Risk Factors for Hepatic Encephalopathy in Hepatocellular Carcinoma after Sorafenib or Lenvatinib Treatment: A Real-World Study

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INTRODUCTION

Although first-line systemic therapies, including **sorafenib (SOR) and lenvatinib (LEN),** has made great progress in prolonging the overall survival of patients with unresectable hepatocellular carcinoma (uHCC), safety is an eternal topic. Most uHCC patients have a basis of liver cirrhosis, which makes the anti-tumor treatment more complicated.

Hepatic Encephalopathy (HE), one of severe complications of cirrhosis, is also a severe adverse event during systemic therapies, which might lead to discontinuation of anti-tumor therapies or even death.

The effects of SOR or LEN on liver function and portal pressure remain controversial. Whether there is a difference in occurrence of HE after SOR or LEN treatment and risk factors for HE during systemic therapies remained to be explore.

AIM

This study aimed to investigate the incidence rate and risk factors for hepatic encephalopathy (HE) among unresectable hepatocellular carcinoma (uHCC) patients with liver cirrhosis who received SOR or LEN treatment.

METHOD

We retrospectively included **uHCC patients with cirrhosis** who received **first-line SOR or LEN** treatment for at least one course from September 2014 to February 2021 in the Fifth Center of The People's Liberation Army General Hospital (PLAGH).Those patients with a history or definite predisposition for HE before treatment were excluded.

Hepatic Encephalopathy Scoring Algorism (HESA), refined according to West Haven Criteria was used in our study.

Receiver operating characteristic (ROC) curve was used to find the optimal cut-off value for continuous variables in predicting HE.

Logistic regression was used to explore factors influencing incidence of HE during TKIs treatment.

RESULTS

Until February 2021, total **454** eligible patients were retrospectively enrolled in this study, **214 in SOR group** and **240 in LEN group**, with similar demographic background, liver function, characteristics of tumors.

At time of data cut-off (2021-12), in accordance with **HESA**, total 9 patients in SOR group developed HE: 3 in grade 2, 5 in grade 3 and 1 in grade 4. While in LEN group, 27 of 240 patients suffered from HE: 1 in grade 1, 14 in grade 2, 4 in grade 3, 7 in grade 4 and 1 without grading. **The incidence rate of HE** in **SOR** group (**4.21%**,95%CI:2%-7%) was significantly lower than that in **LEN** group (**11.25%**,95%CI:7%-15%) (P=0.006). **(Table 1)**

ROC curve suggested that **ammonia, total bile acid, Child-Pugh and duration of treatment** were potential clinical biomarkers in predicting HE (Figure 1). The most optimal cut-off values for variables mentioned above were **38.65 μmol/L, 29.5 μmol/L, 7.5 and 5.6 months**, respectively.

Multivariance logistic regression analysis suggested that **alcoholic cirrhosis** [OR (95%CI): 5.857 (1.519-22.591)] (P = 0.010), **Child-Pugh > 7** [OR (95%CI): 3.023 (1.135-8.055)] (P = 0.027), **blood ammonia ≥ 38.65 μmol/L** [OR (95%CI): 4.693 (1.782-12.358)] (P = 0.002), **Total Bile Acid ≥ 29.5 μmol/L** [OR (95%CI): 11.047 (4.414-27.650)] (P < 0.001), **Lenvatinib treatment** [OR (95%CI): 6.162 (2.258-16.818)] (P < 0.001) and **Duration of treatment ≥ 5.6 months** [OR (95%CI): 4.350 (1.701-11.126)] (P = 0.002) remained to be significantly correlated with HE development during TKIs treatment (Figure 2).

Table 1: Occurrence of Hepatic Encephalopathy

Variables	SOR Group (n = 214, %)	LEN Group (n = 240, %)	P value
Cases of HE	9 (4.2%)	27 (11.3%)	0.006
Grade of HE			
1	0 (0%)	1 (0.4%)	——
2	3 (1.4%)	14 (5.8%)	——
3	5 (2.3%)	4 (1.7%)	——
4	1 (0.5%)	7 (2.9%)	——
Unknown	0 (0%)	1 (0.4%)	——

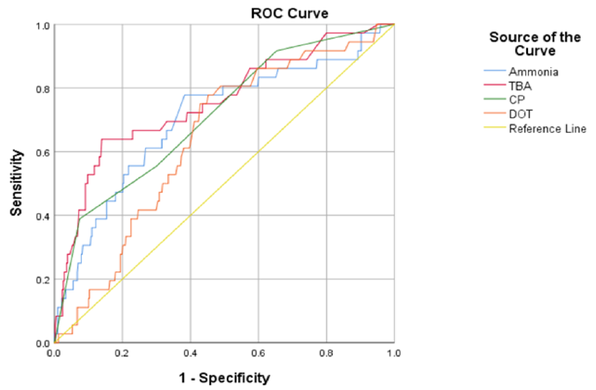

Figure 1: Receiver Operating Characteristic (ROC) curves in Predicting Hepatic Encephalopathy Model.
TBA: total bile acid; CP: Child-Pugh Score; DOT: duration of treatment.

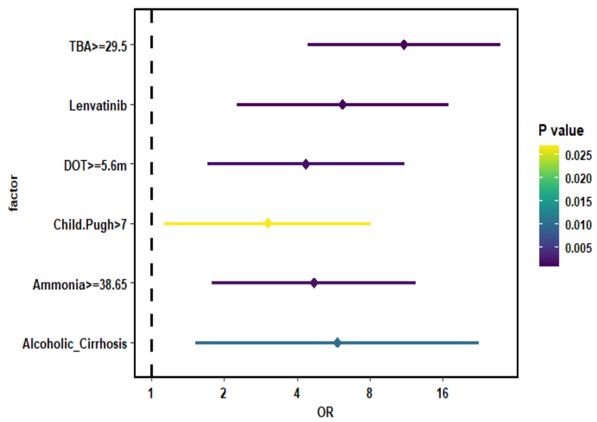

Figure 2: Multivariate Logistic Regression in Exploring Risk Factors for Hepatic Encephalopathy.
TBA: total bile acid (μmol/L); Ammonia (μmol/L); DOT: duration of treatment (months)

CONCLUSIONS

uHCC patients with cirrhosis who receive lenvatinib are more likely to develop HE than sorafenib, with alcoholic cirrhosis, Child-Pugh >7, serum ammonia ≥ 38.65 μmol/L, total bile acid ≥ 29.5 μmol/L, and duration of treatment ≥ 5.6 months to be risk factors for HE. For decompensated cirrhosis patients with uHCC, sorafenib seems to be safer choice.

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