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ORIGINAL ARTICLE

Own Experience of Using Lenvatinib in Patients with Advanced Hepatocellular Carcinoma in Real Clinical Practice based on Moscow City Oncological Hospital №62

Mikhail V. Volkonsky✉, **Roman S. Zhikhorev, Tatiana A. Makarkina, Viktoriia M. Filippova, Yuliya V. Vasileva, Arshak A. Akopyan, Tatyana A. Zhelezkova**

Moscow City Oncological Hospital №62

Abstract

Background. Hepatocellular carcinoma (HCC) (hepatocarcinoma) is the most common (about 85% of cases) malignant liver tumor originating from hepatocytes. According to officially published statistics for the city of Moscow for 2019, 329 people were registered with the first-ever diagnosed C22 malignant neoplasms (liver and intrahepatic bile ducts, including 6.7% of those who were actively identified. The absolute number of such patients registered at the end of the year was 716, which is 5.7 per 100 000 of the population. The contingent accumulation index is 2.2 (the average for Russia is 1.5). With that, 43.1% of patients had stage IV. Mortality rate during the first year after diagnosis is 53.9% (in Russia on the whole, this value is 66.5%). Drug systemic therapy is the method of choice for HCC which is not subject to surgical intervention and local methods of treatment.

Materials and methods. A retrospective analysis of the efficacy and safety of lenvatinib in patients diagnosed with HCC was carried out in real clinical practice at the Outpatient Oncology Care Center of the Moscow City "Oncological Hospital №62". The data analysis covers the period from February 2016 to June 2021. The analysis included 15 patients with a morphologically verified diagnosis of HCC treated with lenvatinib. For the majority of patients, 11 (73.3%) patients received lenvatinib as first-line therapy.

Results. The median progression-free survival was 11.2 months for the entire observation group. In the first line of therapy, the PFS result was the highest and amounted to 12.3 months. The median dose received by patients was 10.9 mg. The level of disease control was 86.6%. The most clinically significant adverse events were grade 2 neutropenia, grade 2 thrombocytopenia, grade 2 asthenia, grade 2–3 hypertension. Lenvatinib had a manageable safety profile.

Conclusion. The performed analysis confirms the data of the REFLECT study on the efficacy of lenvatinib both in healthy patients and in patients with a spectrum of comorbidities with significant (more than 50% of the liver parenchyma) liver damage.

Keywords: hepatocellular cancer, real clinical practice, lenvatinib

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Introduction

Hepatocellular carcinoma (HCC) (hepatocarcinoma) is the most common (about 85% of cases) malignant liver tumor originating from hepatocytes [1].

Along with the TNM Classification of Malignant Tumors (Tumor, Nodus, Metastasis), which is taken into account in the book "The State of Cancer Care for the Population of the Russian Federation", the Barcelona Clinical Liver Cancer classification is also used – it is an improved HCC classification that considers the prevalence of tumor process, the functional state of the liver, the objective condition of the patient and the estimated efficacy of treatment [2].

According to officially published statistics for the city of Moscow for 2019, 329 people were registered with the first-ever diagnosed C22 malignant neoplasms (liver and intrahepatic bile ducts), including 6.7% of those who were actively identified. The absolute number of such patients registered at the end of the year was 716, which is 5.7% per 100 000 of the population. The contingent accumulation index is 2.2 (the average for Russia is 1.5). With that, 43.1% of patients had stage IV. Mortality rate during the first year after diagnosis is 53.9% (in Russia on the whole, this value is 66.5%).

In addition, mortality rate in Moscow for this category is 26.3%, which is lower than the average for Russia (37.3%) and

Information about the authors / Информация об авторах

✉*Mikhail V. Volkonsky* – Cand. Sci. (Med.), Moscow City Oncological Hospital №62. E-mail: mux19@yandex.ru; ORCID: 0000-0003-4060-5015

Roman S. Zhikhorev – oncologist, Moscow City Oncological Hospital №62. ORCID: 0000-0003-2281-7380

Tatiana A. Makarkina – chemotherapist, Moscow City Oncological Hospital №62. ORCID: 0000-0002-1000-4262

Viktoriia M. Filippova – oncologist, Moscow City Oncological Hospital №62. ORCID: 0000-0003-1990-175X

Yuliya V. Vasileva – chemotherapist, Moscow City Oncological Hospital №62. ORCID: 0000-0001-6394-1578

Arshak A. Akopyan – chemotherapist, Moscow City Oncological Hospital №62. ORCID: 0000-0002-0893-9034

Tatyana A. Zhelezkova – oncologist, Moscow City Oncological Hospital №62. ORCID: 0000-0001-5049-6559

✉*Волконский Михаил Викторович* – канд. мед. наук, врач-химиотерапевт ГБУЗ МГОБ №62. E-mail: mux19@yandex.ru; ORCID: 0000-0003-4060-5015

Жихорев Роман Сергеевич – врач-онколог ГБУЗ МГОБ №62. ORCID: 0000-0003-2281-7380

Макаркина Татьяна Андреевна – врач-химиотерапевт ГБУЗ МГОБ №62. ORCID: 0000-0002-1000-4262

Филиппова Виктория Михайловна – врач-онколог ГБУЗ МГОБ №62. ORCID: 0000-0003-1990-175X

Васильева Юлия Владимировна – врач-химиотерапевт ГБУЗ МГОБ №62. ORCID: 0000-0001-6394-1578

Акопян Аршак Александрович – врач-химиотерапевт ГБУЗ МГОБ №62. ORCID: 0000-0002-0893-9034

Железкова Татьяна Андреевна – врач-онколог ГБУЗ МГОБ №62. ORCID: 0000-0001-5049-6559

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Собственный опыт применения ленватиниба у пациентов с распространенным гепатоцеллюлярным раком в условиях реальной клинической практики на базе ГБУЗ «Московская городская онкологическая больница №62»

М.В. Волконский✉, Р.С. Жихорев, Т.А. Макаркина, В.М. Филиппова, Ю.В. Васильева, А.А. Акопян, Т.А. Железкова
ГБУЗ «Московская городская онкологическая больница №62» Департамента здравоохранения г. Москвы, Москва, Россия

Аннотация

Обоснование. Гепатоцеллюлярный рак (ГЦР) наиболее частая злокачественная опухоль печени, исходящая из гепатоцитов. Согласно официально опубликованным статистическим данным, в Москве за 2019 г. число взятых на учет больных с впервые в жизни установленным диагнозом злокачественных новообразований С22 составило 329 человек, из них выявлены активно 6,7%. Абсолютное число таких больных, находившихся на учете на конец года, – 716, что составляет 5,7% на 100 тыс. населения. Индекс накопления контингентов – 2,2 (средний показатель по России составляет 1,5). При этом с IV стадией были 43,1% пациентов. Летальность на 1-м году с момента установки диагноза составила 53,9% (по России этот показатель – 66,5%). Лекарственная системная терапия является методом выбора при ГЦР, не подлежащем хирургическому вмешательству и локальным методам лечения.

Материалы и методы. Проведен ретроспективный анализ эффективности и безопасности ленватиниба у пациентов с установленным диагнозом ГЦР в Центре Амбулаторной Онкологической Помощи ГБУЗ «Московская городская онкологическая больница №62» в условиях реальной клинической практики. В анализ включены 15 пациентов с морфологически верифицированным диагнозом ГЦР, которые получали лечение ленватинибом. Для 11 (73,3%) пациентов ленватиниб был назначен в качестве 1-й линии терапии.

Результаты. Медиана выживаемости без прогрессирования составила 11,2 мес для всей группы наблюдения. Выживаемость без прогрессирования после 1-й линии терапии была наибольшей – 12,3 мес. Частота контроля над заболеванием – 86,6%. Наиболее клинически значимыми нежелательными явлениями были нейтропения 2-й степени, тромбоцитопения 2-й степени, астения 2-й степени, артериальная гипертензия 2–3-й степени. Ленватиниб имел управляемый профиль безопасности. Медианная доза составила 10,9 мг.

Заключение. Проведенный анализ подтверждает данные исследования REFLECT об эффективности ленватиниба как у сохранных пациентов, так и у пациентов со значимым (более 50% паренхимы) поражением печени в спектре сопутствующей патологии.

Ключевые слова: гепатоцеллюлярный рак, реальная клиническая практика, ленватиниб

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for the Central Federal District (31%). This may witness the provision of high-quality medical care and effective patient routing in Moscow [3].

According to the recommendations (National Comprehensive Cancer Network, European Association for the Study of the Liver–European Organisation for Research and Treatment of Cancer, American Association for the Study of Liver Diseases, Russian Society of Clinical Oncology, etc.), drug systemic therapy is the method of choice for HCC which is not subject to surgical intervention and local methods of treatment. The use of systemic targeted therapy lasts until the appearance of objective (confirmed by computed tomography and magnetic resonance imaging) signs of disease progression, intolerable toxicity or decompensation of concomitant diseases [1]. In this case, the main goal of drug treatment is to increase survival and control tumor growth [4–7].

According to the Clinical Guidelines for Hepatocellular Carcinoma approved by the Ministry of Health of the Russian Federation, sorafenib or lenvatinib is recommended in the 1st line of systemic therapy for HCC [1].

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors – VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also has an inhibitory effect on other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor receptors (FGFR 1, 2, 3, 4), platelet-derived growth factor receptor α (PDGFRα), as well as receptor tyrosine kinases *KIT* and *RET*[1].

The administration schedule of lenvatinib depends on the initial weight of the patient: for patients weighing ≥60 kg, treatment begins with a dose of 12 mg/day once; for patients weighing <60 kg, it begins with a single daily dose of 8 mg.

The main registration study of lenvatinib for the treatment of patients with resectable hepatocellular carcinoma is the REFLECT study.

The original design of the non-inferiority REFLECT study was to achieve a primary endpoint of non-inferiority in overall survival (OS). The median OS was similar for both sorafenib and lenvatinib, although numerically the best was seen with lenvatinib (13.6 months for lenvatinib vs 12.3 months for sorafenib; hazard ratio – HR 0.92, 95% CI – confidence interval 0.79–1.06) [7]. Secondary endpoint analysis of progression-free survival (PFS) was 7.4 months for lenvatinib vs 3.7 months for sorafenib; HR 0.66, 95% CI 0.57–0.77 [7].

[1]Patient Information Leaflet for lenvatinib 003398, approved on 30.12.2020. Available at: https://www.rlsnet.ru/mnn_index_id_6709.htm Accessed: 15.01.2022.

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Materials and methods

A retrospective analysis of the efficacy and safety of lenvatinib in patients diagnosed with HCC was carried out in real clinical practice at the Outpatient Oncology Care Center of the Moscow City Oncological Hospital №62. The data analysis covers the period from February 2016 to June 2021.

The analysis includes 15 patients with a morphologically verified diagnosis of HCC who were treated with lenvatinib. All patients had histological verification of the diagnosis, satisfactory liver and kidney function, Eastern Cooperative Oncology Group (ECOG) status 1–2.

Some patients had previous surgical treatment – 5 (33.3%); a large cohort of patients did not have a history of previous surgery – 10 (66.7%). Two patients had HCC after liver transplantation.

Patients were prescribed targeted therapy with lenvatinib at a dose depending on the patient's body weight. Patients weighing over 60 kg had a dose of 12 mg per day, while patients weighing less than 60 kg had a dose of 8 mg per day. In the case of the development of toxicity, the occurrence of adverse events of grade 3 and higher according to the Common Terminology Criteria for Adverse Events classification (CTCAE) 5.0, the dose was reduced according to the drug patient information leaflet. Lenvatinib therapy was continued until disease progression, unacceptable toxicity, or patient refusal to continue treatment. Patients received therapy on an outpatient basis, including regular examinations and follow-up studies according to established standards of care.

The mean age of patients was 63 (44–84) years. Thirteen patients had the ECOG performance status 0–1 (86.7%), and two patients had the ECOG 2 (13%). The distribution according to the initial liver function was as follows: 12 (80%) patients had a functional status corresponding to Child–Pugh A, 3 (20%) patients – Child–Pugh B. Baseline characteristics of patients are presented in table 1.

Six patients (40%) had an initial level of alfa-Fetoprotein (AFP) less than 400 ng/mL; in 4 (26.7%) patients, this level was more than 400 ng/mL; such data were absent for a third patient.

In 7 (46.7%) patients, extrahepatic spread of the disease was identified, in 8 (53.3%) patients, extrahepatic spread of lesions was not reported. With that, the following localizations were noted among extrahepatic spread metastases: bones, subcutaneous metastases.

Five patients (33.3%) had a history of confirmed hepatitis C, two patients (13.3%) had hepatitis B. Eight patients (53.3%) did not have a history of hepatitis B or C.

For the majority of patients, 11 (73.3%) patients received lenvatinib as first-line therapy.

Three patients (20%) received 1st line of prior therapy (sorafenib), 1 patient (6.7%) received 2nd lines of prior therapy (sorafenib and regorafenib).

Analysis

The purpose of this retrospective analysis was to evaluate the efficacy and safety of lenvatinib in real clinical practice at the Moscow City Oncological Hospital №62. The following criteria were used to evaluate the efficacy:

- objective response rate;
- PFS.

Long-term outcomes of treatment, such as one-year, three-, five-year survival, OS, were not assessed in our analysis. To assess the tumor response, various diagnostic methods routinely used in clinical practice, such as computer tomography, magnetic resonance imaging, were used. The tumor response to treatment was assessed according to modified response evaluation criteria in solid tumors (mRECIST).

The safety of therapy was evaluated by reporting adverse events and grading them according to CTCAE 5.0

Results

Effectiveness

The median PFS was 11.2 months (1–20 months) and was estimated as the time from the start of therapy to progression or death from any cause.

Table 1. Baseline characteristics of patients

Parameter	Value
Median age	63 (±10.1) years
Number of cards registered	15
Median weight	70 (±11.2) kg

Table 2. PFS on the presence of hepatitis

Hepatitis	Median PFS, months
Hepatitis B, C	7.0
No hepatitis	13.2

Table 3. Adverse events and their frequency

Adverse event, any severity	Number of patients	Frequency, %
Hypertension	9	60
Hand-foot syndrome	6	40
Toxic hepatitis	2	13.3
Increased alanine aminotransferase, aspartate aminotransferase	1	6.7
Rash	1	6.7

Twenty percent of patients who progressed on lenvatinib received subsequent lines of systemic therapy (nivolumab, regorafenib). Here, the reasons why patients did not receive subsequent lines of therapy were not analyzed. In the first line of therapy, the PFS best result was 12.3 months.

In 2 (13.3%) patients, when receiving lenvatinib, a partial response was recorded as the best; the majority of patients, 73.3%, were able to achieve stabilization when assessed according to mRECIST criteria.

In order to determine clinical predictors of lenvatinib efficacy, PFS was compared depending on concomitant hepatitis B or C (table 2), as well as the presence of an initially elevated AFP level.

When assessing a group of patients with an initially elevated level of AFP, it was noted that with AFP of more than 400 ng/mL, the median PFS was 7.3 months.

It is also worth noted that 9 patients received lenvatinib therapy for a long time, i.e. for more than 7 months. The median duration of therapy for them was 14.3 months.

Safety

Lenvatinib had a manageable safety profile. The median dose received by patients was 10.9 mg.

The most clinically significant adverse events were grade 2 neutropenia, grade 2 thrombocytopenia, grade 2 asthenia, grade 2–3 hypertension. Besides, the phenomena of intoxication, decreased appetite, grade 2–3 rash, exacerbation of arthritis were noted. The most common adverse events are listed in table 3.

It should be noted that an important factor in overcoming toxicity, in clinical observation, was the period of reduction from the time of occurrence of an adverse event. The earlier the discontinuation or dose reduction was undertaken, the faster the side effects were resolved. The data on a decrease in the efficacy of therapy with dose reduction were not identified in this study.

Conclusion

The analysis made, firstly, confirms the data of the REFLECT study on the efficacy of lenvatinib, both in safe patients and in patients with a spectrum of comorbidities with significant (more than 50% of the liver parenchyma) liver damage. Secondly, there is evidence of efficacy in terms of PFS: it is higher than in the REFLECT study (12.3 months vs 7.4 months). Although, it should be noted that the limitations of this study were the small sample size, single-center analysis, and the absence of a comparator group. As in the REFLECT study, patients had an opportu-

nity to receive subsequent lines of therapy, which does not allow us to conclude that the 1st and subsequent lines of therapy are effective in terms of OS. The results obtained and described above contribute to the further study of lenvatinib in monotherapy and in combination with checkpoint inhibitors in the 1st line of therapy as a combinatorial partner to overcome the immunological delay and enhance immune presentation by achieving a rapid antitumor response. We were unable to identify any narrow category of patients who receive the maximum benefit from the prescription of lenvatinib. It should be noted that the prescription of the drug is possible for patients with ECOG 2 status and a spectrum of comorbidities with timely correction of adverse events.

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Authors' contribution. The authors declare the compliance of their authorship according to the international ICMJE criteria. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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