HEPATOTOXICITY IN PATIENTS WITH CANCER PATHOLOGY (DIAGNOSIS, TREATMENT)

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Abstract: The article presents modern theoretical and practical aspects of toxic liver damage in patients with cancer during chemoradiotherapy. Expounded clinical and laboratory parameters hepatocyte damage in patients with cancer. Submitted treatment strategy.

Key words: chemotherapy, cancer, hepatotoxicity

Introduction. Using current clinical protocols therapy hemoblastosis and solid tumors significantly increased the survival of patients with cancer [2,4]. Improving treatment achieved through the use of new drugs and intensification chemotherapy regimens. However, the negative side of polychemotherapy (PCT) are the side effects of anticancer drugs, due to the low selectivity of most chemotherapeutic drugs drugs [2, 4].

According to clinical studies found that drug liver makes about 10% of all adverse reactions linked to the use of these chemotherapeutic drugs [1,5,6,10,12]. In fact, hepatotoxicity develops, perhaps more than that shows official medical statistics because the liver is one of the main parts of biotransformation chemotherapeutic drugs drugs.

In addition to the toxic effect of chemotherapy negative contribution in human liver makes profound immunosuppression caused by both the tumor and treatment, and chronic hepatitis virus infection. In primary or metastatic liver damage is often diffuse or focal infiltration of tumor cells when the process involved portal tracts and sinusoids, which leads to portal hypertension [5,7].

One of the main causes of structural and functional abnormalities of hepatocytes in patients with cancer is endotoxemia syndrome that develops as a result of tumor toxicity, bacterial and viral infections, join, and as a result of massive lysis

of tumor tissue in response to the anticancer drugs. To date, studied and other mechanisms of liver damage when taking medications such as immune mechanism hepatotoxicity. Drug substance or its metabolite may become hapten to proteins of liver parenchyma, causing her immune damage.

It is known that the liver is the organ where most chemotherapeutic drugs metabolized [14]. The literature has accumulated a significant amount of data demonstrating liver monooxygenases involved in their metabolism. Depletion of cytochrome P450 involved in the metabolism of drugs can lead to a decrease in excretion of toxic components that enter the body and cause their accumulation in organs and tissues, disrupt neutralization of endogenous metabolic products or result in the formation of secondary, sometimes more toxic than the original product substances. Reduced effectiveness of this enzyme system increases the toxicity of chemotherapeutic drugs [2,3,11,12]. Yes, according to some studies found that cytotoxic drugs can increase several times the sensitivity of hepatocytes to endotoxin [2]. In addition, the work of most researchers proved that as an opportunity for the removal of harmful substances in the liver of these conditions is problematic, anticancer drugs can cause cumulative toxic effect on its functional state [9,13,15].

Toxic effects of chemotherapeutic drugs drugs is due to a decrease of extraction by hepatocytes and is associated with both a violation of enzyme activity, and in violation of binding to plasma proteins.

Significant role in the development of pathological changes in the liver, is as a viral infection, the risk of which is caused by the transfusion of blood components (red blood cells concentrate, concentrate platelets, fresh frozen plasma). The presence of viral infection can significantly hamper of chemotherapy and contribute to the development of severe complications, even to death. According to the literature, the incidence of viral hepatitis B and C before treatment hemoblastoses is 5.9%, and in remission after chemotherapy - 18.5% and in long term treatment of 72%, including 38% of cases - in phase replication of the virus [4].

When using anticancer drugs often develop their hepatic toxicity effect, which results in a very wide range of morphological variants of liver disease [4.21]. In

particular, the study of methotrexate with liver by type of acute hepatitis may develop hepatic fibrosis of varying degree. For toxicity 6-mercaptopurine and obesity is characterized by necrosis of hepatocytes, the formation of fibrosis portal tracts, cholestatic injury. Toxic hepatitis with hepatic dysfunction may also cause cyclophosphamide, asparaginase, dakarbazyn, idarubicyn, and one of modern anticancer drugs - thalidomide, which has targeted action [7,21]. In hematology also used immunosuppressants, including cyclosporine, also cause toxic liver damage. Development necrosis of the liver can be observed in the treatment of paracetamol [21]. The combination of different drugs may lead to potentiation of hepatotoxicity. Thus, the effect on the liver 6-mercaptopurine increases with concomitant administration of doxorubicin [12.21]. Prolonged treatment with cytotoxic drugs can lead to portal hypertension due to the formation of severe fibrosis. A special form of liver disease in patients with cancer pathology is venoocclusive liver disease that occurs mainly during HIGH chemotherapy. Venookklyuziyna disease characterized hyperbilirubinemia, rapid growth and tenderness of liver, fluid retention with the development of ascites.

In patients with oncopathology are possible irradiation liver damage, which in the acute phase can be characterized by increased levels of transaminases hyperbilirubinemia (jaundice) and ascites. Concurrent use of doxorubicin and vincristine potentiate radiation liver injury. One of the long-term effects of exposure is liver fibrosis. Due to the widespread use of cytotoxic and hormonal agents on malignant disease that has significant immunosuppressive effect, patients in this category are extremely susceptible to infectious diseases. So, hepatitis in these patients may also be due to a wide range of infectious agents: nonspecific lesions in the generalized infections, liver abscesses, fungal diseases and viral hepatitis, particularly determinable cytomegalovirus, herpes simplex and herpes zoster, adenovirus [4.21].

Table 1 shows the cytotoxicity drugs, resulting in the use of developing toxic liver damage [4.21].

Table 1

The frequency and spectrum of hepatotoxicity and the application of chemotherapeutic drugss

Preparation	Description toxicity
6-mercaptopurine	Hepatotoxicity is cholestatic with jaundice or damage of hepatocytes with increased transaminases. Histological examination revealed necrosis of hepatocytes and bile stasis. Hepatotoxicity may occur when using the drug in any dose, but more often when using doses above 2 mg / kg (75 mg/m2) on day.
Asparaginase	In 42-87% of patients seen with jaundice and cholestatic with damage to hepatocytes (increase in transaminases, alkaline phosphatase, bilirubin) in 50% of patients diagnosed with cholestasis without jaundice but with damage to hepatocytes and in more than 87% of developing fatty liver
Blyeomitsyn	In 10% of patients demonstrate abnormal liver function with changing parameters of liver function tests (increase in transaminases, alkaline phosphatase, bilirubin).
Capecitabine	In 20-40% of patients diagnosed cholestatic hepatitis with increased levels of bilirubin, alkaline phosphatase and transaminases; 10% - liver failure.
Carmustin	In 90% of patients after one week of therapy developed abnormal liver function (increased transaminases, alkaline phosphatase), hyperbilirubinemia
Cyclophosphamide	In 1% of patients diagnosed cholestatic hepatitis with increased levels of bilirubin, alkaline phosphatase and transaminases.
Cytarabine	In 2% of patients with liver dysfunction increases gamma glutamyl, transaminases, bilirubin
Daktinomycin	In 15% of hepatotoxic and count, including ascites,

	hepatomegaly, hepatitis, liver function tests change
Floxuridine	Abnormal liver function appears in 50% of patients using intra-arterial infusion
Gemcitabine	In 10-29% of patients noted transient increase in trans and called, in 15-20% - increased alkaline phosphatase and bilirubin
Ifosfamide	In 10% of patients diagnosed with liver dysfunction with an increase in liver trans and called and / or bilirubin in serum
Interleukin-2	In 40% of patients experienced higher bilirubin, 23% p - increase HHTP
Melphalan	In 10% of patients is a transient liver dysfunction with increased HHTP using high doses
Methotrexate	In 17% of patients diagnosed with transient increased trans and called. Using high doses observed toxic hepatitis, the development of fibrosis and cirrhosis.
Mitoxantrone	In 3% of patients may develop jaundice, 10% - abnormal liver function (increased levels of bilirubin, a change of transaminases).
Paclitaxel	Raising trance and called, alkaline phosphatase and bilirubin in serum was observed in 19%, 22% and 7%, respectively. Cases of hepatic necrosis and hepatic encephalopathy origin fatal.
Vinorelbin	Transient increase gamma glutamyl
Cisplatin	In 2-10% of patients observed liver dysfunction with increased levels of liver enzymes and / or hyperbilirubinemia.
Vinkristin	In 1-2% of patients defined hepatotoxicity with increased levels of liver enzymes and / or bilirubin in serum
Doxorubicin	In 1-2% of patients defined hepatotoxicity with increased levels of liver enzymes and / or bilirubin in serum

According to WHO recommendations, distinguish five degrees of intensity of side effects of anticancer drugs, including symptoms and hepatotoxicity (Table 2).

Table 2

Evaluation of toxicity (WHO**)**

Index		The degree of toxicity				
	Rate	0	1	2	3	4
Total bilirubin	<18.81 mmol / l	N	1.26-2.5xN (upper limit of normal)	2.6-5xN (upper limit of normal)	5.1-10xN (upper limit of normal)	≥ 10xN
ALT	<40 U / l	N	1.26-2.5xN (upper limit of normal)	2.6-5xN (upper limit of normal)	5.1-10xN (upper limit of normal)	≥ 10xN
AST	<40 U / l	N	1.26-2.5xN (upper limit of normal)	2.6-5xN (upper limit of normal)	5.1-10xN(Upper limit of normal)	≥ 10xN
alkaline phosphatase	35-129 U / l	N	1.26-2.5xN (upper limit of normal)	2.6-5xN (upper limit of normal)	5.1-10xN (upper limit of normal)	≥ 10xN
gamma glutamyl	5-61 IU / l	N	1.26-2.5xN (upper limit of normal)	2.6-5xN (upper limit of normal)	5.1-10xN (upper limit of normal)	≥ 10xN
Cholesterol	<5.2 mmol / l	N	1.26-2.5xN (upper limit of normal)	2.6-5xN (upper limit of normal)	5.1- 10xN (upper limit of normal)	≥ 10xN
Clinic		-	-	-	Precoma	Hepatic coma

Note: N - upper limit of normal

Given the toxicity developed adjustability doses of cytotoxic drugs depending on liver function. However, most of the studies demonstrated that lower doses of cytotoxic drugs and increasing the period between cycles greatly reduces the effectiveness of therapy and survival in general. The need for treatment of patients with clinically significant hepatic impairment is not in doubt, but the question of compulsory treatment of latent forms of liver failure and prevention of its development is the subject of debate. The success of treatment is determined by the ability to recognize the etiological factor and leading pathogenetic mechanism of its development, and adequately fitted therapy.

Diagnosis of drug-induced liver injury is often difficult, and the doctor must not only collect the patient's history, but also well oriented in its clinical and morphological manifestations. Quite often clinic prevalent symptoms of intoxication as well as varying degrees of jaundice. In response to damage liver cells correspond to the structural changes that capture both parenchymal and mesenchymal tissue.

In severe hepatotoxic lesions may develop hepatic encephalopathy (HE) and liver failure. Stages of HE, in fact, is due to the severity of their potential reversibility. Severity of neuropsychiatric symptoms of HE ranges from light to deep coma stages (Table 3). Symptoms of HE determined clinically and cover changes consciousness, intelligence, behavior and muscle disorders. The main criterion for determining the stages of HE is a state of mind.

Table 3

Stages of hepatic encephalopathy

Stages	**State of Mind**	**Intelligent status**	**Behavior**	**Neuro muscular function**
0 (Latent)	not changed	Concentration-reduced; Memory-reduced	Not changed and	Time for psychometric tests - increased

		(diagnosed with c and le directed study		
I	Disorientation, sleep disturbance and vigor	Logical thinking - reduced f; attention - is reduced, the ability to counting - reduced	Depression, irritability, euphoria, anxiety	Tremor, hyperreflexia, dysarthria (+ +)
II	somnolence	Disorientation in time, the ability to counting - significantly reduced	Apathy, aggression, inadequate response to external stimuli	Asterixis (+), dysarthria (+ +), hypertonicity
III	sopor	Disorientation in space, amnesia	Delirium, primitive reaction	Asterixis (+ +), nystagmus, rigidity
IV	coma	-	-	Atony, areflexia, absence of reaction to pain

In the first stage of HE disturbed sleep rhythm: there daytime sleepiness and insomnia at night. In the second stage increases drowsiness and can go into lethargy. In the third stage to the above symptoms joins disorientation in time and space and

confusion. In some patients develop epileptychninapady, spastic paraplegia. For HE I-III stage sufficiently characteristic flapping tremor or asterixis that is fast flexor and extensor movements in promenezap'yastnyh joints. The fourth stage - the actual coma - characterized by lack of consciousness and response to painful stimuli.

Dedicated stage encephalopathy can consistently pass each other, with the majority of symptoms that appeared in earlier stages, and stored on these.

In addition, isolated latent (hidden) hepatic encephalopathy (HEP) when no clinical symptoms of PE, but further examination revealed a number of neuropsychiatric disorders, such as slowing of cognitive activity and accuracy of fine motor skills. LET regarded as a preliminary stage of severe PE.

For its detection, as well as detailing mental disorders in HE the first and second stages used psychometric testing. There are two groups of tests: tests of cognitive speed response (test connection numbers) and tests the accuracy of fine motor skills (test line or labyrinth). For example, the test connection patient numbers connecting line numbers 1 to 25 printed on a sheet of paper. Evaluation of the test is the time spent on patient his performance, including the time needed for error correction (Table 4).

Table 4

Interpretation of the results of the test connection numbers

Time, s	Balls	Stages of HEP
Less than 40	0	No
41-60	1	0-I
61-90	2	And I-II
91-120	3	II
More than 120	4	II-III

Note that for simplicity and ease of psychometric tests hide certain flaws, which, first of all, is the impact on the results of a large number of endogenous and exogenous factors. Chance HEP can be minimized by using multiple tests in one

patient and interpreting the results in the complex. Sensitivity psychometric tests in detecting LET is 70-80%.

Additional studies in PE include determination of ammonia elektoentsefalohrafiyu (EEG) and other studies.

Determining the level of ammonia. Most patients with HE (90%) the level of ammonia in the blood significantly increased. However, the normal concentration should not be grounds for excluding the diagnosis of PE. Electroencephalography. PE is also accompanied by changes in the EEG, which becomes apparent at stage II: the flattening of the curve alpha rhythm, then the appearance of t-and q-activity. EEG sensitivity in detecting low LET - about 30%. In IE 0-I stage EEG diagnostics performed using visual evoked potentials. Evoked potentials of the brain. It is more sensitive than EEG detection method LET sensitivity which is 80%.

Magnetic resonance spectroscopy (MRS). Particularly sensitive method to detect LLE and to assess the severity of HE (sensitivity in detecting LET approaching 100%).

Positron emission tomography (PET) allows you to verify and refine stage HE. However, MRS, PET is by far the most sensitive method for lifetime diagnosis of HE.

To assess the extent and depth of damage hepatocytes commonly used clinical and biochemical studies of liver cell integrity, its excretory activity, cholestasis, liver functional capacity, mesenchymal and immune reactions. Given that the morphological study of the liver can not spend all patients, analysis of biochemical parameters, with some probability, allows you to specify the level and leading mechanism of liver dysfunction. In clinical practice, it is altered laboratory parameters are often the starting point for the differential diagnosis and determine the form of liver disease and the appointment of immunosuppressive therapy (Table 5). Based on laboratory measurements to judge the severity of the pathological process in the liver, to predict the course of disease, and to assess the effectiveness of the therapy.

Table 5

Interpretation of results in lesions of blood Pec and n ing in patients with cancer

Indicators	Change of	The clinical significance
Bilirubin concentration 'south pairs are efficiently created	N	Cholestasis without jaundice
ALT	N	
Alkaline phosphatase	N	
γ-GTP	increase	
Bilirubin concentration 'south pairs are efficiently created	N	Cholestasis without jaundice but with damage to hepatocytes
ALT	increase	
Alkaline phosphatase	increase	
γ-GTP	increase	
Bilirubin concentration 'south pairs are efficiently created	increase	Cholestasis with jaundice
ALT	increase	
Alkaline phosphatase	increase	
γ-GTP	N	
Bilirubin concentration 'south pairs are efficiently created	increase	Cholestasis with jaundice and hepatic damage
ALT	increase	
Alkaline phosphatase	increase	
γ-GTP	increase	
Alpha fetoproten	increase	Tumor process. For the prediction of hepatocellular carcinoma th

Antinuclear antibodies	increase	Autoimmune liver disorders
Antimitochondrial antibodies	increase	Autoimmune liver disorders
Hammahlobulinemiya	increase	Autoimmune liver disorders

Note: N-norm

Diagnosis of viral liver damage requiring mandatory verification by the adopted complex marker in viral hepatitis (Table 6) [4, 17, 18].

Table 6

Key markers of various hepatitis viruses

Marker	The clinical significance
Hepatitis B (HBV)	
HBsAg - HBV surface antigen	Indicate in HBV infection
HBeAg - nuclear "e" antigen HBV	Indicates the replication of HBV in hepatocytes, high blood infectivity and high risk of perinatal transmission
HBcAg nuclear «core»- antigen HBV	Indicates the replication of HBV in hepatocytes revealed only at morphological study of liver biopsies, blood in free form is not found
Anti-HBc (total) - total antibodies to HBcAg	An important diagnostic marker, especially with negative results indicating HBsAg, used for retrospective diagnosis of hepatitis B
IgM anti-HBc - antibody class M	One of the earliest serum markers of hepatitis B, their presence in the blood indicates an acute infection, chronic hepatitis B and HBV replication mark process activity in the liver

nuclear antigen in	
Anti-HBe - antibody "e" HBV antigen	May indicate the beginning phase of recovery (exception - mutant form of HBV)
HBV DNA - DNA hepatitis B virus	The most accurate marker of the presence and replication of HBV
Hepatitis D (HDV)	
I g M anti-HDV - M class antibodies to hepatitis D	Indicate on HDV replication in the body
I g G HDV-G class antibodies to hepatitis D	Indicate possible infection with HDV or transfer district in infection
HDAg - antigen Hepatitis D	Marker HDV presence in the body
HDV-RNA - RNA virus Hepatitis D	Marker presence and replication of HDV
Hepatitis C (HCV)	
Anti-HCV I g G - Ila class G antibodies	Indicate possible infection with HCV or moved to infection

to hepatitis C	
Anti-HCV core I g M - M class antibodies to a nuclear protein k th and HCV	Indicates the current infection (acute or chronic phase of reactivation
Anti-HCV core I g G - G-class antibodies to a nuclear protein k and thHCV	Indicates HCV infection or past infection
HCV RNA - RNA virus hepatitis C	Marker presence and replication of HCV
Hepatitis G	
HGV-RNA - RNA virus hepatitis G	Marker presence and replication of HGV
Hepatitis TTV	
TTV-DNA - DNA of hepatitis B virus TTV	Marker presence and replication of TTV

In order to confirm the results of various clinical and biochemical studies can be used instrumental methods, primarily ultrasonography and computed tomography (CT).

In order to study the combined detoxification liver function and determine the percentage of functioning hepatocytes using ^{13}C-metatset and new breath test. Metatsetyn that is assigned to a patient undergoes demethylation and decarboxylation by liver enzyme cytochrome P450, as well as a number of chemicals. Violation of these functions seriously affects the ability of the liver to excrete toxic substances. The end product of the metabolism of 13C-metatsetyna is 13SO2, the intensity output through the lungs which gives an indication of the functional state of microsomal enzyme systems of hepatocytes.

Treatment and prevention of damage to hepatocytes in patients with cancer

Program treatment and prevention of hepatotoxicity in patients with cancer patients should be comprehensive and include:

- Dietary measures;
- Drug therapy;
- Installation and removal of additional factors that contribute of hepatotoxicity

Most patients assigned pathogenetic and symptomatic treatment for the prevention and treatment of toxic liver damage on the background of chemotherapeutic drugs treatment. Arsenal drugs purposeful action in the liver damages small. These include: S-ademetionyn, ursodezoksiholevu acid, L-ornithine-L-aspartate and some other [16.21].

S-ademetionin-biologically active substance that is present in all tissues, but the highest concentration is found in the liver. He serves as a necessary structural element in three important biochemical chain: transmetylyuvanni, transsulfuvanni, aminopropilyuvanni. The most important reactions ademetionin-dependent transmetylyuvannya belongs synthesis of phospholipids. Violation transsulfuvannya ademetionin leads to a deficiency of glutathione (endogenous peptide) - one of the most important intracellular detoxifying agents. Lack of glutathione and changes in

the activity of liver GST reduces resistance to the damaging effects of free radicals and other hepatotoxic reactions. Reaction aminopropilyuvannya relates to processes of proliferation of hepatocytes and liver regeneration (polyamine synthesis). We know about antidepressant effect ademetionin. Multi ademetyoninu makes it meaningful clinical application. The drug is licensed for use as a treatment for liver disease and as an antidepressant. As a result, treatment ademetyoninom normalized permeability of cell membranes, the activity of Na +-K +-ATPase, increasing the energy potential of the cells and thus improves the capture components of bile from the blood, their intracellular transport and secretion of bile in the ducts. In cells increases the synthesis and content of thiols (glutathione, taurine, sulfate), which have a protective effect against free radicals, bile acids and other toxic components entering or produced in hepatocytes, including biological substances responsible for the appearance of skin itching [14,15,21].

Evidence of the appointment ademetionin is the appearance of jaundice and hyperfermentemiyi (transaminase elevations) for toxic or viral hepatitis. Appointment ademetionin also shows patients who are infected with hepatitis B and C patients had a history of liver disease in previous courses PCT, as well as patients who planned vysokodoznoyi chemotherapy with bone marrow transplantation. Relatively new evidence for the purpose ademetionin in cancer patients is depression, which is often formed in them. According to many studies, Geptral effective not only as hepatoprotector, but also as an atypical antidepressant.
Drug is initially administered parenterally 5-10 ml (400-800 mg) intravenously or intramuscularly for 10-14 days and then by 400-800 mg (1-2 tablets) two times a day. The duration of treatment is 30 days. If necessary, you can continue or repeat the course. Contraindications to the appointment ademetionin not installed. The protective effect of the drug reduces the number of forced changes chemotherapy protocols related to the liver in 50% of patients. Application ademetionin improves subjective state of patients to reduce symptoms of depression and improve anti-dyspeptic effect.

UDCA-tertiary bile acid formed in hepatocytes and intestine, is hydrophilic and non-toxic. Currently, this drug is used as an immunosuppressive therapy cholestasis. Admission UDCA leads to a reduction in enterohepatic circulation of hydrophobic bile acids, thereby preventing their toxic effects on the membrane of hepatocytes and bile duct epithelium, as well as normalization of antigens on the surface of cell membranes, which reduces their Autoimmunity. In addition, UDCA has choleretic effect resulting circulation at the extrahepatic bile ducts - bazolateralnoyi membrane of hepatocytes. Assigned to UDCA 10-15 mg / kg per day in the disappearance of phenomena cholestasis.

Treatment of concomitant viral hepatitis

As mentioned above, a factor that aggravates hepatotoxic effect of cytotoxic drugs, is concomitant infection with hepatitis B virus. Their etiological treatment in cancer patients is often problematic. On the one hand, there is a need for interruption of treatment of cancer, reducing the effectiveness of therapy. On the other hand, reaching antitumor effect, viral hepatitis may contribute to the formation of cirrhosis or hepatocellular carcinoma [17].

Analysis of current literature has shown that the use of drugs of nucleoside analogues (lamivudin) prevents reactivation of hepatitis B during chemotherapy. Antiviral treatment was recommended for the two groups of patients with hepatitis B after serological diagnosis depending on the phase of the disease (chronic and latent phase flow hepatitis). Patients who have chronic viral hepatitis is set based on the detection of HBsAg in the absence of abnormal liver function, recommended the appointment lamivudinum 100 mg / day for 7 days prior to specific therapy and continued use for one year. In the future, every three months to monitor liver function and PCR reaction for detection of hepatitis B DNA in research, et al. Showed that patients with chronic hepatitis B who were treated lamivudinum during treatment of the underlying disease, reactivation of the virus has been established. For patients with latent hepatitis B (turns HBc antibody) while preserving liver function resulting recommendations have not been established. Appointment of lamivudinum is recommended primarily for patients with latent HBV and liver dysfunction, and in

the absence of changes in indicators transaminase patients can remain under the supervision and control of laboratory indicators of liver. These patients should be performed PCR every three months. However, remember lamivudinum interaction with cytotoxic drugs, the possibility of adverse reactions and the need for prevention, treatment [18,19,20].

Strategies for treating patients with cancer diseases and markers of HCV is currently available in the literature we found. It should be emphasized that interferon appointed in HCV therapy, despite its proven effectiveness and wide application especially in combination with chemotherapy in the treatment of cancer patients found in connection with such neridkisnym side effect of interferon as the development of pancytopenia [4] .

Treatment HE III-IV stages is characterized by high cost and relatively low efficiency. This necessitates early prevention and treatment of diseases associated with the development of HE [1].

Remediation intestine. Cleansing the colon pursues removal of nitrogen-containing substances, especially important in cases of gastro-intestinal bleeding, dietary protein overload and constipation. Very effective use of high enemas that allows you to clean the large intestine to the maximum extent, up to the cecum. This can be achieved by changing the position of the patient: the solution to start the patient on the left side, then continue in the position on the back with painted finish and pelvis in position on the right side. The total volume of the solution is introduced, should not be less than 1000 ml twice a day. As solutions are used sodium acetate buffer (pH 4.5) or lactulose (300 ml per 700 ml of water).

Oral laxatives in severe HE is better to enter through a nasogastric tube. Infusion 1000 ml of 10% aqueous solution of mannitol for 60-90 minutes, causing osmotic diarrhea, provides almost complete elimination of intestinal contents during the subsequent 3-4 hours. In the case of gastrointestinal bleeding mannitol should be administered through a tube to the separation of pure solution of the rectum. In mannitol may be used 20-30% solution of magnesium sulfate (50-100 ml) and

integrated solution consisting of sodium bicarbonate, sodium chloride, potassium chloride, sodium sulfate and polyetylenhlikolyu.

Diet. In patients with any stage of PE should limit the supply of protein from food. When latent PE protein recommended limit to about 40 g / day (0.6 g / kg body weight) for stage III and 30 g / day (0.4 g / kg). In III-IV stages of a patient is optimal nutrition through a tube and parenteral nutrition with protein content of about 20 g / day. Protein in the diet of the patient PE should be submitted preferably vegetable protein and lactalbumin given their better tolerability. Vegetable proteins are richer ornithine and arginine and contain less methionine and aromatic amino acids. In some cases of diet should be completely excluded meat, fish, eggs and cheese. At the same time, long and sharp restrictions protein contributes to the disintegration of endogenous proteins, leading to increased concentrations of nitrogen compounds in the blood, so after receipt of food protein improvement should increase by an average of 10 g in 3 days. After the elimination of signs of HE (in particular on the results of psychometric tests) daily amount of protein can be increased to 80-100 g / day (1.5 g / kg). Calorie intake (1800-2500 kcal / day) provided adequate flow of fat (70-140 g) and carbohydrates (280-325 grams). Meals patient with HE should also contain adequate amounts of vitamins and trace elements, with malabsorption of fat-soluble vitamins showed their parenteral administration [1,5].

Drug therapy. Lactulose, being a disaccharide (1,4-b-halaktozyd-fructose), which is not absorbed, reduces intraintestinal pH prevents growth of bacteria that produce Ammon, absorption of ammonia and aminovmistnyh compounds glutamine breakdown in the lining of the intestine. The positive effect of lactulose treatment shown in multicenter studies. It is achieved in 60-70% of patients with PE and depends on the severity of liver cirrhosis and the degree of portal hypertension. Lactulose assigned 2-3 times a day, the dosage of the drug and the individual is from 30 to 120 ml per day, as a simple but reliable performance criterion considered increasing the frequency of bowel movements to 2-3 times a day. The onset of this effect reflects the decrease in the pH of the colon <6.0. Side effects of lactulose include nausea, vomiting, loss of appetite, bloating, diarrhea and tenesmus. Prolonged

diarrhea can lead to dehydration and electrolyte imbalance, so the selection of doses should follow the rules relating to the frequency of bowel movements, "at least two, no more than three." Some patients do not tolerate lactulose because of its sweet taste, to improve the taste we recommend adding lemon juice. Intermediate metabolites of the urea cycle. This group includes L-ornithine-L-aspartate, L-ornithine-ketoglutarate and arginine Malate. Entered most common L-ornithine-L-aspartate and is available as a solution for intravenous infusion and in the form of granules for oral administration. The mechanism of action of the drug is based on: 1) the stimulation of enzymes involved in the detoxification of ammonia and Ornithine karbamoil transferase and glutamine synthetase 2) inclusion of ornithine and aspartate as substrates in ornitynovyy Krebs cycle urine formation (formation of urea from ammonia) [16.21].

Standard scheme involves the use of intravenous drip 20-30 g of the drug for 7-14 days followed by transition to oral 9-18 g per day. Prolonged use (6-month course to 9 g per day orally) drug effectively prevents recurrence of HE.

Branched chain amino acids (BCAA). Although the amino acid imbalance is regarded as one of the pathogenetic factors of PE, the correlation between the ratio of aromatic amino acids and BCAA the one hand, and the severity of PE, on the other, have been identified. Probably positive clinical effect BCAA infusion caused a decrease in protein catabolism in the liver and muscles as well as improving metabolic processes in the brain. Note that BCAA is an important source of protein for patients with PE who require restriction of protein in the diet. Recommended dosage BCAA 0.3 g / kg / day.

Antibiotics are intended to remove amoniyeprodukuyuchoyi intestinal microflora. Neomycin (dose of 6-8 g / day) are now rarely used because of its oto-and nephrotoxicity. Other antibiotics used in patients with PE include ciprofloxacin, vancomycin and metronidazole. Typically, antibiotics require two groups of patients: those that require strengthening of lactulose as well as those who can not tolerate standard therapy. A major disadvantage of the treatment with antibiotics - limiting their terms of use, making it impossible to use them in the long prevention of PE.

By the basic treatment of progressive PE and commas included glucocorticoids. Assign usually prednisone parenterally at a dose of 1-2 mg / kg. With the development of hemorrhagic syndrome conduct drug hemostatic therapy (fresh frozen plasma, vikasol, ditsynon). In therapy, patients with PE and liver failure are also used efferent treatments - plasmapheresis, hemosorbtion. In severe, progressive hepatic encephalopathy and in patients with hepatic insufficiency only effective treatment is liver transplantation

Materials and methods. We observed were 75 patients (45 men and 30 women) with chronic lymphoproliferative disorders (CLPD), of which 35 patients were diagnosed with B-cell chronic lymphocytic leukemia (B-CLL), 15 - Hodgkin lymphoma (HL) and 25 patients - non-Hodgkin lymphoma (NHL). The average age of patients in our study was 45 ± 0,5 years. Diagnosis CLPD installed under the minimum guidelines of the European Society of Medical Oncology (ESMO, 2008). All patients performed general clinical and laboratory examination. To assess the extent and depth of damage of hepatocytes in patients HLPZ conducted biochemical studies of cell integrity, excretory activity and cholestasis before treatment and after care programs (transaminases, γ-GTP), alkaline phosphatase (ALP).

The degree of endotoxemia assessed by the coefficient of intoxication (CI), which is calculated as the ratio of middle molecules (280 and 254 nm). To confirm the results of clinical and biochemical studies have used instrumental diagnostic methods such as computed tomography (CT), ultrasound liver sonography (ultrasound).

At the time of diagnosis all patients conducted research on viral hepatitis B and C using the ELISA method. Patients with hepatitis B antigen and antibodies to hepatitis C excluded from the study.

For statistical data processing program used «Statistical for Windows». The results and their discussion.

As a result, the study found that in 15 patients on the basis of increasing γ-GTP (68,9 ± 0,4 U / l) was diagnosed with cholestasis without jaundice and hepatic

damage. In five patients revealed increasing ALP and bilirubinemia through direct fractions, based on what was revealed cholestasis with jaundice. Cholestasis without jaundice but with damage to hepatocytes detected in 7 patients. Three patients had cholestasis with jaundice as well as to damage hepatocytes. Data are presented in Table 7.

Table 7.

Variants of cholestasis in patients on HLPZ before therapy

Option cholestasis	Biochemical parameters					
	AST OD / l	ALT d / ODl	alkaline phosphatase OD / l	γ-GTP OD / l	Bilirubin, mmol / l	
					straight j	and non-food and
Cholestasis without jaundice (n = 15)	24.5 ± 0,4	18,8 ± 0,1	36.8 ± 0,3	68,9 ± 0,4	2,1 ± 0,1	15,3 ± 0,2
Cholestasis with jaundice (n = 5)	22,5 ± 0,4	14,8 ± 0,1	78,6 ± 0,1	29,7 ± 0,2	12,5 ± 0,1	16,8, ± 0,1
Cholestasis without jaundice but with injury and hepatocyte (n = 7)	57,8 ± 0,1	61,3 ± 0,3	97,6 ± 0,1	71,9 ± 0,4	3,3 ± 0,1	17,3 ± 0,2
Cholestasis with jaundice, but without hepatocyte damage and (n=3)	53,8 ± 0,1	55,3 ± 0,3	81,6 ± 0,1	65,9 ± 0,4	11,5 ± 0,1	19,8, ± 0,1

As follows from the data presented in Table 7,30 (40%) patients before therapy revealed increasing biochemical parameters that characterize the different options cholestasis syndrome.

With the results of computer research contrast data and ultrasound of the abdomen were excluded specific focal lesions of the liver.
In the other 45 patients with CLPD biochemical indices of damage hepatocytes excretory activity and cholestasis before treatment did not differ from the control group (tab.8).

Table 8.

Biochemical parameters donors and patients with CLPD before treatment

Option cholestasis in	Biochemical parameters					
	AST Od / l	ALT Od / l	alkaline phosphatase Od / l	γ-GTP Od / l	B and L and rub and N, mmol / l	
					straight j	and non-food and
Control group (n = 20)	18.5 ± 0,4	14,8 ± 0,1	22,8 ± 0,3	24,9 ± 0,4	1,1 ± 0,01	15,3 ± 0,2
Patients on CLPD (n = 45)	21,5 ± 0,4	16,8 ± 0,1	23,6 ± 0,1	27,7 ± 0,2	2,5 ± 0,02	16,8, ± 0,1

The program of treatment of 30 patients with the syndrome of cholestasis was included in the drug ademet and on and n (400-800 m g per day) on the background of specific therapy tsytostatych. Patients without evidence of hepatocyte injury and cholestasis in and get well soon tsytostatych therapy.

As a result of follow-up found that 30 of 45 patients who did not receive therapy gepatoprotektoram against tsytostatych therapy revealed increased trans and called and signs of cholestasis (Table 9).

Table 9

Variants of cholestasis in patients with CLPD

Option cholestasis in	Biochemical parameters					
	AST Od / l	ALT Od / l	alkaline phosphatase Od / l	γ-GTP Od / l	Bilirubin, mmol / l	
					Direct and	and non-food
Cholestasis without jaundice (n = 3)	21,6 ± 0,4	15,7 ± 0,1	37,4 ± 0,3	67,5 ± 0,4	1,1 ± 0,1	14,3 ± 0,2
Cholestasis with jaundice (n = 7)	22,5 ± 0,4	13,7 ± 0,1	77,4 ± 0,1	27,4 ± 0,2	13,5 ± 0,1	15,8, ± 0,1
Cholestasis without jaundice but with injury and hepatocyte (n = 12)	102,8 ± 0,1	115,3 ± 0,3	97,6 ± 0,1	73,2 ± 0,4	2,3 ± 0,1	17,3 ± 0,2
Cholestasis with jaundice, but without hepatocyte damage and (n = 8)	51,8 ± 0,1	53,3 ± 0,3	79,6 ± 0,1	61,9 ± 0,4	12,5 ± 0,1	17,8, ± 0,1

Period of clinically significant functional impairment of liver (hyperenzymemia, hyperbilirubinemia, increase of cholestasis) was accompanied by peroxide stress. Rapidly grew signs of endogenous intoxication syndrome. Noted a statistically significant increase in the coefficient of CI ($p < 0.05$). These results confirm the data of other researchers, which describes changes in biochemical parameters indicate a violation detoxication function hepatocytes in patients on background cytostatic therapy.

Patients treated ademetionina against chemotherapeutic drugs therapy, statistically significant normalization of biochemical parameters ($p < 0.05$), which characterized the syndrome of cholestasis and cytolysis. Correction of the liver to allow all patients scheduled chemotherapeutic drugs treatment. After chemotherapy in any patient was not observed deterioration of liver function.

Thus, as a result of the study found that in patients with hematopoietic disease to prevent hepatotoxicity against chemotherapy and to reduce the already developed symptoms hepatopathy necessary purpose in the protocol treatment drugs immunosuppressive therapy cholestasis.

The protective effect ademetionina will reduce the number of forced changes PCT protocols associated with liver damage, in most patients, improve portability PCTs to improve the quality of life of patients during treatment and rehabilitation.

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