A Real-World Study of Optimal Treatment with Anlotinib First-Line Therapy in Advanced Hepatocellular Carcinoma

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Purpose: To observe the efficacy and safety of anlotinib as a first-line treatment for patients with advanced hepatocellular carcinoma (aHCC) in a real-word environment, explore the optimal treatment regimen for patients with aHCC using anlotinib as a first-line treatment.

Patients and Methods: Data from 62 patients with aHCC who received anlotinib single-drug first-line therapy between February 2019 and November 2021. Patients received anlotinib monotherapy, which may be interrupted or discontinued or changed in the event of unacceptable or severe adverse events (AEs) or failure to inhibit tumor progression. The primary endpoint was progression-free survival (PFS) and the secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety.

Results: Among the 62 patients, in the best overall response assessment, there were 12 with complete response (CR; 19.4%), 17 with partial response (PR; 27.4%), 25 with stable disease (SD; 40.3%), and 8 with progressive disease (PD; 14.5%). The ORR and DCR were 46.8% and 87.1%, respectively. Among the 11 patients who received tyrosine kinase inhibitors (TKIs) combined with programmed death 1 (PD-1) inhibitors after disease progression, three (27.3%) had CR, one (9.1%) had PR, three (27.3%) had SD, and four (36.4%) had PD. Therefore, the ORR and DCR were 36.4% and 63.6%, respectively. The median PFS for anlotinib monotherapy was 7.37 months (95% confidence interval [CI]: 5.88–8.86) and the median OS did not reach. AEs occurred in 95.2% of patients during anlotinib monotherapy, with the most common being thrombocytopenia (51.6%). The incidence of grade ≥3 AEs was 38.7%.

Conclusion: Anlotinib is effective and well-tolerated as a first-line treatment for patients with aHCC. Treatment with TKIs and PD-1 inhibitors after disease progression has also shown preliminary efficacy and safety; therefore, sequential therapy with anlotinib-TKIs and PD-1 inhibitors may be an effective treatment for patients with aHCC.

Keywords: hepatocellular carcinoma, anlotinib, sequential therapy, real world

Introduction

Primary liver cancer is one of the six most common cancers and the third leading cause of cancer-related death worldwide in 2020. 1 The number of new cases and deaths due to liver cancer worldwide was approximately 854,000 and 810,000 in 2015, 2 841,000 and 782,000 in 2018, 3 and 906,000 and 830,000 in 2020, 1 with the ratio of mortality to morbidity approaching 1. Because of the high incidence of hepatitis B virus infection, the morbidity and mortality of liver cancer in China remain high. Primary liver cancer is the fifth most common cancer in China, with the second
highest mortality rate and is more commonly found in younger people.\textsuperscript{4–7} Hepatocellular carcinoma (HCC) is the main pathological type of primary liver cancer, accounting for 75–85% of cases.\textsuperscript{8} Current treatment options for HCC include liver transplantation, surgical resection, and local and systemic therapy. Because of the insidious onset of liver cancer, most patients already have advanced stage disease when diagnosed, making radical treatment, such as surgery and liver transplantation, impossible. Without effective treatment, the natural survival time is only 3–4 months,\textsuperscript{9,10} and the overall 5-year survival rate is 10–15\textsuperscript{\%},\textsuperscript{11,12} posing a serious threat to the life and health of Chinese people.

Sorafenib was approved for the treatment of patients with advanced hepatocellular carcinoma (aHCC). Although the median time to progress (mTTP) of aHCC is only 2.8 months and 5.5 months, and the median overall survival (mOS) only 6.5 months and 10.7 months,\textsuperscript{13,14} sorafenib has been the only targeted drug for first-line treatment of aHCC for more than ten years and its dominance was not broken until the approval of lenvatinib in 2018. The median progression-free survival (mPFS) with lenvatinib treatment was 7.2–7.4 months.\textsuperscript{13,14} Atezolizumab combined with bevacizumab, regorafenib, apatinib, pembrolizumab, and camrelizumab has been successively approved for the treatment of aHCC.\textsuperscript{15–19} Although the combination of immune checkpoint inhibitors (ICIs) and different antiangiogenic tyrosine kinase inhibitors (TKIs) has some efficacy in patients with aHCC, combination therapy is more prone to lead to severe adverse reactions than monotherapy,\textsuperscript{15} and the suspension of treatment or dose reduction caused by severe adverse reactions may affect therapeutic efficacy.\textsuperscript{20} Combination therapy greatly increases the economic burden on patients with cancer. Therefore, better tolerability protocols should be explored for the treatment of patients with aHCC to minimize side effects while maximizing therapeutic effects.

Anlotinib (produced by Zhengdatianqing Pharmaceutical Group Co., LTD., Lianyungang City, Jiangsu Province, China) is a novel multitarget oral tyrosine kinase inhibitor that has been approved in China for the treatment of non-small cell lung cancer, small cell lung cancer, soft tissue sarcoma, and medulloid thyroid cancer and has received level 4C evidence in the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 edition). The experimental results showed that anlotinib was superior to sunitinib, sorafenib, and nidanib in terms of antiangiogenesis.\textsuperscript{21} The targets of anlotinib include fibroblast growth factor receptor 1–4 (FGFR1–4), vascular endothelial growth factor receptor 1–3 (VEGFR1–3), platelet-derived growth factor receptor α and β (PDGFRα, β), c-kit, and RET.\textsuperscript{22,23} Anlotinib highly specifically inhibit VEGFR2.\textsuperscript{24} Anlotinib has wide inhibitory effects that are similar to regorafenib inhibitory effects, thus suggesting a broad-spectrum antitumor activity compared to the other TKI.\textsuperscript{25} Immune cells play an intricate role in the tumor microenvironment and tumor neoangiogenesis.\textsuperscript{26} Anlotinib down-regulates the expression of PD-L1 on vascular endothelial cells (VECs) by inactivating AKT pathway, thereby increasing the ratio of CD8/FoxP3 inside tumor and improving the immune microenvironment to inhibit tumor growth.\textsuperscript{21,27} Anlotinib has been shown to be effective and well-tolerated in many patients with HCC, and there are many cases of anlotinib in combination with immunotherapy in clinical practice.\textsuperscript{28–30} In this study, we aimed to observe the efficacy and safety of anlotinib as a first-line treatment for aHCC in the real world, explore the effects of other treatments for patients with disease progression, and explore the optimization of treatment options for such patients in the real world.

**Materials and Methods**

**Etonogestrel Implant**

Data from 62 patients with aHCC who received anlotinib single-drug first-line therapy at the First Affiliated Hospital of Zhengzhou University between February 2019 and November 2021 were retrospectively collected. The inclusion criteria were as follows:\textsuperscript{1} age ≥18 years;\textsuperscript{2} non-resectable HCC diagnosed pathologically or clinically;\textsuperscript{3} at least one measurable lesion according to the RECIST 1.1 criteria;\textsuperscript{4} Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1;\textsuperscript{5} Child–Pugh score for liver function ≤9;\textsuperscript{6} Barcelona Clinic Liver Cancer (BCLC) stage B or C; and\textsuperscript{7} expected survival ≥3 months. The exclusion criteria were:\textsuperscript{1} history of solid organ transplantation or bone marrow suppression;\textsuperscript{2} systemic treatment required for acute autoimmune diseases; and\textsuperscript{3} the presence of autoimmune defects, the need for steroids, or other immunosuppressive treatment.\textsuperscript{4} Prior systemic antitumor therapy with chemotherapy drugs, targeted drugs, and ICIs. As the clinical data and information of patients were collected retrospectively in an anonymized manner, and the data were confirmed to be anonymous and confidential. This study complied with the Declaration of Helsinki, and exempting the
signing of informed consent would not adversely affect the rights and welfare of the subjects. Therefore, an informed consent exemption was obtained from the Ethics Committee of Scientific Research and Clinical Trials of the First Affiliated Hospital of Zhengzhou University. This study was approved by the Ethics Committee of Scientific Research and Clinical Trials of the First Affiliated Hospital of Zhengzhou University. (approval no. 2022-KY-0113-002).

Assessment of Efficacy and Adverse Events
Anlotinib was initially given at 8/10/12 mg/d by the physician in charge after a comprehensive assessment of the patient’s condition, orally before breakfast for 2 weeks, followed by 1 week of withdrawal and 3 weeks (21 days) of treatment. When unacceptable or severe AEs were present or tumor progression was unchecked, the treatment regimen were potentially interrupted, stopped, or modified.

Imaging examinations were performed using enhanced computed tomography (CT), magnetic resonance imaging (MRI), or other available imaging techniques from week 4 following the initiation of anlotinib therapy and every 8 to 12 weeks thereafter. Changes in tumor size were assessed using RECIST 1.1, They were classified into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

AEs were collected in detail and evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 5.0). When grade ≥3 AEs occurred, the physician in charge, based on the instructions and clinical experience, decided to reduce the dose, discontinue treatment, or permanently discontinue the drug until the AEs subsided to level 1 or 2, which can be controlled by the drug.

The primary endpoint of the study was progression-free survival (PFS), and the secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. PFS was defined as the time between the onset of treatment and the appearance of objective tumor progression or death; OS was defined as the time between initial treatment and death from any cause; ORR was calculated as the sum of the percentage of complete and partial responses; and DCR was calculated as the sum of the percentage of stable disease, complete response, and partial response.

Statistical Analysis
Statistical data are expressed as percentages, and differences were analyzed using the χ² or Fisher’s exact test. Non-normally distributed continuous data are described as medians. The Kaplan–Meier method was used to generate PFS curves, the Cox proportional risk model was used to analyze univariate and multivariate factors, and the hazard ratio (HR) and corresponding 95% confidence interval (CI) were obtained. Statistical significance was set at P < 0.05. All statistical analyses were performed using SPSS (version 26.0).

Results
Patient Characteristics
A total of 62 patients with aHCC who received anlotinib as first-line therapy in our hospital between February 2019 and November 2021 were enrolled in this study. Among the 62 patients, with a median age of 55.0 (38.0–78.0) years, 58 (93.5%) had hepatitis B, 1 (1.6%) had hepatitis C, 52 (83.9%) had received previous local or surgical treatment, 27 (43.5%) had portal venous thrombosis (PVT), 18 (29.0%) had extrahepatic metastasis (EHM), 18 (29.0%) had liver occupation greater than 50%, and 42 (67.7%) were evaluated as being BCLC stage C. Fifty-five (88.7%) patients were men. Seventeen (27.4%) patients had Child–Pugh class B liver function, among whom 14 (22.6%) had a Child–Pugh score of 8–9. The baseline patient characteristics are shown in Table 1.

A total of 21 patients experienced a change in treatment regimen because of disease progression, including 11 patients whose treatment regimen changed to TKIs combined with PD-1 inhibitors and had ≥2 radiographic evaluations.

Efficacy
PFS for Anlotinib Monotherapy and OS for Total Duration of Treatment
The median follow-up time was 13.3 months (5.47–35.03). The mPFS for anlotinib monotherapy was 7.37 months (95% CI: 5.85–8.89) (Figure 1). The mOS of all patients during the total follow-up period was not reached, greater than 13.27 months.
(95CI% 10.50–16.04), the 6-month survival rate was 100.0%, and the 1-year survival rate was 82.7%. At the cut-off date, 5 patients had a survival time of more than 2 years. Follow-up of 11 patients who changed treatment regimen to TKIs combined with PD-1 inhibitors showed that mOS was not achieved, greater than 17.00 months (95% CI: 10.24–23.77).

**Overall Response to Anlotinib Monotherapy**

In the best overall response assessment, there were 12 (19.4%) patients with CR, 17 (27.4%) with PR, 25 (40.3%) with SD, and 8 (12.9%) with PD; the ORR and DCR were 46.8% and 87.1%, respectively (Table 2). The ORR and DCR were 43.5% and 83.9% at 3 months and 45.2% and 85.5% at 6 months, respectively.

**Subsequent Treatments**

Among the 11 patients who received TKIs combined with PD-1 inhibitors after disease progression, three (27.3%) achieved CR, one (9.1%) achieved PR, three (27.3%) achieved SD, and four (36.4%) achieved PD. The ORR was 36.4%, and the DCR was 63.6% (Table 2).

**Factors Influencing PFS**

Univariate Cox regression showed that BCLC grade, PVT, and EHM significantly correlated with PFS (P = 0.001, 0.033, and 0.003, respectively). Multivariate Cox analysis showed that EHM (HR: 2.53, 95% CI: 1.19–5.36, P = 0.015), PVT (HR: 1.61, 95% CI: 0.70–3.69, P = 0.262), and BCLC class (HR: 1.97, 95% CI: 1.19–5.36, P = 0.204), indicating that patients with EHM had a 2.53 times higher risk of disease progression relative to patients without EHM (Table 3).
Alpha-Fetoprotein (AFP) Level Changes 1 Month After Anlotinib Monotherapy
AFP levels were determined one month after anlotinib administration. Eighteen patients with AFP levels within the normal range (<8.7 ng/mL) during treatment were excluded. The rate of change in AFP at 1 month was defined as follows: percentage change at 1 month = (AFP level at 1 month − initial AFP level)/initial AFP level. One month after initiation of treatment, 72.7% (32/44) of patients had lower AFP levels than at baseline, with a median AFP change rate of −26.0% (−97.0% to +135.0%).

Adverse Events
During anlotinib monotherapy, four patients (6.5%) stopped taking anlotinib, one patient changed dressing because of intolerance to abdominal distention, one patient stopped taking anlotinib because of poor health condition and loss of appetite, and two patients had grade ≥3 gastrointestinal bleeding and were evaluated by a competent physician and

![Progression-Free Survival](https://doi.org/10.2147/CMAR.S379911)

**Table 2** Overall Response to Treatment

|                | Anlotinib (n=62)\(^a\) | TKIs+PD-1 (n=11)\(^b\) |
|----------------|------------------------|------------------------|
| CR             | 12 (19.4%)             | 3 (27.3%)              |
| PR             | 17 (27.4%)             | 1 (9.1%)               |
| SD             | 25 (40.3%)             | 3 (27.3%)              |
| PD             | 8 (12.9%)              | 4 (36.4%)              |
| ORR            | 29 (46.8%)             | 4 (36.4%)              |
| DCR            | 54 (87.1%)             | 7 (63.6%)              |

**Notes:** \(^a\)Overall response to anlotinib monotherapy. \(^b\)Overall response to the regimen of TKIs combined with PD-1 blockade after progression with anlotinib monotherapy.

**Abbreviations:** TKIs, tyrosine kinase inhibitors; PD-1, programmed death 1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.
stopped taking the drug. In eight patients (12.9%), the dosage was reduced because of AEs with the consent of the physician in charge. The incidence of AEs was 95.2% (59/62) and 38.7% (24/62) for grades 3 and above, respectively. The most common AEs were thrombocytopenia (51.6%), leukopenia (50.0%), hypertension and neutropenia (46.8%), fatigue (43.5%), hand-foot syndrome (41.9%), and total bilirubin (TBIL) elevation (37.1%). The incidence of grade ≥3 AEs was 38.7% (24/62), and the most common grade ≥3 AEs were hypertension (12.9%), TBIL elevation (9.7%), and neutropenia (7.9%). Grade ≥3 bleeding was gastrointestinal bleeding, and one patient died because of gastrointestinal bleeding (Table 4).

The percentage change in the Child–Pugh grade during anlotinib monotherapy is shown in Table 4. Before treatment, 45 (72.6%) of the 62 patients were Child–Pugh class A and 17 (27.4%) were Child–Pugh class B; at the end of anlotinib monotherapy/last follow-up, 35 patients (56.5%) were Child–Pugh class A, 20 (32.3%) were Child–Pugh class B, and 7 (11.3%) were Child–Pugh class C, the change in group distribution was statistically significantly different (P=0.030).

### Table 3 Multivariate Analysis of Factors Associated with PFS

| Variable | Univariable Analysis | Multivariable Analysis |
|----------|----------------------|------------------------|
|          | HR | 95% CI | p  | HR | 95% CI | P value |
| BCLC Stage | 0.29 | 0.13–0.64 | 0.002 | 1.97 | 1.19–5.36 | 0.204 |
| PVT | 2.01 | 1.06–3.81 | 0.032 | 1.61 | 0.70–3.69 | 0.262 |
| EHM | 2.79 | 1.45–5.36 | 0.002 | 2.53 | 1.19–5.36 | 0.015 |

**Abbreviations**: BCLC, Barcelona Clinic Liver Cancer; PVT, portal venous thrombosis; EHM, extrahepatic metastasis.

### Table 4 Safety Profile

| Any Adverse Event (n=62) | AEs ≥3 (n=62) |
|--------------------------|---------------|
| Any adverse event | 59 (95.2%) | 24 (38.7%) |
| HFS | 26 (41.9%) | – |
| Hypertension | 29 (46.8%) | 8 (12.9%) |
| Diarrhea | 21 (33.8%) | – |
| Belching | 7 (11.3%) | – |
| Constipation | 5 (8.1%) | – |
| Skin eruption | 3 (4.8%) | – |
| Myodynia | 1 (1.6%) | – |
| Fatigue | 27 (43.5%) | – |
| Headache | 4 (6.5%) | – |
| Hoarse | 2 (3.2%) | – |
| Bleeding | 12 (19.4%) | 2 (3.2%) |
| Sinus tachycardia | 1 (1.6%) | – |
| Leucopenia | 31 (50.0%) | 4 (6.5%) |
| Thrombocytopenia | 32 (51.6%) | 1 (1.6%) |
| Neutropenia | 29 (46.8%) | 5 (7.9%) |
| Lymphocytopenia | 19 (30.6%) | 3 (4.8%) |
| Cr elevation | 4 (6.5%) | – |
| UA elevation | 10 (16.1%) | – |
| ALT elevation | 9 (14.5%) | – |
| AST elevation | 14 (22.6%) | 2 (3.2%) |
| GGT elevation | 13 (21.0%) | 2 (3.2%) |
| ALP elevation | 10 (16.1%) | – |
| TBIL elevation | 23 (37.1%) | 6 (9.7%) |
| Proteinuria | 10 (16.1%) | – |

**Abbreviations**: HFS, hand–foot syndrome; Cr, creatinine; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; TBIL, total bilirubin.
Among the Child–Pugh class C patients, three had a Child–Pugh score ≥8 before medication (Table 5). ALBI scores before anlotinib monotherapy and at the end of treatment/last follow-up were −2.38 and −2.16, respectively, which was not significantly different (P=0.056).

AEs occurred in all 11 patients who changed their treatment regimen to TKIs and PD-1 inhibitors after disease progression, and three patients (27.3%) developed grade ≥3 AEs.

Discussion

Anlotinib is a multi-target tyrosine kinase inhibitor with antitumor effects in a variety of solid tumors. Anlotinib has shown good efficacy and tolerability as a first- and second-line treatment of advanced liver cancer, and the incidence of treatment-related AEs appears to be lower for anlotinib than for lenvatinib and regorafenib. In first-line treatment with anlotinib combined with penpulimab in patients with advanced unresectable HCC in China, the ORR was 31.0%, the DCR was 82.8%, and the PFS was 8.8 months, demonstrating efficacy and good safety. The purpose of this study was to investigate the efficacy and safety of anlotinib as a first-line treatment for aHCC in a real-world setting, as well as the efficacy of subsequent treatment after disease progression, to optimize anlotinib-based treatment regimens for aHCC.

Most Phase III clinical studies of TKIs strictly limit the baseline conditions of enrolled patients, such as Child–Pugh class A or Child–Pugh score ≤7, platelet count ≥75×10^9/L, Hb ≥85 g/L, bilirubin ≤51.3μmol /L, <50% liver occupation, and without PVT. However, in the real world, some patients with HCC have PVT, thrombocytopenia, leukopenia, and insufficient functional liver reserve. Effective treatment measures are limited; therefore, TKIs are also being tested in clinical practice in these patients. In this study, the inclusion and exclusion criteria were relatively loose, and the baseline status of the patients was very complicated. Of the patients, 29.0% had tumor occupation >50%, 43.5% had PVT, 29.5% had platelet count ≤75×10^9/L, and 13.1% had a decreased white blood cell count; 22.6% of patients had a Child–Pugh score of 8–9; and 50% of patients with platelet count/spleen thickness (PC/SD) ≤1.95 may have had moderate-to-severe esophageal and gastric varices. The baseline condition of our enrolled patients was relatively poor, and the study results objectively reflect the real-world effects of drug treatment.

Our study found that the mPFS of patients receiving first-line anlotinib monotherapy for aHCC was 7.37 months (95% CI: 5.88–8.86), showing a good therapeutic effect. In the first-line treatment of aHCC, the mTTP of sorafenib was 2.8 months (2.63–3.58) and 5.5 months; the mPFS of atezolizumab combined with bevacizumab was 6.8 months, compared with 5.7 months in Chinese patients; lenvatinib’s mPFS reached 7.4 months in the REFLECT study and 5.6 months in another study (95% CI 4.3–6.8). Our data suggest that anlotinib is superior to sorafenib for treating aHCC and has comparable mPFS to that previously reported for lenvatinib. Our study found that the CR, ORR, and DCR reached 19.4%, 46.8%, and 87.1%, respectively, in patients with aHCC treated with anlotinib as first-line treatment, which is similar to that reported previously. The ORR and DCR for sorafenib were 9.2% and 60.5% and for lenvatinib were 24.1% and 75.5%, respectively. Anlotinib is better than sorafenib as a first-line treatment of patients with aHCC and is not worse than lenvatinib. The reason for the better efficacy found in this study may be that only 12.9% of patients had a dose reduction, and long-term full-dose therapy was very helpful in achieving disease control in these patients. Another reason may be that better management and nursing of patients’ hepatitis and cirrhosis allow patients to have sufficient physical condition to receive systemic treatment earlier, which is beneficial for maintaining the Child–Pugh score. Stabilization or reduction of the Child–Pugh score can prolong mPFS, mOS, and post-treatment survival. Third, 51.6% of the patients received local treatment within 1 month of anlotinib treatment. Anlotinib blocks VEGFR at an extremely low half-maximal inhibitory concentration (IC50), which provides efficacy similar to that of

| Table 5 Changes in Liver Function at the Beginning and End of Anlotinib Monotherapy |
|---------------------------------|---------------------------------|-----------------|
|                                | Before Treatment (n=62)         | End of Anlotinib Monotherapy (n=62) | P value |
| Child-Pugh class (A/B/C)       | 45/17/0                         | 35/20/7          | 0.030   |
| ALBI Score                     | −2.38                           | −2.16            | 0.004   |
other VEGFR2 inhibitors at low doses.\textsuperscript{24,37} Among the factors involved in tumor angiogenesis, VEGFR2 is most closely associated with this process. Anlotinib has wide inhibitory effects and highly inhibits VEGFR2 specifically.\textsuperscript{24} Anlotinib can improve tumor immune microenvironment to inhibit tumor growth.\textsuperscript{30} This is the basis of Anlotinib’s remarkable performance.

AFP is a biomarker for predicting tumor volume reduction in patients with HCC; changes in AFP levels can help clinicians understand the efficacy of treatment,\textsuperscript{34,38} with high AFP predictive of poorer OS.\textsuperscript{39} We found a median AFP change rate of $-26.0\% \text{(}-97.0\% \text{to} +135.0\%)$ after 1 month of anlotinib monotherapy, with AFP levels declining from baseline in 72.7\% of patients. In one study of sorafenib, the AFP decreased from baseline in 71.0\% of patients within 4 weeks of starting treatment;\textsuperscript{40} the AFP decreased in 80.0\% (12/15) treated with lenvatinib.\textsuperscript{41} Therefore, anlotinib monotherapy has a fast response rate, no slower than that of sorafenib and lenvatinib. Therefore, early combination therapy is not recommended. By the time of cutoff, 47 patients (75.8\%) were still using anlotinib and 37 patients (59.7\%) were still using anlotinib alone. It can be seen that anlotinib monotherapy can control disease well, and the AEs of anlotinib can be tolerated.

The CR was 21.4\%, ORR was 36.4\%, and DCR was 63.6\% in 11 patients who changed the treatment regimen to TKIs combined with PD-1 inhibitors after disease progression. Ak105-203 showed that the ORR and DCR of anlotinib combined with pembrolizumab as a first-line treatment for patients with aHCC were 31.0\% and 82.8\%, respectively.\textsuperscript{29} IMbrave150 showed that the ORR and DCR of atezolizumab combined with bevacizumab as a first-line treatment for patients with aHCC were 27.3\% (95\% CI: 22.5–32.5) and 73.6\%, respectively.\textsuperscript{15} The ORR and DCR of combination therapy in Chinese patients were 24.6\% (95\% CI, 17.5–32.9\%) and 70.0\% in extended trials.\textsuperscript{33} The ORR of lenvatinib combined with CS1003 in patients with unresectable aHCC was 37.5\%\textsuperscript{42} and that in combination with pembrolizumab was 46.0\%.\textsuperscript{43} These results indicate that changing the treatment regimen to TKIs combined with PD-1 inhibitors can achieve better therapeutic effects after anlotinib monotherapy.

Several studies have examined the safety of anlotinib.\textsuperscript{44–46} The common AEs in this study had similar results to those of previous studies on anlotinib, but compared with previous studies, one patient died due to gastrointestinal bleeding in this study. The PC/SD value of 31 cases in the study was ≤1.95, and the PC/SD value of this patient was 1.95, which may indicate moderate or severe esophageal fundus static varices.\textsuperscript{47} Therefore, it cannot be concluded that the bleeding-related death in the patient was completely caused by the side effects of anlotinib; however, it also suggests that we must pay attention to bleeding risk factors in patients when using TKIs. In the IMbrave150 study, the proportion of sorafenib patients, the incidence of grade ≥3 AEs was 55.1\%, drug withdrawal rate was 10.3\%, dose adjustment or drug interruption was 60.9\%. The incidence of diarrhea was 49.4\% in patients when using TKIs. In the IMbrave150 study, the proportion of sorafenib patients, the incidence of grade ≥3 AEs was 38.7\% (24/62), with 4 patients (6.5\%) discontinuing treatment and 8 (12.9\%) reducing the dose because of AEs. The incidence of diarrhea during anlotinib treatment was 33.8\%, with no grade ≥3 diarrhea. The incidence of grade ≥3 AEs and diarrhea in patients treated with anlotinib is lower than that in patients treated with oral targeted drugs; therefore, patients can take long-term, full doses of anlotinib, which is one reason for the excellent efficacy of anlotinib in patients with advanced HCC.

In conclusion, anlotinib monotherapy has a rapid onset and lasting efficacy, and changing the treatment regimen to TKIs combined with PD-1 inhibitors can also achieve good therapeutic effects after disease progression with anlotinib monotherapy. The treatment of HCC is a long-term process, and the body will face more and larger side effects during the initial combination therapy, which is difficult for patients to tolerate and thus cannot be used for a long time. Moreover, the financial burden on patients is heavy, so we suggest that anlotinib monotherapy should be preferred, and PD-1 inhibitor treatment should be combined after disease progression.

This study has some limitations. First, this was a retrospective study and potential confounding factors could have influenced the results. Second, after progression with anlotinib monotherapy, the sample size of patients treated with TKIs combined with PD-1 blockade therapy was small, and our results require further validation with a larger sample size. Third, most patients were alive at the end of the follow-up, and continued follow-up was required.
**Conclusion**

In the real world, anlotinib has shown favorable efficacy and acceptable toxicity as a first-line monotherapy for aHCC. When combined with PD-1 blockade as a second-line treatment, it also exhibits preliminary efficacy and safety. However, more data are required to confirm these observations.

**Acknowledgments**

We would like to thank the First Affiliated Hospital of Zhengzhou University for their support. We would like to thank Editage for English language editing.

**Funding**

This work was supported by the Beijing Bethune Charity Foundation.

**Disclosure**

The authors declare that they have no competing interests.

**References**

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(7):209–249. doi:10.3322/caac.21660

2. Akinremi-Jumi T, Aberra S, Ahmed M. Global Burden of Disease Liver Cancer Collaboration. et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease Study 2015. *JAMA Oncol*. 2017;3:1683–1691. doi:10.1001/jamaoncol.2017.3055

3. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBCAN sources and methods. *Int J Cancer*. 2019;144:1941–1953. doi:10.1002/ijc.31937

4. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2019;394:1145–1158. doi:10.1016/S0140-6736(19)30427-1

5. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66:115–132. doi:10.3322/caac.21338

6. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: new trends. *J Hepatol*. 2020;72:250–261. doi:10.1016/j.jhep.2019.08.025

7. Harper J, Moses MA. Molecular regulation of tumor angiogenesis: mechanisms and therapeutic implications. *EXS*. 2006;96:223–268.

8. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA Cancer J Clin*. 2018;68:394–424. doi:10.3322/caac.21492

9. Folkman J. Seminars in medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. *N Engl J Med*. 1995;333:1757–1763. doi:10.1056/NEJM199512283332608

10. Boehm T, Folkman J, Browder T, et al. Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance. *Nature*. 1997;390:404–407. doi:10.1038/37126

11. Al-Husein B, Abdalla M, Trepte M, et al. Antiangiogenic therapy for cancer: an update. *Pharmacotherapy*. 2012;32:1095–1111. doi:10.1002/ phar.1147

12. Kerbel RS. A decade of experience in developing preclinical models of advanced- or early-stage spontaneous metastasis to study antiangiogenic drugs, metronomic chemotherapy, and the tumor microenvironment. *Cancer J*. 2015;21:274–283. doi:10.1097/PPO.0000000000000134

13. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10:25–34. doi:10.1016/S1470-2045(08)70285-7

14. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378–390. doi:10.1056/NEJMoa0708857

15. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2019;380:1150–1161. doi:10.1056/NEJMoa1815454

16. Bruix J, Qin S, Merle P, et al. Regorafenib as second-line therapy in Chinese patients with advanced hepatocellular carcinoma: a randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet*. 2017;389:387–398. doi:10.1016/S0140-6736(16)32453-9

17. Li Q, Qin S, Gu S, et al. Apatinib as second-line therapy in Chinese patients with advanced hepatocellular carcinoma: a randomized, placebo-controlled, double-blind, phase III study. *J Clin Oncol*. 2020;38(15_suppl):4507. doi:10.1200/JCO.2020.38.15_suppl.4507

18. Finn RS, Ryoo BY, Merle P, et al. Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). *J Clin Oncol*. 2019;37(15_suppl):4004. doi:10.1200/JCO.2019.37.15_suppl.4004

19. Qin S, Ren Z, Meng Z, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, Phase 2 trial. *Lancet Oncol*. 2020;21:571–580. doi:10.1016/S1470-2045(20)30011-5

20. Zhang Y, Fan W, Wang Y, et al. Apatinib for patients with sorafenib-refractory advanced hepatitis B virus related hepatocellular carcinoma: results of a pilot study. *Cancer Control*. 2019;26:1073274819872216. doi:10.1177/1073274819872216

21. Lin B, Song X, Yang D, et al. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFRβ and FGFR1. *Gene*. 2018;654:77–86. doi:10.1016/j.gene.2018.02.026

22. Shen G, Zhang F, Ren D, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol*. 2018;11:120. doi:10.1186/s13045-018-0664-7
23. Gao Y, Liu P, Shi R. Anlotinib as a molecular targeted therapy for tumors. Oncol Lett. 2020;20:1001–1014. doi:10.3892/ol.2020.11685

24. Xie C, Wan X, Quan H, et al. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. Cancer Sci. 2018;109:1207–1219. doi:10.1111/cas.13536

25. Granitto A, Forgione A, Marinielli S, et al. Experience with regorafenib in the treatment of hepatocellular carcinoma. Therap Adv Gastroenterol. 2021;14:17562842211016959. doi:10.1177/17562842211016959

26. Granitto A, Muratori L, Lalanne C, et al. Hepatocellular carcinoma in viral and autoimmune liver diseases: role of CD4+ CD25+ Foxp3+ regulatory T cells in the immune microenvironment. World J Gastroenterol. 2021;27(22):2994–3009. doi:10.3748/wjg.v27.i22.2994

27. Liu S, Qin T, Liu Z, et al. Anlotinib alters tumor immune microenvironment by downregulating PD-L1 expression on vascular endothelial cells. Cell Death Dis. 2020;11(5):309. doi:10.1038/s41419-020-2511-3

28. Guo W, Chen S, Wu Z, et al. Efficacy and safety of transarterial chemoembolization combined with anlotinib for unresectable hepatocellular carcinoma: a retrospective study. Technol Cancer Res Treat. 2020;19:1533038209665587. doi:10.1177/1533038209665587

29. Han C, Ye S, Hu C, et al. Clinical activity and safety of Penpulimab (anti-PD-1) with anlotinib as first-line therapy for unresectable hepatocellular carcinoma: an open-label, multicenter, phase Ib/II trial (AK105-203). Front Oncol. 2021;11:684867. doi:10.3389/fonc.2021.684867

30. Sun Y, Zhou A, Zhang W, et al. Anlotinib in the treatment of advanced hepatocellular carcinoma: an open-label Phase II study (ALTER-0802 study). Hepatol Int. 2021;15:621–629. doi:10.1007/s12072-021-10171-0

31. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163–1173. doi:10.1016/S0140-6736(18)30207-1

32. Yamashita T, Kudo M, Ikeda K, et al. REFLECT-a phase 3 trial comparing efficacy and safety of lenvatinib to sorafenib for the treatment of unresectable hepatocellular carcinoma: an analysis of Japanese subset. J Gastroenterol. 2020;55:113–122. doi:10.1007/s00535-019-01642-1

33. Qin S, Ren Z, Feng YH, et al. Atezolizumab plus bevacizumab versus sorafenib in the Chinese subpopulation with unresectable hepatocellular carcinoma: phase 3 randomized, open-label IMbrave150 study. Liver Cancer. 2021;10:296–308. doi:10.1159/000513486

34. Wang DX, Yang X, Lin IZ, et al. Efficacy and safety of lenvatinib for patients with advanced hepatocellular carcinoma: a retrospective, real-world study conducted in China. World J Gastroenterol. 2020;26:4465–4478. doi:10.3748/wjg.v26.i30.4465

35. Sasaki R, Fukushima M, Haraguchi M, et al. Response to lenvatinib is associated with optimal RelativeDose intensity in hepatocellular carcinoma: experience in clinical settings. Cancers. 2018;11:1769.

36. Terashima T, Yamashita T, Takata N, et al. Comparative analysis of liver functional reserve during lenvatinib and sorafenib for advanced hepatocellular carcinoma. Hepatol Res. 2020;50:871–884. doi:10.1111/hepr.13105

37. Amino N, Ideyama Y, Yamano M, et al. YM-359445, an orally bioavailable vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor, has highly potent anti-tumor activity against established tumors. Clin Cancer Res. 2006;12:1630–1638. doi:10.1158/1078-0432.CCR-05-2028

38. Kuzuya T, Asahina Y, Tsuchiya K, et al. Early decrease in α-fetoprotein, but not des-γ-carboxy prothrombin, predicts sorafenib efficacy in patients with advanced hepatocellular carcinoma. Oncology. 2011;81:251–258. doi:10.1159/000334454

39. Bruix J, Cheng AL, Meinhardt G, et al. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. J Hepatol. 2017;67:999–1008. doi:10.1016/j.jhep.2017.06.026

40. Kawaoka T, Aikata H, Murakami E, et al. Evaluation of the mRECIST and α-fetoprotein ratio for stratification of the prognosis of advanced-hepatocellular-carcinoma patients treated with sorafenib. Oncology. 2012;83:192–200. doi:10.1159/000341347

41. Kodama K, Kawaoka T, Namba M, et al. Correlation between early tumor marker response and imaging response in patients with advanced hepatocellular carcinoma treated with lenvatinib. Oncology. 2019;97:75–81. doi:10.1159/000499715

42. Shen LYZ, Guo Y, WL JF, et al. A phase Ib study of the PD-1 antagonist CS1003 plus lenvatinib (LEN) in Chinese patients (pts) with the first-line (1L) unresectable hepatocellular carcinoma (uHCC). Ann Oncol. 2020;14(4):987.

43. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus Pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol. 2020;38:2960–2970. doi:10.1200/JCO.20.00808

44. Chi Y, Fang Z, Hong X, et al. Safety and efficacy of anlotinib, a multitargeted angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. Clin Cancer Res. 2018;24:5233–5238. doi:10.1158/1078-0432.CCR-17-3766

45. Cheng Y, Han B, Li K, et al. Effect of anlotinib as a third- or further-line therapy in advanced non-small cell lung cancer patients with different histologic types: subgroup analysis in the ALTER0303 trial. Cancer Med. 2020;9:2621–2630. doi:10.1002/cam4.2913

46. Zhou AP, Bai Y, Song Y, et al. Anlotinib versus sunitinib as first-line treatment for metastatic renal cell carcinoma: a randomized Phase II clinical trial. Oncologist. 2019;24:702–708. doi:10.1634/theoncologist.2018-0839

47. Feng S, Feng HF, Xu J, et al. Value of Fibro Scan and platelet count-to-spleen thickness ratio in predicting the degree of esophageal and gastric varices in liver cirrhosis. J Clin Hepatol. 2021;37:2819–2823.