Efficacy and Safety of Lenvatinib for Advanced Hepatocellular Carcinoma Patients Beyond REFLECT Study Indications in a Real-World Setting in China

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Research Article

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Abstract

Background/purpose: Lenvatinib was found to be non-inferior to sorafenib in a Phase 3 REFLECT trial on advanced hepatocellular carcinoma. However, patients with a liver tumor volume of greater than 50% of total liver volume or with main portal vein tumor thrombus, which often occurs in clinical practice, were excluded from the REFLECT trial. This study aimed to examine the safety and efficacy of lenvatinib on patients beyond REFLECT study indications in a real-world setting.

Method: This was a retrospective, single-center observational study focused on unresectable hepatocellular carcinoma (u-HCC) patients with the tumor accounting for more than 50% of the liver volume or with main portal vein tumor thrombus. From June 2018 to February 2019, 21 u-HCC patients with above characteristics were enrolled. The therapeutic effects were determined using the modified Response Evaluation Criteria in Solid Tumors (m-RECIST) in the 12th week. Grades of adverse events followed with the Common Terminology Criteria for Adverse Events version (CTCAE) 4.0. The median Progression-Free Survival (PFS) and median Over Survival (OS) were determined at the 12th month.

Results: The median observation period was 11.5 months. Fatigue, leukopenia and dysphoria were the most frequent adverse events. Leukopenia, hand-foot skin reaction and decreased appetite were the most frequent adverse events, and were higher than Grade 2. 7 of the patients had elevated Child-Pugh scores, 3 of whom increased from Child-Pugh A to B. All of the adverse events could be controlled by appropriate dose reduction, interruption and symptomatic treatment. No liver function failure occurred. The probability of tumor marker (AFP or PIVKA-II) decline was 100% and 60% at one month and three months after administration respectively. In the m-RECIST evaluation in the 12th week, 0, 7, 7 and 7 patients achieved complete response, partial response, stable disease and progressive disease respectively. The objective response rate was 33.3%. The median PFS and OS was 5.3 and 11.2, respectively. 1 year survival rate was 42.9%.

Conclusion: Lenvatinib treatment can be accomplished with safety and a good response for patients beyond REFLECT study indications in a real-world setting.

Background

Hepatocellular carcinoma (HCC) is a common malignant tumor with morbidity and mortality rates ranking 4th and 2nd in China respectively among all kinds of malignant tumors. Due to its insidious onset, most patients are discovered in the advanced stages. For a long time, sorafenib was the single first-line drug recommended for advanced HCC. As shown in the REFLECT study published in 2017, lenvatinib was non-inferior to sorafenib for overall survival (OS) rate in the first-line treatment of advanced HCC. It was further revealed in the subgroup analysis that lenvatinib was superior to sorafenib in either recent objective response rate (ORR) or future OS for Chinese people. Clinical guidelines issued by multiple professional medical institutions including the Chinese Society of Clinical Oncology (CSCO) currently
classify lenvatinib as a first-line therapy for advanced HCC. However, patients with a liver tumor volume of greater than 50% of the whole liver or main portal vein tumor thrombus were excluded from the REFLECT trial. Considering the importance of determining the safety and efficacy of lenvatinib for these patients, this study aimed to examine the safety and efficacy of lenvatinib for such patients in a real-world setting.

Methods

Study Design and Group

This was a single-center, retrospective observational study in which 21 patients with unresectable advanced HCC were observed from June 2018 to February 2019. The patients suffered either from a tumor accounting for more than 50% of the liver volume or main portal vein tumor thrombus. All of the patients were graded as 0 or 1 in the Eastern Cooperative Oncology Group (ECOG) and classified as Child-Pugh A or B. As this was a study in a real-world setting, most of the patients were given other treatments (including local radiotherapy or the combined utilization of PD-1 inhibitor with lenvatinib). The baseline characteristics are listed in Table 1.

Study Program

The patients received oral lenvatinib of 12 mg/day (body weight > 60 kg and Child-Pugh A) or 8 mg/day (body weight < 60 kg and Child-Pugh B). Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Other treatments in combination with lenvatinib are permitted in a real-world setting. In this study, there were two combined methods. The first was radiotherapy on intrahepatic tumor and/or main portal vein tumor thrombus. The target sections were defined as follows: (1) gross tumor volume (GTV): intrahepatic focus and portal vein tumor thrombus shown in iconography, (2) clinical tumor volume (CTV): intrahepatic focus expanded 3–5 mm from GTV, portal vein tumor thrombus focused at the level of thrombus, including the entire portal vein lumen, expanded 10 mm along the blood vessel to the head and foot, and (3) planning tumor volume (PTV): expanded 5–10 mm to the head and foot, 4 mm to the abdomen and back, and 3 mm to the left and right from CTV. The radiotherapy dose was 95% isodose contour around PTV, liver focus 2Gy×20F and portal vein tumor thrombus 2Gy×25F. Arc intensity modulated radiation therapy (IMRT) was given with a dose of X-ray at 6 MV. In the case of excessive intrahepatic focus of greater than 70% of the whole liver, only portal vein tumor thrombus was radiated. The second method was PD-1 inhibitor for immunotherapy. A sintilimab injection was used as a PD-1 inhibitor through intravenous injection at a 200 mg dose once every three weeks along with lenvatinib. It is allowed to alter other targeted drugs, such as sorafenib and regorafenib after efficacy evaluation for PD.

During the treatment, the lenvatinib (1) remained at the same dosage in case of Grade 1 AE, accompanied by symptomatic treatment or close observation, (2) was reduced by 4 mg in case of Grade 2 AE,
accompanied by symptomatic treatment or close observation, then resumed when AE was at Grade 1 or below, (3) was suspended in the case of Grade 3 AE accompanied by symptomatic treatment or close observation, resumed when AE was at Grade 1 or below, and permanently withdrawn in case AE at Grade 3 or above occurred again, and (4) was permanently withdrawn in the case of Grade 4 AE.

Follow-up Visits

During the treatment, blood pressure was examined once every day, blood routine once every week, hepatic and renal function as well as coagulation function once every two weeks, thyroid function and PRO once every three weeks, tumor marker once every month, and a follow-up visit once every two weeks for any other clinical symptoms. AEs were graded according to CTCAE Version 4.0. Therapeutic effects were determined using the modified Response Evaluation Criteria in Solid Tumors (m-RECIST) 1.1 in the 12th week. The liver was examined by enhanced MRI, and the lungs by regular CT. Imaging evaluations were performed every 3 months.

Statistical methods

The median was calculated for the clinical parameter values and the range was also reported.

Results

Patients’ Characteristics

The study observed 21 patients with unresectable advanced HCC from June 2018 to February 2019, graded at 0 or 1 in ECOG. All the patients failed to meet the inclusion criteria of the REFLECT trial, 15 had a liver tumor volume of greater than 50% of the whole liver, while 13 had main portal vein tumor thrombus. All patients were followed up until February 29th, 2020, and the median follow-up period was 348 days (162 to 465 days). Among them, 16 patients were Child-Pugh A and five were B, 14 patients had prior treatment history, 17 patients received lenvatinib accompanied by radiotherapy, and 15 received lenvatinib accompanied by PD-1 inhibitor. The details are listed in Table 1.

Adverse Effects

AEs occurred to nearly all patients (see Table 2 for details), all of which were Grade 1–3 and no higher than Grade 3. Fatigue, leukopenia and dysphoria were the most frequent AEs, with incidence rates of 90.5%, 76.2% and 71.4% respectively. Leukopenia, hand-foot skin reaction and decreased appetite were the most frequent AEs at Grade 3, with incidence rates of 28.6%, 14.3% and 9.5% respectively.

Efficacy Evaluation

Among these 21 patients, 20 exceeded the normal range in tumor markers, 19 with elevated alpha fetoprotein (AFP) and one with elevated PIVKA-II. The percentages of tumor markers declined in all patients at the 1st and 3rd months by 100% and 60% respectively, as shown in Table 3.
All patients were evaluated for efficacy in the 12th week after lenvatinib treatment using m-RECIST 1.1 evaluation criteria, including 0 patient with completely remission (CR), 3 with partial remission (PR), 10 with stable disease (SD) and 8 with progressive disease (PD) according to target lesions (Fig.1). In addition, 4 patients had new metastatic lesions, of which 2 had new pulmonary metastases, 1 had new liver metastases, and 1 had new bone metastases. Therefore, the patients whose efficacy was evaluated as CR, PR, SD, and PD were 0, 7, 7, and 7, respectively, and with an ORR of 33.3% and disease control rate (DCR) of 66.7%, as shown in Table 4.

The median PFS and OS was 5.3 months and 11.2 months, respectively. 1 year survival rate was 42.9%.

**Discussion**

HCC is a common malignant tumor which ranks 2nd among all cancer diseases that cause death. China has a significant number of cases of hepatitis, as well as cases of liver cancer, accounting for more than half of new liver cancer cases worldwide each year. In a newly published survey on the prevalence of malignant tumors in China, the annual incidence of liver cancer in the country ranks 4th among all cancer types, and the death toll ranks 2nd.[1] Although the physical examination mechanisms are constantly improving, there remains a large number of patients with liver cancer in the advanced stages when they are discovered.[2] At the same time, the prognosis of patients with liver cancer is poor because liver cancer is prone to intrahepatic dissemination and has the characteristics of intrahepatic polycentric carcinogenesis. Despite its limited efficacy, sorafenib has long been recommended as the preferred treatment for patients with advanced HCC.[3]

In 2017, a new multi-targeted drug named lenvatinib appeared in the treatment of advanced liver cancer. This drug can combine with vascular endothelial growth factor receptors (VEGFR) 1–3, fibroblast growth factor receptors (FGFR) 1–4 and platelet-derived growth factor (PDGF)-α to block tumor angiogenesis. At the same time, it can also inhibit other angiogenic tyrosine kinases activity involved in tumor proliferation, thus playing an anti-tumor role. According to the results of a Phase 3 multi-center randomized control clinical study (REFLECT) of advanced HCC using sorafenib, lenvatinib was non-inferior to sorafenib in terms of OS rate in the treatment of advanced HCC.[4] According to the results of this clinical study, several guidelines for the treatment of liver cancer, including that issued by CSCO, recommend lenvatinib as a first-line therapy for advanced HCC.

At present, real world data which meets the inclusion conditions of the REFLECT study has been reported.[5] It is believed that lenvatinib’s toxicity is acceptable in a real-world setting for patients with advanced liver cancer that meet the REFLECT study criteria, and the tumor has a good response rate (ORR of 40%). However, in clinical practice, the liver tumor volume of some HCC patients exceeds 50% of total liver volume, or the main portal vein tumor thrombus has already formed. These patients were excluded from the REFLECT study. For this group of patients, the safety and efficacy of the use of lenvatinib have not been reported. This study observed the use of lenvatinib on such patients in a real-world setting.
With the release of the results of the REFLECT study, the recommendations for the treatment of advanced HCC in the international guidelines for the treatment of liver cancer have been updated to include lenvatinib as a first-line treatment for advanced liver cancer. However, advanced liver cancer covers a wide range of patients, including those with tumors that exceed 50% of liver volume and those with main portal vein tumor thrombus. These patients were excluded from the REFLECT study due to their worse prognosis. Whether this population can tolerate lenvatinib treatment and what level of efficacy it has were unknown. For this reason, we specifically selected these two types of HCC patients as subjects.

Radiotherapy is an important treatment method for patients with main portal vein tumor thrombus,[6] and the study results of the Iphase of lenvatinib in combination with PD-1 inhibitors have been reported.[7] Therefore, in our study, some patients were treated systematically with radiotherapy or PD-1 inhibitors. At the same time, as it was conducted in a real-world setting, this study included patients who had previously been treated with targeted drugs or other topical treatment.

During the 12-week follow-up observation period, we observed that all patients showed AEs to different degrees, and the types of AEs were consistent with previous literature reports.[5, 8 & 9] In this study, however, the incidence of AEs was higher than previously reported. Among the numerous AEs in this study, fatigue, leukopenia and hoarseness occurred in the top three, with 90.5%, 76.2% and 71.4% respectively. In addition to the above three AEs, more than 50% of AEs included decreased appetite, proteinuria, hand-foot skin reaction, dysgeusia, nosebleed, pruritus, rash and constipation. However, among the patients observed in this study, the incidence of serious AEs was not high, and no AEs of Grade 4 were observed in any patient. Among the 21 observed cases, six (all treated with combination radiotherapy) developed Grade 3 leukopenia; three developed Grade 3 hand-foot skin reaction; two developed Grade 3 decreased appetite, rash and diarrhea; and one developed Grade 3 fatigue, hoarseness, nosebleed, thrombocytopenia and hypertension respectively. Since the Phase 1 study of lenvatinib in the treatment of liver cancer focused on its effect on liver function,[10] we also paid particular attention to this and examined the liver function and coagulation function of all patients every two weeks. Among all the patients, the liver function of three patients elevated from Child-Pugh A to B, which resulted in the reduction of lenvatinib, accounting for 18.8%. The Child-Pugh score elevated in seven patients, accounting for 33.3%, but none had Child-Pugh C liver function. The reasons for the high incidence of AEs were as follows: first, all the patients observed in this study were those who exceeded the inclusion criteria of the REFLECT study, so their disease development was more severe than that of the REFLECT study group, with worse tolerance. Second, some patients were more likely to have AEs after receiving radiotherapy or combination therapy such as PD-1 inhibitors. For patients with large liver tumors (accounting for more than 50% of liver volume) or portal vein tumor thrombus, their liver function reserve capacity was weaker due to the reduced number of normal liver cells and liver blood supply, and their liver function score was more likely to elevate under anti-tumor treatment.

Because the current follow-up time for this group of patients is short, it is impossible to accurately evaluate the efficacy of lenvatinib. Even so, we can still initially evaluate the efficacy of lenvatinib in patients with advanced liver cancer beyond REFLECT study indications. In this study, seven, seven and
seven patients achieved PR, SD and PD respectively. The ORR was 33.3%, slightly lower than 40.6% in the REFLECT study\textsuperscript{[4]} and 40.0%\textsuperscript{[5]} in a Japanese study with a real-world setting. In addition, we closely monitored changes in tumor markers in this group of patients and found that at one month after administration, the tumor marker index of all patients decreased, with 70% of patients seeing a decrease of more than 50%. Nonetheless, we also found that the decline in tumor markers was not consistently maintained in all patients, as tumor marker levels elevated again in 40% of patients in the 12th week. This also indicates that some patients are likely to be resistant for three months’ administration of lenvatinib.

Among the patients observed in this group, the median PFS and OS were 5.3 months and 11.2 months, respectively; lower than the data in the Reflect study, which was considered to be related to the lateness of patients enrolled. The Reflect study included patients with stage B and some stage C patients, and excluded those with oversized tumors and portal tumor thrombus. The staging of the patients observed in our group was significantly later than in the Reflect study population. In addition to oral lenvatinib, some patients in this group also received local radiotherapy and PD-1 inhibitor therapy. After lenvatinib progressed, other targeted drugs were subsequently replaced, so they still obtained a relatively long Survival.

For patients with advanced HCC whose liver tumor volume is greater than or equal to 50% of liver volume or with main portal vein tumor thrombus, the current clinical treatment options are limited. Therefore, by observing the safety and efficacy of lenvatinib in these patients in a real-world setting, we can accumulate more experience for clinical practice. However, due to the limited participants in this study and the application of other treatments to some patients in combination with lenvatinib, the results of this study can only be used as a reference for the accumulation of clinical experience and further relevant clinical trials, and the longer-term clinical follow-up data and results are particularly important.

**Conclusion**

Based on this study, we believe that for patients with advanced HCC whose liver tumor volume is greater than or equal to 50% of total liver volume or with main portal vein tumor thrombus, after taking lenvatinib, despite the higher probability of AEs, most of them can tolerate it and show no Grade 4 AEs. This suggests that lenvatinib can achieve a safe response in this group of patients. Some patients may have an elevation in their Child-Pugh score and liver function score after taking lenvatinib, so liver function changes need to be closely monitored during treatment, and the dose of lenvatinib can be reduced if necessary. Compared with the participants in the REFLECT study, the effective rate of lenvatinib in this group of patients is slightly lower. The observation of long-term efficacy requires more case accumulation and further follow-up.

**Declarations**

**Funding** (Not applicable)
Conflicts of interest/Competing interests (The authors declare that they have no conflict of interest.)

Availability of data and material (All data used and/or analyzed during the current study are available from the corresponding author on reasonable request.)

Code availability (Not applicable)

Authors' contributions (Guangxin Li conceived and designed the research. Yu Zhang, Yanmei Yang and Gong Li collected the data and performed the data analysis. Guangxin Li wrote the paper.)

Ethics approval (The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Medical Ethics Committee of Beijing Tsinghua Changgung Hospital.)

Consent to participate (Not applicable)

Consent for publication (Not applicable)

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Tables

Table 1 Clinical Baseline Characteristics

| Baseline Characteristics                                      | Participants (21) |
|---------------------------------------------------------------|-------------------|
| Gender (male: female)                                         | 19: 2             |
| Age (median)                                                  | 47 (31–69)        |
| Weight                                                        | 64 (49–76)        |
| ECOG (0:1)                                                    | 15: 6             |
| Have you ever been treated (yes: no)                          | 14: 7             |
| Time from onset to taking lenvatinib (months)                 | 3 (1–33)          |
| Have you used targeted drugs before (yes: no)                 | 09:12             |
| Viral infection (HBC: HCB: none)                              | 20: 1: 0          |
| Child-Pugh grading (A: B)                                    | 16: 5             |
| Applied lenvatinib with radiotherapy simultaneously or within 3 months (yes: no) | 17: 4             |
| Applied lenvatinib to PD-1 inhibitor (yes: no)                | 15: 6             |
| Liver tumor volume: liver volume > 50% (yes: no)              | 15: 6             |
| Main portal vein tumor thrombus (yes: no)                     | 13: 8             |
| Inferior vena cava tumor thrombus (yes: no)                   | 01:20             |
| Transfer of other organs before taking lenvatinib (yes: no)   | 07:14             |
| Platelet count × 10⁹/L before taking lenvatinib (median)      | 169 (60–530)      |
| AFP value (ng/ml) before taking lenvatinib (median)           | 3,966 (2.52–640,851) |

Table 2 Adverse Events and Grading
| Side Effect                        | G1 | G2 | G3 | G4 | G5 | Total Amount | Proportion (%) |
|-----------------------------------|----|----|----|----|----|--------------|----------------|
| Fatigue                           | 14 | 04 | 01 |    |    | 19           | 90.5           |
| Leukopenia                        | 03 | 07 | 06 |    |    | 16           | 76.2           |
| Hoarseness                        | 09 | 05 | 01 |    |    | 15           | 71.4           |
| Decreased appetite                | 08 | 03 | 02 |    |    | 13           | 61.9           |
| Albuminuria                       | 10 | 03 |    |    |    | 13           | 61.9           |
| Hand-foot skin reaction           | 08 | 02 | 03 |    |    | 13           | 61.9           |
| Dysgeusia                         | 09 | 04 |    |    |    | 13           | 61.9           |
| Nosebleed                         | 08 | 02 | 01 |    |    | 11           | 52.4           |
| Pruritus                          | 07 | 04 |    |    |    | 11           | 52.4           |
| Rash                              | 06 | 03 | 02 |    |    | 11           | 52.4           |
| Constipation                      | 07 | 04 |    |    |    | 11           | 52.4           |
| Diarrhea                          | 03 | 04 | 02 |    |    | 09           | 42.9           |
| Oral hemorrhage                   | 07 | 02 |    |    |    | 09           | 42.9           |
| Thrombocytopenia                  | 02 | 06 | 01 |    |    | 09           | 42.9           |
| Ventosity                         | 06 | 02 |    |    |    | 08           | 38.1           |
| Hypertension                      | 04 | 02 | 01 |    |    | 07           | 33.3           |
| Hypoproteinemia                   | 06 | 01 |    |    |    | 07           | 33.3           |
| Nausea                            | 06 | 01 |    |    |    | 07           | 33.3           |
| Mucositis                         | 04 | 03 |    |    |    | 07           | 33.3           |
| Elevated bilirubin                | 05 | 02 |    |    |    | 07           | 33.3           |
| Aopecia                           | 06 | 01 |    |    |    | 07           | 33.3           |
| Arthralgia                        | 07 |    |    |    |    | 07           | 33.3           |
| Fever                             | 03 | 03 |    |    |    | 06           | 28.6           |
| Acites                            | 05 | 01 |    |    |    | 06           | 28.6           |
| Oral dysfunction                  | 05 |    |    |    |    | 05           | 23.8           |
| Stomachache                       | 04 | 01 |    |    |    | 05           | 23.8           |
| Muscle pain                       | 05 |    |    |    |    | 05           | 23.8           |
| Eczema                            | 03 | 01 |    |    |    | 04           | 19.1           |
Eczema 03 03 14.3
Lalopathy 01 01 04.7
Cramp 01 01 04.7
Anemia 01 01 04.5

Table 3 Changes in Tumor Marker

| At the 1st Month | At the 3rd Month |
|------------------|-----------------|
| Elevate          | Elevate         |
| Decline: < 50%   | Decline: > 50%  |
| 0                | 8               |
| 0%               | 40%             |
| 6                | 7               |
| 30%              | 35%             |
| 14               | 7               |
| 70%              | 25%             |

Note: 21 patients were observed, including 18 with elevated AFP, 2 with elevated PIVKA-II in patients with normal AFP, and 1 with normal AFP and PIVKA-II.

Table 4 Short-term Efficacy

| CR | PR | SD | PD |
|----|----|----|----|
| Participants | 0 | 7 | 7 | 7 |
| Proportion (%) | 0.0 | 33.3 | 33.3 | 33.3 |

Figures
21 patients were evaluated for efficacy in the 12th week after lenvatinib treatment using m-RECIST 1.1 evaluation criteria, including 0 patient with completely remission (CR), 3 with partial remission (PR), 10 with stable disease (SD) and 8 with progressive disease (PD) according to target lesions. In addition, 4 patients had new metastatic lesions, of which 2 had new pulmonary metastases(No.13 and No.18), 1 had new liver metastases(No.4), and 1 had new bone metastases(No.12).