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Original Article

Comparison of the clinical efficacy of donafinil and lenvatinib in the treatment of intermediate and advanced hepatocellular carcinoma

Qinzhen He[1], Mengguang Guo[1], Yanhong Ya[1], Jinli Huang[1], Aiqiu Liu[1], Wexiang Jing[2]

[1]*Oncology Department, No. 1 People's Hospital of Hechi, Hechi 546300, Guangxi, China;* [2]*Surgery Department, No. 1 People's Hospital of Hechi, Hechi 546300, Guangxi, China*

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Abstract: Objective: To compare the therapeutic effects of donafinil and lenvatinib in the treatment of patients with intermediate–advanced hepatocellular carcinoma (HCC). Methods: A total of 100 patients with intermediate--advanced HCC who received donafinib or lenvatinib treatment in Hechi First People's Hospital, Hechi People's Hospital, the Second Affiliated Hospital of Guangxi University of Science and Technology, and other centers from January 2021 to June 2022 were retrospectively analyzed. The patients were classified into a donafinil group (n=50) and a lenvatinib group (n=50) according to the treatment method. The therapeutic effects and adverse reactions of the two groups were compared, as well as the changes in alpha-fetoprotein (AFP), Golgi glycoprotein 73 (GP-73), and glypican-3 (GPC3) before and after treatment. Results: The objective remission rate in the lenvatinib group was less than that in the donafenib group (20% VS 32%, $P > 0.05$). Disease control rates were higher in the donafinib group than in the lenvatinib group (70% VS 50%, $P < 0.05$). A comparison of survival time between the two groups showed that the survival rate and progression-free survival in the Donafenib group were higher than those in the Lunvatinib group ($P < 0.05$), and the main risk factor affecting the survival rate was the number of multiple tumors. There was no statistically significant difference in the rate of adverse reactions between the two groups ($P > 0.05$). The levels of AFP, GP-73, and GPC3 in the two groups were significantly lower than those before treatment ($P < 0.05$). Conclusion: Both donafenib and lenvatinib can effectively treat patients with middle and advanced hepatocellular carcinoma, and the local control rate of donafenib is higher than that of lenvatinib. The treatment of intermediate–advanced hepatocellular carcinoma patients with donafinib has better clinical efficacy than levatinib, which can effectively reduce the severity of patients' disease and prolong their survival time.

Keywords: Hepatocellular carcinoma, donafenil, lenvatinib

Introduction

Hepatocellular carcinoma (HCC) is a malignant tumor of the liver with a high incidence and short course of disease. According to the latest statistics, the number of new cases of liver cancer in the world is up to 900,000 each year, and the number of deaths is up to 830,000, with high morbidity and mortality [1, 2]. In the early stage of liver cancer, it is difficult to detect and diagnose, and the tumor development rate is fast, with high recurrence and aggressiveness, etc., leading to the delayed diagnosis and losing the best opportunity for surgical treatment [3, 4]. In the past, patients with liver cancer who lost surgical treatment were mainly treated with sorafenib and other therapeutic means [5, 6]. However, the efficacy of sorafenib is limited, the improvement of patients' symptoms is not obvious, and the risk of adverse reactions in patients is high [7]. Therefore, it is still very important to find an effective treatment. Donafenib is an updated version of sorafenib, which is a multi-target and multi-kinase inhibitor. Relevant studies [8] have shown that Donafenib can play a strong anti-tumor effect. Lenvatinib is also the main drug for the treatment of middle and advanced liver cancer. Al-Salama ZT et al. [9] pointed out that lenvatinib can achieve a therapeutic effect by inhibiting tumor growth and metastasis. At present, for intermediate--advanced liver cancer, several

studies [10, 11] have reported that targeted drugs such as donafinib and lenvatinib have good efficacy in the treatment of middle and advanced liver cancer, but no recommendation has been made on which drug should be used first, and there are few reports on the efficacy comparison between the two drugs. Therefore, we aimed to explore the clinical efficacy of donafinib and lenvatinib in the management of patients with intermediate--advanced hepatocellular carcinoma, to suggest a basis for clinical treatment.

Materials and methods

General information

This study was a retrospective analysis. Clinical data were collected from 100 patients with intermediate--advanced hepatocellular carcinoma treated with donafinib or envatinib in hospitals from January 2021 to June 2022, including 61 males and 39 females. Centers including the First People's Hospital of Hechi, the People's Hospital of Hechi, and the Second Affiliated Hospital of Guangxi University of Science and Technology were included. The cases were classified by treatment into 50 cases of donafinil and 50 cases of envatinib. The research was conducted with the informed consent of the patients and their families. This study was approved by No. 1 People's Hospital of Hechi Ethics Committee.

Inclusion and exclusion criteria

Inclusion criteria: (1) Consistent with the guidelines for the diagnosis and treatment of primary liver cancer (2019 edition) [12]; (2) Barcelona Clinical Liver Cancer (BCLC) is Phase B or Phase C; (3) Age ≥ 18 years; (4) Patient demographic information, laboratory examination results, follow-up data, and other data are complete. Exclusion criteria: (1) Those with serious abnormalities in the function of organs such as the kidney and heart; (2) Those taking other related drugs during the treatment period; (3) Those who are allergic to therapeutic drugs; (4) Those with serious complications.

Treatment methods

Donafenil group: Patients were treated with Donafenil tablets (Manufacturer: Suzhou Zejing Biopharmaceutical Co., Ltd.; Approval number: National medicine approval HT20210020; Specification: 0.1 g×10 pieces ×4 boards/box) 200 mg/time, twice a day, for 12 weeks.

Lenvatinib group: Patients were given oral envatinib (Manufacturer: Eisai Co., Ltd.; Approval number: National drug approval HT20200044; Specification: 4 mg×10 capsules ×3 plates/box), 8 mg per time, once a day for patients with body weight < 60 kg; Patients with body weight ≥ 60 kg were given 12 mg once a day for 12 weeks.

Observation indicators

(1) Clinical efficacy was assessed according to the mRECIST criteria and classified as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Objective remission rate ORR = (CR+PR) a number of cases/total number of cases ×100%. Disease control rate DCR = (CR+PR+SD) number of cases/total number of cases ×100%. (2) Serum levels of AFP, GP-73, and GPC3 before and after treatment were observed in the two groups. The above indicators were measured by enzyme-linked immunosorbent assay (ELISA). (3) Patients in both groups were observed for adverse effects, such as diarrhea and hypertension. The current research started follow-up from the date of initial treatment. Time to death, progression-free survival (PFS), and survival time (OS) of patients were recorded during the follow-up period. The follow-up cut-off date was August 31, 2022. PFS indicates the time from the start of treatment until disease progression or death from any cause. OS indicates the period from the patient's diagnosis of intermediate to middle and advanced hepatocellular carcinoma to the date of last follow-up or death. In this study, clinical efficacy, AFP, GP-73, GPC3, PFS, and OS were the main observation indexes, and adverse reactions were the secondary observation indexes.

Statistical methods

The SPSS 23.0 program was employed for data analysis and processing. Quantitative data with a normal distribution were expressed as $\bar{x} \pm s$, and the inter-group comparison was conducted using independent t-test. Counted data were described by [n (%)], and the chi-square test was applied for inter-group comparisons. A rank sum test was employed to compare ranked

Table 1. Comparison of general data between the two groups ($\bar{x} \pm s$, n)

Factor	Donafenib (n=50)	Lenvatinib (n=50)	X^2/t value	*P* value
Gender [n (%)]				
Male	31 (62.00)	30 (60.00)	0.042	0.838
Female	19 (38.00)	20 (40.00)		
Age ($\bar{x} \pm s$)	50.38 ± 6.72	51.70 ± 7.77	-0.909	0.366
Weight ($\bar{x} \pm s$)	59.14 ± 5.98	58.84 ± 5.15	0.269	0.789
BCLC [n (%)]				
B period	21 (42.00)	23 (46.00)	0.162	0.687
C period	29 (58.00)	27 (54.00)		
Number of tumors [n (%)]				
single	26 (52.00)	27 (54.00)	0.040	0.841
multiple	24 (48.00)	23 (46.00)		
Tumor metastasis [n (%)]				
yes	28 (56.00)	26 (52.00)	0.161	0.688
no	22 (44.00)	24 (48.00)		

data. The Kaplan-Meier method was adopted for survival analysis. Log-rank test was employed to compare the rate of survival of patients of different subgroups. $P < 0.05$ was considered a significant difference.

Results

Comparison of two groups of general data

There was no significant difference in gender, age, weight, BCLC stage, tumor number, or metastasis between the two groups (all $P > 0.05$), as shown in **Table 1**.

Comparison of efficacy between the two groups

The objective remission rate (ORR) after treatment was 32.00% in the donafinib group, which was higher than the 20.00% in the lenvatinib group; however, the difference did not reach statistical significance ($P > 0.05$). The disease control rate (DCR) was significantly higher than that in the lenvatinib group ($P < 0.05$), as shown in **Table 2**.

Comparison of levels of different indicators before and after treatment between the two groups

Before treatment, the comparison of AFP, GP-73, and GPC3 levels between the two groups was not significant (all $P > 0.05$). The levels of AFP, GP-73, and GPC3 were lower after treatment compared with those before treatment (all $P < 0.05$). AFP, GP-73, and GPC3 decreased more in the donafinil group than in the lenvatinib group (all $P < 0.05$), as shown in **Table 3**.

Adverse reactions

Adverse reactions occurred in 59% (59/100) of the patients. Rash was the most common adverse effect in both donafinib and lenvatinib groups (32% VS 28%), followed by hypertension (22% VS 28%), diarrhea (18% VS 16%), and weight loss (18% VS 16%); however, there was no significant difference in adverse reactions between the two groups ($P > 0.05$), as shown in **Table 4**. All the above adverse reactions were treated and treated accordingly, and no grade IV adverse reactions occurred in any patients.

Comparison of PFS and OS between the two groups

Mortality was less in the donafinil group than in the lenvatinib group [28% (14/50) vs 44% (22/50)]. The survival rate was higher in the donafinib group than in the lenvatinib group ($P < 0.05$), as shown in **Figure 1**. Progression-free survival was longer in the donafinib group than in the lenvatinib group ($P < 0.05$), as shown in **Figure 2**.

Analysis of related factors affecting survival rate

This study was divided into a death group and a survival group according to the death of patients. As shown in **Table 5**, there was a significant difference in the number of tumors between the two groups ($P < 0.05$). Variables with statistical significance by univariate analysis were included as independent variables (multiple tumors =1, single tumor =0), and death was taken as a dependent variable (yes =1, no =0). The results of multivariate logistic regression analysis showed that having multi-

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

Group	CR	PR	SD	PD	ORR (%)	DCR (%)
Donafenib (n=50)	2 (6.00)	14 (28.00)	19 (38.00)	15 (30.00)	16 (32.00)	35 (70.00)
Lenvatinib (n=50)	2 (6.00)	8 (16.00)	15 (30.00)	25 (48.00)	10 (20.00)	25 (50.00)
χ^2/Z		-1.970			4.355	4.167
P		0.049			0.113	0.041

Note: Z: represents the result of rank sum test for rank data; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: Disease control rate.

Table 3. Comparison of different indexes before and after treatment between the two groups ($\bar{x} \pm s$)

Group	AFP (ng·mL^{-1})		GP-73 (μg·L^{-1})		GPC3 (μg·L^{-1})	
	Pre-treatment	After treatment	Pre-treatment	After treatment	Pre-treatment	After treatment
Donafenib (n=50)	721.19 ± 56.22	406.97 ± 121.39*	164.55 ± 19.41	106.39 ± 37.28*	11.73 ± 1.99	7.22 ± 2.61*
Lenvatinib (n=50)	721.87 ± 54.23	459.86 ± 130.26*	163.17 ± 15.12	120.61 ± 32.16*	11.98 ± 1.99	8.14 ± 1.99*
t	-0.062	-2.101	0.396	-2.042	-0.626	-1.991
P	0.951	0.038	0.693	0.044	0.533	0.049

Note: Compared to before treatment, *$P < 0.05$.

Table 4. Adverse reactions of the two groups after treatment [n (%)]

Adverse reaction	Donafenib [n (%)]	Lenvatinib [n (%)]	χ^2 value	*P* value
diarrhea	9 (18.00)	8 (16.00)	0.071	0.790
rash	16 (32.00)	14 (28.00)	0.190	0.663
hypertension	11 (22.00)	14 (28.00)	0.480	0.488
weight loss	9 (18.00)	8 (16.00)	0.071	0.790

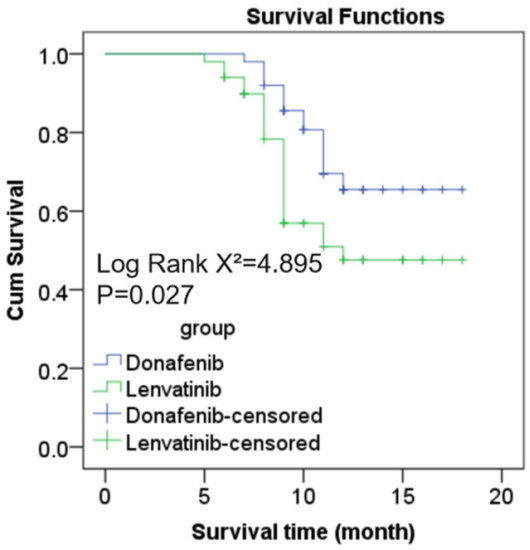

Figure 1. Comparison of OS survival curves between the two groups.

ple tumors was an independent risk factor affecting the survival rate of patients, as shown in **Table 6**.

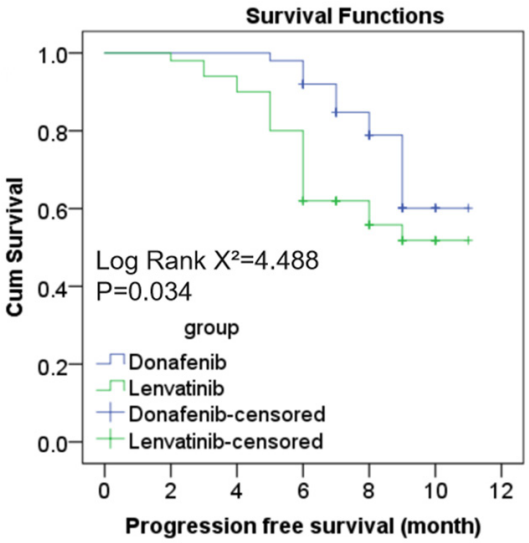

Figure 2. Comparison of PFS survival curves between the two groups.

Discussion

Intermediate--advanced liver cancer develops rapidly, is more prone to complications, and the survival time is short. To increase the patient's survival time, systemic therapy must be given to the patient. Systemic therapy is beneficial in reducing the progression of the patient's disease and improving the patient's prognosis [13]. At present, the main treatment methods for middle and advanced liver cancer include chemotherapy, targeted therapy, and immunotherapy [14]. Chemotherapy is currently the

Table 5. Analysis of single factors affecting survival rate of patients

Factor	Death group (n=36)	Survival group (n=64)	χ^2/t value	*P* value
Gender [n (%)]				
Male	22 (61.11)	39 (60.94)	0.000	0.986
Female	14 (38.89)	25 (39.06)		
Age ($\bar{x}$ ± s)	52.78 ± 6.96	50.06 ± 7.29	1.817	0.072
Weight ($\bar{x}$ ± s, kg)	58.64 ± 5.91	59.19 ± 5.38	0.472	0.638
BCLC [n (%)]				
B period	16 (44.44)	40 (62.50)	3.048	0.081
C period	20 (55.56)	24 (37.50)		
Number of tumors [n (%)]				
single	12 (33.33)	41 (64.06)	8.734	0.003
multiple	24 (66.67)	23 (35.94)		
Tumor metastasis [n (%)]				
yes	18 (50.00)	28 (43.75)	0.362	0.547
no	18 (50.00)	36 (56.25)		

Table 6. Logistic regression analysis of factors related to survival rate

Factor	B	SE	Wald	*P*	HR value (95% CI)
Number of tumors	1.271	0.439	8.379	0.004	3.565 (1.508-8.432)

main treatment modality for patients with unresectable hepatocellular carcinoma. However, the therapeutic effect of chemotherapy is limited because of the different severity of the patient's disease and the increased drug resistance of cancer cells. With the clinical application of molecularly targeted drugs such as donafinib and lenvatinib, the treatment effect of liver cancer has been improved. By inhibiting tumor division and proliferation, molecularly targeted drugs can inhibit the formation of tumor new blood vessels and achieve a therapeutic effect, thus prolonging the survival time of patients [15].

Donafinib is an updated version of sorafenib. Donafinib is a multi-target, multi-kinase inhibitor that exerts potent antitumor effects by inhibiting Raf kinase and affecting tumor cell proliferation while inhibiting tumor angiogenesis [16]. Lenvatinib is the main drug for the treatment of middle and advanced liver cancer, which mainly inhibits the formation of tumor neovascularization, thereby reducing the vascular permeability of the tumor microenvironment and inhibiting tumor growth and metastasis to achieve therapeutic effect [17]. This research was conducted to compare the clinical efficacy of donafinil and lenvatinib in patients with intermediate--advanced hepatocellular carcinoma. The results indicated that the objective remission rate and disease control rate of patients with intermediate--advanced hepatocellular carcinoma treated in the lenvatinib group were less than those in the donafinib group. Survival analysis of patients in both groups indicated that patients in the donafinib group had higher survival and progression-free survival than in the lenvatinib group. The adverse effects were essentially the same in both groups. The results were similar to those of Luo [18]. Therefore, it is hypothesized that donafinil has good clinical efficacy in treating patients with intermediate--advanced hepatocellular carcinoma and can effectively prolong the survival of patients.

AFP is a glycogen protein synthesized and secreted by liver cells, which will be extensively analyzed when the liver is damaged and is closely related to the occurrence of liver cancer and various tumors. Currently, it is one of the diagnostic markers of liver cancer in clinical practice [19, 20]. A number of studies [21, 22] have indicated that GP-73 can be used as a diagnostic indicator of hepatocellular carcinoma. GP-73 is a transmembrane protein that is expressed at a low level or even with no expression in normal human hepatocytes. When the body's hepatocytes are infected by viruses, the level of GP-73 can be increased. Glypican-3 (GPC3) can control cell growth and differentiation by binding with heparin-binding protein. It is not expressed in normal human liver cells but is abnormally elevated in patients with liver cancer. Several studies [23, 24] have confirmed that GPC3 is highly expressed in hepatoma patients and can be applied as a diagnostic marker for hepatocellular carcinoma. The results of this research indicated that the levels of AFP, GP-73, and GPC3 were significantly

decreased in both groups after drug treatment compared to the pre-treatment period. This result indicates that both donafinil and lenvatinib could reduce the levels of AFP, GP-73, and GPC3 in patients with intermediate--advanced liver cancer, which was consistent with the results of Liu et al. [25, 26]. The results showed that the two drugs had an antitumor effect during the treatment, and both could reduce the symptoms of patients.

Advantages and limitations

In this research, we analyzed the therapeutic effects of donafinil and lenvatinib to provide a basis for the clinical treatment of intermediate--advanced hepatocellular carcinoma. However, there are still some limitations of this research. Although the effectiveness of donafinil and lenvatinib was verified. However, the clinical outcomes may have been overestimated because of the small sample size, and insufficient and uneven follow-up time in this study. In subsequent research, more comprehensive research is required to confirm the clinical effects of donafinil and lenvatinib.

Conclusion

In conclusion, both donafinib and lenvatinib can effectively treat intermediate--advanced liver cancer. The objective remission rate and disease control rate of these patients in the lenvatinib group were lower than those in the donafinib group. The results of the survival analysis indicated that patients in the donafinil group had a longer survival time and progression-free survival time than those in the lenvatinib group. The rate of adverse reactions was comparable between the two groups. This indicates that donafinil has higher clinical efficacy than lenvatinib in intermediate--advanced liver cancer. In the clinical treatment of these patients appropriate drugs can be reasonably selected according to their conditions and drug acceptance to prolong the survival time.

Disclosure of conflict of interest

None.

Address correspondence to: Wexiang Jing, Surgery Department, No. 1 People's Hospital of Hechi, Hechi 546300, Guangxi, China. Tel: +86-0778-3212583; E-mail: weixiangj@126.com

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