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ORIGINAL RESEARCH

Impact of Type of Lenvatinib Resistance on Prognosis and Second-Line Regimen in Patients with Virus-Associated HCC

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Background: Lenvatinib is the first-line treatment option for patients with advanced hepatocellular carcinoma (HCC); however, the impact of lenvatinib resistance on patient prognosis is unknown.

Methods: We recruited all patients with advanced HCC who received first-line lenvatinib treatment between February 2019 and February 2023 at two medical centers in China, according to the selection criteria. The patients were divided into primary and secondary resistance groups based on tumor progression within 3 months. The Kaplan-Meier method was used to calculate progression-free survival (PFS) and overall survival (OS). Logistic regression and Cox proportional hazards models were used to explore factors influencing drug resistance and prognosis. The study end points were drug resistance, PFS, and OS.

Results: A total of 531 patients met the study criteria, with 169 (31.8%) and 362 (68.2%) patients in the primary and secondary groups, respectively. An alpha-fetoprotein (AFP) concentration > 400 ng/mL was an independent risk factor for primary drug resistance. Patients in the primary group had a significantly shorter median OS (11.0 vs 31.0 months, P<0.001) than those in the secondary group. The 1-, 2- and 3-year cumulative survival rates in the primary group were 46.3%, 22.2%, and 10.1%, while those in the secondary group were 82.3%, 59.1% and 44.9%, respectively. Compared to tyrosine kinase inhibitor (TKI) monotherapy, longer median PFS (4.0 vs 7.0 months, P=0.008) and OS (11.0 vs 23.0 months, P=0.024) were achieved with the combination of a TKI plus a PD-1 inhibitor as a second-line therapy after lenvatinib resistance.

Conclusion: There is a high rate of primary resistance to lenvatinib in patients with HCC and the prognosis for those with primary resistance is poor. TKI combined with PD-1 inhibitors should be preferentially recommended for lenvatinib-resistant patients.

Keywords: hepatocellular carcinoma, resistance, lenvatinib, programmed cell death protein-1 inhibitor, tyrosine kinase inhibitor, second-line

Introduction

Hepatocellular carcinoma (HCC), the most common pathological type of primary liver cancer, is a major public health problem, with an incidence of one million new cases per year globally.[1] Surgery is the optimal treatment strategy, with a 5-year survival rate of 50–70% in patients with early-stage HCC.[2] Because of the insidious onset of HCC, 70–80% of patients are initially diagnosed at intermediate to advanced stages, and can only receive nonsurgical treatment, making systemic therapy the cornerstone of treatment for these patients.[2,3] In addition, promising treatment options such as herbal therapies are being developed.[4] Viral hepatitis is the predominant etiological factor in patients with HCC. It has been reported that more than 70% of Chinese patients with HCC have a background of hepatitis virus infection.[5]

The recent development of several tyrosine kinase inhibitors (TKIs) and programmed cell death protein-1 (PD-1) inhibitors has dramatically improved the prognosis of patients with advanced HCC. There are three globally recognized

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first-line treatment options for HCC: sorafenib, lenvatinib, and atezolizumab plus bevacizumab (A + T).[6] Sorafenib, the most representative TKI for patients with HCC, has been the only treatment option for patients with progressive HCC for 10 years, since it was recommended as a first-line treatment option for HCC patients in 2007.[7] However, it prolongs survival by only 2.8 months compared with a placebo.[7] In 2018, lenvatinib was approved for use in advanced HCC after the results of a REFLECT-based study showed that lenvatinib was non-inferior to sorafenib in terms of efficacy.[8] In 2020, A + T revolutionized the treatment landscape of HCC and was approved as a first-line combination therapy by the Food and Drug Administration (FDA).[9] Despite the impressive success of these therapies, the median progression-free survival (PFS) is less than 8 months, indicating that more than half of the patients will develop resistance beyond this period.

Drug resistance is the biggest obstacle to prolonging patient survival. Resistance mechanisms are complex, and in the case of lenvatinib, there is not only resistance related to the targets (fibroblast growth factor receptors 1–4 [FGFR1–4] and vascular endothelial growth factor receptors 1–3 [VEGFR1–3]) of lenvatinib therapy, but also resistance related to epithelial-mesenchymal transition, autophagy, and ferroptosis.[10] Despite the discovery of more than 10 different mechanisms of lenvatinib resistance, clinical translation has not yet been achieved. Resistance is often categorized as primary or secondary.[11] Primary resistance is inherent in patients, whereas secondary resistance develops after prolonged drug therapy. Theoretically, the impact of the two types of resistance on patient prognosis is substantial. However, this hypothesis needs to be urgently elucidated.

The emergence of resistance is an indication that the drug has lost its efficacy; therefore, clarifying the optimal second-line regimen is critical for prolonging survival. However, no studies of second-line regimens after lenvatinib failure have been reported. The second-line treatment regimens recommended by various guidelines are based on a study of sorafenib.[6] To prolong the survival of HCC patients the clarification of the 2nd line treatment regimen after the occurrence of resistance to lenvatinib is extremely urgent. Therefore, this study was conducted to investigate the factors influencing lenvatinib resistance, the impact of lenvatinib on survival, and the optimal second-line treatment regimen.

Materials and Methods

Study Design and Participants

This retrospective study was conducted at the Affiliated Hospital of Guizhou Medical University and the Fifth Medical Center of the General Hospital of the People's Liberation Army in China. We screened all patients with HCC treated with first-line lenvatinib between February 2019 and February 2023 at both medical centers. The inclusion criteria were as follows: (1) definitive diagnosis of HCC visualized by imaging, (2) Child-Pugh class A/B, (3) at least one measurable tumor lesion, and (4) at least one imaging evaluation performed within 3 months from the start of lenvatinib therapy. The exclusion criteria were as follows: (1) other tumors; (2) immune monotherapy; (3) non-adherence to lenvatinib; (4) death within 1 month; (5) non-hepatitis B virus (HBV)/hepatitis C virus (HCV) infection; (6) intolerance; or (7) missing follow-up data. This retrospective study was approved by the ethics committees of both medical centers and complied with the 1975 revision of the Declaration of Helsinki. All patients received systemic therapy at standardized doses according to harmonized instructions. Those who met the study criteria were divided into primary resistance (primary group) or secondary resistance (secondary group) groups. The baseline characteristics of the participants were collected at two time points: initiation of lenvatinib and initiation of second-line treatment after lenvatinib treatment failure.

Related Definitions and Study Endpoints

Resistance was the primary endpoint of this study. Primary resistance was defined as tumor progression within 3 months of lenvatinib initiation. Secondary resistance was defined as tumor progression that occurred more than 3 months after lenvatinib initiation. Secondary endpoints were overall survival (OS) and PFS. OS was defined as the time interval from treatment initiation to death from any cause or the end of the study, whichever occurred first. PFS was defined as the time from the initial dose to the first radiologically confirmed tumor progression or death from any cause. Radiological responses were recorded using dynamic computed tomography (CT) or magnetic resonance imaging (MRI) at baseline and every 8–12 weeks after treatment initiation.

Statistical Analysis

Categorical data are expressed as frequencies with proportions and were analyzed using the chi-square test. The Kaplan-Meier method was used to calculate PFS and OS and to plot the curves. The Log rank test was used to compare the cumulative survival rates of the two groups and a risk curve was drawn. Logistic regression and Cox proportional hazards models were used to explore factors influencing drug resistance and prognosis. Variables with $P \leq 0.05$ in univariate analysis were subjected to stepwise multivariate analysis. A two-tailed P-value ≤ 0.05 represented statistical significance. Statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA), and Kaplan-Meier survival curves were obtained using the XIANTAO platform (https://www.xiantaozi.com).

Results

Patient Characteristics

Between February 2019 and February 2023, a total of 634 patients with advanced HCC treated with first-line lenvatinib at both centers were screened. Of these, 103 patients were excluded, mainly including coexistence of other primary tumors in 7 cases, immune monotherapy in 9 cases, failure to take medication as prescribed in 10 cases, death within one month of receiving treatment in 12 cases, absence of HBV or HCV infection in 14 cases, lenvatinib intolerance in 23 cases, and lack of follow-up data in 28 cases (Figure 1).

Follow-up was stopped in February 2024 and the median follow-up time was 23 (95% CI: 21–29) months.531 patients met the study criteria, including 169(31.8%) in the primary group and 362(68.2%) in the secondary group. Of

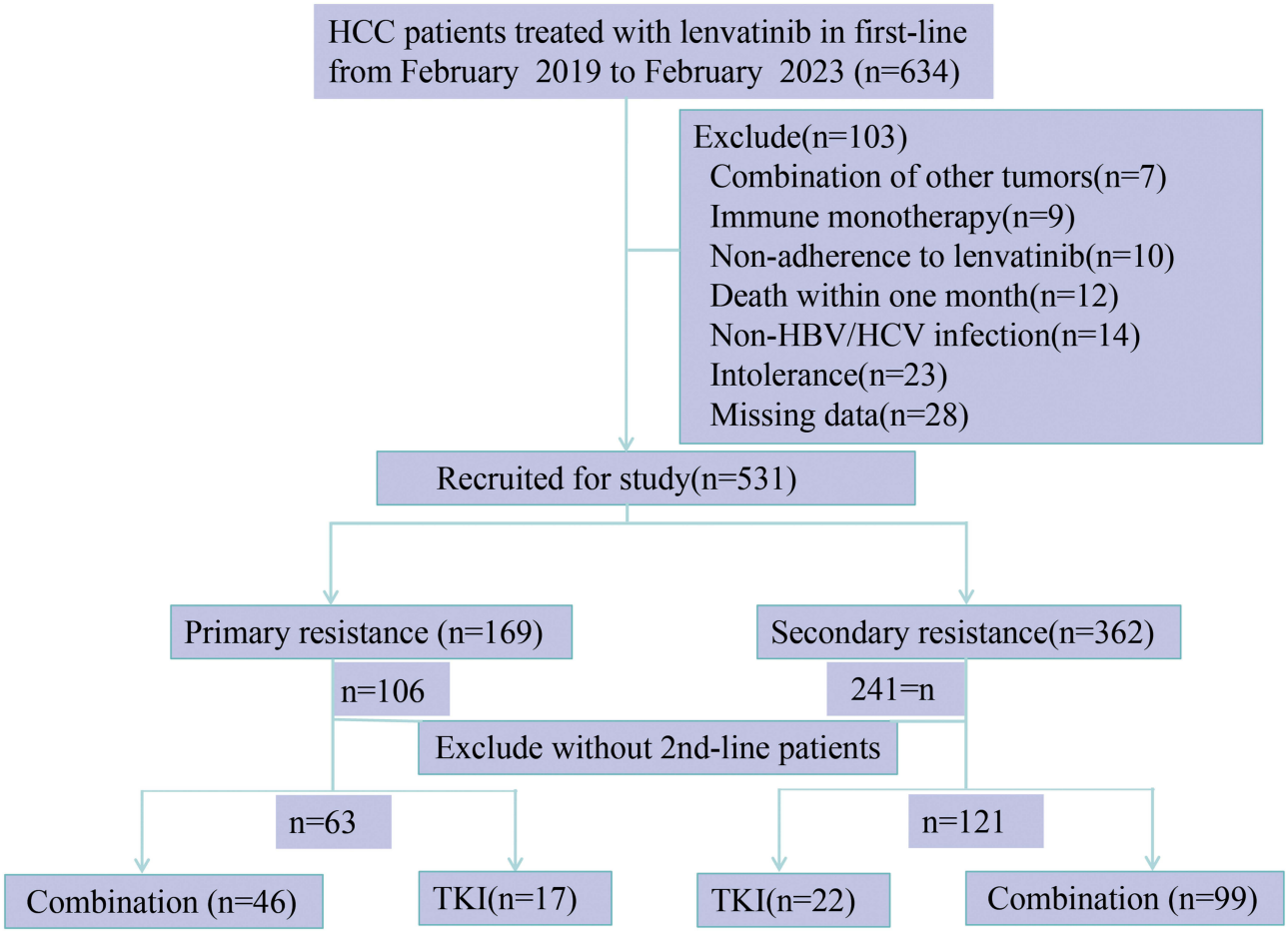

Figure 1 Patients flow chart.

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; TKI, any tyrosine kinase inhibitor; Combination, PD-1 inhibitor combined with TKI.

these patients,77.4%(n=411) were male. There were 513(96.6%) patients with HBV infection and 18(3.4%) patients with HCV infection. There were 306(57.6%) patients with Barcelona Clinic Liver Cancer (BCLC) stage C, 276(52.0%) with extrahepatic metastasis, and 148(27.9%) with Child-Pugh class B (Table 1).

During the follow-up period, 184 patients received second-line treatment, including 63(34.2%) in the primary group and 121(65.8%) in the secondary group. In the primary group, 17 patients received TKI monotherapy, whereas 46 received TKI in combination with a PD-1 inhibitor. In the secondary group, 99 patients received combination therapy, while 22 received TKI monotherapy (Figure 1). A total of 39 patients were treated with 2nd-line TKIs, including the drugs sorafenib (n=18, 46.2%), regorafenib (n=14,35.9%), apatinib (n=4, 10.3%), and donafenib (n=18, 7.7%). The specific combination therapies (n=145) included lenvatinib plus sintilimab (n=66,45.5%), lenvatinib plus camrelizumab (n=29, 20.0%), lenvatinib plus tislelizumab (n=13, 9.0%), lenvatinib plus other PD-1 inhibitors (n=8, 5.5%), regorafenib plus a PD-1 inhibitor (n=12, 8.3%), and other combination therapy options (n=17, 11.7%).

Factors Associated with Resistance

The results of the analysis of risk factors associated with drug resistance were presented in Table 1 and Supplementary Table 1. We found that extrahepatic metastasis (HR: 1.97, 95% CI: 1.36–2.87, P<0.001), AFP>400ng/mL (HR: 2.00, 95% CI: 1.37–2.90, P<0.001), tumor size>5cm (HR: 1.46, 95% CI: 1.01–2.11, P=0.046), and BCLC, C stage (HR: 1.98, 95% CI: 1.35–2.91, P<0.001) were risk factors for primary resistance to lenvatinib by univariate analysis. Our multifactorial analysis showed that AFP>400ng/mL (HR: 1.76, 95% CI: 1.19–2.61, P=0.005) was the only independent risk factor for primary resistance.

Resistance and Prognosis

We divided all eligible patients into primary and secondary groups according to the type of resistance and then into subgroups according to the course of treatment, compared cumulative survival rates by Log rank test and plotted risk curves. When all patients were analyzed, the median PFS was 2.3 months in the primary group and 10.6 months in the secondary group (P<0.001) (Supplementary Figure 1); and the OS was 11 months in the primary group and 31 months in

Table 1 Baseline Characteristics of the Study Population and Primary Resistance to Lenvatinib: Univariate Analysis

	Primary Group (n=169)	Secondary Group (n=362)	HR (95% CI)	P value
Age>50, years, n (%)	128(75.7)	283(78.1)	0.87(0.57–1.34)	0.532
Male sex, n (%)	148(87.6)	305(84.3)	1.32(0.77–2.25)	0.315
Diabetes, n (%)	35(20.7)	53(14.6)	1.52(0.95–2.44)	0.081
Hypertension, n (%)	63(37.3)	119(32.9)	1.21(0.83–1.78)	0.319
Smoking, n (%)	75(44.4)	138(38.1)	1.30(0.89–1.88)	0.171
Drinking, n (%)	67(39.6)	124(34.3)	1.26(0.87–1.84)	0.228
HBV, n (%)	161(95.3)	352(97.2)	0.57(0.22–1.48)	0.248
Vascular invasion, n (%)	52(30.8)	106(29.3)	1.07(0.72–1.60)	0.727
Extrahepatic metastasis, n (%)	107(63.3)	169(46.7)	1.97(1.36–2.87)	<0.001
Portal hypertension, n (%)	76(45.0)	180(49.7)	0.83(0.57–1.19)	0.307
Splenomegaly, n (%)	125(74.0)	243(67.1)	1.39(0.93–2.09)	0.112
Cirrhosis, n (%)	130(76.9)	287(79.3)	0.87(0.56–1.35)	0.538
AFP>400ng/mL, n (%)	78(46.2)	109(30.1)	2.00(1.37–2.90)	<0.001
ALT>40U/L, n (%)	52(30.8)	113(31.2)	0.98(0.66–1.45)	0.918
AST>40U/L, n (%)	84(49.7)	167(46.1)	0.87(0.60–1.25)	0.443
Tumor size>5cm, n (%)	77(45.6)	132(36.4)	1.46(1.01–2.11)	0.046
Child, B stage, n (%)	48(28.4)	100(27.6)	1.04(0.69–1.56)	0.852
BCLC, C stage, n (%)	116(68.6)	190(52.5)	1.98(1.35–2.91)	<0.001

Abbreviations: HBV, hepatitis B virus; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Tumor size, maximum tumor diameter; BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio.

the secondary group (P<0.001) (Figure 2a). The 1-, 2-, and 3-year cumulative survival rates in the primary group were 46.3%, 22.2%, and 10.1%, respectively, whereas those in the secondary group were 82.3%, 59.1%, and 44.9%, respectively (Figure 2a). The median OS in the primary group was also significantly shorter than that in the secondary group (14.0 vs 36.0 months, P<0.001) in all patients receiving second-line treatment (n=184) if the survival time was calculated for from the initiation of lenvatinib treatment (Figure 2b). When the survival time was calculated from the initiation of second-line therapy, the median PFS (5.0 vs 8.0 months, P=0.001) and median OS (12.0 vs 25.0 months, P<0.001) were both shorter in the primary group than in the secondary group (Figure 2c and d).

The above results showed that patients with primary resistance had a worse prognosis than those with secondary resistance. To exclude the effect of the treatment regimen, we further performed subgroup analyses based on different second-line treatment regimens. In all patients who received TKI monotherapy, median PFS (3.0 vs 8.0 months, P=0.035) and median OS (7.0 vs 19.0 months, P=0.004) were significantly shorter in the primary group than in the

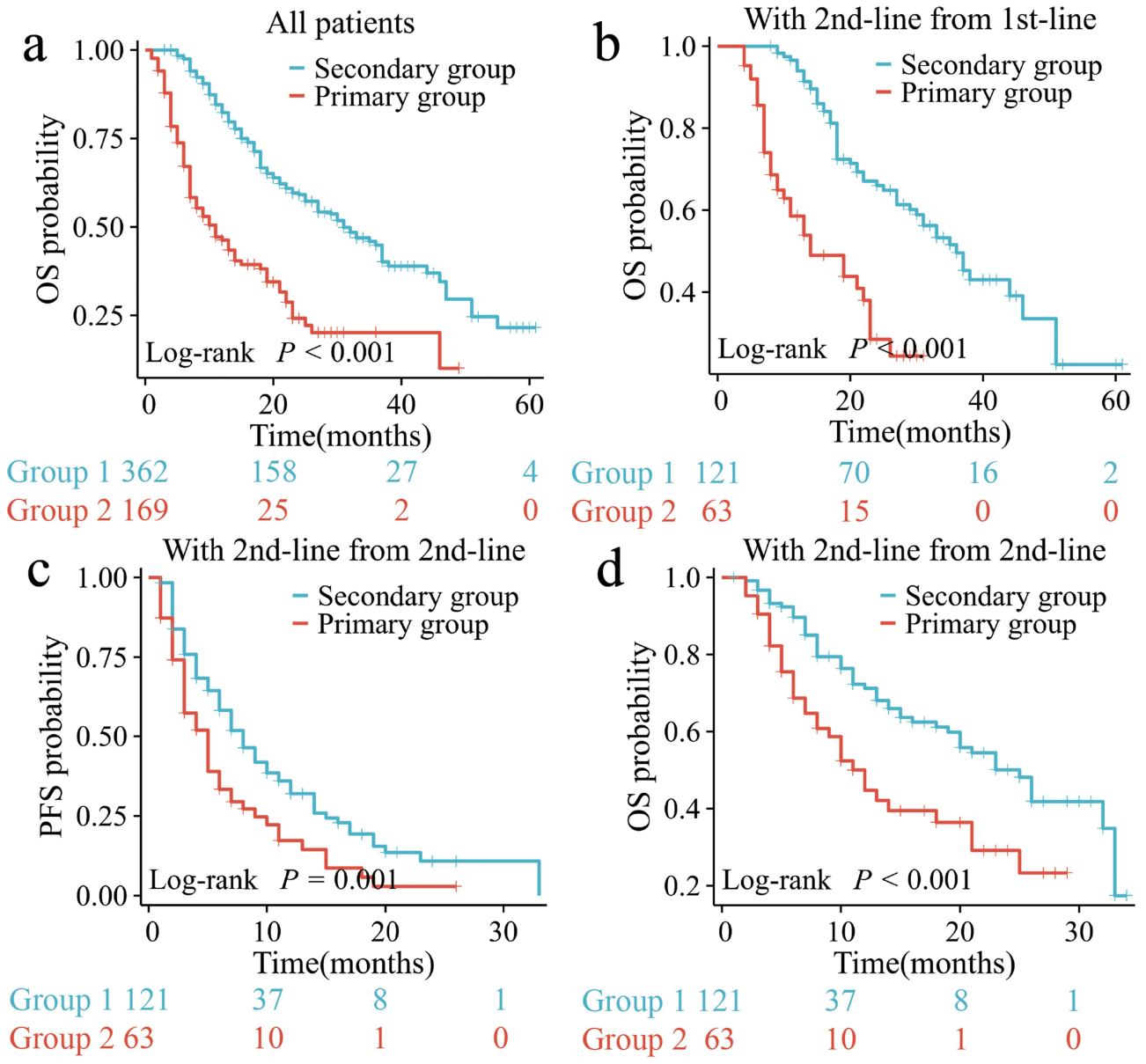

Figure 2 The K-M survival curve is used to calculate the overall survival (OS) of all patients (**a**), the OS of patients receiving second-line treatment with survival time calculated from the start of lenvatinib treatment (**b**), and the progression-free survival (PFS) (**c**) and OS (**d**) of patients receiving second-line treatment with survival time calculated from the start of second-line treatment.

secondary group (Figure 3a and d). In all combination-treated patients, those on the TKI plus PD-1 inhibitors (PFS:6.0 vs 8.0 months, P=0.011; OS:14.0 vs 25.0 months, P=0.039) regimen or the lenvatinib plus sintilimab (PFS:5.0 vs 15.0 months, P=0.001; OS:10.0 vs 32.0 months, P=0.003) regimen showed a poorer prognosis in the primary group than in the secondary group (Figure 3).

Additionally, we performed univariate and multivariate analyses of PFS and OS in patients receiving second-line therapy. Univariate analysis revealed that primary resistance, TKI treatment, extrahepatic metastasis and BCLC, C stage were associated with shorter PFS and OS. The results of this multifactorial analysis showed that PFS was shorter in patients with primary resistance (HR 1.64, 95% CI 1.15–2.34, P=0.007), undergoing TKI monotherapy (HR 1.61, 95% CI 1.08–2.39, P=0.019) and OS was shorter in those with primary group (HR 1.93, 95% CI 1.25–2.99, P=0.003), undergoing TKI monotherapy (HR 1.84, 95% CI 1.13–2.98, P=0.014) (Table 2).

Second-Line Therapy and Prognosis

Among all patients receiving second-line treatment (n=184), the combination group had a significantly longer median PFS (4.0 vs 7.0 months, P=0.008) and OS (11.0 vs 23.0 months, P=0.024) than the TKI group (Figure 4a and b). This is consistent with the results of the multi-factor analysis presented inTable 2. Our results also showed no significant difference in baseline characteristics between the two groups of patients (Supplementary Table 2), further confirming the conclusion that second-line combination therapy was superior to monotherapy.

To explore the best of the 2-line combination regimens, we divided the combination regimens into subgroups for analysis. Unfortunately, we did not find the best combination regimen in the following subgroup analyses, including lenvatinib + PD-1 inhibitors versus other TKIs plus PD-1 inhibitors (P=0.164), lenvatinib plus sintilimab versus other

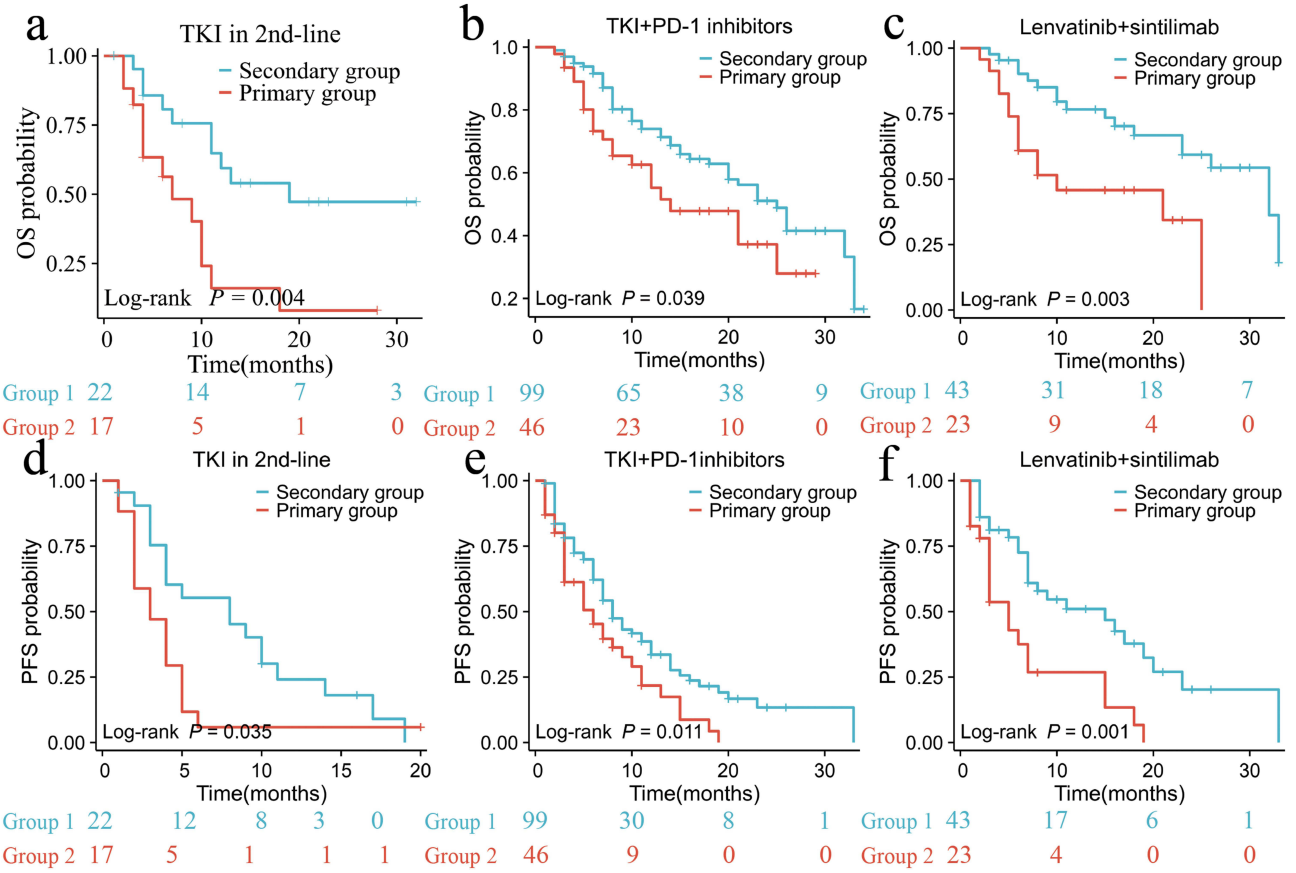

Figure 3 K-M survival curves were used to analyze overall survival (OS) and progression-free survival (PFS) after receiving different 2-line treatment regimens, including TKI monotherapy (**a** and **d**), TKI plus PD-1inhibitors (**b** and **e**), and lenvatinib plus sintilimab (**c** and **f**).

Table 2 Analysis of Prognostic Risk Factors in Patients with 2nd-Line Treatment

	Progression-free Survival		Overall Survival	
Univariate analysis	HR (95% CI)	P value	HR (95% CI)	P value
Primary resistant	1.77(1.24–2.52)	0.002	2.02(1.32–3.11)	0.001
TKI	1.52(1.03–2.25)	0.035	1.70(1.06–2.73)	0.029
Age>50, years	0.83(0.55–1.26)	0.377	0.80(0.49–1.30)	0.368
Male sex	1.29(0.77–2.15)	0.331	0.98(0.52–1.84)	0.941
Diabetes	0.98(0.60–1.60)	0.943	1.09(0.61–1.97)	0.770
Hypertension	1.08(0.76–1.53)	0.662	0.74(0.48–1.15)	0.179
Smoking	1.04(0.74–1.48)	0.811	1.43(0.95–2.16)	0.089
Drinking	1.15(0.81–1.62)	0.445	1.44(0.95–2.18)	0.086
HBV	1.45(0.59–3.56)	0.412	0.66(0.28–1.52)	0.324
Vascular invasion	1.01(0.65–1.57)	0.974	0.82(0.46–1.45)	0.488
Extrahepatic metastasis	1.76(1.25–2.49)	0.001	1.72(1.14–2.61)	0.010
Portal hypertension	1.33(0.94–1.88)	0.110	1.25(0.83–1.90)	0.291
Cirrhosis	1.48(0.96–2.27)	0.075	1.15(0.68–1.93)	0.605
AFP>400ng/mL	0.90(0.62–1.29)	0.561	1.22(0.79–1.89)	0.371
ALT>40U/L	1.33(0.92–1.91)	0.132	1.03(0.65–1.63)	0.903
Tumor size>5cm	1.31(0.92–1.87)	0.133	1.10(0.72–1.69)	0.664
Child, B stage	1.45(0.95–2.21)	0.084	1.40(0.85–2.30)	0.182
BCLC, C stage	1.58(1.12–2.24)	0.010	1.57(1.03–2.38)	0.035
Multivariate analysis				
Primary resistant	**1.64(1.15–2.34)**	**0.007**	**1.93(1.25–2.99)**	**0.003**
TKI	**1.61(1.08–2.39)**	**0.019**	**1.84(1.13–2.98)**	**0.014**
Extrahepatic metastasis	**2.03(0.97–4.26)**	**0.060**	**2.26(0.95–5.40)**	**0.065**
BCLC, C stage	**0.84(0.40–1.77)**	**0.648**	**0.71(0.30–1.71)**	**0.450**

Abbreviations: TKI, tyrosine kinase inhibitor; HBV, hepatitis B virus; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; Tumor size, maximum tumor diameter; BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio; CI, confidence interval.

TKI plus PD-1 inhibitors (P=0.157), lenvatinib plus sintilimab versus lenvatinib plus other PD-1 inhibitors (P=0.635) and lenvatinib plus sintilimab versus lenvatinib plus camrelizumab (P=0.501) (Figure 4c–f).

Discussion

To the best of knowledge, this is the first multicenter real-world study to analyze the prognosis of patients with advanced HCC according to the type of lenvatinib resistance. Our findings suggest that primary resistance results in a significantly shorter PFS and OS than secondary resistance. We also found that AFP >400ng/mL was the only independent risk factor for primary drug resistance. After lenvatinib resistance, the prognosis was better for patients who continue to receive the combination of TKI plus PD-1 inhibitors than for those who receive compared to TKI monotherapy.

Lenvatinib, an oral tyrosine multitarget inhibitor, is one of the three first-line options for treating HCC globally (sorafenib, lenvatinib, and A + T). Several Phase III trials of A + T combination therapy have shown that sorafenib has lost its prime position as a first-line therapy.[9] However, the role of first-line lenvatinib treatment remains controversial due to the absence of head-to-head clinical trials.

The current first-line status of lenvatinib can be understood from several perspectives. First, from the of available perspective clinical trials, patients treated with lenvatinib had better PFS (7.4 vs 3.7 months; P<0.001) and objective response rate (ORR) (24.1% vs 9.2%; P<0.001) than those treated with sorafenib.[8] Transarterial chemoembolization (TACE) plus lenvatinib has better time-to-progression (TTP) (4.7 vs 3.1 months; P=0.029) and ORR (53.1% vs 25.0%, P=0.039) than TACE plus sorafenib.[12] Second, although no prospective studies have compared A+T with lenvatinib, data from retrospective studies have shown no statistically significant differences in OS or TTP between the two regimens.[13] Third, sorafenib is associated with a higher incidence of palmar-plantar erythrodysesthesia (63% vs 30%) and diarrhea (50% vs 43%) than lenvatinib.[8] The A+T regimen is associated with a higher rate of grade 3 or 4 adverse events than

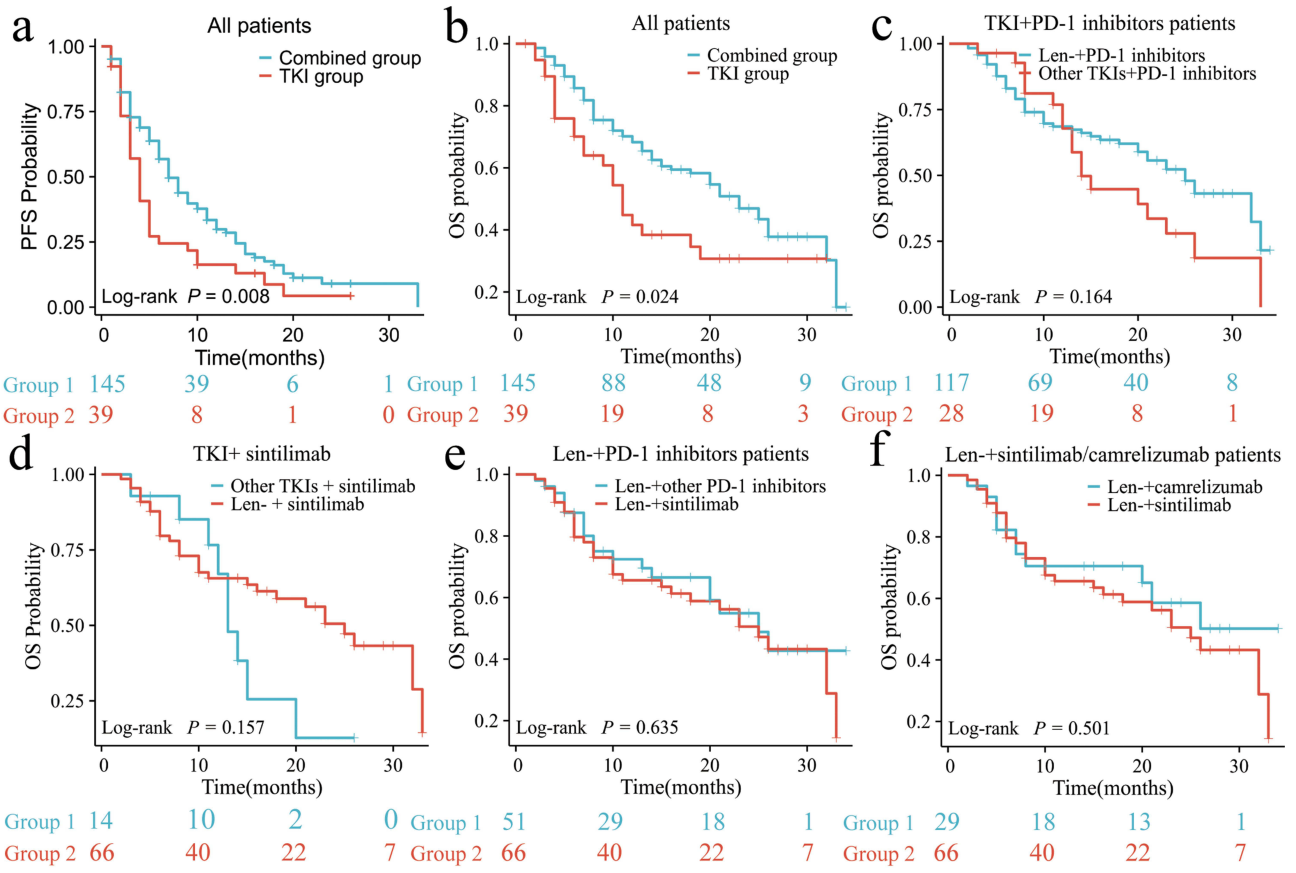

Figure 4 Progression-free survival (PFS) (**a**) and overall survival (OS) (**b**) were analyzed with K-M survival curves between the TKI group and the combination group, and comparisons of OS in 4 different subgroups (**c–f**).

lenvatinib (84.9% vs 69.8%; P=0.009).[13] In addition, the A+T regimen is not applicable to patients with a high risk of bleeding or autoimmune diseases. Fourth, a cost-effectiveness analysis showed that lenvatinib remained a cost-saving measure compared to sorafenib in 64.87% of the simulations.[14] Despite the lack of results from a cost-effectiveness analysis of lenvatinib versus the A+T regimen, a cost-effectiveness analysis of sorafenib versus the A+T regimen showed no benefit from the A+T regimen.[15] These results suggest that lenvatinib is more cost-effective than the A+T regimen. Fifth, when it comes to the etiology of HCC, A+T is not suitable for non-viral hepatitis virus-associated HCC,[16] and lenvatinib is associated with a longer OS than A+T in patients with non-alcoholic steatohepatitis/non-alcoholic fatty liver disease.[13] Furthermore, the efficacy of lenvatinib is not significantly different for all etiologies.[17] Sixth, there was better adherence to the oral administration of lenvatinib was better than adherence to the intravenous administration of the A+T regimen. Therefore, lenvatinib is a superior first-line treatment option for most patients.

Lenvatinib has great potential, mainly because of its long median PFS. The median PFS for lenvatinib was 7.4 months in the REFLECT trial and 8.1 months in the LEAP 002 trial.[8,18] These results exceed the 6.9 months for the A+T regimen in the IMbrave 150.[16] Lenvatinib has shown promising results, but still cannot escape the end of drug resistance. In the REFLECT trial, showed that the disease control rate for lenvatinib was only 72.8%, indicating that approximately 30% of the patients did not benefit from lenvatinib.[8] Consistent with our findings, 31.8% of the patients developed primary resistance. The median PFS after lenvatinib treatment was only 2.3 months. However, secondary resistance was associated with a median PFS of 10.6 months and a median OS of an astounding 31 months. These two drug-resistant types exemplify a major difference in survival, providing great value for survival prediction.

Lenvatinib has multiple therapeutic targets (FGFR1-4, VEGFR1-3, platelet-derived growth factor receptor α [PDGFR α], KIT-ligand [stem cell factor receptor], and RET [rearranged during transfection]). The abnormal expression of any of these targets may induce lenvatinib resistance. Additionally, high expression levels of c-mesenchymal-epithelial transition factor

(c-MET), fibronectin (FN), and frizzled-10 (FZD10) are closely associated with lenvatinib resistance. Resistance involves multiple pathways, including the FZD10/β-catenin/c-Jun/MEK/ERK,[19] ITGB8/HSP90/AKT,[20] NF1/Ras/MAPK axes,[21] etc. Although relevant resistance-target inhibitors may be effective against lenvatinib resistance, the complexity of the resistance network hinders clinical translation. Identifying the predictors associated with lenvatinib resistance can be extremely helpful in managing the antitumor processes. Our study found that AFP>400ng/mL was the only independent risk factor for primary resistance. Based on our results, the A + T regimen should be prioritized as the first-line treatment regimen for patients with AFP>400ng/mL. However, such a conclusion needs to be made with caution because we included few factors in the analysis and the number of cases was small.

Currently, clinicians determine drug resistance primarily through imaging assessments (tumor progression is defined as drug resistance). In clinical practice, the most common means of overcoming resistance is to change or add another antitumor regimen. Precise sequential therapy is the best method to prolong patient survival. There are five FDA-approved second-line treatment options for HCC, based on study results after sorafenib failure, including cabozantinib, regorafenib, pembrolizumab, ramucirumab (AFP ≥400 ng/mL), and ipilimumab + nivolumab.[22] The results of a study based on the A+T regimen showed that lenvatinib was the preferred regimen after A+T treatment.[23] In addition, a retrospective study showed no significant differences in prognosis between patients undergoing with sorafenib a immunotherapy regimens after lenvatinib treatment failure.[24] This is inconsistent with our findings that TKI+PD-1 inhibitors have longer PFS and OS in lenvatinib second line therapy compared to TKI. There may be two reasons for this. First, in the study by Mara et al 59.6% of the patients had virus-related HCC, compared with 100% in our study.[24] This is the main reason because immunotherapy is not beneficial for non-viral HCC.[25] Secondly, the immunotherapy mentioned in the study by Mara et al was a combination regimen (A+T) in 44.1% of patients, while the remaining patients may have received immune monotherapy. However, 100% of the patients in our study received a combination regimen. There is also evidence that immune monotherapy is significantly less effective than lenvatinib treatment plus immunotherapy.[26] Of course, we explored the best of the combination regimens. The results of the analysis comparing, lenvatinib + PD-1 inhibitors with those of other TKIs+ PD-1 inhibitors were not significantly different. This also indicates that the addition of a PD-1 inhibitor after lenvatinib treatment failure was an effective approach. This is expected, because even if an alternative TKI is used, there may be a risk of cross-resistance and patients may be less adherent to the new drug. No significant differences were also observed in the analysis comparing lenvatinib in combination with different PD-1 inhibitors.

This study has some limitations. First, this was a retrospective study, which may have resulted in information and selection biases. Second, we did not include patients with nonviral-associated HCC and therefore we could not perform an analysis of such patients. Third, because of the limited number of cases, second-line treatment regimens were analyzed primarily based on TKIs or TKIs combined with PD-1 inhibitors, and specific TKI regimens were not analyzed. Therefore, data from prospective studies are urgently needed to determine the factors associated with lenvatinib resistance and inform the selection of second-line treatment regimens.

Conclusions

The high rate of primary resistance to lenvatinib in patients with HCC has a serious impact on patient prognosis. AFP >400 ng/mL as the only independent risk factor for primary resistance to lenvatinib and should be recommended to guide the choice of the first-line treatment regimen. The combination of TKI + PD-1 inhibitors are an effective second-line treatment strategy and should be recommended when lenvatinib resistance occurs.

Statement of Ethics

This study was approved by Ethics Committee of the Fifth Center of Chinese PLA General Hospital (approval number: KY-2023-8-54-1) and Ethics Committee of the Affiliated Hospital of Guizhou Medical University (approval number: 2023-934). Since the study was a retrospective study, the Ethics Committee withdrew the requirement for informed consent of patients. All data in the article were obtained from the eHealth system, and we are committed to using these data only to support the conclusions of this article.

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Disclosure

All authors declare no conflicts of interest and consent to the publication of the article.

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