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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

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Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

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რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

ერტენზიით დაავადებული იყო 71 (35,32%) ექიმი, მათ შორის 30 (14,93%) - მამაკაცი, 41 (20,39%) – ქალი: I ხარისხის არტერიული ჰიპერტენზია - 46 (22,88%), მათ შორის 30 (14,92%) - ქალი, 16 (7,96%) – მამაკაცი; II ხარისხის არტერიული ჰიპერტენზია - 25 (12,44%), მათ შორის 20 (9,95%) - ქალი, 5 (2,59%) – მამაკაცი.

შრომის მავნე პირობებში მომუშავე ექიმებს შორის არტერიული ჰიპერტენზიის განვითარებასა და პროგრესირებაზე მოქმედი სამედიცინო-სოციალური ფაქტორებისა და ემოციური გამოფიტვის გაანალიზების შემდგომ, ავტორები დაასკვნიან, რომ არც ერთი რისკ-ფაქტორი არ შეიძლება ერთმანეთისაგან დამოუკიდებლად იყოს განხილული.

ინდივიდური პროფილაქტიკის წარმატება დამოკიდებულია რისკ-ფაქტორების მქონე პირების დროულ გამოვლენასა და პროფილაქტიკური ჩარევის განხორციელებაზე. მეორადი პროფილაქტიკა გამოიხატება დაავადების ადრეული სტადიის გამოვლენაში და სამკურნალო-პროფილაქტიკური ღონისძიებების გატარებაში. ამ სტრატეგიების რეალიზების ერთ-ერთ მთავარ პრობლემას წარმოადგენს მოსახლეობის ჯანსაღი ცხოვრების წესის პირობების უზრუნველყოფა.

არტერიული ჰიპერტენზიისა და რისკის ფაქტორების გავრცელება მედიცინის მუშაკებს შორის საკმარისად მაღალია, ისევე როგორც არაორგანიზებულ პოპულაციაში; ამასთან, სახეზეა დაბალი გათვითცნობიერებულობა საკუთარი დაავადების შესახებ და მკურანლობის დაბალი ეფექტურობა.

MODERN APPROACHES IN MANAGEMENT OF CHILDREN WITH CHRONIC HEPATITIS B IN REMISSION OF ACUTE LYMPHOBLASTIC LEUKEMIA

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Coming into the third millennium, the world of medical science, in addition to its outstanding achievements in the field of public health, brought with it a number of unresolved problems. One of them World Health Organization (WHO) considers the problem of chronic liver disease such as chronic hepatitis B and C, which has recently become wide spread and also came into ten main causes of death worldwide [1]. In the "Global report of WHO about hepatitis" 2017 (WHO Global hepatitis report, 2017) is indicated that the overwhelming majority of these people, unable to make timely diagnosis and treatment, are at risk of slow development of chronic liver disease, cancer and death. The morbidity and mortality rate of this pathology is increasing and according to WHO experts, it will double by 2020. "Thus, in the present, said Dr Margaret Chan, Director-General of WHO [2], hepatitis is recognized as one of the main problems of public health that requires urgent actions".

Among chronic diffuse liver diseases, viral hepatitis B, which is a global medico-social problem that is associated with widespread prevalence in both adults and children, the tendency to chronic and the development of severe naturally occurring consequence (cirrhotic effects, hepatocellular carcinoma), is very important [3].

According to WHO experts, from 400 million up to 2 billion people are infected worldwide by hepatitis B virus [3]. Among them, 257 million people live with chronic hepatitis, 1.4 million people die each year from this pathology, which is equivalent to the total number of deaths from tuberculosis and HIV [4].

It should be noted that on a global scale, the prevalence of hepatitis B varies greatly in different regions of the world. It is 1.6% (15 million) of the population in the European Region, while 3.3% (21 million people) in the Eastern Mediterranean region [5].

The problem of chronic hepatitis B is extremely urgent in Ukraine as well. According to O.Golubovska's data [6], in the last decade, the prevalence of this pathology has increased among the adult population. Ukraine is one of the regions with an average prevalence of chronic hepatitis B (HCV) in the population, with an average detection rate of HBsAg-carriers estimated at 2% [7]. According to official figures in Ukraine about 2 million people are suffering from chronic hepatitis. This problem is also relevant in the pediatric population [8-10]. The number of children suffering from chronic hepatitis in Ukraine had a tendency to increase. So, every year, there are 3,500 children which are registered with viral hepatitis B [11].

It should be noted that in the adult population acute hepatitis B is transformed into chronic in 10-15% of cases, while in the pediatric population this percentage is much higher and is 90%, especially at an early age [3,4]. What is especially dangerous in terms of severe disabling and sometimes fatal consequences (liver cirrhosis and hepatocellular carcinoma). According to the literature sources [12,13] in children CHB is found in all age groups.

Recently, a special contingent of patients with chronic hepatitis which had appeared on the background of oncohematologic pathology had made its appearance in the practice of pediatric infectious diseases [14-17]. This group of patients are under the high risk of getting infected by viral hepatitis and includes children with hemophilia, malignant tumors of blood and lymphoid tissues [9,15]. High prevalence of viral hepatitis in patients with oncohematological diseases (OGD) is due to the intensity of parenteral interventions, massive haemotransfusions load, high frequency of invasive research methods [14].

The damaging of the liver by viral hepatitis in children with OGD has dualistic character [19]. Firstly, it is caused by a viral infection itself, and secondly, by a state immunosuppression resulting from oncopathology, prolonged hepatotoxic action of polychemotherapy (PCT), and other drugs which are used as concomitant therapy [18,19]. It has been established that the risk of hepatitis B virus infection in patients with OGD increases directly in proportion to the number of units of blood and its

preparations which had been obtained during transfusions [9].

The frequency of the prevalence of markers of viral hepatitis B (HBV) and C (HCV) among patients in hematology diseases varies widely from 3.9 to 97% according to data of different authors [9,15,20,21].

According to data of prof. Reisis A.R. [14], infectivity rate by viral hepatitis B and C in children with oncopathology reaches 79%. Due to the data of Kramarev S.O. [9], after examination of 151 patients with cancer, the markers of HBV-infection were found in 29.2% of children, HCV-infection in 70, 8% of patients. According to Belarussian author Romanova O.N. and her co-authors (2013), among the 806 patients with oncopathology that were treated at the Republican Scientific and Practical Center of Pediatric Oncology, Hematology and Immunology, frequency of HBV-infected children was 42.2%, markers of HCV-infection were found in 28.1% of patients, mixed infection were established in 23.3% of patients. According to various authors, the vast majority of children with OGD are getting infected by hepatitis B and C viruses within the first year from the start of treatment for the underlying disease, actually during the period of maximum intensity of chemotherapy [15].

In conditions when 60-80% of children with acute lymphoblastic leukemia (ALL) presently are recovering, the development of hepatitis in these children is a very serious problem which sometimes makes it necessary to interrupt the treatment of the underlying disease and the threat of relapse. According to the literature data, that chemotherapy of OGD helps accelerate the replication of the virus and increases the risk of rapid progression of hepatitis [14, 15].

However, according to the most literature sources, the most frequently observed OGD patients have a latent subclinical course of HBV infection with the development of unicteric forms and a high degree of viral load [9, 10, 20, 22].

In children, the development of CHB on the background of oncopathology, in particular acute lymphoblastic leukemia, is accompanied by significant changes in the immune status (increasing of the level of CD 8+ cell, decreasing of CD 4+ cells and their ratio of CD 4+/CD 8+) [14,20,23]. According to some authors, the development of severe hepatitis on a backround of chemotherapy is connected with the circulation of anti-HBe (+) of mutant strain of HBV [21]. This statement coincides with the results of a multicenter study in 250 clinics in Japan in the late 1990s [24]. Some publications indicate a delay in the development of HBe seroconversion to anti-HBe, which significantly complicates the etiologic diagnosis [20].

Today, in many developed countries of the world the problem of viral hepatitis B and C in OCG patients has been eliminated, as all transfused blood products are carefully checked by quantitative PCR methods that allow to detect a very low concentrations of the virus (up to 5-10 IU / ml) [1, 4]. In Ukraine transfusional transmission of HBV is essential, as in the most blood transfusion station testing of donor blood is performed by ELISA with determination of antibodies to the virus hepatitis B and in rare cases RT-PCR method of measurement range of 100 to 200 IU / mL can be used [9].

However, the infectivity rates of HBV and HCV–infections in patients with OCG, especially in children population of Ukrainian hospitals are still not known. Nowadays there are any official statistics on this issue. A small number of published works in recent years is devoted to the study of the immune status, features of antiviral treatment and evaluation of its effectiveness in immunocompromised patients [9].

Regarding the treatment of patients with hepatitis B, it should be noted that current guidelines that exist and approved in Ukraine are not effective enough and need improvement. Management of viral hepatitis that develop on the background of oncopathology, such guidelines do not exist at all and therapeutic tactics in these cases to such patients in modern guidelines are presented unequivocally.

Today, there are three groups of antiviral agents for the treatment of CHB on the background of oncopathology: synthetic nucleosides (and their analogues), cytokines (IL -2, TNF-α), interferons [25-27]. Since the 1980s, interferons (IFN-α), which have antiproliferative and immunomodulatory effects, are the most widely used. However, in recent decades, nucleoside / nucleotide analogues (NAs) have become increasingly widespread in using in pediatrics [28-30]. Since 2014, the recommendations of many international organizations for the study of liver diseases (ESPGHAN, AASLD, APASL) had allowed the using in children of 5 drugs, including IFN-α and four representatives of NAs (lamivudine, adefovir dipivoxil, entecavir, tenofovir disoproxil fumarate) [25,31-33].

Injection IFN-α is a first-line drugs for the treatment of children with chronic hepatitis B, ranging from 1 year of age, except for patients with decompensated liver cirrhosis [9,14]. Lamivudine and entecavir are allowed for 2-year-old children, however, currently lamivudine is limited because of the rapid development of resistance and the appearance of mutations in the HBV DNA genome. Adefovir and tenofovir are allowed in use in children aged over 12 years old because of the development of nephrotoxicity and mineral reduction of bones. These drugs, as well as entacavir, are highly effective in management of lamivudine-resistant CHB and wild-strain HBV [25, 34]. In case of detection of hepatitis B markers in children with oncopathology it is recommended to use nucleoside/nucleotide analogues at least 12 months after its termination [3,15,28]. According to Kramarev S.O. and co-authors' data [9], the most appropriate time for initiation of antiviral therapy in OGD patients is at least 36 months after the end of polychemotherapy and radiotherapy.

Many clinical trials in recent years had tested the effectiveness of the usage of antiviral monotherapy and combined therapy against viral hepatitis B and C [9,14,15,18,19,35-37]. Thus, in the works of Usta M. [19], Dikici B [35], it was shown that combined therapy (lamivudine + IFN-α) lasting about 12 months in children with oncohematological diseases and chronic hepatitis B is more effective compared with monotherapy by lamivudine.

Similar researches were carried out by the staff members of the Department of Pediatric Infectious Diseases of the National Medical University named after Boghomolets O.O. (Kyiv, Ukraine) [9]. They described in their studies three main different treatment regimens for HBV-infection in children with OGD, among which the most effective were combination of lamivudine at a dose of 3 mg/kg/day with interferon-alpha (IFN-α) in dose of 5 million IU/m^2 with short course (up to 1 month) with secondary IFN-α withdrawal and continued taking lamivudine . However, according to international guidelines, it is advisable for patients with OGD to administer entacavir according to body weight and age in combination with interferons [38,39]. According to the author's data, the proposed treatment regimen can effectively prevent HBV reactivation and avoid the inconvenience of remonitoring of HBV DNA. Nowadays entecavir or tenofovir are better and more effective drugs than limivudine in terms of the prevention of CHB [32]. Following with the recommendations of Law et al. [26] prophylactic antiviral therapy should be continued for at least 12 months. after chemotherapy or even later on.

At the same time, the proposed schemes of antiviral treatment in OGD patients may be used after clinical and laboratory remission of the underlying disease. The onset of this remission is individual and can range from 1 to 3 years. In such patients, it is advisable to use supportive therapy to reduce the incidence of endogenous intoxication, severity of clinical syndromes, preventing of progression of viral hepatitis B and improve quality of life.

In patients with viral hepatitis B supportive treatment involves the using of hepatoprotectors and enzyme drugs [40].

Among the large number of hepatoprotectors, which were registered in Ukraine, some affect on cytolysis (bioflavanoid drugs), others – affect on the fibrotic processes in the liver and cytokine balance (aminoacid hepatoprotectors, ursodesoxycholic acid) [41]. Taking into account, many issues have been reported about the study of the role of various hepatoprotectors in liver diseases in both adults and children [42,43].

Having analised A.R. Rezys and E.A. Nurmuhametova's data, had been astimated that in patients with hepatitis B and C in the period of intensive chemotherapy, administration of hepatoprotector such as ademethionine reduces the level of ALT, reduces the number of forced changing of polychemotherapy protocols due to impaired of liver function (from 88.6 to 29.7%) and has the influence on breaks duration between courses of treatment.

At that time in literature were published a big amount of scientific studies about liver diseases management and effectiveness analysis after administration of arginine- betaine drug. According to Hospodarsky I.Ya. and his co-authors' issues, [41] the use of an arginine-betaine drug in patients with viral hepatitis C with liver fibrosis of F2 - F3 (according to METAVIR scale), who had completed the course of antiviral treatment, promotes the normalization of liver enzymes level, the disappearance of cytolytic syndrome, and leads to a decreasion of inflammation and the severity of fibrotic changes in the liver parenchyma (according to FibroTest).

According to Berezenko V.S. and et al. data, [44] in children with liver steatosis and nonalcoholic steatohepatitis to prevent the risk of transformation of the disease in more severe and irreversible stage its nessesary to administer arginine- betaine drug to reduce the degree of fatty liver infiltration, hepatomegaly , pain and feeling of heaviness in the right subcostal region of the abdomen .

Similar results were obtained by other Ukrainian authors. So according to Abaturov A.E. and co-authors issues [45], in 50% of children aged 7-15 years with non-alcoholic fatty liver disease after three months of treatment with arginine- betaine drug (at a dose of 1 sachet, twice daily), were established signifant decreasing in the manifestations of asthenovegetative and dyspeptic syndromes, was detected stable tendention to normalization of arterial blood pressure and body weight stabilization, decreasing the level of cytolytic enzymes (ALT, AST) and manifestation of dyslipidemia, reducing the frequency of detection of hepatomegaly in 2.5 times, compared with the basic condition at the beginning of treatment.

All of the above has led us to use in children with chronic hepatitis B against the background of the OGD of the arginine-betaine substance in the form of "Betargin" (manufactured by Farmatis SA for Farm Union BSIZ Development France / Ukraine; registration number 05.03.02 - 03 / 28649 from 04/25/14). For OGD patients this hepatoprotector can be an excellent alternative in remission period.

Arginine-betaine drug is a complex of aminoacids, which directly effects on the functioning of the liver in viral hepatitis, hepatotoxicity, steatosis, cirrhosis and remove the consequences of hepatotoxic action of drugs, toxic agents, conditions which are associated with violations of protein metabolism.

The components of this agent, namely: arginine and betaine can enhance liver detoxification function, help maintain nitrogen balance, have antioxidant effects, and thus to reduce hypoxia and inflammation level, normalize microcirculation in the liver and improve portal vein heamodynamics , improve intracellular metabolism in hepatocytes, stimulate their activity and regeneration, participate in lipid metabolism, prevent the risk of thrombus formation and progression of atherosclerosis. These positive effects of aminoacids have been proven by foreign researchers. For example, Japanese scientists S. Kakumitsu and his co-authors [46], studied the effect of L - arginine on hepatic blood flow. Its vasodilating effect had been proven by increasing of NO–synthesis level and portal blood flow, as well as its antihypoxic effect in patients with liver cirrhosis.

A team of scientists from Canada and Hong-Kong (2008) studied antifibrotic effect of L - arginine in experimental models of liver fibrosis in laboratory mices. In the course of scientific studies, it was established that the injection of L – arginine had shown the effectiviness of reducing of oxidative stress and decreasing of collagen formation [47].

Regarding to betaine chemical substance, according to American scientists issues (Sandeep M. et al. [48]), betaine significantly effects on the severity of symptoms in chronic hepatitis, in particular, it helps the digestive process in the case of high acidity, reduces acidosis, eliminates dyspeptic symptoms (nausea, feeling of heaviness in the stomach, bloating), etc. , and also decrease homocysteine level and reduces the incidence of side effects from the cardiovascular system.

The aim of the study is to evaluate the effectiveness of "Betargin" in the complex managment of patients with chronic hepatitis B in remission of acute lymphoblastic leukemia.

Similar studies have not been reported in Ukraine.

Material and methods. This investigation was conducted by the Department of Pediatric Infectious Diseases of National Pirogov Memorial Medical University, Vinnytsya. Presented results of the treatment of 41 children with chronic hepatitis B in remission ALL, aged from 3 to 17 years, who were under clinical observation in the Vinnytsia Oblast Children's Clinical Infectious Diseases Hospital, Khmelnytsky city infectious hospital, Zhytomyr Regional Children's Hospital and Ivano-Frankivsk Regional clinical infectious hospital during 2013-2017 years. The duration of HBV-infection in patients was 2 years. It should be noted that the diagnosis of ALL was established according to the official documentation of the oncology dispensaries.

The treatment of patients was carried out according to the protocol of the treatment of children with diseases of the digestive system, approved by Order of the Ministry of Health of Ukraine № 59 approved at 29.01.2013 years.

During the study, all children were divided into two representative groups. Comparison group (group A) was formed by 18 children with chronic hepatitis B in remission of ALL who were under clinical observation and received basic therapy according to approved protocols. The main group (group B) included 23 patients with chronic hepatitis B in remission ALL, which except basic therapy received arginine-betaine substance as " Betargin" drug. The control group consisted of 30 healthy children.

This agent was used as a sachet or glass container. The dosage was carried out according to the instructions. Children aged older than 3 years used the agent up to 1 sachet (or 1 glass containers) dissolved in 1/2 cup of drinking water (100 ml) 3

times per day (TID) after meals. The course of treatment lasted for 2 months.

The determination of the effectiveness of arginine-betaine substance in sick children with chronic hepatitis B in remission of ALL conducted according to the following criteria: the dynamics of clinical symptoms and syndromes; estimating at the beginning and after 2 months of treatment the main laboratory indexes (total bilirubin and its fractions, alaninaminotransferase (ALT), aspartateaminotransferase (AST), alkaline phosphatase (ALP), gammaglutaniltranspherase (GGT)), also indexes of lipidogram (lipoproteids of high, low and very low density (HDLP, LDLP, VLDLP), cholesterol level (CL), triglycerides (TG)).

It should be noted that except presented markers in children, the level of multifunctional plasma protein osteopantin (OPN) was determined, which is a key at cytokine regulating of the revive of tissue. Its expression is the highest in addition to macrophages , neutrophils and dendritic cells , also in the liver in Kupffer cells, macrophages, stellate cells (Wang et et al, 2000), due to that fact OPN promotes the body's response to the infection and damaging of the hepatocytes (Ramaiah and Rittling , 2007). Osteopontin is the most important component of the endoplasmic matrix that promotes liver fibrosis and acts as a biomarker of its severity.

The level of osteopontin in the serum of blood were determined by immunoferment assay of test system of Human Osteopontin Quantikine, complex ELISA according to the manufacturer's instructions (RDD - systems, Dos Too , Minneopolis , MN , the USA), having a detection level of OPN dose from 0,006 to 0,024 ng/ml.

Diagnosis verification of CHB was carried out on the basis of detection in blood of HBV-patients of HBV DNA by PCR method (using test systems "NNF DNA – technology", Russia). By the enzyme linked immunosorbent analysis method (ELISA) were defined antigens and antibodies (HBsAg, HBeAg, anti-HBsAg, anti HBcAg, anti HBeAg) the production NBO diagnostic system (Nyzhniy Novgorod, Russia).The evaluation of activity of necroinflammatory process and the degree of fibrosis was performed by using Fibrotest (laboratory « Synevo»), the stage of fibrosis was determined by METAVIR diagnostic scale.

The study was performed in accordance with the requirements of medical statistics, with the written consent of the parents of the examined children according to legislation of Ukraine. The obtained data were analysed using Microsoft Excel 2010 and Statistica 6 (StatSoft Inc., the USA) computer software by using descriptive and comperative analysis methods.The critical significance level was assumed to be 5% ($p<0.05$), and the probability of differences in the samples was determined by the parametric method (Student's t-test).

Results and discussion. In the course of investigational process, it was found, that the main clinical manifestations in patients with chronic hepatitis B in remission of ALL were asthenovegetative, dyspeptic syndrome, abdominal pain syndrome and right subcostal abdominal region, also hepatosplenomegaly.

The dynamics of clinical features in children with chronic hepatitis B in remission of ALL depending on medical tactics is presented in Table 1.

It should be noted, that in children of group A (15 (83.3%) as well as in patients from group B (19 (82.6%)) before the treatment, asthenovegetative syndrome took place. The children complained of slight fatigue, weakness, irritability, poor appetite. After carrying out the therapy, asthenovegetative syndrom in children of group B was manifested significantly less (8.6%), comparing with patients from group A (33.3%) ($p<0.05$). A similar pattern was observed with dyspeptic syndrome. Thus, in group A patients at the beginning of the treatment this clinical syndrome occurred in 66.6% (12) patients, after treatment the number of patients decreased by half and was established at the level of 38.8% (7 patients). While children in group B after administered therapy total amount of these patients were only 3 (13.1%), which was clinically significantly less than in group A 38.8% (7 patients) ($p<0.05$).

The clinical picture of children with chronic hepatitis B in remission of ALL was characterized also by abdominal pain syndrome, but this syndrome was less presented, comparing with asthenovegetative syndrome. For example, 4 (22.2%) patients in group A had recurrent abdominal pain before treatment, also 5 patients (27.7%) had pain in the right subcostal abdominal region, after treatment these symptoms were estimated in 3 (16.6%) and 2 (11.1%) children, respectively. Whereas in group B patients, abdominal pain syndrome was noted before treatment in 5 children (21.7%), pain in the right subcostal abdominal region was diagnosed in 6 patients (26.1%). In spite of that, after treatment in only 1 patient (4.3%) the pain in the right subcostal abdominal region was registered, and abdominal pain syndrome had not been reported in any patient.

Table 1. Dynamics of the clinical picture in patients with CHB in remission of ALL depending on the chosen therapeutic tactics (in %)

Clinical symptoms	Group A (n=18)				Group B (n=23)			
	Before treatment		After treatment		Before treatment		After treatment	
	n	%	n	%	n	%	n	%
Astenovegitative syndrome	15	83,3	6	33,3 ♦	19	82.6	2	8,6 * #
Dyspeptic syndrome	12	66,6	7	38,8 ♦	15	65,2	3	13,1 * #
Abdominal pain syndrome	4	22,2	3	16.6	5	21.7	0	0
Pain in the right subcostal abdominal region	5	27.7	2	11,1	6	26.1	1	4,3 #
Hepatomegaly	8	44.4	7	38,8	10	43,4	3	13,1 * #
Splenomegaly	5	27.7	4	22,2	6	26.1	4	17.3

*Notes: *- ($p<0.05$) significant difference between indicators in group B;*
♦ - ($p<0.05$) significant difference between indicators in group A;
 # - ($p<0.05$) significant difference between the examined groups after treatment

One of the most clinically significant symptoms of chronic hepatitis B in children was hepatosplenomegaly. It should be noted, that almost in half of children, in both groups, as in group A - 44.4% (8 patients), and group B - 43.4% (10 patients) before treatment was reported data about liver enlargment. After administered therapy the number of children with hepatomegaly was significantly reduced and was in group B - 13.1% (3 children), compared with group A - 38.8% (7 children), respectively ($p<0.05$).

Comparing with hepatomegaly, splenomegaly took place in a much smaller number of patients. At the beginning of the treatment, it was diagnosed in 5 children of group A (27.7%) and in children of group B (26.1%) (6 patients) of cases, respectively. After the completing of administered therapy, total number of patients which were examined with splenomegaly, was decreased, but this percentage was smaller and made up respectively 17.3% (4 patients) in group B and slightly more children in group A - 22.2% (4 patients), respectively.

The dynamics of cytolytic and cholestasis indexes in patients with chronic hepatitis B in remission of ALL depending on different treatment regimens.

Before the treatment, all examined patients had cytolytic syndrome, which was expressed by increased level of ALT and AST enzymes (Table 2) in serum.

Thus, ALT levels in both examined groups was significantly higher than in healthy children 15.5 [14,0-19,0] mmol /L and was 81.5 [42,0-131.0], but in group A ($p<0.05$) and 81.0 [59.0-140.0] and in group B children, respectively ($p<0.05$). After administered therapy the level of this indexes in children of group B was significantly lower (42.0 U/L), than in patients from group A 69.0 [50.0-77.0], respectively ($p<0.05$).

A similar trend was observed with AST level. So, in the children of group A at the beginning of treatment, the level of AST was 50.0 [35.0 - 67.0] U/L and after treatment it decreased in 10 U/l and was 40.0 [28,0- 56,0] U/l. Whereas in children of group B after therapy, the level o AST decreased by half and its level was 28,0 [19,0 - 6 0,0] IU/l ($p<0,05$) (Table 2).

Except serum transaminases enzymes, total bilirubin and its fractions were checked for all patients. It should be noted that regardless of the fact that a considerable part of patients had an increased level of transaminases enzymes, instead of it the total bilirubin and its fractions level remained within the normative ranges. Thus, in group A, total bilirubin was 16.55 [7.0 - 18.39] mmol/L, mainly due to the indirect fraction of 7.95 [5.3-12.4] mmol/L. After the completion of administered therapy, there was a tendency in decreasing of total bilirubin level to 14.40 [10.0 - 19.39] μmol/l, and slightly increasing in the indirect bilirubin fraction level at 10.9 [8.1 - 13.4] μmol/l were reported. A similar pattern was observed in the patients from group B. For all of this, after therapy the level of direct bilirubin in patients in this group was significantly lower and was 3.2 [2.1-4.2] μmol/l , unlike the children of group A had 5.05 [2.1-6.0] μmol/l ($p<0.05$).

The main markers of cholestasis in children as alkaline phosphatase and gamaglutamatransferase were estimated. Only these indices were determined in both study groups. It should be noted that the level of ALP enzyme, as in group A 227,3 [184,0-263,0] μmol/h/l, and in group B - 232,0 [193,0-282,0] μmol/h/l was significantly higher than in healthy children 154.0 [146.0-167.0] mmol/h/l. After treatment, the level of ALP enzyme was decreased significantly in both study groups, but in children of group A it decreased by 1/5, compared with patients of group B - by more than 1/3 part. Thus, at the beginning of treatment, the level of ALP was 232.0 [193.0-282.0] μmol/h/l, and after treatment was 165.0 [117.0-208.0] μmol/h/l, respectively ($p<0,05$) (Table 2).

Table 2. The level of the main indexes of cholestasis in the dynamics during administration of different treatment regimens in patients with CHB in remission of ALL (Me [C25- C75])

Index	Group A (n=18)		Group B (n=23)		Control group (n=30)
	Before treatment	After treatment	Before treatment	After treatment	
ALT, IU/l	81.5 * ♦ [42,0-131,0]	69,0 # ♦ [50,0-77,0]	81,0 ^ ♦ [59,0-140,0]	42,0 ♦ [25,0-77,0]	15.5 [14,0-19,0]
AST, IU/l	50.0 * ♦ [35,0-67,0]	40,0 ♦ [28,0-56,4]	53,0 ^ ♦ [32,0-86,0]	28,0 [19,0-60,0]	26,0 23,0-30,0]
Total bilirubin, μmol / l	16.55 ♦ [7,0-18,39]	14.40 ♦ [10,0-19,39]	12.60 ♦ [7,3-15,6]	12.70 ♦ [6,8-15,6]	6.15 [5,11-7,33]
Direct bilirubin, μmol/l	4.48 ♦ [2,0-6,1]	5.05 # ♦ [2,1-6,0]	3.70 ♦ [2,8-5,4]	3.2 ♦ [2,1-4,2]	1.39 [1,21-1,65]
Indirect bilirubin, μmol/l	7.95 ^ ♦ [5,3-12,4]	10,9 ♦ [8,1-13,4]	8.0 ^ ♦ [4,2-11,9]	9.5 ♦ [5,2-11,5]	5.01 [3,89-6,30]
ALP, Mmol/hour/l	227.3 * ♦ [1 84 , 0-2 63 , 0]	1 79 , 50 ♦ [1, 49 , 0-2 04 , 0]	232,0 ^ ♦ [1 93 , 0-282.0]	1 65 , 0 [1 17 , 0-20 8 , 0]	154.0 [146,0-167,0]
GGT, Mmol//hour/l	14,0 * [12,0-19,0]	13,0 [10-17,0]	15,0 ^ [10,0-18,0]	12,0 ♦ [9,0-14,0]	15.0 [10,0-18,0]

notes: ^ - (p <0.05) significant difference between indicators in group B;
** - (p <0.05) significant difference between indicators in group A;*
 # - (p <0.05) significant difference between the main groups after the end of treatment;
♦ - (p <0.05) significant difference with control group

Table 3. Characteristic of lipid metabolism in patients with CHB in remission of ALL on the background of different treatment regimens (Me [C25 - C75])

Index	Group A (n=18)		Group B (n=23)		Control group (n=30)
	Before treatment	After treatment	Before treatment	After treatment	
Cholesterol, mmol/l	4.43 * ♦ [4,26-4,67]	4.15 # ♦ [3,90-4,72]	4,30 ^ ♦ [3,78-4,60]	3.48 ♦ [3,02-3,78]	3.04 [2,81-3,27]
TG, mmol/l	0.74 * [0,55-0,92]	0.67 [0,50-0,78]	0.76 ^ ♦ [0,71-0,85]	0.62 [0,58-0,72]	0.67 [0.59-0.78
HDLP, mmol/l	1.57 * ♦ [0,92-1,77]	1.60 ♦ [1,18-1,72]	1.40 ^ ♦ [1,23-1,64]	1.45 ♦ [1,33-1,70]	1,79 [1,60-1,90]
LDLP, mmol/L	2.40 * ♦ [2,02-3,05]	2.30 # ♦ [1,94-2,86]	2.53 ^ ♦ [2,26-2,89]	2.06 ♦ [1,98-2,34]	1.99 [1,60-2,10]

notes: ^ - (p <0.05) significant difference between group B indicators;
** - (p <0.05) significant difference between indicators in group A; # - (p <0.05) significant difference between the main groups after the end of treatment; ♦ - (p <0.05) significant difference with the control group*

Table 4. The level of OPN in the study groups, depending on the prescribed regimens of treatment, Me [C25-C75] ng/ml

Index	Group A (n=18)		Group B (n=23)		Control group (n=30)
	Before treatment	After treatment	Before treatment	After treatment	
OPN ng / ml	233.98 ♦ [156,2-500,0]	178 , 1 5 # ♦ [124,6-389,2]	250.38 ^ ♦ [198,88-408,72]	104.92 [73,2-46,25]	94.0 [79,0-112,0]

notes: ^ - (p <0.05) significant difference between indexes in group B;
** - (p <0.05) significant difference between indexes in group A; # - (p <0.05) significant difference between indexes in the main groups after completion of treatment; ♦ - (p <0.05) significant difference with the control group*

The level of GGT enzyme in both groups of study were in the relevant normal ranges (Table 2).

For the detailed analysis of the lipid spectrum of patients' serum, the levels of high- and low-density lipoproteins fractions, triglycerides and cholesterol levels were determined in all patients (Table 3).

Before the beginning of the treatment, lipid metabolism indexes in children of the both study groups were not significantly different, but these indexes were different from those in healthy children group. So the level of cholesterol, in children of group A was 4,43 [4,26-4,67] mmol/L, as well as in group B - 4,30 [3,78-4,6] mmol/l and it was significantly higher, compared to healthy children - 3.04 [2.81-3.27] mmol/l (p<0.05). After treatment, cholesterol level was significantly decreased in both study groups, but in children who had received arginine-betaine substance, cholesterol level was significantly lower 3.48 [3.02 - 3.78] mmol/l compared with group of children that did not receive this agent 4.15 [3.90-4.72] mmol/L.

The similar pattern was observed after analysis of LDLP level. Early treatment levels of HDL were significantly higher in both study groups, compared with those in healthy children. In the process of treatment LDLP level was decreased significantly in group A patients - 2.30 [1.94-2.86] mmol/L, as well as in group B patients , but in children who received arginine- betaine substance the level of this index was the lowest and was at range as 2.06 [1.98 - 2.34] mmol/l (p<0.05).

Unlike LDLP, the level of HDLP at the beginning of treatment was reduced in both study groups, in group A it was 1.57 [0.92-1.77] mmol/L, in group B - 1.40 [1.23-1,64] mmol/l, unlike in healthy children 1,79 [1,60-1,90] (p<0,05). After the completion of therapy in both study groups, the level of HDLP had slightly increased. It should be noted that, despite the fact that children with chronic hepatitis B in remission of ALL, at baseline levels of LDLP and cholesterol were higher, and the content of triglycerides increased insignificantly and was 0.76 mmol/L in both study groups. After the treatment, the level of triglycerides decreased to normative laboratory ranges.

During the scientific research, the level of serum osteopontin was estimated in patients with CHB in remission of ALL and healthy children. It was found that before the treatment, the level of OPN in children of group B was 250,38 [198,88 - 408,72] ng/ml, in group A patients - 233,98 [156,2 - 500,0] ng/ml and it was significantly higher compared with the children from the control group - 94.0 [79.0 - 112.0] ng/ml (p<0.05) (Table 4).

In two months after treatment completion in both these groups, the level of serum OPN was decreased, but in the children who received arginine-betaine substance in complex treatment, the value of OPN index was significantly lower 104.92 [73.2 - 146,25] ng/ml than in group A children - 178.15 [124.6 - 389.2] ng/ml (p<0.05).

Conclusions.

1) Administration of arginine – betaine substance in the complex treatment of the patients with chronic hepatitis B in remission of ALL had shown the results in a significant improvement in the general condition of children due to the reduction (p <0.05) of frequency of manifestation of astenovegitative (8.6% vs 33 , 3% of the comparison group), dyspeptic (13.1% vs. 38.8%), abdominal pain syndrome (4.3% vs. 11.1%) and hepatomegaly (13.1% vs. 38.8%).

2) Using arginine-betaine drug in patients with chronic hepatitis B in remission of ALL promotes the rapid decreasing of liver enzymes and reducing cholestasis signs. At the time of completion of treatment, the level of ALT enzyme in patients in the main group was 1.6 times lower (p <0.05) than in the comparison group.

3) Detailed analysis of the lipid serum profile had shown that in examined children who in the complex therapy received arginine-betaine substance, detoxification function of the liver had improved, the indices of lipid metabolism had became normal.

The tendency in decreasing levels of cholesterol, LDLP, tryglycerides and increasing of HDLP were reported.

4) Under the influence of the administration of arginine-betaine substance, can be reported decreased level of OPN which represented as a noninvasive biomarker of liver fibrosis and has profibrotic activity. In children with CHB in remission of ALL, administration of "Betargin" in complex treatment had shown an antifibrotic effect, which is confirmed by the decreased ($p<0.05$) of the serum OPN level to 104.92 [73.2– 146.25] against 178.15 [124,6-389,2] ng / ml in the comparison group.

REFERENCES

1. Global Hepatitis Report. World Health Organization. Geneva, 2017.
2. Информационный бюллетень ВОЗ (2017). http://www.who.int/bulletin/volumes/95/ru.
3. Management of chronic hepatitis B in childhood. — ESPGHAN clinical practice guidelines / Sokal E.M. et al. // J. Hepatol. 2013. № 59 (4). P. 814–829.
4. Сергеєва Т.А. Епідеміологія гепатиту В в Україні: офіційна статистика, реалії, проблеми, перспективи. // Клінічна імунологія, алергологія, інфектологія. 2017. 5 (102). с. 9–20.
5. Висоцька О.І., Голубовська О.А. Актуальні питання протидії поширенню соціально-небезпечних гемоконтактних вірусних інфекцій в сучасній системі громадського здоров'я України: роль первинної медичної допомоги. // Україна. Здоров'я нації. 2018. No 3 (50). С. 11–16.
6. Golubovska O. Local situation in Ukraine. 3rd Central and Eastern European Meeting on Viral Hepatitis and Co-infection with HIV. Reviews in Antiviral therapy & Infectious Diseases (Ljubljana, Slovenia, 27-28.09.2017). Ljubljana, 2017
7. Чернега Н.Ф. Сучасні підходи до діагностики і лікування вірусних гепатитів у дітей раннього віку. Науковий вісник Ужгородського університету, серія «Медицина». 2014. Вип. 2 (50). С.190–195.
8. Березенко В. С., Царьова О. В. Характеристика фіброзу печінки у дітей з хронічним вірусним гепатитом с за окремими прямими та непрямими маркерами. // Вісник морфології. 2016. Т. 22. No 1. С. 113–117.
9. Вирусные гепатиты В и С у детей с онкогематологической патологией / Крамарев С.А. и др. // Актуальная инфектология. 2016. No 1(10). С. 53–58.
10. Особливості перебігу хронічних гепатитів у дітей раннього віку / Шадрін О.Г, Ковальчук А.А., Дюкарева С.В., Басараба Н.М. // Дитячий лікар. 2013. No4 (25). С.46–49.
11. Крючко Т.О., Несін І.М. Сучасні аспекти діагностики та терапії хронічного вірусного гепатиту при вірусній етіології у дітей. // Дитячий лікар. 2012. No 8. С. 29–33.
12. Денисова М.Ф., Музика Н.М. Порівняльна клініко-параклінічна характеристика дітей із хронічними вірусними гепатитами В і С. // Child`s Health. 2008. No 5 (14).
13. Музика Н.М. Порівняльна клініко-параклінічна характеристика хронічних вірусних гепатитів у дітей та удосконалення їх патогенетичної терапії : автореф. дис. на здобуття наук. ступеня канд. мед. наук : 14.01.10. Київ, 2006. 25 с.
14. Рейзис А.Р. Принципы интерферонотерапии вирусных гепатитов у детей с онкогематологическими заболеваниями. // Вопросы гематологии / онкологии и иммунопатологии в педиатрии. 2002. No 1. С. 48–50.
15. Романова О.Н., Коломиец Н.Д., Гущина Л.М. Хронические вирусные гепатиты у детей со злокачественными новообразованиями. // Клиническая инфектология. Паразитология. 2013. No 2 (5). С. 129–136.
16. The impact of hepatitis viruses on chronic lymphoproliferative disorders--preliminary results / Vladareanu A.M. et al. // J Med Life. 2010. Vol. 3(3). P. 320-329.
17. Yazici O., Sendur M.A.N., Aksoy S. Hepatitis C virus reactivation in cancer patients in the era of targeted therapies. // World J. Gastroenterol. 2014. № 20 (22). P. 6716-6724. DOI: 10.3748/wjg. v20.i22.6716.
18. Булиева Н.Б. Особенности вирусных гепатитов у больных гемобластозами. // Мир науки, культуры, образования. 2012. No1 (32). С. 260–264.
19. Chronic hepatitis B in children with or without malignancies: A 13-year follow-up / Usta M., Urgancı N., Yıldırmak Z.Y., Vural S.D. // World J Gastroenterol. 2015; 21(7): 2073-2079.
20. Бойко Я.Є. Особливості пошкодження печінки у дітей з гострою лімфобластною лейкемією в процесі протокольної терапії: автореф. дис. на здобуття наук. ступеня канд. мед. наук : 14.01.31. Київ, 2001. 16 стр.
21. Рейзис А.Р., Нурмухамедова Е.А. Клиническая онкогематология. ГЭОТАР. 2001. Гл.37. С. 539–553
22. Царьова О.В. Клініко-діагностичні критерії прогресування хронічних вірусних гепатитів В та С у дітей: автореф. дис. на здобуття наук. ступеня канд. мед. наук. Київ, 2017. 21.
23. Россина А.Л., Смирнов А.В., Моисеенко Е.И., Киселев А.В., Гаврилова И.Е., & Маякова С.А. (2003). Лечение хронических гепатитов в и с у детей с онкогематологическими заболеваниями рекомбинантным интерфероном б2b. Детские инфекции, (1), 27-28.
24. McMahon B.J. The natural history of chronic hepatitis B virus infection. // Hepatology. 2009. P. S45–55.
25. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. World Health Organization. Geneva, 2015.
26. Law M.F., Ho R., Cheung C.K. Prevention and management of hepatitis B virus reactivation in patients with hematological malignancies treated with anticancer therapy. // World J Gastroenterol. 2016. Vol. 22 (28). P. 6484–500. DOI: 10.3748/wjg. v22.i28.6484.
27. Management of chronic hepatitis B in childhood. — ESPGHAN clinical practice guidelines / Sokal E.M. et al. // J. Hepatol. 2013. № 59 (4). P. 814–829. DOI: 10.1016/j. jhep.2013.05.016.
28. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. // J. Hepatol. 2012. № 30 (2). doi: 10.1016/j.jhep.2012.02.010.
29. EASL Clinical Practice Guidelines on the management of chronic hepatitis B virus infection. // J. Hepatology. 2017.
30. Treatment of children with chronic hepatitis B virus infection in United States patient selection and therapeutic options / Jonas M.M. et al. // Hepatology. 2010. P. 1–14.
31. Hepatology. A clinical textbook. 7th Edition 2016 / Mauss S. et al. Hamburg: Medizin Fokus Verlag. 2016. 709 p.
32. Jonas M.M., Lok Anna.S.F. Antiviral Therapy in Management of Chronic Hepatitis B Viral Infection in Children: A Systematic Review and Meta- analysis. // Hepatology. 2016. Vol. 63. P. 307–318.
33. Komatsu H., Inui A., Fujisawa T. Pediatric hepatitis B treatment.// Annals of translational medicine. 2017. Vol. 5 (3) 37. 1–13.
34. Comparison of treatments of chronic hepatitis B in children with lamivudine and alpha-interferon combination and alpha-interferon alone / Dikici B. et al. // Pediatr Int. 2002. Vol. 44. P. 517–521.
35. Current therapeutic approaches in childhood chronic hepatitis B infection: a multicenter study / Dikici B. et al. // J Gastroenterol Hepatol. 2004. Vol. 19. P. 127–133.

36. Mieli-Vergani G., Vergani D. Treatment of hepatitis B virus in children: why, whom, how? // Indian Journal of Gastroenterology. 2006. Vol. 25. P. 121–124.
37. Treatment of children with chronic hepatitis B virus infection in United States patient selection and therapeutic options / Jonas M.M. et al. // Hepatology. 2010. P. 1–14.
38. Law MF, Ho R, Cheung CK, et al. Prevention and management of hepatitis B virus reactivation in patients with hematological malignancies treated with anticancer therapy. // World J Gastroenterol. 2016;22(28):6484–6500. doi:10.3748/wjg. v22.i28.6484
39. Komatsu H, Inui A, Fujisawa T. Pediatric hepatitis B treatment. // Ann Transl Med. 2017;5(3):37.
40. Вірусний гепатит В у дітей. Уніфікований клінічний протокол первинної, вторинної (спеціалізованої), третинної (високо-спеціалізованої) медичної допомоги. Київ, 2016. 44.
41. Господарський І.Я., Грушко В.В., Волинець К.В. Можливості і проблеми застосування гепатопротекторів у хворих на хронічний гепатит С після завершення противірусної терапії. // Сучасна гастроентерологія. 2015. No 2(82). С. 57–60.
42. Денисова М.Ф., Чернега Н.Ф., Музыка Н.Н. Бетаргин в комплексном лечении ацетонемического синдрома у детей. // Современная педиатрия. 2014. No8 (64). С.1–6.
43. Колеснікова О.В., Потапенко А.В. Динаміка кардіометаболічних показників на тлі комплексної терапії у хворих на субклінічний гіпотиреоз в поєднанні з неалкогольним стеатозом печінки. // Український журнал медицини, біології та спорту. 2016. No3 (5). С. 71–75.
44. Причини розвитку, діагностика та підходи до лікування стеатозу печінки та неалкогольного стеатогепатиту у дітей / Березенко В.С, Михайлюк Х.З., Диба М.Б., Ткалик О.М. // Современная педиатрия. 2014. No4 (60). С. 1–6.
45. Эффективность гепатопротекторной терапии бетаин-аргининовым комплексом «Бетаргин» при применении у детей с неалкогольной жировой болезнью печени / Абатуров А.Е., Крючко Т.А., Кривуша Е.Л., Пода О.А. // Современная педиатрия. 2018. No3 (91). С. 1-9.
46. Kakumitsu, S., Shijo, H., Yokoyama, M., Kim, T., Akiyoshi, N., Ota, K., Kubara, K., Okumura, M. and Inoue, K. (1998), Effects of l-arginine on the systemic, mesenteric, and Hepatic circulation in patients with cirrhosis. // Hepatology, 27: 377-382.
47. Tung-Ming Leung, George L. Tipol et al. Endothelial nitric oxide synthase is a critical factor in experimental liver fibrosis. // Int J. Exp. Path. (2008), 89, 241-250
48. Sandeep Mukherjee, Tamara Bernard, Kusum Kharbanda, Anthony J. Barak, Michael F. Sorrell, Dean J. Tuma. Impact of Betaine on Hepatic Fibrosis and Homocysteine in Nonalcoholic Steatohepatitis – A Prospective, Cohort Study // The Open Translation Medicina Journal, 2011; 3: 1-4.

SUMMARY

MODERN APPROACHES IN MANAGEMENT OF CHILDREN WITH CHRONIC HEPATITIS B IN REMISSION OF ACUTE LYMPHOBLASTIC LEUKEMIA

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The aim of the study is to assess the effectivity of the drug «Betargin» in complex management of patients with chronic hepatitis B (CHB) in remission of acute lymphoblastic leukemia (ALL).

The research had shown the results of treatment of 41 children with CHB in remission of ALL aged from 3 to 17 years old, who were on dispensary observation in Vinnytsia Regional Children's Clinical Infectious Diseases Hospital during 2013-2017 years. Patients were devided into the following groups: the comparison group (group A), which included 18 children with CHB in remission of ALL, who received basis therapy; the main group (group B) which consisted of 23 patients with CHB in remission of ALL, who got betaine arginine complex («Betargin») in addition to basis therapy. The control group was formed out of 30 healthy children. Determination of effectivity of the proposed treatment regimen was performed by studying the indicators of cholestasis, cytolysis, hepatocellular insufficiency, and lipid metabolism. To assess the liver's fibrosis level and necroinflammatory activity we used the determination of the level of plasma osteopontin in the serum using the enzyme-linked immunosorbent assay (ELISA) method: Human Osteopontin Quantikine (RDD systems, Dos Too, Minneapolis, MS, USA). The verification of the diagnosis of CHB was based on the detection of specific markers of HBV-infection in blood using ELISA and PCR analysis.

During our scientific research we established that using betaine arginine complex in management of CHB in remission of ALL led to considerable improvement of children's general condition, namely due to reducing ($p<0,05$) the incidence of asthenovegetative (8.6% against 33.3% in the comparison group), dyspeptic (13.1% against 38.8%) as well as pain syndromes (4.3% against 11%) and hepatomegaly (13.1% against 38.8%). The activity of ALT in the main group was in 1.6 times less ($p<0,05$) than in comparison group at the end of the course of treatment. «Betargin» has an antifibrotic effect which is confirmed by a decrease in the level of plasma osteopontin up to 104,92 ng/ml against 178,15 ng/ml in the comparison group ($p<0,05$).

Keywords: children, acute lymphocytic leukemia, arginine-betaine complex, chronic hepatitis B, betargin.

РЕЗЮМЕ

СОВРЕМЕННЫЕ ПОДХОДЫ К ЛЕЧЕНИЮ ДЕТЕЙ С ХРОНИЧЕСКИМ ГЕПАТИТОМ В В РЕМИССИИ ОСТРОГО ЛИМФОБЛАСТНОГО ЛЕЙКОЗА

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Цель исследования - оценка эффективности препарата «Бетаргин» в комплексном лечении больных хроническим вирусным гепатитом В в ремиссии острого лимфобластного лейкоза.

Представлены результаты лечения детей (n=41) с хроническим вирусным гепатитом В (ХВГ) в ремиссии лимфобластного лейкоза (ЛБЛ) в возрасте от 3 до 17 лет. Дети находились на диспансерном наблюдении в Винницкой областной клинической детской инфекционной больнице в период с 2013 по 2017 гг. В ходе исследования дети распределены на две репрезентативные группы: сравнения (группа А) - 18 детей с ХВГ в ремиссии ЛБЛ, которые получали базисную терапию. В основную группу (группа В) вошли 23 пациента с ХГВ в ремиссии ЛБЛ, которые, кроме базисной терапии, получали аргинин-бетаиновый препарат «Бетаргина». Контрольную группу составили 30 здоровых детей.

Определение эффективности предложенной схемы лечения проводили путем изучения показателей холестаза, цитолиза, печеночно-клеточной недостаточности, липидного обмена. Для оценки степени фиброза печени и некровоспалительной активности определяли уровень плазменного остеопонтина в сыворотке крови методом имменоферментного анализа (ИФА) с набором Human Osteopontin Quantikine (RDD-системы, Dos Too, Minneapolis, MK, США). Верификация диагноза ХВГ проводилась на основании обнаружения в крови маркеров HBV-инфекции методом ПЦР и ИФА.

В результате исследования установлено, что использование аргинин-бетаинового препарата в комплексном лечении больных ХГВ в ремиссии ЛБЛ привело к значительному улучшению общего состояния детей за счет уменьшения ($p<0,05$) частоты проявлений астено-вегетативного (уменьшение до 8,6% против 33,3% в группе сравнения), диспепсического (13,1% против 38,8%), болевого синдромов (4,3% против 11%) и гепатомегалии (13,1% против 38,8%). Применение препарата «Бетаргин» способствует быстрому снижению цитолитических ферментов. Активность аланинаминотрансферазы у больных основной группы была в 1,6 раз ниже ($p<0,05$), чем в группе сравнения. Улучшилась детоксикационная функция печени, нормализировались показатели липидного обмена. «Бетаргин» обладает антифибротическим эффектом, что подтверждается снижением уровня остеопонтина плазмы крови до 104,92 против 178,15 нг/мл группы сравнения ($p<0,05$).

რეზიუმე

თანამედროვე მიდგომები ქრონიკული B ჰეპატიტის მქონე ბავშვების მკურნალობაში მწვავე ლიმფობლასტური ლეიკოზის რემისიის ფაზაში

ი.ნეზგოდა, ლ.მოროზი, შ.სინგხი, ო.სინგხი

ვინიცას ნ.პიროგოვის სახ. ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა პრეპარატ ბეტარგინის ეფექტურობის შეფასება ქრონიკული B ჰეპატიტის მქონე ბავშვების კომპლექსურ მკურნალობაში მწვავე ლიმფობლასტური ლეიკოზის რემისიის ფაზაში.

წარმოდგენილია 3-17 წლის ასაკის ქრონიკული B ჰეპატიტის მქონე ბავშვების (n=41) მკურნალობის შედეგები მწვავე ლიმფობლასტური ლეიკოზის რემისიის ფაზაში. ბავშვები იმყოფებოდნენ დისპანსერული მეთვალყურეობის ქვეშ ვინიცას საოლქო კლინიკურ ინფექციურ საავადმყოფოში 2013-2017წწ. პერიოდში. კვლევის მსვლელობისას ბავშვები განაწილდა ორ რეპრეზენტატულ ჯგუფად: შედარების ჯგუფი (ჯგუფი A) შეადგინა 18 ბავშვმა ქრონიკული B ჰეპატიტით მწვავე ლიმფობლასტური ლეიკოზის რემისიის ფაზაში,რომლებიც იღებდნენ ბაზისურ თერაპიას. ძირითად ჯგუფში (ჯგუფი B) შევიდა 23 პაციენტი ქრონიკული B ჰეპატიტით მწვავე ლიმფობლასტური ლეიკოზის რემისიის ფაზაში, რომლებიც, ბაზისური თერაპიის გარდა, იღებდნენ არგინინ-ბეტაინის პრეპარატს "ბეტარგინის" სახით. საკონტროლო ჯგუფი შეადგინა 30 ჯანმრთელმა ბავშვმა. შემოთავაზებული სქემის ეფექტურობა განისაზღვრა ქოლესტაზის, ციტოლიზის, ღვიძლ-უჯრედული უკმარისობის, ლიპიდური ცვლის მაჩვენებლების შესწავლის გზით. ღვიძლის ფიბროზის ხარისხის და ნეკროანთებითი აქტივობის შეფასების მიზნით განისაზღვრა პლაზმის ოსტეოპონტინის დონე სისხლის შრატში იმუნოფერმენტული ანალიზის მეთოდით Human Osteopontin Quantikine ნაკრების გამოყენებით (RDD-სისტემები, Dos Too, Minneapolis, MK, აშშ). ქრონიკული B ჰეპატიტის დიაგნოზი ვერიფიცირებული იყო სისხლში HBV-ინფექციის მარკერების კვლევის საფუძველზე პოლიმერაზულ-ჯაჭვური და იმუნოფერმენტული ანალიზის მეთოდებით.

დადგენილია, რომ არგინინ-ბეტაინის პრეპარატის გამოყენებამ ქრონიკული B ჰეპატიტის მქონე პაციენტების კომპლექსურ მკურნალობაში მწვავე ლიმფობლასტური ლეიკოზის რემისიის ფაზაში განაპირობა ბავშვების ზოგადი მდგომარეობის მნიშვნელოვანი გაუმჯობესება ასთენიურ-ვეგეტატური გამოვლინებების (შედარების ჯგუფში – 8,6%, ძირითად ჯგუფში – 33,3%), დისპეპსიური მოვლენების (შედარების ჯგუფში – 13,1 %, ძირითად ჯგუფში – 38,8%), ტკივილის სინდრომის (შედარების ჯგუფში – 4,3%, ძირითად ჯგუფში – 11%) და ჰეპატომეგალიის (შედარების ჯგუფში – 13,1% ძირითად ჯგუფში – 38,8%) ($p<0,05$) შემცირების ხარჯზე. პრეპარატ ბეტარგინის გამოყენება ხელს უწყობს ციტოლიზური ფერმენტების მკვეთრ შემცირებას. ალანინტრასფერაზას აქტივობა ძირითადი ჯგუფის პაციენტებში 1,6-ჯერ ნაკლები იყო ($p<0,05$), ვიდრე შედარების ჯგუფში. გაუმჯობესდა ღვიძლის დეტოქსიკაციური ფუნქცია, ნორმალიზდა ლიპიდური ცვლის მაჩვენებლები. ბეტარგინს აქვს ანტიფიბროზული ეფექტი, რაც დასტურდება სისხლის პლაზმაში ოსტეოპონტინის დონის შემცირებით - 104,92 ნგ/მლ *vs* 178,15 ნგ/მლ (შედარების ჯგუფში, $p<0,05$).