Original Article

Efficacy and safety of regorafenib as second-line treatment for patients with hepatocellular carcinoma and macrovascular invasion and(or) extrahepatic metastasis

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Background: Macrovascular invasion and(or) extrahepatic metastasis are the main clinical characteristics of Chinese patients with hepatocellular carcinoma (HCC) after entering the second-line treatment. The aim of this study was to explore the efficacy and safety of regorafenib as a second-line treatment for these patients with HCC.

Methods: We selected 253 patients with primary liver cancer who were treated in Henan Cancer Hospital from June 2017 to September 2020. According to the inclusion and exclusion criteria, 63 patients with HCC with macrovascular invasion and/or extrahepatic metastasis were finally included. The clinical data of patients were obtained by consulting the electronic medical record system and through telephone follow-up. The median overall survival (mOS), duration of drug use, and disease control rate (DCR) of patients were evaluated, and the Cox regression model was used to analyze the risk factors of prognosis.

Results: The mOS of 63 patients with HCC administered regorafenib as second-line treatment was 9.6 months, the duration of drug use was 3.8 months, and the DCR was 59% (37/63). Cox multivariate analysis showed that overall survival (OS) was closely related to the level of alpha-fetoprotein (AFP) and treatment method but not to the type of first-line drug. The mOS of patients with AFP ≥400 ng/mL was 7.4 months, which was significantly lower than that of those with AFP <400 ng/mL (12.5 months) (P=0.0052). The mOS of patients treated with regorafenib alone was 6.8 months, which was significantly lower than that of those treated with regorafenib combined with immunotherapy (24.3 months) and intervention therapy (17.5 months) (P<0.0001). The mOS of patients using regorafenib as second-line treatment in the first-line sorafenib group and first-line nonsorafenib group were 9.5 and 9.6 months, respectively (P=0.9766). The grade ≥3 adverse events (AEs) with an incidence of more than 10% included hand-foot syndrome, increased bilirubin, decreased albumin, and elevated transaminase, with incidences of 22%, 14%, 11%, and 10%, respectively.

Conclusions: As second-line treatment for patients with HCC with macrovascular invasion and(or) extrahepatic metastasis, regorafenib has definite efficacy and tolerable adverse reactions. It is the preferred drug for the second-line treatment of patients with advanced HCC.

Keywords: Hepatocellular carcinoma (HCC); extrahepatic metastasis; macrovascular invasion; regorafenib

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Introduction

Regorafenib is a multitarget and small-molecule tyrosine kinase inhibitor (TKI), which has multiple effects such as inhibiting tumor proliferation, mitigating vascular proliferation, and reversing immune tolerance (1). It entered China on March 22, 2017, and was approved by the Chinese Food and Drug Administration (CFDA) in December for patients with hepatocellular carcinoma (HCC) who had previously received sorafenib treatment. Regorafenib has established itself as a second-line treatment of HCC through a phase III clinical study of regorafenib (RESORCE) (2) that confirmed regorafenib can significantly improve the overall survival (OS) and progression-free survival (PFS) of patients with unresectable advanced HCC in second-line treatment compared with placebo. However, the RESORCE study has limitations in its applicability to Chinese patients with HCC because of the differences in race, pathogenic factors, performance status, presence of macrovascular invasion and(or) extrahepatic metastasis, use of local therapies, and first-line treatment protocols. Reviewing the RESORCE study, first of all, there are not only ethnic differences between Chinese and Western patients but also different pathogenic factors for liver cancer. Hepatitis C infection is the main pathogenic factor for liver cancer in Western populations (3), while hepatitis B infection is the main pathogenic factor for Chinese patients (4-6). These differences may lead to different outcomes to regorafenib treatment. Second, In the RESORCE study, 100% of patients used sorafenib as first-line treatment. However, in the first-line treatment of liver cancer, there are not only targeted drugs such as sorafenib (7) and lenvatinib (8) but also programmed cell death ligand 1 (PD-L1) inhibitors (9), programmed cell death 1 (PD-1) inhibitors, bevacizumab (10), and oxaliplatin-containing chemotherapy (11). Whether different first-line treatment protocols can affect the efficacy and outcome of second-line regorafenib treatment has not yet been reported. Third, macrovascular invasion and(or) extrahepatic metastasis are the main clinical characteristics of Chinese patients with liver cancer after entering the second-line treatment (12). The prognosis of these patients is poor, with the median survival between 2.7–4.2 months (13). These patients were a minority and not fully represented in the RESORCE trial therefore it is unclear if they would derive benefit from regorafenib treatment. Fourth, according to European and American diagnosis and treatment guidelines of advanced HCC once the patient has developed macrovascular invasion and(or) extrahepatic metastasis and has entered second-line treatment, single-drug systematic therapy is recommended (14-16). This can include regorafenib, cabozantinib (17), ramucirumab (18), apatinib, tislelizumab (19), pembrolizumab (20) etc., but the efficacy is poor, and the PFS and OS are short, which cannot satisfy clinical needs. Although, there are no controlled trials supporting the use of combination therapy as a second-line treatment, a few small single-arm studies have shown that sorafenib or regorafenib combined with immunotherapy or local therapy is superior to use of a single targeted drug for unresectable advanced HCC (21-23). However, whether patients with macrovascular invasion and/or extrahepatic metastasis can benefit from the combination therapy and its safety remains unclear. In view of these issues, Thus, the purpose of this study was to evaluate the efficacy of regorafenib as second-line treatment for real world Chinese patients with HCC patients with macrovascular invasion and/or extrahepatic metastasis. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/

Highlight box

Key findings

- This study is the first to investigate whether this subset of Chinese patients with macrovascular invasion and/or extrahepatic metastases could benefit from second-line therapy with regorafenib in the real world. Results have confirmed that the efficacy of regorafenib was not affected by first-line sorafenib or other treatments.

What is known and what is new?

- The RESORCE study has established regorafenib as a second-line treatment for intermediate and advanced hepatocellular carcinoma (HCC).
- Our study first confirmed that regorafenib has definite efficacy and tolerable adverse reactions in Chinese HCC patients with macrovascular invasion and/or extrahepatic metastasis. In addition, we also verified that first-line treatment regimens had no significant impact on the efficacy of second-line regorafenib treatment.

What is the implication, and what should change now?

- Our study preliminarily confirmed that regorafenib combined with immunotherapy or local intervention was superior to regorafenib monotherapy. Next, we will design a prospective study to further validate our inference.

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Methods

Participants and inclusion and exclusion criteria

We selected all patients with primary liver cancer who were treated in Henan Cancer Hospital from June 2017 to September 2020 using the neighbor system (n=253). According to the inclusion and exclusion criteria, 63 patients with HCC with macrovascular invasion and/or extrahepatic metastasis were finally included. 63 patients were divided into two groups with group 1 having 43 patients whom were treated with first-line sorafenib and second-line regorafenib. In group 2, 20 patients were treated with first-line nonsorafenib (including 15 patients receiving apatinib, 2 patients receiving lenvatinib, 1 patient receiving apatinib plus camrelizumab, 1 patient receiving anlotinib plus camrelizumab, and 1 patient receiving lenvatinib plus toripalimab) and second-line regorafenib; when differentiating second-line treatment methods, 63 patients were placed into a regorafenib monotherapy group (31 patients) or regorafenib combination therapy group (32 patients). In the combination therapy group, 5 patients were treated with regorafenib combined with immunotherapy, and 27 patients were treated with regorafenib combined with intervention therapy [including transcatheter arterial chemoembolization (TACE), radiofrequency, portal vein particle implantation, etc.]. The patients' clinical data were obtained by consulting the electronic medical record system and telephone follow-ups. The follow-ups were conducted every two cycles until the patient passed. The median follow-up time was 22.5 months. The inclusion criteria were as follows: (I) patients with HCC proven by histological or clinical diagnosis; (II) extrahepatic metastasis and(or) macrovascular invasion confirmed by imaging [according to Cheng's classification (24), portal vein tumor thrombus (PVTT) can be classified as type I, invasion of the portal vein branches of the liver lobe or segment; type II, invasion of the left or right branches of the portal vein; type III, invasion of the main portal vein; and type IV, invasion of the superior mesenteric vein]; (III) Child-Pugh score of ≤7 points; (IV) patients treated in our hospital, with complete clinical and pathological data; (V) at least two cycles of oral regorafenib; (VI) patients with measurable lesions; and (VII) patients failed to previous systemic therapy. Meanwhile, patients were excluded if they had fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma; or had central nervous system metastases. This study was conducted with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Affiliated Cancer Hospital of Zhengzhou University (No. 2021-053) and has been registered on ClinicalTrials.gov. (registration No. NCT05024539). Individual consent for this retrospective analysis was waived.

Study methods

The general clinical characteristics, pathological characteristics, treatment methods, and outcomes of patients were collected for statistical analysis. OS, duration of drug use, and disease control rate (DCR) were calculated according to the follow-up results. OS was defined as the time from the beginning of regorafenib administration to death, and duration of drug use was defined as the time from the beginning of regorafenib administration to the end of administration, and DCR was defined as the proportion of patients whose efficacy evaluation was complete response (CR), partial response (PR), or stable disease (SD).

Statistical analysis

SPSS 25.0 software (IBM Corp.) and GraphPad Prism 9 (GraphPad Software) were used for analysis. Variables with nonnormal distribution are expressed as medians. Kaplan-Meier Log-rank test was used to draw survival curves to calculate the influence of different factors on survival. The Cox regression model was used to analyze the risk factors of prognosis. A P value <0.05 was considered statistically significant.

Results

OS, duration of drug use, and DCR of patients in second-line regorafenib treatment of liver cancer

The general characteristics of all patients are shown in *Table 1*. The OS of the 63 patients with HCC with macrovascular invasion and/or extrahepatic metastasis being administered regorafenib as second-line treatment was 9.6 months (*Figure 1A*), and the duration of drug use was 3.8 months (*Figure 1B*). Among the 63 patients, 1 patient reached CR, 5 patients reached PR, and 31 patients reached SD, representing a DCR of 59% (37/63) (*Figure 1C*).

Table 1 General characteristics of 63 patients with HCC with macrovascular invasion and(or) extrahepatic metastasis

Characteristic	Patients (n=63)
Gender	
Male	59 [94]
Female	4 [6]
Median age, years	52
ECOG	
0–1	48 [76]
2	15 [24]
Child-Pugh grade	
Grade A	57 [90]
Grade B ≤7 points	6 [10]
AFP	
<400 ng/mL	32 [51]
≥400 ng/mL	31 [49]
Viral infection	
Hepatitis B infection	63 [100]
Hepatitis C infection	0 [0]
No definite virus infection	0 [0]
Cirrhosis	
Yes	47 [75]
No	16 [25]
Macrovascular invasion	39 [62]
Portal vein invasion	32 [52]
Cheng type I	1
Cheng type II	21
Cheng type III	8
Cheng type IV	2
Other types of macrovascular invasion except portal vein invasion	7 [10]
Extrahepatic metastasis	49 [78]
Pulmonary metastasis	29
Lymph node metastasis	19
Bone metastasis	8
Pleural or peritoneal metastasis	8
Metastasis to a single organ	31
Metastasis to ≥2 organs	18
Macrovascular invasion and extrahepatic metastasis	25 [40]
Treatment order	
First-line sorafenib; second-line regorafenib	43 [68]
First-line non-sorafenib; second-line regorafenib	20 [32]

Data are presented as n [%]. HCC, hepatocellular carcinoma; ECOG, Eastern Cooperative Oncology Group; AFP, alpha fetoprotein.

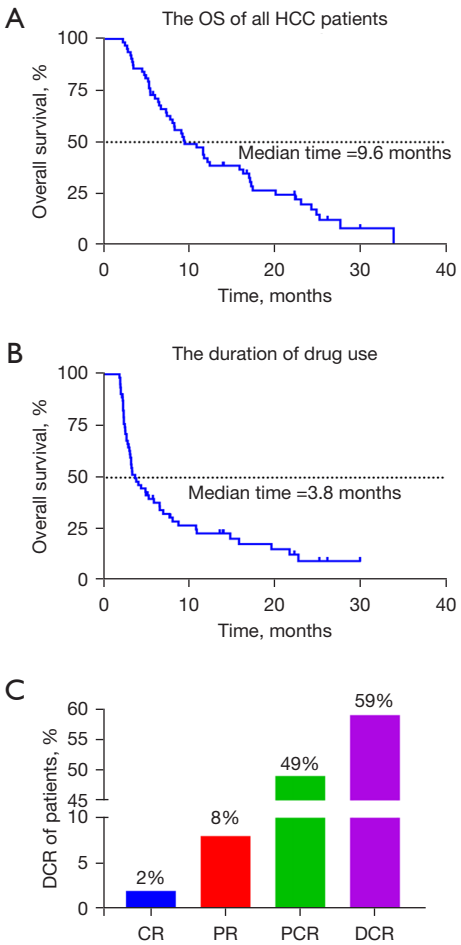

Figure 1 The treatment response of patients with HCC administered regorafenib as second-line treatment. (A) The OS, (B) duration of drug use, and (C) DCR of patients in second-line regorafenib treatment of liver cancer. OS, overall survival; HCC, hepatocellular carcinoma; CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate.

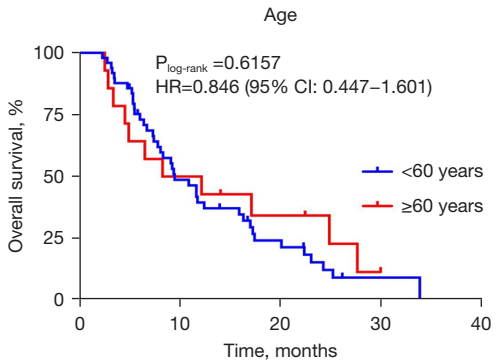

Figure 2 Kaplan-Meier curves of the association between age and overall survival in 63 patients with HCC. HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma.

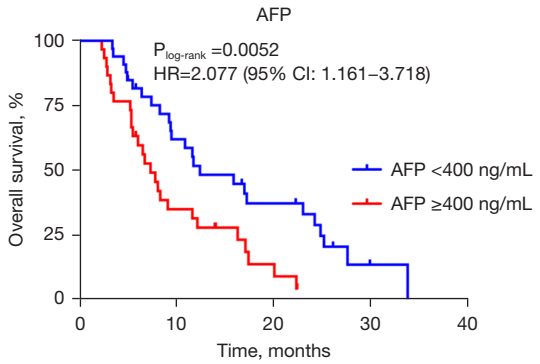

Figure 4 Kaplan-Meier curves of the association between AFP and overall survival in 63 patients with HCC. AFP, alpha fetoprotein; HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma.

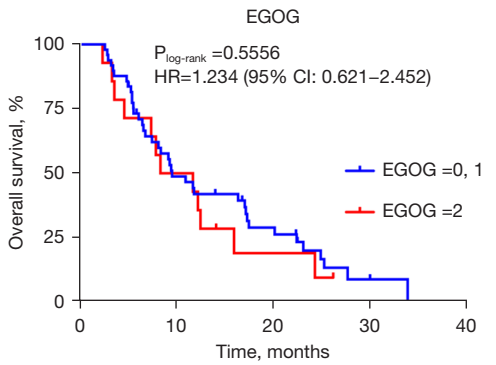

Figure 3 Kaplan-Meier curves of the association between ECOG status and overall survival in 63 patients with HCC. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma.

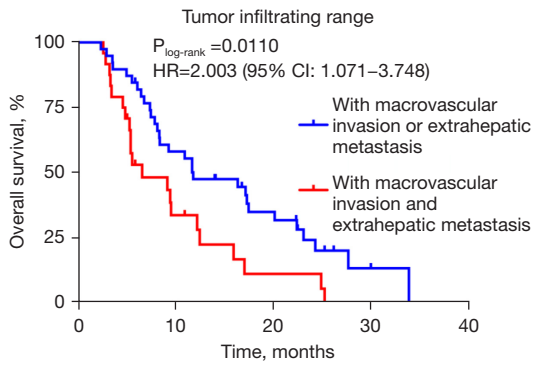

Figure 5 Kaplan-Meier curves of the association between macrovascular invasion/extrahepatic metastasis and overall survival for different subgroups. HR, hazard ratio; CI, confidence interval.

Relationship between OS and age, Eastern Cooperative Oncology Group (ECOG) score, tumor marker alpha fetoprotein (AFP), tumor invasion range, treatment order and treatment methods

Among the 63 patients, 14 were ≥60 years old, with a median OS (mOS) of 9.6 months, and 49 were <60 years old, with a mOS of 10.3 months. In between the two age groups there was no statistical significance in mOS (P=0.6157) (*Figure 2*); According to the ECOG score, 48 patients were ECOG 0–1, with a mOS of 9.6 months, and 15 patients were ECOG 2, with a mOS of 10.1 months. There was also no statistical significance in terms of mOS between the two groups (P=0.5556) (*Figure 3*); Among these 63 patients, there were 31 patients with AFP ≥400 ng/mL and 32 patients with AFP <400 ng/mL. The mOS of patients with AFP ≥400 ng/mL was 7.4 months, and the mOS of patients with AFP <400 ng/mL was 12.5 months, which represented a statistically significant difference (P=0.0052) (*Figure 4*). In terms of tumor invasion range, 25 patients with both macrovascular invasion and extrahepatic metastasis had a mOS of 6.6 months, while 38 patients with either macrovascular invasion or extrahepatic metastasis had a mOS of 11.8 months, which did represent a statistically significant difference (P=0.0110) (*Figure 5*). When comparing treatment order, 43 patients were treated with first-line sorafenib and second-line regorafenib, with a mOS of 9.5 months. Twenty patients that were treated with first-line nonsorafenib had a mOS of 9.6 months. There was no statistical difference between the two groups in mOS (P=0.9766) (*Figure 6A*). Additionally, 43 patients were treated

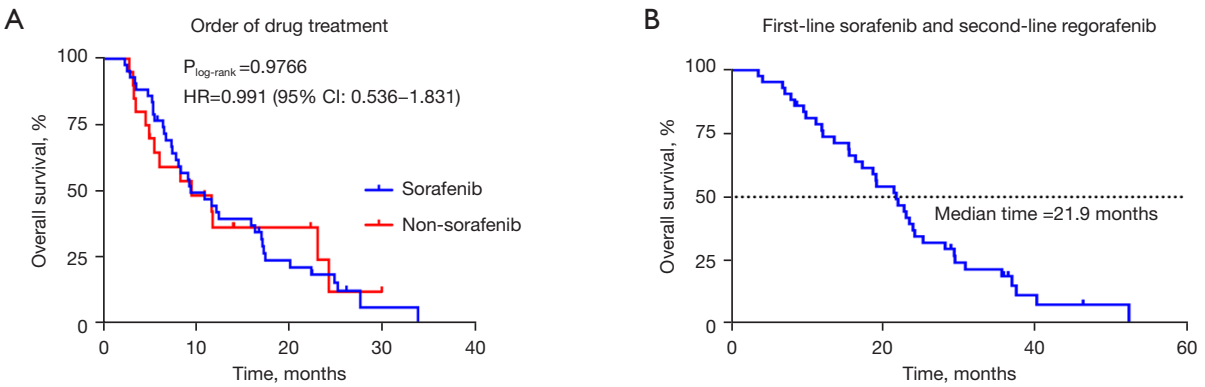

Figure 6 Kaplan-Meier curves of the association between order of drug treatment and overall survival in 63 patients with HCC. HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma.

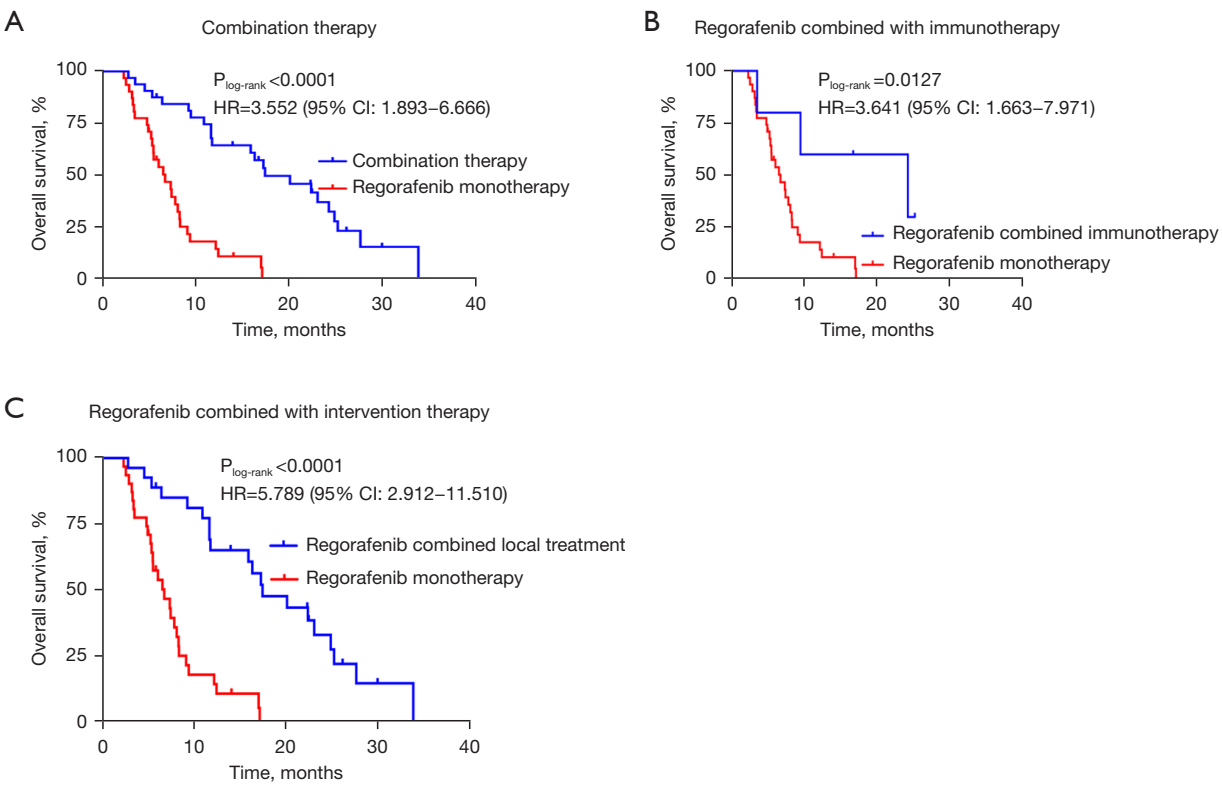

Figure 7 Kaplan-Meier curves of the association between treatment methods and overall survival in 63 patients with HCC. HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma.

with sequential therapy of first-line sorafenib and second-line regorafenib, with a total OS of 21.9 months (*Figure 6B*). Among the 63 patients, 31 patients received regorafenib monotherapy, with a mOS of 6.8 months, and 32 patients received regorafenib combination, with a mOS of 17.5 months, which showed a statistically significant difference (P<0.0001) (*Figure 7A*). The mOS of the regorafenib combined with immunotherapy was 24.3 months, which was significantly different compared with the regorafenib monotherapy group (P=0.0127) (*Figure 7B*). The mOS of regorafenib combined with intervention therapy was 17.5 months. There was a statistical difference when compared to the regorafenib

Table 2 Multivariate Cox analysis of the factors associated with shorter OS in 63 patients with HCC

Variable	Multivariate analysis		
	HR	95% CI	P
AFP grouping	2.429	1.218–4.939	0.013
Treatment order	1.970	0.952–3.933	0.059
Treatment method	4.922	2.213–11.420	0.000
Invasive range	1.917	0.957–3.814	0.064
Age	0.479	0.216–0.978	0.055
ECOG	0.837	0.385–1.680	0.633

OS, overall survival; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein; ECOG, Eastern Cooperative Oncology Group.

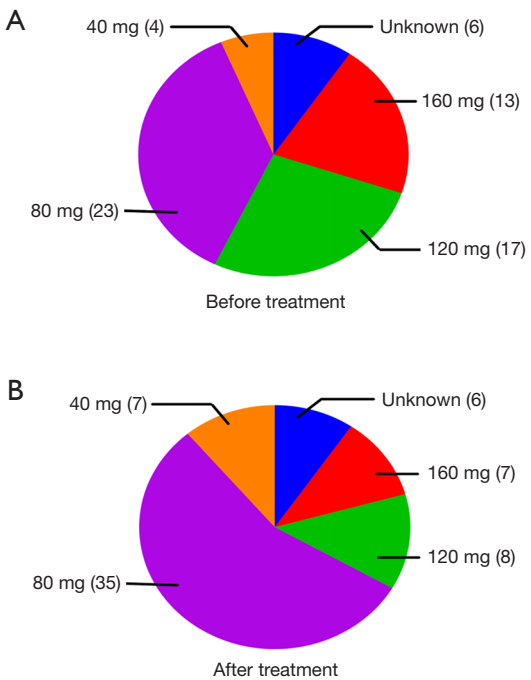

Figure 8 Pie chart of regorafenib dose in 63 patients with HCC. HCC, hepatocellular carcinoma.

monotherapy group (P<0.0001) (*Figure 7C*).

Multivariate analysis results of OS

The analysis of AFP level, treatment order, treatment methods, invasive range, age, ECOG, and prognosis found that the level of AFP and treatment methods were the main factors affecting the prognosis. The prognosis of patients with a high AFP level and of those receiving regorafenib monotherapy was worse than that of patients with a low AFP level and of those receiving combination therapy (*Table 2*).

Dose of regorafenib

Among the 63 patients, 6 patients did not know the specific dose, 13 patients (21%) took 160 mg dose of regorafenib initially, 17 patients (27%) took 120 mg, 23 patients (37%) took 80 mg, and 4 patients (6%) took 40 mg (*Figure 8A*). During the treatment period, 24 (38%) patients decreased the dose because of adverse events (AEs), 2 (3%) increased the dose, 1 increased the dose from 40 to 80 mg, and 1 patient increased the dose from 80 to 120 mg. The proportion of patients receiving final doses of regorafenib of 160, 120, 80, and 40 mg was 11%, 13%, 56%, and 11%, respectively (*Figure 8B*).

AEs

The AEs recorded included hand-foot syndrome, fatigue, anorexia, nausea and vomiting, hypertension, diarrhea, abdominal pain, skin rash, trachyphonia, increased bilirubin, decreased albumin, elevated transaminase, thrombocytopenia, leukopenia, and hemorrhage. Most of the patients experience grade 1–2 AEs, and some experienced grade 3 AEs. The grade ≥3 AEs with an incidence of more than 10% included hand-foot syndrome, increased bilirubin, decreased albumin, and elevated transaminase, with incidences of 22%, 14%, 11%, and 10%, respectively. There were no related deaths, and 3 patients had upper gastrointestinal bleeding (*Table 3*).

Discussion

Most patients with liver cancer in China are diagnosed in the middle and late stages once diagnosed and treated, and the disease progression is rapid. After first-line treatment, most patients entering the second-line treatment have macrovascular invasion, especially portal vein invasion or extrahepatic metastasis, which are important factors affecting the prognosis of liver cancer (25). Once patients have portal vein invasion and extrahepatic metastasis, the tumor can rapidly cause liver function damage, tumor intrahepatic dissemination, portal hypertension, ascites, and dysfunction of other metastatic organs. Therefore, we selected patients with macrovascular invasion and(or)

Table 3 AEs in patients with HCC treated with regorafenib

AEs	All grades	Grade ≥3
Hand-foot syndrome	35 [56]	14 [22]
Fatigue	26 [41]	3 [5]
Anorexia	15 [24]	0 [0]
Nausea and vomiting	8 [13]	0 [0]
Hypertension	15 [24]	4 [6]
Diarrhea	10 [16]	1 [2]
Abdominal pain	5 [18]	0 [0]
Skin rash	6 [10]	0 [0]
Trachyphonia	4 [7]	0 [0]
Increased bilirubin	13 [21]	9 [14]
Decreased albumin	17 [27]	7 [11]
Thrombocytopenia	21 [33]	5 [8]
Leukopenia	19 [30]	0 [0]
Hemorrhage	3 [5]	3 [5]
Elevated transaminase	24 [38]	6 [10]

Data are presented as n [%]. AEs, adverse events; HCC, hepatocellular carcinoma.

extrahepatic metastasis to determine whether they can benefit from the second-line treatment of regorafenib in clinical practice. From June 2017 to September 2020, we included 63 patients with HCC with macrovascular invasion and(or) extrahepatic metastasis according to the inclusion and exclusion criteria. The results showed that the mOS of patients receiving second-line regorafenib treatment was 9.6 months, the duration of drug use was 3.8 months, and the DCR was 59%. The mOS was similar to the 10.9 months of the total population of the RESORCE study and the 7.9 months of Chinese subgroup population, which was better than the 2.7–4 months in previous study (13). It has been suggested that regorafenib can improve the prognosis of patients with HCC. When comparing the RESORCE clinical trial to our study the final results showed that the different pathogenic factors did not affect the responsiveness to regorafenib. The results of the clinical trial are consistent with those of real-world studies (2,26). In addition, the International Liver Cancer Association (ILCA) conference in 2020 reported a retrospective study conducted by a research team from the Cancer Prevention and Treatment Center of Sun Yat-sen University (27). Forty-one patients with advanced HCC who failed first-line sorafenib treatment and then received regorafenib treatment were included. The mOS of second-line regorafenib treatment was not reached, and the median PFS was 6.6 months. The mOS of this study was longer than that of our real-world study, which may be due to the differences in patients' selections. The patients we selected were all patients with macrovascular invasion or extrahepatic metastasis, which further demonstrated that they are the main factors contributing to the poor prognosis of liver cancer. In addition, we chose the duration of regorafenib as our observation indicator, and not PFS. we found the formation of sublesions around the primary lesions of the liver to be the most common path of liver cancer progression during the study. When a new lesion appears, this is evaluated as PD according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. However, in real world practices, this does not entail a change in systemic therapy. Instead, patients would be referred for local therapy to control the disease while continuing their systemic therapy. Therefore, we used the duration of drug use as our observation indicator, which is more representative of real clinical practice. The median duration of drug use reached 3.8 months, which was longer than the 2.8 months of the Chinese subgroup in the RESORCE trial and was considered to be attributable to the local therapy in some patients.

In Cox multivariate analysis, it was found that OS was not related to the patient's age and whether sorafenib was used in first-line treatment, but rather to the AFP level and whether regorafenib was combined with immunotherapy or intervention therapy. In our study, there were 49 (78%) patients younger than 60 years old and 14 (22%) patients older than 60 years old, indicating that young and middle-aged patients were the major aged-related subgroups of liver cancer. Moreover, 100% of the 63 patients had hepatitis B virus infection, and 75% had liver cirrhosis. Therefore, the whole course of the disease in patients conformed to a tripartite hepatitis-liver cirrhosis-liver progression, which is in line with the results of a previous study (28). The mOS of patients in our study <60 years old was 10.3 months, and >60 years old was 9.6 months. The responsiveness to regorafenib therapy was not affected by age.

In order to evaluate whether the first-line treatment protocol affects the efficacy of second-line regorafenib treatment, 63 patients were divided into a sorafenib followed by regorafenib group and nonsorafenib followed by regorafenib group, with the mOS of these two groups being 9.5 and 9.6 months, respectively (P>0.05). This indicated

that first-line treatment protocol had no significant impact on the efficacy of second-line regorafenib treatment (29). In the RESORCE trial, the total OS of sorafenib followed by regorafenib reached 26 months, and this result was confirmed by many real-world studies, such as the 17.5-month OS reported in Japan (30), the 25.8-month OS reported in South Korea (31), and the 28-month OS reported in Spain (32). In our study, 43 patients were treated with sorafenib followed by regorafenib, and the total OS reached 21.9 months, which was shorter than the 26 months of the RESORCE study but longer than the 17.5 months of the real-world study in Japan (30). It also showed that the differences in patients' general conditions directly affected the total OS.

AFP, a reliable tumor marker in HCC, has been shown to not only promote the proliferation of liver cancer cells but can also play an immunosuppressive role by inhibiting the activity of lymphocytes and the phagocytosis of phagocytes (33). Among the 63 patients in our study, 31 patients with AFP ≥400 ng/mL had a mOS of 7.4 months, while 32 patients with AFP <400 ng/mL had a mOS of 12.5 months. The mOS of the two groups was significantly different (P=0.0052), and the prognosis of patients with high AFP was worse, which may be related to the fact that AFP can promote tumor growth and immunosuppression.

Among 63 patients in our study, 39 had macrovascular invasion, 32 of whom had portal vein invasion. The reason why the portal vein is so commonly invaded is that the formation of arteriovenous fistula in the tumor focus and the establishment of the liver cirrhosis lobe can significantly increase the pressure of the portal vein and promote the reflux of portal vein blood, greatly slowing down its flow rate. Additionally, the portal vein mainly collects blood from the intestinal tract, and thus there are many nutrients in the blood in this area. Consequently, due to the high level of nutrition and low flow rate, tumor cells are more able to remain in the portal vein and can quickly reproduce to form PVTT. Consistent with previous study (34), there were 49 patients with extrahepatic metastasis, with the lungs, lymph nodes, bone, pleura or peritoneum being the main metastatic sites. Our results showed 25 patients with both extrahepatic metastasis and macrovascular invasion had a mOS of 6.6 months, which was far lower than the mOS of 11.8 months in patients with only macrovascular invasion or extrahepatic metastasis. This further indicated that macrovascular invasion and extrahepatic metastasis also belong to the terminal stage of the disease, and the prognosis was very poor; however, these factors were not found to be statistically significant in the multivariate analysis, and perhaps more cases are needed to verify this speculation.

Once HCC treatment enters the second-line and macrovascular invasion and(or) extrahepatic metastasis occur, the European and American guidelines and Chinese liver cancer diagnosis and treatment guidelines or CSCO guidelines mainly focus on single-drug, systematic therapy, including with regorafenib, apatinib, cabozantinib, ramucirumab, etc. However, the PFS under such treatment is 2–3 months, and the OS is 7–10 months, which is clinically unsatisfactory (12,17,35). At present, the clinical studies are attempting to combine multiple treatment methods, for instance, a targeted drug combined with immunotherapy or a targeted drug combined with local therapy. Liu *et al.* (22) using regorafenib combined immunotherapy such as toripalimab, sintilimab or tislelizumab, the effective rate was 18.8%, PFS reached 5.9 months, and OS reached 12.9 months. Xu *et al.* (36) used apatinib combined with camrelizumab for first-line and second-line treatments of unresectable HCC, achieving a mOS of 20.1 and 21.8 months, respectively. In our study, five patients received a combination of regorafenib and immunotherapy, which yielded a mOS of 24.3 months and was statistically significant compared with that of patients receiving regorafenib alone. Theoretically, targeted drugs and immunosuppressants such as PD-1 and PD-L1 inhibitors have synergistic effects. Antiangiogenic drugs can promote the maturation of antigen presentation cells, make local blood vessels of tumors more regular, and reverse the immunosuppressive microenvironment, allowing for more mature T cells to enter the tumor and creating conditions for PD-1 and PD-L1 inhibitors to exert their effect (37). The combination of targeted drugs and local therapy has a similar theoretical basis. Local therapy, such as TACE, hepatic arterial infusion chemotherapy (HAIC) and trans-arterial radioembolization (TARE) (38) can rapidly reduce the local tumor load, cause local tumor hypoxia, increase the secretion of a large number of angiogenic factors, and promote the formation of new blood vessels. Targeted drugs mainly refer to antiangiogenic drugs that can inhibit angiogenesis through multiple pathways, producing synergistic effects (39). It was previously believed that patients with PVTT should not be locally treated for HCC. The main reason for this was the belief that HCC has two blood supply systems: the hepatic artery and portal vein. Once patients are treated with hepatic artery embolization and PVTT is present, there is a risk

of rapid deterioration of liver function (40). However, in recent years, a large number of studies have shown that the formation of PVTT is a relatively slow process, so there is abundant collateral circulation around PVTT, and the risk of hepatic failure is small even with TACE and other treatments (41,42). Furthermore, the current treatment of PVTT itself also includes the implantation of a portal vein stent, placement of portal vein particles, radiotherapy of PVTT, and other methods. In addition, some studies have shown that even if extrahepatic metastasis occurs, the progression of intrahepatic lesions is the most important path of progression. Many recent studies have also shown that sorafenib or lenvatinib combined with TACE has a good effect on patients with unresectable HCC (21,43,44). Regorafenib, as a second-line treatment drug for HCC, has also shown effectiveness and tolerability in combination with TACE in some small sample studies (23,45). The 63 patients we included in our study were divided into two groups according to treatment method: one group was treated with regorafenib alone, while the other group was treated with combination therapy. In the combination therapy group, 5 patients could not receive local therapy but received regorafenib combined with immunotherapy, while the other 27 patients received regorafenib combined with local therapy. The results showed that the mOS of patients receiving both regorafenib combined with immunotherapy and regorafenib combined with local therapy was significantly longer than that of patients receiving regorafenib alone. Similarly, the local treatment methods in the combination group showed diversity according to the type of recurrence and include TACE of liver lesions, radiofrequency, and ion implantation of PVTT. This additionally highlights the complexity of liver disease progression and the need for multidisciplinary consultation for patients with advanced disease.

In terms of the overall dose of regorafenib, although the standard dose is 160 mg, our study showed that an initial dose of 160, 120, 80, and 40 mg accounted for 21%, 27%, 37%, and 6%, respectively. During the treatment, 24 patients (38%) reduced the dose, and 2 patients increased the dose. The final dose of 160, 120, 80, and 40 mg accounted for 11%, 13%, 56%, and 11% of these patients, respectively. This suggests that the standard dose of 160 mg was poorly tolerated in Chinese patients with liver cancer, and 80 mg was the dose that most patients could tolerate. Due to the small number of cases and relatively scattered doses, the dose-related clinical data of nearly 10% of patients (6 patients) were not obtained, so the dose-related single-factor or multi-factor analysis could not be conducted.

We also recorded the common AEs of regorafenib, including hand-foot syndrome, fatigue, anorexia, nausea and vomiting, hypertension, diarrhea, abdominal pain, skin rash, trachyphonia, and proteinuria, among others, most of which were grade 1–2. However, some AEs were unique to patients with liver cancer, such as increased bilirubin, elevated transaminase, hypoproteinemia, upper gastrointestinal bleeding, and thrombocytopenia. The occurrence of these AEs was related to the liver cancer itself, the formation of liver cirrhosis, hypersplenism, collateral circulation, TACE, radiofrequency ablation, and other local treatments. The grade ≥3 AEs with an incidence of more than 10% included hand-foot syndrome, increased bilirubin, decreased albumin, and elevated transaminase, with incidences of 22%, 14%, 11%, and 10%, respectively, indicating that the adverse reactions of monotherapy or combination therapy of regorafenib were tolerable.

Conclusions

It can be seen from our study that regorafenib, as a second-line treatment drug for liver cancer, still has a good effect on patients with advanced liver cancer who have macrovascular invasion or extrahepatic metastasis. In particular, the OS of patients receiving regorafenib combined with immunotherapy or intervention therapy was significantly longer than that of patients receiving regorafenib alone. The overall adverse reactions are tolerable, and no new adverse reactions were observed. It should be noted that regorafenib has been included within the scope of medical insurance reimbursement, with a high performance to cost ratio, and is worth popularizing in the second-line treatment of liver cancer. However, our study is retrospective in nature, which has several drawbacks. For example, evaluation for the initial dose of regorafenib, dose adjustment, and combination drug therapy are highly subjective, and the adverse reactions and specific drug dose of patients cannot be completely obtained. The above factors may affect the further interpretation of the results to a certain extent. Therefore, our team is conducting a prospective clinical study of regorafenib combined with local therapy and immunotherapy to obtain more reliable conclusions.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Affiliated Cancer Hospital of Zhengzhou University (No. 2021-053). Individual consent for this retrospective analysis was waived.

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