Гепатоцеллюлярная карцинома, ассоциированная с гепатитами В и С, у монголоидов и европеоидов Северо-Восточной Азии

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Более половины всех случаев гепатоцеллюлярной карциномы в мире выявляют в странах Азии. На территории Северо-Восточной Азии, где в сопредельных регионах проживают монголоиды и европеоиды, клинико-эпидемиологические особенности гепатоцеллюлярной карциномы исследованы недостаточно.

Цель исследования – сравнительная клинико-эпидемиологическая характеристика гепатоцеллюлярной карциномы и определение диагностической значимости некоторых сывороточных онкомаркеров в этнических группах монголоидов и европеоидов.

Материал и методы. Исследования проведены на сопредельных территориях Монголии и азиатской части России в районе озера Байкал (Иркутская область). Всего обследовано 300 больных гепатоцеллюлярной карциномой, в том числе 195 монголов из Улан-Батора и 105 русских, постоянно проживающих в Иркутской области.

Результаты и обсуждение. В Монголии 93% случаев гепатоцеллюлярной карциномы ассоциированы с вирусными гепатитами, причем на долю гепатита В приходится 34,5% случаев, что существенно отличает Монголию от азиатской части России. Среди неинфекционных факторов риска в Монголии существенную роль играет чрезмерное употребление алкоголя.

Заключение. В связи с недостаточной чувствительностью определения альфа-фетопротеина в этнической группе монголоидов необходим поиск новых молекулярных маркеров. Показана альтернативная возможность использования остеопонтин и глипикан-3 в качестве сывороточных предикторов гепатоцеллюлярной карциномы, диагностическая чувствительность которых выше альфа-фетопротеина и не различается в этнических группах монголоидов и европеоидов.

Ключевые слова:
гепатоцеллюлярная карцинома, факторы риска, альфа-фетопро-теин, остеопонтин, глипикан-3, монголоиды, европеоиды

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Hepatocellular carcinoma associated with hepatitis B and C in mongoloids and caucasians of North-East Asia

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More than half of all cases of hepatocellular carcinoma in the world are detected in Asian countries. However, not the territories of northeastern Asia, where Mongoloids and Caucasians live in adjacent territories, the clinical and epidemiological features of hepatocellular carcinoma have been insufficiently studied.

The aim – comparative clinical and epidemiological characteristics of hepatocellular carcinoma and determination of the diagnostic significance of some serum cancer markers in the ethnic groups of Mongoloids and Caucasians.

Material and methods. The studies were carried out in the adjacent territories of Mongolia and the Asian part of Russia in the area of Lake Baikal (Irkutsk region). A total of 300 patients with hepatocellular carcinoma were examined, including 195 Mongols from the city of Ulan Bator and 105 Russians permanently residing in the Irkutsk region.

Results and discussion. In Mongolia 93% of hepatocellular carcinoma cases are associated with viral hepatitis, with hepatitis B accounting for 34.5% of cases, which significantly distinguishes Mongolia from the Asian part of Russia. Excessive alcohol consumption is a significant non-infectious risk factor in Mongolia.

Conclusion. In connection with the insufficient sensitivity of the determination of alpha-fetoprotein in the ethnic group of Mongoloids, it is necessary to search for new molecular markers. An alternative possibility of using osteopontin and glypican-3 as serum predictors of hepatocellular carcinoma, the diagnostic sensitivity of which is higher than alpha-fetoprotein and does not differ in the ethnic groups of Mongoloids and Caucasians, has been shown.

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Introduction

Hepatocellular carcinoma (liver cancer) ranks 5th among all cancers. It has been established that the main risk factors for the development of hepatocellular carcinoma (HCC) are chronic forms of the course of hepatitis B, C, D [1, 2]. In developing countries, infection with hepatitis viruses is detected in 75–90% of patients with HCC [1]. More than half of all patients with hepatitis B and C in the world are concentrated in Asian countries [3, 4]. The highest prevalence rates of diseases associated with the outcomes of viral hepatitis are also observed here: liver cirrhosis and hepatocellular carcinoma [5].

In addition to infectious agents, factors that provoke carcinogenesis include disorders of lipid and carbohydrate metabolism, alcohol abuse, autoimmune liver damage, exposure to hepatotoxic chemical compounds [2, 6]. In the Russian Federation, HCC, in addition to infection with hepatitis B (HBV) and C (HCV) viruses, is associated with such risk factors as metabolic syndrome (17.4%) and alcoholic hepatitis (8.7%) [7].

Due to the absence of clinical symptoms at an early stage of the disease, HCC is usually diagnosed late at stages III-IV by classification TNM. Therefore, the search for predictors in the form of serum tumor markers or molecular witnesses of the presence of a tumor (liquid biopsy) is of great importance. Historically, one of the first HCC tumor markers is hepatic alpha-fetoprotein (AFP). Its increase of more than 20 ng/ml in the patient's blood dictates the need for examination to exclude HCC, and the level above 400 ng/ml makes it possible to ascertain the presence of a tumor with a high probability [8, 9]. Nevertheless, the diagnostic value of this tumor marker is limited by insufficient sensitivity, which stimulates the search for new, more effective predictors. The promising new generation tumor markers include osteopontin and glypican-3 [10, 11]. However, their diagnostic effectiveness in the context of various ethnic groups has not been studied enough.

We are aimed to give a clinical and epidemiological characteristics of hepatocellular carcinoma in ethnic groups of Mongoloids and Caucasians living in the adjacent territories of northeast Asia, and to determine the diagnostic sensitivity of some serum tumor markers in the surveyed cohorts.

Material and methods

Clinical and epidemiological studies were carried out in two large contiguous territories of northeastern Asia: Mongolia and the Asian part of Russia (Irkutsk region).

The territories of Mongolia and the Irkutsk region are characterized by a large area and an uneven population density. Mongolia covers an area of more than 1570 thousand km², and the population is 2.75 million people [12]. Irkutsk region is located on an area of 774.8 thousand km², with a population of 2.4 million people [13]. Both territories are comparable in terms of climatogeographic and demographic indicators, but differ in the ethnic composition of the living population. In Mongolia, representatives of the Khalkha Mongols make up the majority of the country's population (96.0%) [12]. The territory of the Irkutsk region is dominated by Caucasians – 96.3% [13].

Epidemiological studies were carried out for 10 years, from 2000 to 2019. To study the incidence of HCC, data from the Department of Health of the Executive Agency of the Government of Mongolia and the Ministry of Health of the Irkutsk Region were used. To analyze the clinical manifestations of HCC, we used the questionnaire method and the study of medical records. In total, 300 patients with HCC were examined, including 195 Mongols from Ulan Bator and 105 Russians permanently residing in the Irkutsk region. The research protocol was carried out in accordance with the Declaration of Helsinki [14]. Informed consent was obtained from all patients. The degree of alcohol dependence was assessed using the Audit scale [15]. With an indicator of more than 16 points on the Audit scale, the fact of regular consumption of alcohol was stated. Anti-HCV, HBsAg and anti-HBc were determined in all patients with HCC. The diagnosis of HCC was made taking into account the criteria of the European Association for the Study of Liver Diseases (EASL) [9].

Material was collected at the National Cancer Center (Ulaanbaatar), General Hospital No. 3 of Ulaanbaatar City, National Center for Communicable Disease (Ulaanbaatar) and at the Irkutsk Regional Oncological Dispensary.

The AFP level in the blood serum was determined on an Architect system I1000SR automatic analyzer (USA, Abbott) by the chemiluminescent method. Osteopontin (OPN) and glypi-

Dynamics of the long-term incidence of HCC (per 100,000 population) in the Irkutsk region (circles) and Mongolia (triangles)

Table 1. Comparison of baseline patients and tumor characteristics in patients with hepatocellular carcinoma in Asian and Caucasian ethnicities, $M \pm m$

Variables	Ethnic group of Mongolians (n=195)	Ethnic group of Caucasians (n=105)	p
Age, years	61.7±10.5	63.1±1.5	>0.05
Gender: male, n (%)	108 (55.4±3.6)	58 (55.2±4.9)	>0.05
History of jaundice, n (%)	120 (61.5±3.5)	24 (22.9±4.1)	<0.001
History of blood transfusion, n (%)	38 (19.5±2.8)	15 (14.3±3.4)	>0.05
Alcohol drinking >16 units by score Audit, n (%)*	57 (29.2±3.3)	16 (15.2±3.5)	<0.01
Presence of liver cirrhosis, n (%)	125 (64.1±3.4)	88 (83.8± 3.6)	<0.001
Total bilirubin, umol/l	22.2±8.6	67.9±18.7	<0.05
Albumin, g/l	37.0±4.0	28.9±1.3	>0.05
ALT, U/l	103.0±10.9	98.4±33.8	>0.05
AST, U/l	78.0±9.8	158.5±40.1	>0.05
Diabetes, n (%)	7 (3.6±1.3)	5 (4.8±2.1)	>0.05
Obesity (BMI >30 kg/m ²), n (%)	32 (16.4±2.7)	12 (11.4±3.1)	>0.05
Smoking, n (%)	30 (15.4±2.6)	20 (19.0±3.8)	>0.05
Hepatitis B markers, n (%)	67 (34.4±3.4)	18 (17.1±3.7)	<0.001
Hepatitis C markers, n (%)	89 (45.6±3.6)	46 (43.8±4.8)	>0.05
Co-infections HBV + HCV, n (%)	28 (14.4±2.5)	12 (11.4±3.1)	>0.05
AFP, ng/ml	196.0±130.9	458.3±271.2	>0.05
OPN, ng/ml	275.5±34.2	193.5±32.3	>0.05
GPC-3, ng/ml	1.18±0.16	1.76±0.26	>0.05
TNM stage I, n (%)	20 (10.3±2.2)	6 (6.5±2.6)	>0.05
TNM stage II, n (%)	30 (15.4±2.6)	23 (24.7±4.5)	>0.05
TNM stage III, n (%)	88 (45.1±3.6)	53 (57.0±5.1)	>0.05
TNM stage IV, n (%)	57 (29.2±3.3)	23 (24.7±4.5)	>0.05
Extrahepatic metastasis, n (%)	36 (18.5±2.8)	30 (28.6±4.4)	>0.05

* – questioning on the Audit scale was conducted in 90 patients from Mongolia and 76 from Russia.

can-3 (GPC-3) levels were determined by ELISA using Human Osteopontin Platinum ELISA/BMS 2066 (Affymetrix eBioscience) and ELISA Kit for Glypican 3, SEA971Hu, (Cloud-Clone Corp.). The determination of the cut off for each tumor marker was carried out by us earlier on the basis of calculating the highest value of the Youden index [16].

Methods of statistical material processing

Statistical processing of the data obtained was carried out by comparing two samples, assessing long-term morbidity and correlation analysis. Intensive epidemiological rates were calculated per 100,000 population. Statistical processing of the results was performed using Epidemiology/Biostatistics Tools for Windows (Wayne W. LaMorte, MD, PhD, MPH Copyright 2006; USA). To identify the reliability of differences in indicators in the compared groups, the Student's test and the chi-square test (χ^2) were used. The critical level of statistical significance was taken as $p \leq 0.05$.

Results

Despite the close climatic, geographical and demographic indicators, the incidence rate of HCC significantly differed in the comparison territories (Figure). As of 2019, the incidence rate in Mongolia exceeded the corresponding value in the Irkutsk region by 7.6 times 68.0 and 9.1 per 100 000 population, respectively; $p < 0.001$.

As can be seen from Table 1, both groups were dominated by male patients over the age of 60 years. In the ethnic group of

Mongols, jaundice in the past and regular use of alcohol were more often in the anamnesis of life. Of the etiological factors, in $1/3$ of patients in Mongolia, HCC was associated with HBV, which is significantly more frequent than in the Irkutsk region ($p < 0.001$). At the same time, in Caucasians, HCC developed mainly at the stage of liver cirrhosis ($p < 0.001$), and a higher average level of total bilirubin in the blood serum was also revealed ($p < 0.05$).

The comparability of the groups in terms of age-sex composition and stages of HCC made it possible to analyze the diagnostic significance of serum tumor markers in the compared ethnic groups (Table 2). Exceeding cut off value in both groups was most often observed when determining OPN. An increase in the level of GPC-3 was detected only in half of the patients with HCC. The proportion of HCC patients with an increased

Table 2. The proportion of patients with HCC in the ethnic groups of Caucasians and Mongoloids in whom the level of tumor markers in the blood serum exceeded the cut off, $M \pm m$, %

Index	Mongolians (n=195)	Caucasians (n=105)	p
AFP >20.0 ng/ml	134 (68.7±3.3)	86 (81.9±3.8)	<0.01
OPN >80.0 ng/ml	163 (83.6±2.7)	78 (74.3±4.3)	>0.05
GPC-3 >1.0 ng/ml	110 (56.4±3.6)	68 (64.8±4.7)	>0.05

level of OPN and GPC-3 did not depend on ethnicity, while an increase in the AFP level above 20 ng/ml was significantly more frequent in the ethnic group of Caucasians.

Discussion

The study showed that the level of long-term incidence of HCC in the Irkutsk region does not differ from other regions of Russia [17, 18], and in Mongolia is comparable to China and Korea, which are hyperendemic territories [1, 4].

Assessment of the movement of the incidence of HCC in long-term dynamics showed similar trends in its growth in Mongolia and in the Irkutsk region ($r^2=0.81$; $p<0.01$). However, the average values of absolute growth indicate more unfavorable trends in the spread of HCC in Mongolia.

In both comparison areas, HCC is more common in males over the age of 60. As you know, the predominance of men is characteristic of this pathology and varies in different countries of the world in the ratio of men: women from 1.4:1 to 4:1 [1, 6]. It is noteworthy that in Mongolia, despite the inclusion of hepatitis B vaccination in the vaccination calendar since the 90s of the last century, a fairly large proportion of HCC associated with HBV remains. In addition, it is necessary to take into account the high incidence of co- and superinfection of HBV and HDV in Mongolia [19]. The combination of HBV and HDV is accompanied by a 30-fold increase in the risk of developing HCC compared with monoinfection [2].

The differences in the frequency of detection of liver cirrhosis in HCC patients are evidently due to the prevalence of HBV patients among Mongoloids. As you know, the mechanism of the carcinogenic action of HBV and HCV is different. The oncogenicity of HCV is mediated by the chronic inflammatory process and the development of liver cirrhosis. In HBV, HCC develops due to the integration of viral DNA into the hepatocyte genome, often against the background of minimal liver fibrosis [2].

The question of the role of genetic factors in the predisposition to the development of HCC has been repeatedly discussed [6, 20]. Clinical observations have shown that representatives of the Mongoloid race are more likely to develop HCC than Caucasians. High-risk groups include Asian, Africans and Hispanics [1, 2, 21].

This study has shown that, along with AFP, other proteomic tumor markers, in particular, OPN and GPC-3, can be used to diag-

nose HCC. OPN is an integrin-binding glycoprophosphoprotein that is produced in increased amounts in many malignant neoplasms. GPC3 belongs to the glypican-proteoglycan family. An increased level of GPC3 is detected in 50–55% of patients with HCC and only in 5% of patients with liver cirrhosis [22]. The stand-alone value of GPC3 for the diagnosis of HCC is limited due to its low sensitivity. Of greatest interest is OPN, an increase in which in the blood of HCC patients over 80 ng/ml was found in 74% of Caucasians and 83% of Mongoloids.

The AFP content in the blood above 20 ng/ml was found in representatives of the Caucasian race much more often than in the Mongoloids. It is possible that the AFP level was influenced by the prevalence of patients with liver cirrhosis in the group of Caucasians, in which there is an increase in the AFP level regardless of the presence or absence of liver cancer [1, 20]. At the same time, ethnic characteristics cannot be ruled out. Similar trends have been identified for the Chinese population. According to Parikh N.D., 2017, when comparing the AFP level in HCC patients, Chinese and Euro-Americans, the oncomarker content above 100 ng/ml was more often found in the latter [23]. Due to the insufficient diagnostic sensitivity of AFP in representatives of Mongoloids in Japan, a system for the combined determination of three tumor markers in the blood has been developed: AFP, AFP-L3 and DCP, which turned out to be more effective [24, 25]. Currently, this combination of serum HCC predictors is being tested in a number of European countries [26].

Conclusion

Mongolia among the countries of the Asian continent in terms of the incidence of HCC, along with China and Korea, belongs to the hyperendemic regions. In this country, 93% of all HCC cases are associated with viral hepatitis, with HBV accounting for 34.5% of cases, which significantly distinguishes Mongolia from the Asian part of Russia. Excessive alcohol consumption is a significant non-infectious risk factor in Mongolia. In connection with the insufficient sensitivity of AFP determination in the ethnic group of Mongoloids, it is necessary to search for new molecular markers. An alternative possibility of using osteopontin and glypican-3 as serum predictors of HCC was shown, the diagnostic sensitivity of which is higher than AFP and does not differ in the ethnic groups of Mongoloids and Caucasians.

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