022 to September'2022 from the date of randomization to next 6 months or till death whichever one will be earlier. Department of Hepatology, Sir Salimullah Medical College Mitford Hospital. A total of 24 patients with patients diagnosed as advanced Hepatocellular Carcinoma by imaging, inclusion criteria were patients with Hepatocellular Carcinoma (Diagnosed histologically or cytologically or by imaging criteria with CT or MRI) with no option of resection of Barcelona Clinic Liver Cancer- (BCLC) stage B or C and exclusion criteria were Patients with very early-stage Hepatocellular Carcinoma BCLC stage 0, BCLC stage A, BCLC stage D, with obvious invasion to bile duct, who received previous systemic therapy for Hepatocellular Carcinoma, with jaundice (serum bilirubin ³3 mg/dl), with aminotransferases ³5ULN, with other co-morbid conditions (COPD, CKD, Heart failure, IHD, pregnancy) and divided into two arms. 24 patients had treated with the groups of Lenvatinib and Sorafenib. Participants of the study will be recruited by randomization from patients admitted in the department of Hepatology, Sir Salimullah Medical College Mitford Hospital and diagnosed as a case of advanced Hepatocellular Carcinoma with no option of resectibility. 14 patients were given Lenvatinib and 10 patients were given Sorafenib. Informed written consent was taken from each subject. The ethical review committee of Sir Salimullah Medical College approved the research protocol before starting this study.

**Operational Definition:**

**Hepatocellular carcinoma (HCC)[8]** is the sixth most common cancer in the world and the second most common cause of cancer death.The incidence of HCC varies in different countries, depending on the prevalence of chronic liver disease.The aetiological agent of HCC is known in more than 90% of cases.

**Child Pugh Score[8]**

- Encephalopathy: None = 1 point, Grade 1 and 2 = 2 points, Grade 3 and 4 = 3 points

- Ascites: None = 1 point, slight = 2 points, moderate = 3 points
- Bilirubin: under 2 mg/ml = 1 point, 2 to 3 mg/ml = 2 points, over 3 mg/ml = 3 points
- Albumin: greater than 3.5mg/ml = 1 point, 2.8 to 3.5mg/ml = 2 points, less than 2.8mg/ml = 3 points
- Prothrombin Time* (sec prolonged): less than 4 sec = 1 point, 4 to 6 sec = 2 points, over 6 sec = 3 points

**Barcelona Clinic Liver Cancer (BCLC) Staging[9]**

There are 5 stages to the BCLC staging system.

**Stage 0** (Very early stage)

This means the tumour is less than 2cm, you feel well (PS 0) and your liver is working normally (Child-Pugh A).

**Stage A** (Early stage)

This means there is a single tumour of any size, or up to 3 tumours all less than 3 cm. You feel well and are active (PS 0), and your liver is working well (Child-Pugh A or B).

**Stage B** (Intermediate Stage)

This means there are many tumours in the liver, but you feel well (PS 0) and your liver is working well (Child-Pugh A or B).

**Stage C** (Advanced stage)

This means the cancer has spread into the blood vessels, lymph nodes or other body organs. Or you do not feel well and are less active (PS 1 or 2). Your liver is still working well. (Child-Pugh A or B).

**Stage D**

This means you have severe liver damage (Child-Pugh C), or you are not well and need help to look after yourself (PS 3 or 4).

**Results:**

Table I resembles socio-demographic characteristics of respondents. It is evident that, majority of the patients were from 51-60 years of age group. On the other hand, 28% of respondents were non-schooling or illiterate. In case of financial issues, 24% patient's incomes were between 10,000 to 20,000.

**Table I:** Socio-demographic Characteristics of respondents:

Distribution of study population according to the age

| Age Group (years) | Frequency (%) |
|---|---|
| 31-40 | 5 (20.8%) |
| 41-50 | 6 (25%) |
| 51-60 | 8 (33%) |
| 61-70 | 3 (12.5%) |
| >70 | 2 (8.35) |

Distribution of study population according to their education

| | |
|---|---|
| Primary | 6 (24%) |
| SSC | 1 (4%) |
| HSC | 2 (8%) |
| Graduation | 4 (16%) |
| Post-graduation | 4 (16%) |
| No-Schooling | 7 (28%) |

Distribution of study population according to their monthly income (Bangladeshi Taka -BDT)

| | |
|---|---|
| <10,000 | 5 (20%) |
| 10,000-20,000 | 6 (24%) |
| 20,000-30,000 | 3 (12%) |
| 30,000-40,000 | 3 (12%) |
| 40,000-50,000 | 3 (12%) |
| >50,000 | 2 (8%) |

Figure 1 illustrates distribution of study population according to the gender. Majority (92%) of patients were male

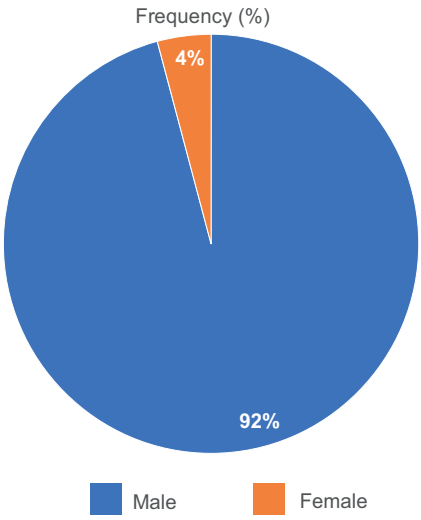


**Figure 1:** Distribution of study population

**Table II :** Clinical Manifestation of the participants (n= 24)

| Clinical Manifestation | Name of drug | Present (f/%) | Absent (f/%) |
|---|---|---|---|
| Jaundice | Lenvatinib | 5 (20.8%) | 9 (37.5%) |
| | Sorafenib | 2 (8.3%) | 8 (33.3%) |
| Flapping Tremor | Lenvatinib | 3 (12.5%) | 11 (45.8%) |
| | Sorafenib | 2 (8.3%) | 8 (33.3%) |
| Ascites | Lenvatinib | 6 (25.0%) | 8 (33.3%) |
| | Sorafenib | 5 (20.8%) | 5 (20.8%) |
| Oedema | Lenvatinib | 2 (8.3%) | 12 (50%) |
| | Sorafenib | 3 (12.5%) | 7 (29.1%) |

Table II showed clinical manifestation of the participants. Those patients who used Lenvatinib, 20.8% of patients had jaundice. Only 5 patients of Lenvatinib, had jaundice whereas, 6 patients had ascites.

Table III resembles distribution of study population according to the BCLC Staging and Child Pugh Score. According to BCLC staging, 16.6% patients were at stage B using Sorafenib. On the other hand, 45.8% patients were in Stage A according to Child Pugh Score using Lenvatinib.

Table IV showed comparison of outcome of Lenvatinib and Sorafenib among the study population. It is evident that, AST level is reduced comparing with baseline to 3months. Moreover, Sorafenib reduced ALP from 214.9 U/L to 98.3 U/L within 3 months.

**Table III:** Distribution of study population according to the BCLC Staging and Child Pugh Score
BCLC Staging

| Name of drug | Stage B (f/%) | Stage C (f/%) |
|---|---|---|
| Lenvatinib | 7 (29.1%) | 7 (29.1%) |
| Sorafenib | 4 (16.6%) | 6 (25.0%) |
| Child Pugh Score | | |
| Name of drug | A (f/%) | B (f/%) |
| Lenvatinib | 11 (45.8%) | 3 (12.5%) |
| Sorafenib | 8 (33.3%) | 2 (8.3%) |

*BCLC: Barcelona Classification of Liver Cancer

**Table IV :** Comparison of Outcome of Lenvatinib and Sorafenib among the study population:

| Lenvatinib (Baseline) (Mean, ±SD) | | Lenvatinib (3 months) (Mean, ±SD) | Sorafenib (Baseline) (Mean, ±SD) | Sorafenib (3 months) (Mean, ±SD) |
|---|---|---|---|---|
| ALT (U/L) | 61.3 (32.91) | 64. 5(±23.3) | 67.9 (±34.09) | 65.9 (±24.09) |
| AST (U/L) | 87.2 (37.76) | 63.0 (±22.6) | 93.4 (±55.5) | 63.2 (±28.7) |
| ALP (U/L) | 141.6 (105.7) | 109.4 (±63.6) | 214.9 (±131.66) | 98.3 (±51.9) |

**Discussion:**

Being a global problem, HCC, is a prominent burden on the health-care system and produce obstacles in productive capacity in the lower socio-economic to middle-income countries, mostly caused by HCV and HBV infections. Different kinds of strategies and social awareness has been raised against this social alarming threat.[10]

In our comparative study, it was conducted from the date of randomization to next 6 months or till death whichever one will be earlier. Department of Hepatology, Sir Salimullah Medical College Mitford Hospital. A total of 24 patients with patients diagnosed as advanced Hepatocellular Carcinoma by imaging, inclusion and exclusion criteria and divided into two arms. 24 patients had treated with the groups of Lenvatinib and Sorafenib. The aim of the study was to assess and compare the outcome of Lenvatinib versus Sorafenib in the management of Hepatitis B virus related Hepatocellular Carcinoma.

In previous Asian-pacific region studies, the incidence of HCC is higher in men when compared to women, 213 patients with HCC in 1999–2005 in which 83.1% were male patients [10]. Similarly, in our study, Majority (92%) of patients were male.

In this study, A huge number of patients were from 51-60 years of age group. Globally, incidence rates of HCC positively correlate with age and peak incidence occurs approximately at 75 years old.[11]

In a previous clinical study, the Lenvatinib group, 8 and 35 patients were classified to have BCLC stage B and C disease, respectively, at the time of drug initiation. In the sorafenib group, 8 and 47 patients were classified to have BCLC stage B and C disease, respectively.[12] However, in our study, according to BCLC staging, 16.6% patients were at stage B using Sorafenib. In the similar study, majority of patients (95.8%) had well-preserved liver function (Child-Pugh class A) at the time of initial Lenvatinib treatment.[13] Furthermore, in our study, similarly a large 45.8% patients were in Stage A according to Child Pugh Score using Lenvatinib.

In our clinical study, Lenvatinib and Sorafenib both have positive changes of clinical parameters in HCC patients. Both drugs reduced AST and ALP from baseline to 3 months significantly. In another study, we have found similar findings whereas AST ALP were also altered in a positive way [14].

In this study, in Lenvatinib group there were significant reduction of tumor sizes in comparison to Sorafenib group according to mRECIST criteria which was found statistically significant. Similar study in China and Germany found similar results in reduction of tumor sizes by Lenvatinib.

**Conclusion:**

In spite of having changes in epidemiology and etiology of HCC, there is a new hope that, Lenvatinib positively changes the clinical outcome in HCC patients specially in tumor size reduction.

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**Conflict of Interest:**

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

**Ethical Approval:**

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Sir Salimullah Medical College. Written informed consent was taken from all the patients before taking part of the study.

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