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VIRAL HEPATITIS OF CHILDREN WITH ONCOHEMATOLOGICAL DISEASES IN YAKUTIA

This article presents data on chronic viral hepatitis of children with oncohematological diseases. There were evaluated clinical and laboratory data of 11 children with chronic viral hepatitis B and C, among which 10 patients were with monoinfection and 1 was with mixed hepatitis

B + C. It also presents results of treatment of chronic viral hepatitis with interferon-alpha in children with hematologic malignancies.

Keywords: chronic hepatitis C, chronic hepatitis B, oncohematological diseases, children, interferon- α .

Chronic viral hepatitis B is a serious problem of health care in general and of pediatrics in particular. The proportion of hepatitis C in children was 40,8 %, another 5 % of CHC proceeds in УДК: 616.36-002.2:616-053.2(571.56) combination with CHB, 1 % in combination with G, and about 1 % of chronic hepatitis C patients have markers of hepatitis viruses B and D [4].

The greatest frequency of detections of markers of hepatitis B and C is marked in some regions of Russia, one of which is the Republic of Sakha (Yakutia). According to official data, 11,6 % of the whole population and 4,5 % of indigenous population in Yakutia were positive for HBsAg and anti-HCV, respectively. The frequency of HBsAg carriage in pregnant women was twofold higher than the corresponding federal rate (2 % and 1,1 %, respectively). The frequency of detection of HBsAg in children aged 0 to 14 years in the Arctic uluses of Sakha (Yakutia) is 4,2 % while it is 2,7 % in the central zone of Russia [3, 4, 6, 7].

Infection with hepatitis B virus (HBV) and C (HCV) of children with an acute leukemia (AL) is very high. According to A.R. Reyzis it reaches 75 %, of them 25-30 % of patients are infected with HBV, 35-45 % with HCV and they are often combined. The reason for such a high hepatitis virus infection is a massive blood transfusion-load, state of profound immunosuppression, toxic injury of liver on the background of polychemotherapy (PCT) [2, 3]. Under circumstances when currently 60-80 % of children recover from AL, hepatitis becomes a serious problem for them in the future [2].

On the application of IFN-alpha in the treatment of chronic viral hepatitis C in children with acute hepatitis diseases, the elimination of the virus occurs in 47,6 % of cases [4].

Patients and methods. We studied the case records of children diagnosed with AL, who received and receives treatment in the hematology department (HD) of Republican Hospital No.1 affiliated to the National Centre of Medicine for the period from 2000 to 2008. 83 children were diagnosed with AL, including 64 children (77,1 %) with an acute lymphoblastic leukemia (ALL) and 19 children (22,9 %) with an acute nonlymphoblastic leukemia (ANLL). Viral damage of liver was diagnosed in 10 children (12 %) of 83 patients with AL. Hepatitis C virus was diagnosed in 6 children (7,2 %), hepatitis B virus in 3 children (3,6 %) and 1 patient was diagnosed with mixed-hepatitis B + C. 8 patients with VH suffered from ALL (12,5 % of all children with ALL), one child suffered from an acute myeloid leukemia (AML) (5 .3 % of all ANLL) and one boy suffered from biphenotypic leukemia. One girl was diagnosed with histiocytosis from Langerhans' cells.

All patients with viral hepatitis were diagnosed on the basis of research methods of EIA and PCR (qualitative and quantitative). All patients took check studies before and after the therapy: determination of antibodies to the thyroid gland, EEG, blood count, general urinalysis, biochemical blood tests every month during the therapy; PCR (qualitative and quantitative) after 1, 3, 6, 9 and 12 months of the therapy. PCR control was performed on a quarterly basis after the completion of treatment.

The effectiveness of antiviral therapy was assessed on the basis of recommendations of the American Association for the Study of Liver Diseases. Therapy was considered effective if the patient had experienced an SVR, i.e. the absence of the genome of the virus in the blood for 6 or 12 months after treatment. Early virological response was evaluated after 3 months of treatment and used for SVR predicting. Pre-early virological response was assessed after 1 month of therapy and was also used to predict SVR [1, 8].

Results and discussion. All patients entering the hematology department are screened for markers of viral hepatitis (VH). Only one patient out of all with AL was diagnosed with chronic viral hepatitis B before admission. This child was detected with HBsAg. Other markers of HBV were not defined.

Serologic tests of patients with HCV showed anti-HCVcor, anti-NS with two or more pools, so everyone has been diagnosed with new-onset chronic hepatitis C. HBsAg, anti-HBcor IgG and anti-HBcor Ig M were found in all children with viral hepatitis B and HBeAg was found in only one child.

The presence of an active replication was confirmed by a PCR analysis. Among patients with HBV DNA HBV was found in all children, RNA HCV was detected in 5 of 6 patients. The

active replication of DNA HBV was replaced by RNA HCV in a patient with mixed-hepatitis. The remission period in this patient was actually absent.

Serological markers of hepatitis B were first identified mainly on the stage of treatment - consolidation of remission (in 8 children with ALL, one patient with histiocytosis from Langerhans' cells), at the stage of maintenance therapy in 2 patients (1 child with ALL, 1 with AML). Patients with AL experience the major transfusion-load during the polychemotherapy – induction of remission, which protracts 43 days. Thus, the average number of blood transfusions (concentrated or washed red blood cells) in the induction of children with HV was – $6,75 \pm 1.2$ times, transfusion of FFP – $2,57 \pm 0.7$ times, platelet concentrate – $26,5 \pm 3.4$ doses, albumin – $4,4 \pm 0.2$ times.

Only one patient had visual manifestation of jaundice in the form of sclera icteritiousness and dark urine, but the increase of the overall level of bilirubin in the blood serum (up to 0.31) occurred in 3 patients. All the children had mild hepatomegaly. Hyperenzymemia was determined in 6 children (4 patients with HBV and 2 patients with HCV). Increased ALT levels ranged from 49,3 to 124 U/l and averaged $71,8 \pm 12$ U/l, AST levels varied from 47 to 86 U/l and averaged $58,3 \pm 5,6$ U/l. In some children lesion of the biliary system was noted (4 patients): AP increase by 2-4 times (normal 98-279 U/l) and GGT in 4-6 times (normal). However, it should be noted that all the changes of biochemical parameters were determined on the background of polychemotherapy both in the presence of an active replication of HBV or HCV, and remission. Patients without HV which were treated with chemotherapy had also hyperenzymemia, and hyperbilirubinemia to a lesser extent. Thus, we cannot clearly recognize toxic and viral infection of hepatocytes in patients with AL and HV during the exacerbation period.

An US revealed homogeneous diffuse changes in the liver parenchyma with an average echo-density – 6 children, elevated echo-density – 4 children; fine-grained echostructure was detected in 2 children. No one had changes in the intrahepatic bile duct and portal vein. Induration of the gallbladder's walls occurred in 5 patients.

Treatment of hepatitis (toxic or viral) in children with AL was performed pathogenetically in the hematological department. Hepatoprotective drugs (SAMe, urosfolk, inosine, tocopherol acetate, succinic acid) were mainly used. Somewhat better biochemical parameters were noted on the background of the therapy. Antiviral therapy was not performed.

During the treatment one patient with biphenotypic AL and CHBV (his diagnose was set before the start of polychemotherapy) died at the stage of consolidation of remission. The cause of death was an acute hepatic failure.

Children who had successfully completed the polychemotherapy were taken for a specialized control by a hepatologist. If hematological remission maintained 3 months and some more, then antiviral therapy was considered. Indication for the therapy was a proven viremia.

RNA HCV was detected in 3 months after the completion of polychemotherapy in 2 patients. These patients had a low viral load ($<600\,000$ IU/ml) and normal levels of ALT and AST. Antiviral therapy has been appointed as the drug Intron A 3 MIU 3 times a week. Both children had pre-early and early virological response, therefore the selected treatment regimen was left unchanged. Against the background of the interferon therapy there were no side effects in these children. The feverish reaction to the first injection did not exceed 38° C. Further the temperature rise was observed in 1 patient, but not above $37,5^{\circ}$ C. Changes in the blood count were not found.

In one patient after the completion of the antiviral therapy a persistent virological response was marked until 12 months. In the second patient the relapse was recorded in the third month after the end of the antiviral therapy.

In one patient the active replication of RNA HCV was detected 12 months after the completion of chemotherapy. In two patients with HCV an exacerbation was diagnosed in 1.5 years.

Therapy treatment: Intron A 3 MIU 3 times a week. 2 children had a pre-early and early virological response; one boy had not the early virological response. This patient was assigned to a daily intake of Intron A 3 MIU. All patients had side effects to treatment in the form of febrile reaction to the injection, muscle aches, decreased appetite and low mood. Changes in the blood count were not found. The patient with a daily administration of this drug had no differences in severity of side effects.

The persistent virological response was achieved in one patient within 6 months. The two patients are currently completing a course of antiviral therapy (40 and 42 weeks). Estimation of the efficiency will be carried out within the next 12 months.

Conclusion. Thus, the infection of children with AL HV is 12,0 %, including hepatitis B – 3,6 %, hepatitis C – 7,2 %, mixed-hepatitis B + C – 1,2 %. Markers of hepatitis were detected mainly at the stage of polychemotherapy - consolidation of remission, i.e., hepatitis B virus occurs during the induction of remission, when children experience the greatest transfusion-load. Clinical manifestation of the liver disease on the background of chemotherapy could be caused by a toxic or viral agent. Antiviral therapy of hepatitis B is conducted 3 months after the completion of polychemotherapy at the persistent clinical and hematologic remission.

For efficient prevention and early diagnosis of parenteral viral hepatitis in children with the oncohematological pathology it is necessary to:

- * conduct strict blood control of donors for hepatitis B and C,
- * test patients receiving polychemotherapy for markers of viral hepatitis at least 1 time in 3 months,
- * carry out the control of the active replication once every 3 months for children with a diagnosis of viral hepatitis.

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