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HEMATOLOGICAL ADVERSE EVENTS ON THE BACKGROUND OF ANTIVIRAL THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C

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Abstract. Currently, the main etiotropic method of treating chronic hepatitis C is combination therapy with standard interferon-a (IFN-a) or pegylated interferon-a (PIFN-a) in combination with ribavirin. Despite significant advances in AVT in CHC patients, adverse events may occur during treatment, which force either to reduce the dosage of drugs or stop treatment altogether.

Keywords: Antiviral therapy, adverse events, anemia, hepatitis C

Relevance. To date, HCV infection remains an urgent problem of modern medicine, which is due to a wide, consistently high incidence and ubiquitous distribution, as well as significant economic costs for diagnostic and therapeutic processes. According to the World Health Organization (WHO), in 2010 alone, the number of carriers of the hepatitis C virus in the world was more than 170 million people. At the same time, 3-4 million new cases of hepatitis C (HCV) are registered annually, and the situation is likely to continue to worsen.

Purpose. To study the scientific literature on the problem of adverse events in patients with hepatitis C taking antiviral therapy.

The most common reasons for dose reduction are depression, cytopenias, and impaired thyroid function. Among the adverse events (AEs) of antiviral therapy for chronic hepatitis C, in terms of their importance, hematological changes — anemia, neutropenia, thrombocytopenia — are in the first place. Hematological disorders as the reason for dose reduction and discontinuation of combined antiviral therapy for CHC occur in 25% and 3% of cases, respectively. The development of hematological AEs against the background of AVT reduces the quality of life of patients, sometimes accompanied by the development of complications that require a temporary or permanent reduction in the dose of antiviral drugs or their cancellation. At the same time, the frequency of SVR formation decreases. In this regard, AVT requires the prevention and correction of hematological AEs. Currently, for the prevention and correction of AEs, drugs are used, stimulating various sprouts of hematopoiesis. However, among specialists in the field of CVH treatment, there is no consensus on the effect of growth factors on achieving a sustained virological response (SVR), as well as on the incidence of infectious and other complications of AVT.

Before presenting the material on AEs that accompany patients with CHC, it is advisable to dwell on the mechanisms of action of the interferon system in chronic viral liver diseases and modern ideas about antiviral therapy for HCV infection.

Today, the world's main antiviral drug for the treatment of viral hepatitis is interferon-alpha, in particular its recombinant preparations.

Interferons belong to the system of cytokines and are low molecular weight peptides with antiviral, immunomodulatory, antitumor and antiproliferative activity,

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which allows us to consider them as polyfunctional bioregulators with a very wide range of biological effects. There are three classes of interferons:

1. Interferon-a (leukocyte, synthesized by activated monocytes and B-lymphocytes).
2. Interferon-P (fibroblast, synthesized by fibroblasts and epithelial cells, macrophages).
3. Interferon-y (immune, synthesized by activated T-lymphocytes).

According to the predominant mechanism of action, interferons are divided into 2 types. The first type includes interferons-a and b, which carry out non-specific protection of all types of body cells from the penetration and reproduction of biological objects - carriers of alien genetic information (viruses and some other pathogens prone to intracellular parasitism). They are produced immediately after meeting with the pathogen, their action is aimed at localizing the pathogen and preventing its spread in the body. The main action of IFN-R is local, aimed at preventing the spread of the infectious agent from the place of its introduction. If there is no inactivation of the infectious agent at the site of introduction and it circulates in the body, its contact with lymphocytes and macrophages induces the production of IFN-a.

The second type includes interferon-y, which is involved in the regulation of the development of the main stages of the adaptive immune response. It begins to be produced at subsequent stages of the infectious process by already sensitized T-lymphocytes and is actively involved in the specific immune response cascade.

Since the discovery of interferons (A. Isaac, D. Lindenman, 1957) to date, many biological effects of these compounds have been identified. First of all, the ability to suppress the replication of various intracellular infectious agents (viruses, bacteria, rickettsia, protozoa) has been established. Found antiproliferative, antitoxic, antimutagenic, as well as a wide range of immunoregulatory effects of interferons. At the same time, the biological action of interferons is characterized by both universality and specificity. A significant contribution to understanding the mechanisms of action of interferons was made by analyzing the experience of using interferon preparations, both of natural origin and those obtained on the basis of recombinant technologies. The interaction of interferons with cells begins at the level of surface receptors. At present, the existence of common specific receptors for a- and ß-interferons has been proven, while interferon-y has its own receptors. It should be noted that different cells express different amounts of interferon receptors on their surface, which explains the unequal cellular sensitivity to the drug. Having penetrated inside the cell, interferon-a activates genes encoding the production of effector proteins, which ultimately realize antiviral effects.

The Jak-Stat signaling pathway plays an important role in the mechanism of interferon-associated bone marrow suppression. The signaling pathway includes the activation of Janus kinase (Jak 1) and tyrosine kinase (Tuk 2), which is initiated by the binding of alpha interferons to the interferon heterodimeric complex. Consequently, signal transmitters and transcription activators Stat 1 and Stat 2 are activated, penetrating into the nucleus, where the promotion of interferon-stimulated genes occurs. As a result, the mechanisms of apoptosis of bone marrow (BM) stem cells, a decrease in protein synthesis in hematopoietic cells, an increase in the

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production of BM stem cells and their depletion occur. All this leads to a decrease in the production, differentiation and maturation of BM cells, which ultimately results in the formation of cytopenias. Thus, interferons do not have a direct antiviral effect, but affect the replication of the pathogen by actively including virus-containing cells in the metabolic processes. A number of the same events that lead to the antiviral effect of IFN-a underlie its antiproliferative action. It's extremely important since the antifibrotic effect of the drug is of great importance in the treatment of patients with CVH. At the same time, under the influence of IFN-a, the expression of antigens of the main histocompatibility complex of class I, which present viral antigens to T-lymphocytes, increases. This leads to easier recognition of virus-containing cells and their destruction by immunocompetent cells of the body.

Today, recombinant interferons-a-2a and -a-2b are predominantly used in the treatment of chronic viral hepatitis. They are created thanks to genetic engineering technology using the human interferon-a2 gene and Escherichia coli as a producer. To achieve a therapeutic effect, it is necessary to create, and most importantly, maintain the required dose of the drug in the patient's body. In this regard, in recent years, pegylated (prolonged) forms of IFN-a (PIFN-a-2a and PIFN-a-2b) have been created. Due to the addition of a large inert polyethylene glycol molecule to IFN-a, the molecular weight of the drug increased significantly. This made it possible to slow down its clearance from the body and maintain a high concentration of the drug in the blood for a week after the injection.

The goal of antiviral therapy for CHC is to achieve persistent suppression of viral replication and remission of chronic viral hepatitis. The main criterion for prescribing etiotropic therapy for patients with CHC is active viral replication (HCV RNA) against the background of an active inflammatory process in the liver (increased ALT, histological signs) and/or extrahepatic manifestations. To date, a large amount of data has accumulated on the evaluation of the therapeutic effect of IFN-a in CHC. The current treatment of chronic viral hepatitis C is a combination therapy with standard interferon-a or pegylated interferon-a in combination with ribavirin at times determined by the genotype of the virus.

Depending on various initial factors, from 40 to 80% of patients respond positively to treatment, but some patients either initially do not respond to therapy, or the effect is temporary, and after discontinuation of the drug, a relapse of HCV infection develops. Work on optimizing existing therapy continues, as the problem cannot be considered solved. The study of viral kinetics during antiviral therapy made it possible to change the views on the duration of therapy depending on the variant of the virological response and the level of initial viremia. Thus, the presence of a “rapid” virological response under the condition of low viremia before treatment made it possible to reduce the AVT period to 16 weeks in patients with genotype 2/3, and to 24 weeks in patients with genotype 1.

Considerable attention is paid to the factors (predictors) that determine a positive response to interferon therapy. These include: a short duration of the infectious process, young age, female sex, uncomplicated premorbid background (alcoholism, drug addiction, immunodeficiency, autoimmune and concomitant chronic diseases), increased ALT activity, initially low levels of HCV RNA, absence

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of mixed hepatitis, signs severe cholestasis, severe fibrosis and cirrhosis of the liver, side effects of interferon.

Undesirable effects of etiotropic therapy in patients with chronic hepatitis C.

During interferon therapy in patients with CHC, a number of undesirable side effects occur, which reduce the quality of life, adherence to treatment, and the frequency of achieving SVR. Side effects occur in 25-50% of patients in the first days of therapy. Their frequency increases in the presence of liver cirrhosis in middle-aged and elderly people, with longer periods of treatment (48 or 72 weeks) and high doses of IFN-a. In some patients with CHC, undesirable effects of therapy are the reason for its withdrawal. In patients receiving combined treatment with IFN-a and ribavirin, the frequency of withdrawal is 14%, in those on IFN-a monotherapy - 13%. The use of PIFN-a (2a and 2b) in the combined antiviral therapy for CHC did not add new undesirable effects, however, more frequent weight loss was noted, the appearance of local reactions to the administration of the drug and the development of hematological disorders (anemia, sunneutropenia, thrombocytopenia), necessitating a change in the dose of IFN-a and / or ribavirin in 32-42% of patients or their cancellation in 10-14%. With a duration of combination therapy up to 24 weeks and a dose of ribavirin up to 800 mg, the frequency of serious adverse events is 3-5%. The frequency of discontinuation of the drug in patients with cirrhosis of the liver does not differ from that in patients without cirrhosis.

Undesirable side effects are divided into four groups: the first group includes frequent (more than 20% of patients) that do not require changes in doses and treatment regimens; in the second group - relatively infrequent (in 10-20% of patients), which may require dose reduction or discontinuation of therapy; the third group consists of rare severe (frequency less than 1% of cases) or life-threatening (less than 0.1% of cases), which require mandatory discontinuation of treatment; the fourth group - irreversible side effects that significantly worsen the quality of life of patients with chronic hepatitis C leading to disability.

The most common adverse effects of interferon therapy are flu-like syndrome, asthenia, depression, weight loss, irritation at the injection site. Flu-like syndrome is characterized by fever, malaise, headache, loss of appetite, aching muscles and joints, and sweating. The maximum body temperature occurs approximately 4 hours after the injection of IFN-a. When using PIFN-a, a “second wave” is possible after 24-72 hours. This symptom complex develops, as a rule, at the beginning of therapy. As its duration increases, after 2-3 weeks, the severity of these phenomena decreases. Influenza-like syndrome is effectively eliminated by prescribing paracetamol (0.5-2 g / day) or other non-steroidal anti-inflammatory drugs, active fluid intake is recommended. The introduction of IFN-a in the evening allows some of the side effects to be transferred to the sleep period. This side effect rarely requires discontinuation of treatment. With the appearance of skin itching and rash, irritation at the injection site, corticosteroid or zinc-containing ointments, NSAIDs for external use are used. Changing the site of administration of the drug and the appointment of antihistamines reduce the severity of the skin syndrome. The incidence of cough during antiviral therapy ranges from 5-7% to 22-23%, regardless of the treatment regimen (monotherapy or combination treatment) and the type of interferon therapy

(PIFN-a or IFN-a; 2a or 2b). Drinking at least 2 liters of fluid per day, the use of licorice root, thyme herbs can be useful in controlling this symptom, however, in some patients; antiviral therapy has to be abandoned due to an increasing cough during treatment. Hair loss is reduced with external use of zinc or minoxidil-containing agents (zinc pyrithione), or oral zinc preparations. Dyspeptic syndrome (anorexia, nausea, vomiting, diarrhea, abdominal pain) is observed in 20% of cases. Weakness is noted in 53% of patients receiving antiviral therapy, and in 17% of patients it is significant. Among the risk factors for its occurrence are the female sex, age over 50 years, cirrhosis of the liver, depression, vascular purpura, anemia. In 10% of cases, weakness is combined with extrahepatic manifestations - arthralgia, myalgia, paresthesia, Sjögren's syndrome, skin itching and reflects the presence of mixed cryoglobulinemia. The Meltzer triad (weakness, arthralgia, skin purpura) present before treatment in CHC patients with cryoglobulinemia causes increased asthenia during antiviral therapy. With the development of weakness, pronounced asthenic syndrome, physical activity, physical exercises in the aerobic respiration mode and an increase in the volume of fluid taken are recommended.

Conclusion. Thus, the side effects of antiviral drugs in patients with hepatitis C is an urgent problem of modern medicine, requiring a careful approach in early diagnosis and complex selection of treatment.

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