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Lenvatinib Therapy in Patients with Unresectable Hepatocellular Carcinoma in Real Clinical Practice

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Aim. To determine lenvatinib treatment outcomes in patients with advanced unresectable hepatocellular carcinoma (uHCC) in real clinical practice.

Patients and methods. A multicenter retrospective observational study included 58 patients with a confirmed uHCC diagnosis receiving lenvatinib. At baseline, ECOG, Child-Pugh and BCLC scores were assessed. The objective response rate (ORR), disease control rate (DCR), median overall survival (OS) and median progression-free survival (PFS) rates were assessed. In addition, adverse effects (AE) during treatment were monitored.

Results. The median OS and PFS comprised 14.6 (95 % CI 10.6–18.6) and 11.1 months (95 % CI 8.31–13.8), respectively. The ORR amounted to 32.8 %, while DCR reached the level of 79.3 %. The levels of ORR and DCR were not statistically significantly different between the patients with stages B and C according to the BCLC staging system, with grades 0 and 1 according to ECOG, with classes A and B according to the Child-Pugh score, with viral and non-viral HCC etiology, with and without extrahepatic spread, and with and without portal vein invasion. Patients with alpha-fetoprotein (AFP) blood levels <200 ng/mL showed significantly higher ORR and DCR compared to those with AFP levels >200 ng/ mL (44.4 % vs. 13.6 %, $p = 0.015$; and 88.9 % vs. 63.6 %, $p = 0.021$, respectively). The uHCC stage according to BCLC, ECOG functional status, Child-Pugh class, presence or absence of extrahepatic spread and viral etiology had no effect on the OS and PFS median levels. Patients with macroscopic portal vein invasion had a significantly lower PFS compared with those lacking this complication: 3.97 (0.00–8.07) vs. 11.1 (8.46–13.7), $p = 0.053$. AFP levels ≥200 ng/mL adversely affected survival rates: median OS comprised 12.0 (5.95–18.9) months in the group of patients with AFP ≥200 ng/mL vs. 16.1 (8.73–23.5) months in the group of patients having AFP <200 ng/mL, $p = 0.020$. AEs were registered in 81.0% ($n = 47$) of patients. Among the most common AEs were arterial hypertension (32.8 %), weakness (24.1 %), weight loss (12.1 %) and appetite loss (10.3 %). Due to AEs, lenvatinib was withdrawn in 5 (8.6 %) patients.

Conclusion. Lenvatinib confirmed its efficacy and safety in patients with uHCC in real clinical practice. The treatment outcome might be affected by AFP levels and the presence of macroscopic portal vein invasion. Further comparative studies into treatment regimens applied in real clinical practice are required.

Keywords: liver cancer, hepatocellular carcinoma, HCC, targeted therapy, lenvatinib, real clinical practice

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Ленватиниб у пациентов с нерезектабельной гепатоцеллюлярной карциномой в реальной клинической практике

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Цель исследования: определить результаты лечения пациентов с неоперабельной гепатоцеллюлярной карциномой (нГЦК) на поздних стадиях, которые получали ленватиниб в условиях реальной клинической практики.

Материал и методы: в многоцентровое ретроспективное наблюдательное исследование вошли 58 пациентов с подтвержденным диагнозом нГЦК, получающие ленватиниб. На исходном уровне выполнялась оценка по шкалам ECOG, Чайлд-Пью и BCLC. Оценивали частоту объективного ответа (ЧОО), частоту контроля заболевания (ЧКЗ), медиану общей выживаемости (ОВ), медиану выживаемости без прогрессирования (ВБП), также контролировали нежелательные явления (НЯ) на фоне терапии.

Результаты: Медиана ОВ составила 14,6 месяца (95 % ДИ 10,6–18,6), а медиана ВБП — 11,1 месяца (95 % ДИ 8,31–13,8). ЧОО составила 32,8 %, ЧКЗ достигла уровня 79,3 %. ЧОО и ЧКЗ статистически значимо не различалась между пациентами со стадией В и С по шкале BCLC, с балльной оценкой 0 и 1 по шкале ECOG, с классом А и классом В по шкале Чайлд–Пью, у пациентов с вирусной и невирусной этиологией ГЦК, с внепеченочным распространением и без него, а также у пациентов с инвазией в воротную вену и без нее. Пациенты с уровнем альфа-фетопротеина (АФП) в крови <200 нг/мл показали достоверно более высокую ЧОО и ЧКЗ по сравнению с уровнями >200 нг/мл (44,4 % против 13,6 %, $p = 0,015$; и 88,9 % против 63,6 %, $p = 0,021$ соответственно). Стадия нГЦК по BCLC, функциональный статус по шкале ECOG, класс по шкале Чайлд-Пью, наличие/отсутствие внепеченочного распространения, вирусная этиология не оказывали влияния на медиану. Пациенты с макроскопической инвазией в воротную вену имели достоверно более низкую ВБП по сравнению с пациентами без таковой 3,97 (0,00–8,07) vs. 11,1 (8,46–13,7), $p = 0,053$. Уровень АФП ≥200 нг/мл отрицательно влиял на показатели выживаемости: медиана ОВ составила 12,0 (5,95–18,9) месяца в группе пациентов с АФП ≥200 нг/мл vs. 16,1 (8,73–23,5) месяца в группе пациентов с АФП <200 нг/мл, $p = 0,020$. НЯ зарегистрированы у 81,0 % ($n = 47$) пациентов. Наиболее распространенными НЯ были артериальная гипертензия (32,8 %), слабость (24,1 %), снижением массы тела (12,1 %), потеря аппетита (10,3 %). Ленватиниб был отменен из-за НЯ у 5 (8,6 %) пациентов.

Выводы: ленватиниб подтвердил эффективность и безопасность для пациентов с нГЦК в условиях реальной клинической практики. На результаты лечения могут влиять уровень АФП и наличие макроскопической инвазии в воротную вену. Необходимы дальнейшие сравнительные исследования различных режимов терапии в реальной клинической практике.

Ключевые слова: рак печени, гепатоцеллюлярная карцинома, таргетная терапия, ленватиниб, реальная клиническая практика

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Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the fourth leading cause of cancer death worldwide. However, the incidence of liver cancer is expected to continue to increase as the prevalence of chronic liver disease continues to rise steadily. The morphological type of liver cancer is HCC in more than 80% [1]. Over the past decade, mortality from liver cancer in the Russian Federation has consistently exceeded the incidence, which is associated with the complexities of early diagnosis, the lack of effective screening, and cancer alertness of allied healthcare professionals. [2]. The crude incidence rate of HCC in 2019 was 6.53; the adjusted incidence rate

was 3.48 per 100,000 population, while 16.7% of patients received expert treatment [3].

In a situation where late detection of the disease often does not allow curative treatment, systemic therapy for unresectable HCC (uHCC) remains the only opportunity to increase survival and improve the quality of life of patients. The prognosis of the course of the disease and treatment options for patients with hepatocellular carcinoma depend on the tumor burden, the degree of hepatic dysfunction, and the overall performance status of a patient [4–6].

The topic of HCC treatment is currently drawing particularly close attention due to the systemic therapy enhancement. The REFLECT, an international multicenter, randomized, open-label, phase III clinical trial [7, 8] prompted clinicians involved in the treatment of HCC patients to deeply analyze additional aspects, such as detailed characteristics of the tumor process, assessment of the liver function, as well as the balance of these indicators in groups in terms of their possible impact on the primary results obtained. An example of such an assessment was the study by A. Briggs et al. published in 2020 [9]. The most important prognostic factors are microvascular infiltration, extrahepatic spread of the tumor, alpha-fetoprotein (AFP) level in blood plasma, stages B and C in accordance with the BCLC clinical classification of liver cancer, scores on the ALBI scale (a model for assessing the liver function based on laboratory-identified levels of albumin and bilirubin, albumin-bilirubin ratio only), subsequent therapy [10, 11, 12]. A number of studies have shown that the survival of patients during treatment depends on the stage of the disease, liver function, past hepatitis (viral, toxic, and metabolic). Liver cirrhosis is an independent prognostic factor [13].

Therapy options for HCC, unlike other malignant neoplasms, have an additional limitation associated with the liver function affected by the tumor in presence of cirrhotic changes. The REFLECT study demonstrated non-inferiority of lenvatinib in first-line therapy in patients with uHCC versus sorafenib which is the only systemic treatment option that improved overall survival (OS) in patients with this pathology [7, 9]. Median OS was 13.6 months on lenvatinib versus 12.3 months on sorafenib (hazard ratio = 0.92) [8].

The results obtained in 2018 allowed lenvatinib to be ranked high among a small number of multikinase inhibitors that could be prescribed to this group of patients. Lenvatinib has established itself as a modern drug therapy for HCC with a favorable efficacy and safety profile based on the results of the REFLECT study [7]. In this study, lenvatinib was non-inferior to sorafenib in patients with uHCC securing an increase in overall survival: median progression-free survival (PFS) on lenvatinib was 7.4 months, while on sorafenib it was 3.7 months [7, 14]. This led to the approval of lenvatinib as a first-line treatment for uHCC. However, unresolved issues of managing patients with inoperable HCC and the prospects for the use of this drug still remain. The efficacy of antitumor treatment with lenvatinib in patients with decompensated liver function of Child-Pugh class B and at the intermediate stage B according to the Barcelona Clinic Liver Cancer (BCLC) classification [7].

In 2019, A. Alsina et al. presented the results of a sub-analysis of the REFLECT study, which allowed a more detailed assessment of the benefits of using lenvatinib as initial therapy and the options of subsequent lines with other drugs [15]. The patients who got subsequent lines of antitumor treatment shown promising results on OS as compared to patients who got only 1st line.

There is currently growing interest in real-world data (RWD) studies [16, 17]. This is due to unresolved issues remaining after prospective phase III studies, where there are limitations in the selection of comparison groups and research methods, which makes it difficult to interpret their results to a wider patient population. RWD complementing phase III studies help to establish the evidence necessary for inclusion in clinical recommendations and drug lists [18–21].

Purpose: to establish the results of treatment of patients with advanced uHCC who received lenvatinib based on real-world data.

Materials and methods

A multicenter, retrospective, observational study was conducted to assess the efficacy and tolerability of lenvatinib in patients with uHCC. The study analyzed the medical records of patients with uHCC treated at six centers: Sverdlovsk Regional Oncology Center (Yekaterinburg), Republican Clinical Oncology Center of the Ministry of Health of the Republic of Bashkortostan (Ufa), Chelyabinsk Regional Clinical Center of Oncology and Nuclear Medicine (Chelyabinsk), Moscow City Oncology Hospital No. 62 of the Department of Health of the City of Moscow (Moscow region), Republican Clinical Oncology Center of the Ministry of Health of the Republic of Tatarstan named after Professor M.Z. Sigala (Kazan), Orenburg Regional Clinical Oncology Center (Orenburg).

The study involved 58 patients whose response to treatment was adequately assessed.

Inclusion criteria:

- Confirmed uHCC
- Therapy with lenvatinib

Exclusion criteria:

- Decompensated liver cirrhosis
- Insufficient clinical data
- Follow-up period of less than 3 months after lenvatinib prescription

Confirming HCC diagnosis

The diagnosis was confirmed based on the results of a histological examination (morphological verification), or if signs characteristic of HCC were identified in a cirrhotic liver according to multiphase computed tomography (CT) or magnetic resonance imaging (MRI): diffuse (not annular) contrast enhancement of a >1 cm tumor in the late arterial phase and washout of the contrast agent in the venous phase; in tumor nodes of >2 cm in size, a pseudocapsule detected in a delayed (equilibrium) phase; tumor growth by 50 % in less than 6 months or an increase in the tumor size by at least 5 mm in 6 months. These Liver Imaging Reporting and Data System (LI-RADS) radiological classification criteria are approved for use by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) [22–24]. Randomized trials have shown that the LI-RADS category 4–5 has a high specificity (95–100 %) for high-risk HCC patients with a nodule size of >10 mm [25–27].

Dosage regimen for lenvatinib

In the study patients, lenvatinib (Lenvima®, Eisai Co., Ltd., Tokyo, Japan) was administered orally according to the Prescribing Information in the period from 14.10.2018 to 17.11.2021. Patients weighing <60 kg received lenvatinib at a dose of 8 mg once daily; patients weighing ≥60 kg received it at a dose of 12 mg once daily; and patients with Child-Pugh class B received lenvatinib at a dose of 8 mg once daily, regardless of weight.

Study methods

Baseline characteristics, including age, sex, body weight, underlying liver disease, and specific tumor characteristics, i.e. date of diagnosis, tumor etiology and stage at diagnosis according to the BCLC scale, macrovascular and portal vein invasion, extrahepatic spread, and previous treatment were assessed retrospectively. At baseline, data were obtained on the assessment of the severity and degree of cirrhosis compensation on the Child-Pugh scale, the patient's performance status using the scale of the Eastern Cooperative Oncology Group (ECOG), and the AFP blood level.

The intermediate HCC stage (B according to BCLC) is characterized by a multinodular asymptomatic liver tumor without macrovascular invasion, the patient's performance status being satisfactory (ECOG score of 0), the severity of cirrhosis scored as Child-Pugh A/B, while the advanced stage (C according to BCLC) is characterized by the presence of a tumor of any size, invasion of the main hepatic vessels and/or extrahepatic spread, severity of cirrhosis scored as Child-Pugh A/B, ECOG score of 0–2.

As the disease progressed, the lenvatinib was discontinued according to the manufacturer's instructions. In addition to tumor progression, other reasons for treatment discontinuation were analyzed, such as worsening of liver function and adverse events (AEs).

Response was assessed every 2–3 months by CT or MRI according to the response evaluation criteria in solid tumors mRECIST. The outcome was qualified as complete and partial response (CR, PR), stabilization of the disease (SD), and progression of the disease (PD). The disease control rate (DCR) was defined as the proportion of patients who have achieved complete/partial response and stable disease as the best radiological response.

Patients were followed up until death or data cutoff. Patients who were alive but had their last documented visit more than 6 months before database lock were considered lost to follow-up.

Ethical considerations

The study was conducted in accordance with Good Clinical Practice (GCP; 2016, Astana) and Clinical Practice Guidelines of the Russian Federation (Order of the Ministry of Health of the Russian Federation No. 200n, 2016). All procedures in this study met the ethical standards of the World Medical Association's Declaration of Helsinki (Fortaleza, Brazil, 2013). Informed consent was not required due to the retrospective nature of the study.

Documentation of statistical methods

Statistical analysis was done using the SPSS Statistics 26.0 software (IBM Corp., Armonk, NY, USA). Baseline characteristics were described as numbers, percentages and medians with ranges. Overall survival (OS) was defined as the interval from the date of treatment initiation to the date of death or the end of the follow-up period. The time period between the start of lenvatinib and the date of the first radiographically confirmed PD was used to determine progression-free survival (PFS). Median OS and PFS were estimated using the Kaplan–Meier

Table 1. Patients included in the study

Indicator*	All group (n = 58)
Age, years	60,7 (22,0–78,7)
Sex	
men	45 (77,6 %)
women	13 (22,4 %)
Hepatocellular carcinoma cause	
viral hepatitis B	5 (8,6 %)
viral hepatitis C	27 (46,6 %)
non virus-related	26 (44,8 %)
Liver cirrhosis	42 (72,4 %)
ECOG functional status	
0	11 (19,0 %)
1	41 (70,7 %)
2	6 (10,3 %)
BMI, kg/m^2	26,9 (16,9–42,6)
AFP level at baseline (normal <10 ng/mL)	76,0 (1,02–74000)
below 200 ng/mL	36 (62,1 %)
over 200 ng/mL	22 (37,9 %)
Child–Pugh class	
A	37 (63,8 %)
B	20 (34,5 %)
C	1 (1,7 %)
BCLC stage	
A	2 (3,4 %)
B	24 (41,4 %)
C	32 (55,2 %)
Presence of macroscopic portal vein invasion	7 (12,1 %)
Extrahepatic spread	13 (22,4 %)

*Data are presented as median (min–max) or abs. numbers (%)

method. Chi-square, Fisher's exact test and log-rank tests were used to analyze differences between the subgroups of the study. Relative risks were expressed as a hazard ratio (HR) with a 95 % confidence interval (95 % CI). The significance of the results was determined at a significance level of p <0.05.

Results

The mean age of patients in the study group was 60.7 (range 22 to 78) years. There were 3 times more men than women – 45 (77.6 %) and 13 (22.4 %) patients, respectively. The baseline characteristics of patients are presented in Table 1.

The most common BCLC stages were B (n = 24, 41.4 %) and C (n = 32, 55.2 %). Thirty-seven (63.8 %) patients and 20 (34.5 %) patients were classified as Child-Pugh class B. Five patients (8.6 %) had a history of hepatitis B virus, and 27 (46.6 %) patients had that of hepatitis C virus. Most patients had a score of 0 or 1 on the ECOG scale: 11 (19.0 %) and 41 (70.7 %), respectively. Only 7 patients (12.1 %) had macroscopic portal vein invasion, and 13 (22.4 %) patients had extrahepatic spread. The median serum AFP levels were 76.0 ng/mL in the range of 1.02 to 74,000 ng/mL, and in 22 (37.9 %) patients, the baseline AFP level was ≥200 ng/mL, while 16 (27.6 %) patients had it as ≥400 ng/mL.

Prior to starting lenvatinib, 14 (24.1 %) patients had received prior HCC treatment. Surgical treatment was received by 7 patients (12.1 %). The most common local treatment was transarterial chemoembolization (TACE), with 6 patients (10.3 %) receiving at least one procedure. Four patients received prior drug treatment for HCC. Lenvatinib was prescribed as first-line systemic

therapy in 54 (93.1 %) patients. During the entire follow-up, 30 patients died (51.7 %), 28 patients were alive at the time of the last follow-up examination, of which 14 were still on lenvatinib.

The mean duration of treatment with lenvatinib was 9.7 ± 6.9 months (median 7.9, range 1 to 30 months). Dose reduction was required in 14 cases (24.1 %), and treatment interruption was necessary in 13 cases (22.4 %). Lenvatinib treatment discontinuation and drug withdrawal was associated with disease progression in 32 (55.2 %) patients, while in 5 (8.6 %) cases the drug was discontinued due to side effects; worsening of liver function with an increase in hepatic impairment was observed in 7 (12.1 %) patients (Table 2).

The median overall survival was 14.6 months (95 % CI 10.6-18.6) and the median progression-free survival was 11.1 months (95% CI 8.31 ÷ 13.8). The objective response was obtained in 19 (32.8 %) patients, and the disease control rate reached the level of 79.3 % (Table 3).

The ORR did not show statistically significant difference between patients with BCLC stage B and patients with BCLC stage C (29.2 % (7/24) vs. 31.3 % (10/32), $p = 0.867$), with ECOG score of 0 and 1 at treatment initiation (54.5 % (6/11) vs. 24.4 % (10/41), $p = 0.054$), with Child-Pugh class A and B (29.7 % (11/37) vs. 35.0 % (7/20), $p = 0.683$), in patients with viral and non-viral etiology of HCC (28.1% (9/32) vs. 38.5% (10/26), $p = 0.404$), with and without extrahepatic spread (38.5 % (5.13) vs. 31.1% (14/45), $p = 0.619$) and also with and without main portal vein invasion (42.9 % (3/7) vs. 31.4 % (16/51), $p = 0.544$).

The DCR was also comparable between patients with BCLC stage B and patients with BCLC stage C (79.2 % (19/24) vs. 78.1% (25/32), $p = 0.925$), with ECOG score of 0 and 1 at treatment initiation (90.9 % (10/11) vs. 80.5% (33/41), $p = 0.417$), with Child-Pugh class A and B (83.8 % (31/37) vs. 70.0 % (14/20), $p = 0.223$), in patients with viral and non-viral etiology of HCC (81.3 % (26/32) vs. 76.9 % (20/26), $p = 0.686$), with and without extrahepatic spread (92.3% (12/13) vs. 75.6 % (34/45), $p = 0.189$), and also with and without main portal vein invasion (57.1 % (4/7) vs. 82.4 % (42/51), $p = 0.121$).

Patients with the AFP level of less than 200 ng/mL showed a significantly higher objective response rate to therapy and the disease control rate compared with AFP levels ≥200 ng/mL (44.4 % (16/36) vs. 13.6 % (3/22), $p = 0.015$; and 88.9 % (32/36) vs. 63.6 % (14/22), $p = 0.021$, respectively).

Further, treatment efficacy was assessed in terms of patient survival depending on the main prognostic factors evaluated (Table 4).

The intermediate and advanced stages of the disease according to the Barcelona Clinic Liver Cancer (BCLC) classification, which takes into account the tumor process prevalence, liver function, the patient's objective status and the expected efficacy of treatment, also did not show statistically significant differences between median PFS (stage B: 12.2 (9.54–14.9) months, stage C: 9.70 (5.23–14.2) months, $p = 0.669$) and OS (stage B: 14.6 (10.8–18.4) months, stage C: 14.3 (6.00–22.7) months, $p = 0.619$) (Fig.1).

During treatment with lenvatinib, the patient's ECOG performance status did not have a statistically significant impact on the median PFS (score 0: 8.87 (7.14–10.6), score 1: 11.6 (9.44–13.7) months, $p = 0.632$) and OS (score 0: 14.6 (11.3–17.9), score 1: 12.9 (10.0-15.7) months, score 2: 5.07 (0.0–15.8) months, $p = 0.225$).

Liver function and liver disease compensation assessed by the Child-Pugh class did not

Table 2. Changes in lenvatinib regimen ($n = 58$)

Changes	*n*	%
Drug withdrawal due to:	44	75.9
Adverse effects	5	8.6
Disease progression	32	55.2
Growing liver failure	7	12.1
Dose reduction	14	24.1
Treatment breaks	13	22.4
Second-line therapy after lenvatinib:	20	34.5
Regorafenib	15	25.9
Sorafenib	2	3.45
Other	3	5.17

Table 3. Clinical response to lenvatinib therapy (n = 58)

Confirmed objective tumor response	*n*	%
Combined response (CR)	1	1.7
Partial response (PR)	18/58	31.0
Stable disease (SD)	27/58	46.6
Objective response rate (CR+PR)	19/58	32.8
Disease control rate (CR+PR+SD)	46/58	79.3
Disease progression	12/58	20.7
Number of deceased patients	30/58	51.7
Progression-free survival median (95%CI), months	11.1 (8.31–13.8)	
Overall survival median (95%CI), months	14.6 (10.6–18.6)	

Table 4. Long-term outcomes of lenvatinib therapy depending on the main prognostic factors (n=58)

Long-term outcome	Factor		*P*
	ECOG 0, *n* = 11	ECOG 1, *n* = 41	
PRS median (95%CI), months	8,87 (7,14–10,6)	11,6 (9,44–13,7)	0,632
OS median (95%CI), months	14,6 (11,3–17,9)	12,9 (10,0–15,7)	0,225
Disease progression*	9 (81,8 %)	23 (56,1 %)	0,120
	BCLC B, n = 24	BCLC C, n = 32	
PRS median (95%CI), months	12,2 (9,54–14,9)	9,70 (5,23–14,2)	0,669
OS median (95%CI), months	14,6 (10,8–18,4)	14,3 (6,00–22,7)	0,619
Disease progression*	15 (62,5 %)	20 (62,5 %)	1,000
	Child-Pugh A, n = 37	Child-Pugh B, n = 20	
PRS median (95%CI), months	10,7 (7,65–13,8)	11,6 (7,21–15,9)	0,512
OS median (95%CI), months	14,3(11,5–17,2)	19,6 (5,80–33,3)	0,639
Disease progression*	21 (56,8 %)	15 (75,0 %)	0,174
	Viral etiology		
	Yes, n = 32	No, n = 26	
PRS median (95%CI), months	12,2 (8,94–15,5)	8,87 (4,56–13,2)	0,386
OS median (95%CI), months	12,9 (9,25–16,5)	14,6 (5,95–23,3)	0,795
Disease progression*	18 (56,3 %)	18 (69,2 %)	0,314
	Macroscopic portal vein invasion		
	Yes, n = 7	No, n = 51	
PRS median (95%CI), months	3,97 (0,00–8,07)	11,1 (8,46–13,7)	0,053
OS median (95%CI), months	8,37 (1,74–15,0)	14,6 (6,76–22,5)	0,167
Disease progression*	6 (85,7 %)	30 (58,8 %)	0,169
	Extrahepatic spread		
	Yes, n = 13	No, n = 45	
PRS median (95%CI), months	12,0 (11,0–12,9)	10,3 (7,26–13,3)	0,775
OS median (95%CI), months	19,6 (8,68–30,5)	14,3 (11,5–17,2)	0,340
Disease progression*	6 (46,2 %)	30 (66,7 %)	0,180
	AFP <200 ng/mL n = 36	AFP ≥200 ng/mL n = 22	
PRS median (95%CI), months	12,0 (10,1–13,8)	7,30 (3,70–10,9)	0,141
OS median (95%CI), months	16,1 (8,73–23,5)	12,0 (5,95–18,9)	0,020*
Disease progression*	22 (61,1 %)	14 (63,6 %)	0,849

* on the cut-off date

have an impact on PFS (score A: 10.7 (7.65–13.8) months, score B: 11.6 (7.21–15.9) months, $p = 0.512$) and OS (score A: 14.3 (11.5–17.2) months, score C: 19.6 (5.80–33.3) months, $p = 0.639$).

The viral etiology did not have an impact on survival rates. The duration of PFS with a history of viral hepatitis B or C was 12.2 (8.94–15.5) months; with other causes – 8.87 (4.56–13.2) months, $p = 0.386$. OS reached the level of 12.9 (9.25–16.5) and 14.6 (5.95–23.3), $p = 0.795$ (Fig. 2).

Patients with macroscopic portal vein invasion had a significantly lower PFS as compared with patients without it – 3.97 (0.00–8.07) vs. 11.1 (8.46-13.7), $p = 0.053$ (Fig. 4). At the same time, in terms of OS in patients with macroscopic invasion, only a trend towards lower median values was observed: 8.37 (1.74–15.0) vs. 14.6 (6.76–22.5), $p = 0.167$ (Fig. 3).

In the presence or absence of extrahepatic spread of the tumor process, the duration of PFS and OS periods did not show statistically significant difference: 12.0 (11.0–12.9) vs. 10.3 (7.26–13.3), $p = 0.775$ and 19.6 (8.68–30.5) vs. 14.3 (11.5–17.2), $p = 0.340$, respectively.

High levels of AFP (greater than 200 ng/mL) prior to treatment had a negative impact on survival rates. PFS was 7.30 (3.70–10.9) vs. 12.0 (10.1–13.8) months with AFP of less than 200 ng/mL, $p = 0.141$. OS had a significantly lower value of 12.0 (5.95–18.9) months in the group of patients with AFP ≥ 200 ng/mL vs. 16.1 (8.73–23.5) months in the group of patients with AFP of < 200 ng/mL, $p = 0.020$ (Fig. 4).

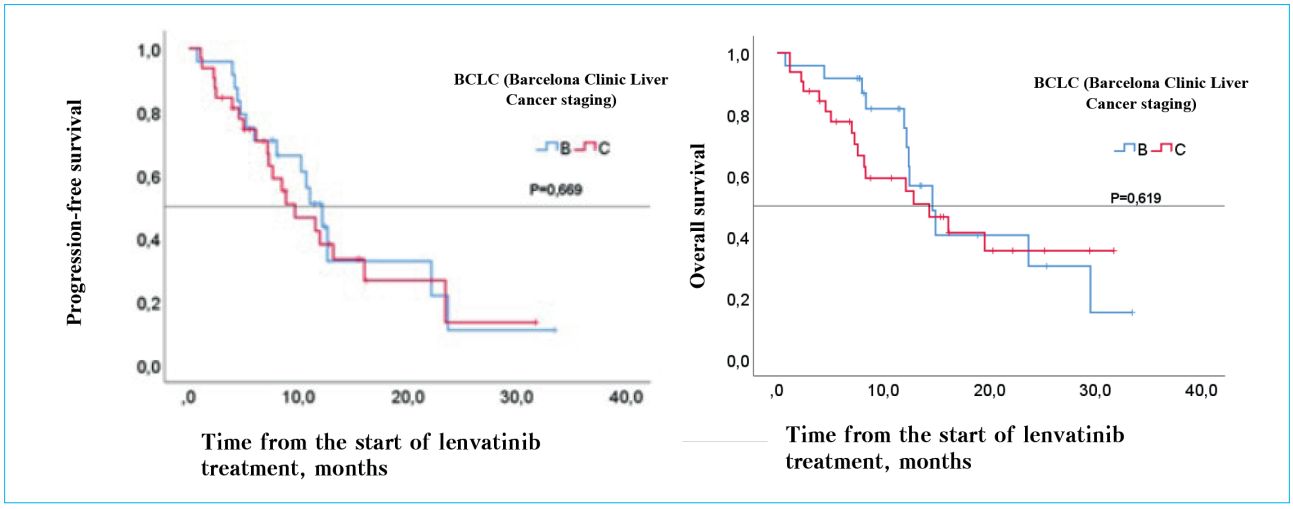

Fig. 1. PFS and OS depending on the BCLC stage.

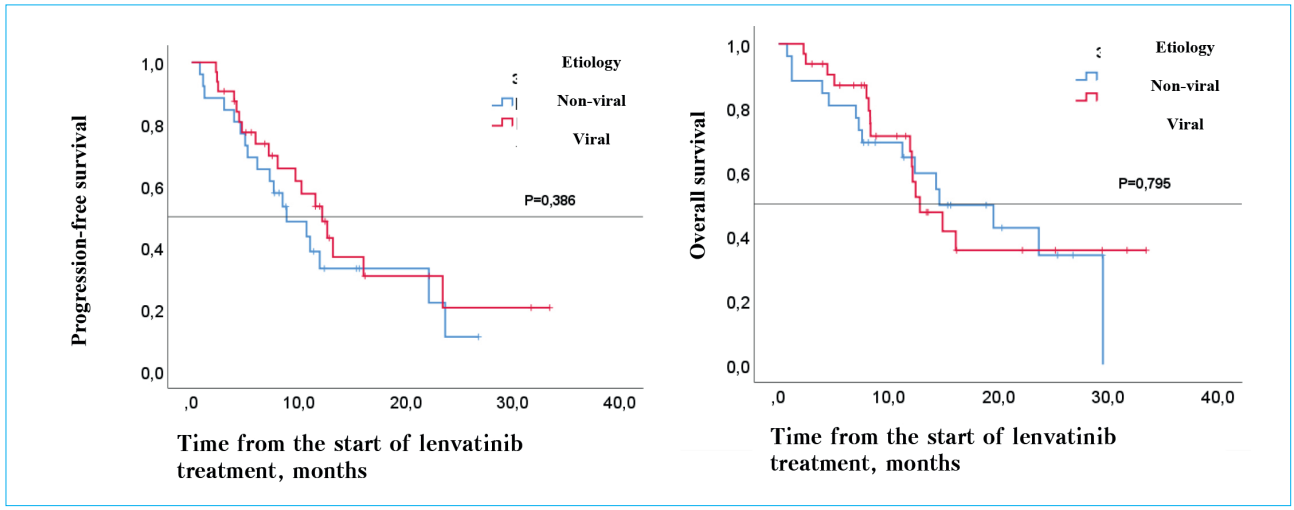

Fig. 2. PFS and OS depending on viral etiology

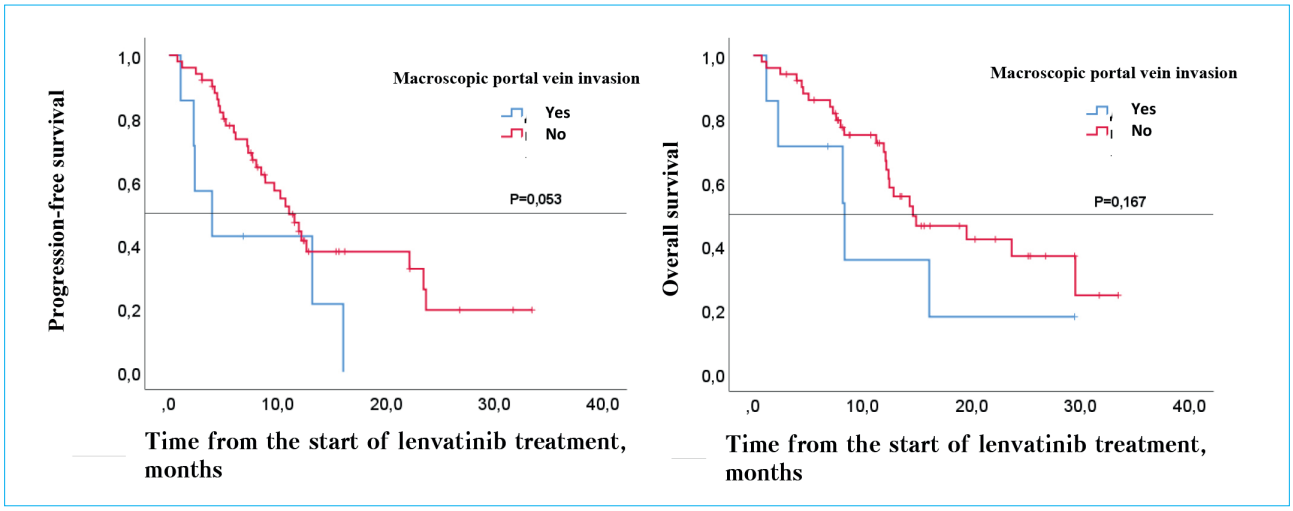

Fig. 3. PFS and OS depending on the presence/absence of macroscopic portal vein invasion

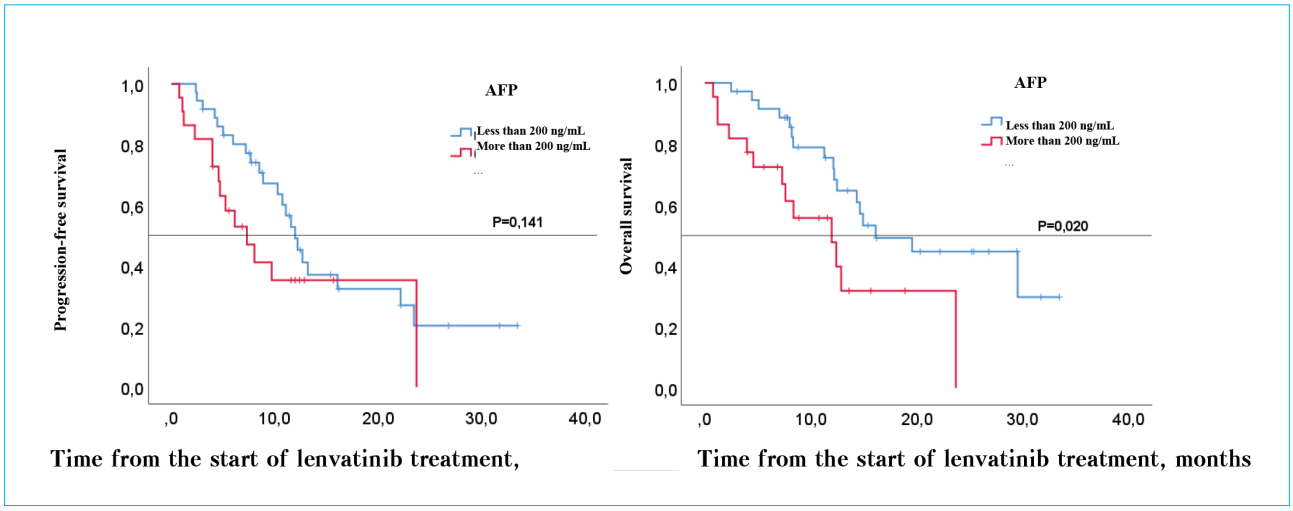

Fig. 4. PFS and OS depending on the AFP level

Subsequent second-line systemic anti-tumor treatment was received by 20 patients (34.5 %) (Fig. 5). Regorafenib was the most commonly prescribed drug (n = 15; 25.9 %), followed by sorafenib (n = 3; 5.17 %), ramucirumab (n = 1, 1.72 %), and pembrolizumab (n = 1, 1.72 %). Immunotherapy was given in 3 cases (5.17 %). In 12/20 patients (60.0 %), disease stabilization was observed. Median PFS from the 2nd line initiation was 6 months (3.97–8.03), median OS – 7,6 months (5.07–10.1)

The Cox proportional hazard analysis showed that patients with macroscopic portal vein invasion or AFP levels ≥200 ng/mL before treatment had a tendency to disease progression (Fig. 6). The risk of progression in presence of macroscopic portal vein invasion is 2.4 times higher than in its absence (p = 0.086). High levels of AFP increase the likelihood of progression by 1.7 times (p = 0.154).

In patients with an AFP level ≥200 ng/mL before treatment initiation, the probability of survival decreases by 2.4 (1.1–5.0) times (Fig. 6). The relative risk also tends to increase by 1.8 times (0.7–4.9) with an ECOG performance status score 1 and by 2 times (0.7–5.1) with macroscopic portal vein invasion, with a significance of p = 0.205 and p = 0.208, respectively.

Adverse events during treatment with lenvatinib were reported in 82.8 % (n = 47) of patients. The most common AEs were hypertension (32.8 %), fatigue (24.1 %), body weight loss (12.1 %), decreased appetite (10.3 %).

With regard to liver-related side effects, 4 patients (6.9 %) had an increase in transaminases

during treatment, 3 (5.12 %) developed hepatotoxicity, and 2 (3.45 %) developed bilirubinemia.

Among 48 patients with AEs, 30 (62.5 %) had disease progression and 23 (47.9 %) patients died. The median values of PFS and OS in the subgroups of patients with and without AEs were 11.6 (9.41–13.7) versus 4.20 (3.58–4.83) months (p = 0.122) and 16,1 (8.52–23.8) versus 4.43 (0.00–11.6) months (p < 0.001), respectively.

Discussion

Systemic therapy with tyrosine kinase inhibitors (TKIs) or immunotherapeutic agents is used to increase survival in patients with advanced (BCLC C) HCC. Sorafenib has been established as the standard first-line treatment for uHCC since 2007, when the SHARP study demonstrated that sorafenib improved median overall survival (OS) compared with placebo in patients who had not previously received systemic therapy (10.7 vs. 7.9 months, hazard ratio = 0.69, p <0.001) [28]. In 2018, based on the REFLECT study, lenvatinib became the new drug of choice, which should be introduced into the uHCC treatment regimen [7,8]. However, in real-world clinical use, there are patients who remained outside the scope of the REFLECT study, including patients who received lenvatinib in the second line therapy, patients with ECOG 2, Child-Pugh class B, and BCLC substages B2 and B3 [12, 29, 30]. Therefore, real-world data are of key importance for expanding the evidence base.

T. Sho et al. studied 105 patients with uHCC in a real clinical setting, 64 of whom did not meet the inclusion criteria for the REFLECT study [12]. Among these 64 patients, 28 had a history of TKI treatment, 27 had Child-Pugh class B, 14 had HCC at ≥50 % of liver, 6 had decreased platelets, 7 had bile duct invasion, and 5 had portal vein invasion. The results of our work are comparable to the results of this study: the objective response rate in our study was 32.8 % vs. 53.5 % in the study by T. Sho et al.; the disease control rate was 79.3 and 91.9 %, respectively. Median PFS in our study was 11.1 months, while in the study by T. Sho et al. it was 9.8 months. In our study, lenvatinib showed a better safety profile than that the study by T. Sho et al.: drug withdrawal due to side effects occurred in 8.6 % and 27.6 % of cases, respectively. Differences may be explained by varying baseline characteristics of included patients with uHCC: in the study by T. Sho et al., the majority had an ECOG score of 0, while in our study it was 1; the AFP level was 14.0 and 76.0, respectively.

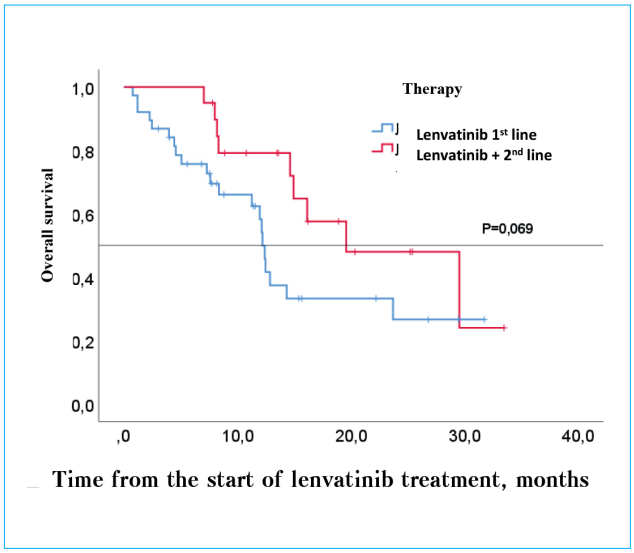

Fig. 5. OS depending on the presence/absence of subsequent second-line systemic anticancer treatment

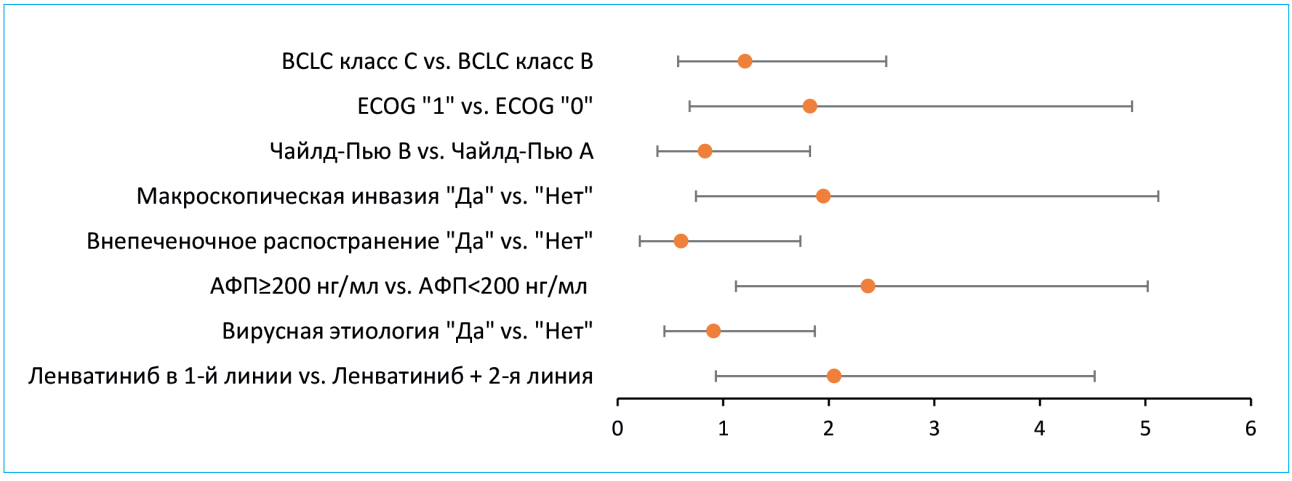

Fig. 6. Effects of major predictors on OS by the results of univariate Cox proportional hazards analysis

Table 5. Adverse effects (n=58)

Adverse effect (any severity degree)	*n*	%
Arterial hypertension	19	32.8
Weakness	14	24.1
Weight loss	7	12.1
Appetite loss	6	10.3
Skin toxicity	4	6.90
Thrombocytopenia	4	6.90
ALT/AST above normal	4	6.90
Hepatotoxicity	3	5.12
Bilirubinemia	2	3.45
Diarrhea	2	3.45
Palmar-plantar erythrodysesthesia	2	3.45
Increased pain syndrome	2	3,45
Nausea	1	1.72
Polyneuropathy	1	1.72
Fistulas	1	1.72
Increased body temperature	1	1.72
Nephrotic syndrome	1	1.72

In REFLECT, median OS on lenvatinib was 13.6 months and median PFS was 7.4 months [7, 8]. In our study, median OS was 14.6 months and median PFS was 11.1 months. The fact that the parameters are comparable confirms the efficacy of lenvatinib in real-world clinical use in various groups of patients with uHCC, including those not studied in the scope of REFLECT.

The use of systemic anticancer therapy in the 2nd line after progression on lenvatinib contributed to an increase in median OS by more than 1.5 times and the probability of survival by 2 times compared with patients who received lenvatinib only in the 1st line, however, the differences did not reach statistical reliability. Studies on a larger sample of patients are needed to test this trend.

The results of comparative studies of lenvatinib with sorafenib in real-world clinical use have recently been published [31,32]. In both studies, lenvatinib was superior to sorafenib. Further, median OS, median PFS and DCR were also comparable with the results obtained in our study.

The recently published results of the IMbrave150 study showed that the combination of atezolizumab + bevacizumab also demonstrated better OS and PFS compared to sorafenib in patients with uHCC: median OS was 19.4 months on the combination vs. 13.4 on sorafenib; median PFS was 6.9 months on the combination vs. 4.3 months, $p < 0.001$ [33]. At the same time, a comparative study of real-world data did not demonstrate differences between groups of patients with uHCC who were prescribed atezolizumab + bevacizumab or lenvatinib, neither in terms of median OS, nor in terms of median PFS. Investigators concluded that these regimens were comparable in efficacy and safety [34]. However, the cost of therapy with the combination of atezolizumab + bevacizumab is prohibitive: a pharmacoeconomic study demonstrated that atezolizumab + bevacizumab combination therapy has clinical benefits, but is not cost-effective compared to sorafenib for first-line treatment of unresectable or metastatic HCC from a US payer perspective [35]. Therefore, lenvatinib or sorafenib remain the preferred first-line regimen for these patients.

Conclusion

Lenvatinib confirmed its efficacy and safety in patients with uHCC based on real-world data. However, the treatment outcome may vary depending on such factors as AFP levels and the presence of macroscopic portal vein invasion. Further pharmacoeconomic and comparative clinical studies of real-world data will help broaden our knowledge of the prospects for the use of various regimens of systemic therapy in patients with uHCC.

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