Lenvatinib With or Without Immune Checkpoint Inhibitors in Subsets of Advanced Hepatocellular Carcinoma

Yu-Xian Teng,1,* Ping-Ping Guo,2,* Ke-Zhang Qin,1,* Kang Chen,1 George Papatheodoridis,1 Bang-De Xiang,1 Liang Ma,1 Jian-Hong Zhong1

1Department of Hepatobiliary Surgery, Guangxi Liver Cancer Diagnosis and Treatment Engineering and Technology Research Center, Guangxi Medical University Cancer Hospital, Nanning, China
2Department of Ultrasound, Guangxi Medical University Cancer Hospital, Nanning, China
3Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens “Laiko”, Athens, Greece

*Yu-Xian Teng, Ping-Ping Guo, and Ke-Zhang Qin contributed equally to this work.

Abstract

Objectives: Targeted agents combined with immune checkpoint inhibitors (ICIs) for advanced hepatocellular carcinoma (HCC) may improve survival for some patients. This study aims to identify the patients who are most likely to benefit from combination therapy.

Methods: The study included 45 patients receiving lenvatinib while other 65 patients receiving lenvatinib plus ICIs between January 2019 and August 2020. Clinical and laboratory data were evaluated and compared.

Results: The median follow-up was 20.5 months in the lenvatinib and 18.0 months in the combination group. The corresponding median overall survival was 9.3 and 13.0 months (p=0.004), respectively. Subgroup analyses found that lenvatinib plus ICIs was associated with better overall survival in patients younger than 60 years, males, without MAFLD as well as with BMI <23 kg/m², cirrhosis, HBV infection, total tumor volume ≥982 cm³, tumor burden score of ≥10.4 or α-fetoprotein ≥200 ng/ml.

Conclusion: Lenvatinib plus ICIs therapy seems to be more effective in advanced HCC patients with viral etiology, low BMI, or high tumor load.

Keywords: Hepatocellular carcinoma, Immune checkpoint inhibitors, Lenvatinib, Overall survival

The efficacy of targeted agents combined with immune checkpoint inhibitors (ICIs) has been shown to be better than that of targeted agents alone in patients with advanced hepatocellular carcinoma (HCC), but not all patients benefit from combination therapy.1-5 Identifying the patients who are most likely to benefit from each therapy is critical for improving their overall management. The subgroup analyses of IMbrave150,6 CheckMate 4597 and KEYNOTE-2408 suggested that the effects of targeted immunotherapy in advanced HCC depend on liver disease aetiology.9 Namely, patients with non-viral HCC appeared to have no significant benefit from ICIs. Two other cohorts also supported the ineffectiveness of ICIs in non-alcoholic fatty liver disease related HCC.9 In fact, patients with non-alcoholic fatty liver disease related HCC have significant different survival after hepatic resection or lenvatinib monotherapy than those with other etiology-related HCC.10-12

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Address for correspondence: Jian-Hong Zhong; Liang Ma, MD. Guangxi Medical University Cancer Hospital, He Di Rd 71, Nanning 530021, China
Phone: +86 771 5310253 E-mail: zhongjianhong@gxmu.edu.cn; malianggxyd@163.com
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Nowadays, many basic researches have investigated the biomarkers of response and sensitivity to ICIs therapy. However, these studies use very sophisticated methods. Histopathologic biomarker to predict the response and sensitivity to ICIs therapy would be a therapeutic target for enhancing the efficacy of ICIs therapy. Cytokeratin 19 (CK19) and Ki-67 are two items that routinely reported in histopathology after HCC resection. Some studies found CK19 and Ki-67 are associated with immune microenvironment and molecular classification in HCC. However, no study investigated the role of CK19 and Ki-67 as histopathologic biomarker to predict the response and sensitivity to ICIs therapy.

Whether additional factors affect the efficacy of ICIs in patients with HCC has not been clarified. This brief report explored the factors influencing the efficacy of lenvatinib with or without ICIs in advanced HCC based on data from real-world clinical practice. Moreover, the role of CK19 and Ki-67 as histopathologic biomarker to predict the response to ICIs therapy was also investigated.

Methods

The cohorts of this study were previously described. However, subgroup analysis to reveal the subsets with the best benefit from combination therapy was not performed. In the combination cohort, ICIs included pembrolizumab (n=5), camrelizumab (n=31), sintilimab (n=21), toripalimab (n=7) and tislelizumab (n=1). The definition of metabolic dysfunction-associated fatty liver disease (MAFLD) was based on presence of steatosis in >5% of hepatocytes, in addition to body mass index (BMI) ≥23 kg/m², type 2 diabetes mellitus or metabolic dysregulation. The independent effects of baseline factors including age, gender, BMI, steatosis, MAFLD, cirrhosis, hepatitis B virus (HBV) infection, total tumor volume, tumor burden score and α-fetoprotein on the efficacy of the two groups (lenvatinib alone vs lenvatinib+ICI) were assessed by multivariable analyses. Objective response was not reported in this brief report because of the small sample size in some subgroups.

The definition of tumor burden score was described previously. It is defined using distance from the origin on a Cartesian plane incorporating maximum tumor size (x-axis) and number of lesions (y-axis). The total tumor volume is calculated by the addition of the volume of each individual tumor.

All included patients had Child-Pugh class A or B liver function, an Eastern Cooperative Oncology Group performance status of 0 or 1 at the time of lenvatinib initiation. As histology data was missing in some patients, liver cirrhosis could not be graded. The median duration of lenvatinib therapy was 10.2 (1.2-23.7) months in the combination group and 8.2 (1.1-23.7) months in the lenvatinib monotherapy group, respectively. Patients in the combination group were treated with a total of 508 cycles of ICIs (median 7, range 1-21).

Results

Patients in the lenvatinib group were significantly older, while all other baseline characteristics were comparable between the two groups (Table 1). The follow-up was

| Variable | Lenvatinib (n=45) | Lenvatinib + ICI (n=65) | p |
|----------|------------------|------------------------|---|
| Median age, y | 56 | 51 | 0.020 |
| Male gender, n (%) | 42 (93.3) | 55 (84.6) | 0.233 |
| Mean BMI (kg/m²) | 22.8 | 22.8 | 0.997 |
| BMI ≥23 kg/m², n (%) | 17 (37.8) | 28 (43.1) | 0.694 |
| Type 2 diabetes, n (%) | 4 (8.9) | 7 (10.8) | 1.000 |
| Hypertension, n (%) | 11 (24.4) | 7 (10.8) | 0.69 |
| Triglycerides (>1.70 mmol/L), n (%) | 5 (11.1) | 5 (7.7) | 0.738 |
| High-density lipoprotein (<1.0 mmol/L for man and <1.3 mmol/L for women, n (%) | 14 (31.1) | 25 (38.5) | 0.544 |
| >5% steatosis, n (%) | 21 (46.7) | 19 (29.2) | 0.072 |
| MAFLD, n (%) | 14 (31.1) | 14 (21.5) | 0.274 |
| Liver cirrhosis, n (%) | 32 (71.1) | 52 (80.0) | 0.362 |
| HBV infection*, n (%) | 20 (44.4) | 40 (61.5) | 0.084 |
| Anti-HCV, positive, n (%) | 2 (4.4) | 4 (6.2) | 1.000 |
| Mean total tumor volume, cm³ | 984.4 | 982.5 | 0.993 |
| Mean tumor burden score | 10.4 | 10.7 | 0.809 |
| α-fetoprotein ≥200 ng/mL, n (%) | 25 (55.6) | 41 (63.1) | 0.553 |

*Not including patients with other etiology; BMI, body mass index; MAFLD, metabolic dysfunction-associated fatty liver disease.
updated on 15 October 2021. The median follow-up was 20.5 months in the lenvatinib and 18.0 months in the combination group. At the time of analysis, 35 (77.8%) and 33 (50.8%) deaths occurred in the lenvatinib and the combination group, respectively. Patients in the combination group had significantly better overall survival than those in the lenvatinib group (hazard ratio=0.51; 95% confidence interval, 0.31-0.84; Fig. 1a); median overall survival was 13.0 and 9.3 months, respectively.

And then, subgroup analysis based on patients with and without MAFLD was performed. Each group had 14 patients with MAFLD. The two groups had similar OS (hazard ratio=0.54; 95% confidence interval, 0.22-1.33; Fig. 1b). However, among those without MAFLD, patients with combination therapy had statistically higher OS than those with lenvatinib monotherapy (hazard ratio=0.51; 95% confidence interval, 0.28-0.93; Fig. 1c).

Subgroup analyses based on other variables were also performed. Lenvatinib plus ICIs compared to lenvatinib was associated with better overall survival in patients younger than 60 years, males as well as with BMI <23 kg/m², cirrhosis, HBV infection, total tumor volume ≥982 cm³, tumor burden score of ≥10.4 or ß-fetoprotein ≥200 ng/ml (Fig. 2).

Twenty-two patients have undergone hepatic resection before lenvatinib plus ICIs therapy for recurrent HCC.\[17\] All these patients were with postoperative histopathological analysis for CK19 and Ki-67. Seven (31.8%) of them were positive with CK19 expression. The median expression of Ki-67 was 40% (range 5% to 80%). Patients without CK19 expression have higher overall (hazard ratio=0.42; 95% confidence interval, 0.09-1.86; Fig. 3a) and progression-free survival trend (hazard ratio=0.27; 95% confidence interval, 0.07-1.01; Fig. 3b). However, patients with Ki-67 low expression (n=11) had very similar overall (hazard ratio=0.89; 95% confidence interval, 0.23-3.39; Fig. 3c) and progression-free survival (hazard ratio=0.49; 95% confidence interval, 0.16-1.49; Fig. 3d) with those with high expression.

Table 1. Hazard ratios for OS analyses in patients with and without MAFLD.

| Subgroup          | No. | Hazard ratio (95% CI)       | P value |
|-------------------|-----|-----------------------------|---------|
| Age, yr           |     |                             |         |
| < 60              | 86  | 0.467 (0.269-0.811)         | 0.007   |
| ≥ 60              | 24  | 0.913 (0.339-2.455)         | 0.857   |
| Gender            |     |                             |         |
| Male              | 97  | 0.470 (0.280-0.791)         | 0.004   |
| Female            | 13  | 0.830 (0.213-3.233)         | 0.789   |
| Body mass index   |     |                             |         |
| < 23              | 65  | 0.449 (0.242-0.832)         | 0.011   |
| ≥ 23              | 45  | 0.620 (0.292-1.342)         | 0.229   |
| Status 5%         |     |                             |         |
| Present           | 40  | 0.495 (0.231-1.059)         | 0.070   |
| Absent            | 70  | 0.542 (0.290-1.013)         | 0.055   |
| MAFLD             |     |                             |         |
| Present           | 28  | 0.531 (0.212-1.331)         | 0.177   |
| Absent            | 82  | 0.506 (0.288-0.890)         | 0.018   |
| Liver cirrhosis   |     |                             |         |
| Present           | 84  | 0.536 (0.309-0.932)         | 0.027   |
| Absent            | 26  | 0.424 (0.160-1.127)         | 0.085   |
| Etiology          |     |                             |         |
| HBV infection a   | 60  | 0.487 (0.242-0.980)         | 0.044   |
| Others            | 50  | 0.581 (0.300-1.124)         | 0.107   |
| Total tumor volume|     |                             |         |
| < 982             | 75  | 0.581 (0.317-1.067)         | 0.080   |
| ≥ 982             | 35  | 0.398 (0.183-0.863)         | 0.020   |
| Tumor burden score|     |                             |         |
| < 10.4            | 50  | 0.551 (0.253-1.196)         | 0.132   |
| ≥ 10.4            | 60  | 0.451 (0.245-0.829)         | 0.010   |
| ß-fetoprotein, ng/ml|   |                             |         |
| < 200             | 44  | 0.793 (0.366-1.718)         | 0.556   |
| ≥ 200             | 66  | 0.370 (0.201-0.681)         | 0.001   |

Figure 1. Overall survival analyses for patients treated with lenvatinib monotherapy vs lenvatinib plus immune checkpoint inhibitors. (a) Kaplan–Meier curves for total population; (b) Kaplan–Meier curves for patients with MAFLD; (c) Kaplan–Meier curves for patients without MAFLD. CI, confidence interval; HR, hazard ratio; ICIs, immune checkpoint inhibitors; Len, lenvatinib.

Figure 2. Subgroup analyses of total population.
aIncluding patients with hepatitis B virus infection.
bNot including patients with other etiology.

Figure 3. Overall survival analyses for patients treated with lenvatinib monotherapy vs lenvatinib plus immune checkpoint inhibitors. (a) Kaplan–Meier curves for total population; (b) Kaplan–Meier curves for patients with MAFLD; (c) Kaplan–Meier curves for patients without MAFLD. CI, confidence interval; HR, hazard ratio; ICIs, immune checkpoint inhibitors; Len, lenvatinib.
Discussion

This study has several interesting findings. First, the conclusions of previous reports\(^5\) that NAFLD-related HCC is less responsive to immunotherapy are further supported by our results coming from an HBV endemic region, as patients with HBV infection and those without NAFLD were found to benefit most from the combination of lenvatinib with ICIs. Second, lenvatinib plus ICIs appeared to improve the overall survival in patients with HCC and low BMI, which is in contrast with reports for better efficacy of ICI therapy in patients with advanced non-small cell lung cancer and high BMI.\(^{21}\) In any case, both studies support the use of baseline BMI as a stratification factor in future ICIs trials. Third, HCC patients with high tumor load as reflected by total tumor volume, tumor burden score, and \(\alpha\)-fetoprotein levels\(^{19,22}\) were more likely to benefit from combination therapy. Fourth, the statistical significance of CK19 expression as a biomarker may be achieved when included larger sample size. Actully, the expression of CK19 is a biomarker among patients with HCC after hepatic resection or after regorafenib therapy.\(^{23-25}\) Therefore, these variables may also serve as predictors of efficacy of combination therapy in patients with advanced HCC.

In conclusion, lenvatinib plus ICIs therapy seems to be more effective in advanced HCC patients with viral etiology, low BMI, or high tumor load.

Disclosures

Ethics Committee Approval: This study was approved by the institutional review board of Guangxi Medical University Cancer Hospital (number LW2021026).

Conflict of Interest Disclosures: Dr Papatheodoridis has served as lecturer/advisor for Bayern, Ipsen and Roche; the other authors have nothing to disclose.

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References

1. Ren Z, Xu J, Bai Y, Xu A, Cang S, Du C, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. Lancet Oncol 2021;22:977–90.
2. Finn RS, Ikeda M, Zhu AX, Sung MW, Baron AD, Kudo M, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol 2020;38:3960–70.
3. Lan XB, Papatheodoridis G, Teng YX, Zhong JH. The upward trend in the immunotherapy utilization for hepatobiliary cancers. Hepatobiliary Surg Nutr 2021;10:692–5.
4. Deng ZJ, Li L, Teng YX, Zhang YQ, Zhang YX, Liu HT, et al. Treatments of hepatocellular carcinoma with portal vein tumor thrombus: current status and controversy. J Clin Transl Hepatol 2022;10:147–58.
5. Liu HT, Jiang MJ, Deng ZJ, Li L, Huang JL, Liu ZX, et al. Immune checkpoint inhibitors in hepatocellular carcinoma: current progresses and challenges. Front Oncol 2021;11:737497.
6. Finn RS, Qin S, Ikeda M, Galle PR, Dureex M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894–905.
7. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). Ann Oncol 2019;30:v874–5.
8. Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. J Clin Oncol 2020;38:193–202.

9. Pfister D, Nunez NG, Pinyol R, Govaere O, Pinter M, Szydlowska M, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021;592:450–6.

10. Liu L, Xie S, Teng YX, Deng ZJ, Chen K, Liu HT, et al. Outcomes of liver resection for metabolic dysfunction-associated fatty liver disease or chronic hepatitis B-Related HCC. Front Oncol 2021;11:783339.

11. Rimini M, Kudo M, Tada T, Shigeo S, Kang W, Suda G, et al. Non-alcoholic steatohepatitis in hepatocarcinoma: new insights about its prognostic role in patients treated with lenvatinib. ESMO Open 2021;6:100330.

12. Chin KM, Prieto M, Cheong CK, Di Martino M, Ielpo B, Goh BKP, et al. Outcomes after curative therapy for hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: a meta-analysis and review of current literature. HPB (Oxford). 2021;23:1164–1174.

13. Wu H, Li Y, Shi G, Du S, Wang X, Ye W, et al. Hepatic interferon regulatory factor 8 expression suppresses hepatocellular carcinoma progression and enhances the response to anti-programmed cell death protein-1 therapy. Hepatology. 2022 Jan 6. Doi: 10.1002/hep.32316. [Epub ahead of print].

14. Xiang J, Zhang N, Sun H, Su L, Zhang C, Xu H, et al. Disruption of SIRT7 increases the efficacy of checkpoint inhibitor via MEF2D regulation of programmed cell death 1 Ligand 1 in Hepatocellular Carcinoma cells. Gastroenterology 2020;158:664–78.e24.

15. Kurebayashi Y, Ojima H, Tsujikawa H, Kubota N, Abe Y, et al. Landscape of immune microenvironment in hepatocellular carcinoma and its additional impact on pathological and molecular classification. Hepatology 2018;68:1025–41.

16. Moldogazieva NT, Zavadskiy SP, Sologova SS, Mokhosoev IM, Terentiev AA. Predictive biomarkers for systemic therapy of hepatocellular carcinoma. Expert Rev Mol Diagn 2021;21:1147–64.

17. Chen K, Wei W, Liu L, Deng ZJ, Li L, Liang XM, et al. Lenvatinib with or without immune checkpoint inhibitors for patients with unresectable hepatocellular carcinoma in real-world clinical practice. Cancer Immunol Immunother. 2021 Sep 24. doi: 10.1007/s00262-021-03060-w. [Epub ahead of print].

18. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73:202–9.

19. Sasaki K, Morioka D, Conci S, Margonis GA, Sawada Y, Ruzzene A, et al. The tumor burden score: a new "Metro-tick-et" prognostic tool for colorectal liver metastases based on tumor size and number of tumors. Ann Surg 2018;267:132–41.

20. Toso C, Trotter J, Wei A, Bigam DL, Shah S, Lancaster J, et al. Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. Liver Transpl 2008;14:1107–15.

21. Kichenadasse G, Miners JO, Mangoni AA, Rowland A, Hopkins AM, Sorich MJ. Association between body mass index and overall survival with immune checkpoint inhibitor therapy for advanced non-small cell lung cancer. JAMA Oncol 2020;6:512–8.

22. Hsu CY, Huang YH, Hsia CY, Su CW, Lin HC, Loong CC, et al. A new prognostic model for hepatocellular carcinoma based on total tumor volume: the Taipei Integrated Scoring System. J Hepatol 2010;53:108–17.

23. Zhuo J, Lu D, Lin Z, Yang X, Yang M, Wang J, et al. The distinct responsiveness of cytokeratin 19-positive hepatocellular carcinoma to regorafenib. Cell Death Dis 2021;12:1084.

24. Zhang J, Qi YP, Ma N, Lu F, Gong WF, Chen B, et al. Overexpression of Epacam and CD133 Correlates with Poor Prognosis in Dual-phenotype Hepatocellular Carcinoma. J Cancer 2020;11:3400–6.

25. Obiorah IE, Chahine J, Ko K, Park BU, deGuzman J, Kallakury B. Prognostic implications of arginase and cytokeratin 19 expression in hepatocellular carcinoma after curative hepatectomy: correlation with recurrence-free survival. Gastroenterology Res 2019;12:78–87.