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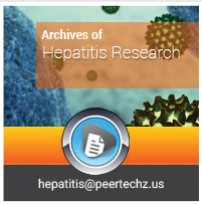

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ARCHIVES OF Hepatitis Research OPEN ACCESS JOURNAL

ISSN: 2641-2977 DOI: https://dx.doi.org/10.17352/ahr

Short Communication

Viral hepatitis B in patients with hematological malignancies (Overview)

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Received: 12 January, 2023
Accepted: 28 January, 2023
Published: 30 January, 2023

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Keywords: Hepatitis B; Safety of blood transfusion; Activation of hepatitis B; Oncohematological patients

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Abstract

The review presents current data on the role of viral hepatitis B in oncohematological patients. Possible ways of infection, prevention of infection, and activation of hepatitis B in this category of patients are considered. The specific features of the course of hepatitis B in various clinical situations are described: against the background of other viral infections and in the conduct of specific anti-leukemia therapy.

Introduction

Viral hepatitis is a group of diseases that occur with a predominant lesion of the liver, manifested by an increase in its size and impaired functionality, as well as symptoms of intoxication to varying degrees of severity and in some cases jaundice [1]. Hepatitis B is a potentially life-threatening liver infection caused by the Hepatitis B Virus (HBV). This disease is a serious public health problem worldwide. The infection can become chronic with a high risk of death from cirrhosis and liver cancer [2]. According to various estimates, the number of patients (carriers) of HBV in the Russian Federation is 6-8 million people [3]. Hepatitis virus infection is often registered among the able-bodied population, which is the main source of donor personnel.

Methodology

The aim of the study is to systematize and analyze own and literature data on the diagnosis, prevention of infection, and activation of hepatitis, as well as the clinical course of hepatitis B in patients with myeloblastosis.

The problem of viral hepatitis acquires significant relevance in oncohematological patients, which is associated with the peculiarities of their treatment: cytostatic therapy, and repeated blood transfusions.

Liver damage in patients with various forms of hemoblastosis is one of the most frequent complications during chemotherapy or Hematopoietic Stem Cell Transplantation (HSCT). According to our data, an increase in the size of the liver was observed in 70-80% of patients with acute leukemia in the primary active phase, due to its leukemic infiltration. In patients in the relapse phase who had been receiving cytotoxic drugs for a long time, according to ultrasound data, hepatomegaly, a zone of low echogenicity along the contour of the diaphragm, inflammatory infiltration in the liver, dilation of the common bile duct were detected in all cases. There was an increase in the size of the spleen, dilation of the portal system veins, an increase in the activity of alanine aminotransferase (ALT), a decrease in the activity of the prothrombin complex, factor V and fibrinogen concentration, hyperbilirubinemia was detected in some patients, which indicates toxic hepatitis caused by the use of cytostatic drugs [1].

Similar changes were found in 40% of patients with multiple myeloma with the disease for more than 4 years, i.e. who received various chemotherapy programs: hepatomegaly, a zone of reduced echogenicity along the contour of the diaphragm

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up to the "erasure" of the hepatic pattern, increased ALT activity, and in 1/3 of patients - moderate hyperbilirubinemia due to direct fractions, there is a decrease in the activity of excessive reproduction [1]. Patients receiving chemotherapy or immunosuppressive therapy for hematological tumors are at high risk of hepatitis B and C infection.

In addition, with hematological tumors – both during primary diagnosis and especially during chemotherapy, a decrease in hemoglobin levels <80 g/ l is often observed, which is an indication for transfusion of donor red blood cells. Blood transfusion is associated with the risk of developing a number of reactions and infectious complications, including viral hepatitis B and C [4]. It should be noted that the detection of hepatitis B in oncohematological patients significantly worsens the prognosis, especially in elderly patients [5]. The resulting complication requires the appointment of antiviral therapy. This often requires reducing the dose of antitumor drugs, up to their cancellation, and increasing the intervals between treatment cycles, which negatively affects the course of the underlying disease and reduces the patient's survival. This determines the need to increase the effectiveness of preventive measures carried out in oncohematological hospitals and improve the diagnosis of viral hepatitis in this group of patients [1]. A common complication in patients with hemoblastosis receiving long-term cytostatic and hemocomponent therapy is the development of toxic hepatitis with impaired liver function and possible infection and/or activation of viruses, in particular hepatitis B virus.

The frequency of detection of HBsAg in patients hospitalized in the hematology clinic of the Russian Research Institute of Hematology and Transfusiology was 6.4% in 2001 and 4.2% in 2015, its fluctuations in some years were extremely insignificant [6]. Such a high percentage of detection of hepatitis B markers is due, firstly, to cytotoxic damage to the liver, and secondly, to the frequent use of hemocomponent therapy in this category of patients. Reactivation of the virus as a result of chemotherapy of malignant diseases is an urgent problem that hematologists face today [7,8]. The incidence of HBV reactivation among patients with varying subtypes of hematological malignancy is similar. Prophylaxis with anti-HBV agents clinically reduced the risk of hepatitis B reactivation [9]. The high probability of such HBV reactivation dictates the need for adequate treatment of HBsAg-positive patients since this can contribute to the progression of liver damage, including lightning hepatitis. The German Society of Hematology and Medical Oncology recommended mandatory HBV, HCV and HEV screening in patients prior to undergoing high-dose chemotherapy and autologous HSCT [10]. It demonstrated the efficiency of lamivudine prophylaxis in preventing HBV reactivation in patients with resolved infection [11].

Interestingly, liver damage associated with hepatotoxicity, hepatitis B and C aggravates the course of the effectiveness of therapy for hepatitis E. It was noted that the majority of patients with hepatitis E who did not respond to ribavirin treatment had a pre-existing disease, including hepatotoxicity associated with drug therapy, chronic hepatitis B infection, and hepatitis C infection [12].

An important factor aggravating the course of the underlying disease in oncohematological patients is the development of opportunistic infectious diseases, the leading of which are infections caused by the herpes virus. They are characterized by a widespread, lifelong resistance and high level of infection in oncohaematological patients during HSCT [13]. At the same time, the effect of HBV on the activation of herpes viruses should be noted. A statistically and clinically significant increase in the proportion of individuals with markers of acute HHV-6 infection among hematological patients infected with HBV was revealed. Interestingly, no such pattern was found in relation to other herpes viruses (HSV-1,2, CMV, EBV) [14].

The frequency of detection of the hepatitis B virus marker (HBsAg) in oncohematological patients largely reflects the level of transfusion of infected blood components that were not detected during laboratory control. Therefore, a qualitative examination of donors for the presence of markers of active blood-borne infections is the main condition for ensuring the safety of blood transfusion. Blood donors are examined for the presence of markers of hepatitis B (HBsAg), Hepatitis C (HCV) - antibodies to HCV, Human Immunodeficiency Virus (HIV) - antibodies to HIV-1, HIV-2, and p24 antigen, as well as syphilis – antibodies to *Treponema pallidum*. Of these infectious agents, only hepatitis B is one of the infections that can be controlled by methods of specific prevention, based on active vaccination. This has made a significant contribution to reducing the incidence of hepatitis B. However, the disease still continues to be registered. Careful selection of the donor contingent has led to the fact that the risk of infection of recipients with latent infections during blood transfusion, including viral hepatitis B and C, has become lower, but it remains. The study of the dynamics of HBsAg detection in donors for the period from 2010 to 2016 revealed its gradual decrease and correlates with the overall decrease in the incidence of hepatitis B in the country. Laboratory examination of donors for blood-borne infections is carried out constantly. The introduction of nucleic acid amplification (NAT) technologies has significantly reduced the period of the infectious window. However, with a very low viral load, even the use of amplification methods, especially in the case of "silent" forms of HBV infection, can lead to a false negative result. Therefore, along with donors, regular screening of oncological and oncohematological patients receiving immunosuppressive therapy is recommended [15,16]. Such a new method as the next-generation sequencing method, capable of detecting minor populations of HBV mutations, provides a diagnostic advantage, lays the foundation for the development of screening methods, and allows for the study of the virological and pathogenesis aspects of hepatitis B [17].

Recently an electronic alert system has been developed. The system increased viral hepatitis screening in patients receiving hematological treatment and led to improvements in the management of these patients, including avoiding HBV reactivation [18].

In this regard, it should be noted that it is necessary to continue determining the activity of alanine aminotransferase (ALT) as a surrogate producer of hepatitis. Donors who were

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found to have elevated ALT levels earlier than HBV markers were excluded from blood donation. This turned out to be the only barrier due to which infected blood components were not used for transfusion [19]. A high level of ALT activity should be considered as a reason for a more thorough examination of donors, in order to identify not only infectious but also general somatic pathology. This indicates the need for a more thorough approach to ensuring the safety of blood transfusion in immunosuppressive oncohematological patients.

As mentioned above, unlike other viral hepatitis, hepatitis B refers to infections with controlled specific prevention, and vaccination plays a crucial role in preventing the spread of infectious diseases. However, it has been shown that protective immunization, determined by the titer of anti-HB antibodies, can drop to a critical level over the years, especially if infection occurs with an HBV variant that differs from the vaccine [20]. Vaccination leads to the production of antibodies in recipients and allows for a sharp decrease (up to 90%) in the prevalence of hepatitis B.

However, additional vaccination is not recommended for vaccinated oncohematological patients in the absence of detectable amounts of HBsAg before chemotherapy. Live antiviral vaccines are contraindicated during chemotherapy or hematopoietic stem cell transplantation. Vaccination should be carried out 2 weeks before the start of chemotherapy and is contraindicated during treatment and for 6 months after chemotherapy and immunotherapy. Revaccination can be carried out 3 months after the end of these types of treatment [21].

Conclusion

Thus, the presented data indicate the need to expand the monitoring of serological markers and sensitive molecular diagnosis of hepatitis B for all patients requiring chemotherapy or hematopoietic stem cell transplantation due to the need to choose a vaccination strategy, antiviral and immunosuppressive therapy.

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