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PREVENTION AND TREATMENT OF DRUG-INDUCED LIVER INJURY IN PATIENTS WITH BREAST CANCER AND OVARIAN CANCER

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Abstract

Introduction: *Drug-induced liver injury is one of the most serious problems in hepatology. In most cases the abolition of the "causative" drug is a sufficient condition for the reverse development of pathological changes. However, in the case of chemotherapy for cancer patients, the abolition of hepatotoxic drug is impossible without creating an immediate or delayed threat to the patient's life.*

Objective: *To develop optimal schemes for the prevention and treatment of drug-induced liver injury by studying of its characteristics of with various chemotherapy regimens in patients with breast cancer and ovarian cancer.*

Material and methods: *The screening group included 291 patients who underwent chemotherapy courses for breast cancer and ovarian cancer. The diagnosis and type of drug-induced liver injury was based on laboratory data (alanine aminotransferase and/or alkaline phosphatase increased above 2 norms) and the exclusion of other etiologies of liver diseases. Chemotherapy hepatotoxicity was assessed using the Shaposhnikov scale. The degree of hepatic encephalopathy was determined using a critical flicker frequency test. Depending on chemotherapy mode, groups of the patients were divided into subgroups: cyclophosphamide + Methotrexate+ Fluorouracil, Doxorubici + Cyclophosphamide, Epirubicin + Cyclophosphamide + 5-fluorouracil, Paclitaxel + Cisplatin, Carboplatin + Cyclophosphamide. According to the type of drug-induced liver injury, patients with cholestatic type received preparations, with cytolytic type – S-adenosylmethionine for 8 weeks.*

Results and its discussion: *It was found that the most common side effect of chemotherapy is leukopenia, anemia and increase in level of alanine aminotransferase and alkaline phosphatase. The use of ursodeoxycholic acid and S-adenosylmethionine as an accompanying therapy significantly reduces the level of alanine aminotransferase and alkaline phosphatase degree of hepatotoxicity and hepatic encephalopathy, clinical improves the quality of life of patients and contributes to a more rapid elimination of symptoms of astheno-vegetative, dyspeptic and pain syndromes.*

Conclusion: *It has been proven that the use of a differentiated approach to the choice of a hepatoprotector: S-adenosylmethionine in hepatocellular type, ursodeoxycholic acid - in cholestatic type of drug-induced liver injury for 8 weeks in patients with oncological profile allowed to carry out the planned therapy without deviations from the protocol.*

Keywords: *drug-induced, liver injury, encephalopathy*

Introduction

Drug-induced liver injury is various clinical and morphological variants of liver damage that develop in response to taking medications. Hepatotoxicity is a complex of metabolic, degenerative, inflammatory and necrotic changes in the liver, leading to secondary cellular, organic and

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systemic changes in the body with the development of intoxication and multiple organ failure [*Björnsson E.S., Hoofnagle J.H., 2016*]. This injury occur with a frequency of one case per 1000 patients up to one case per 100,000 patients who take drugs in therapeutic doses. More than 1000 drugs that have the ability to cause liver damage are currently registered in the world [*Stephens C. et al., 2014*]. Many drugs are potentially hepatotoxic. Every year the range of drugs that cause liver damage is expanding: in 1991, there were reports of 748 such drugs, in 1992 - about 808, by the beginning of 2000 - about 1000, and the list of such drugs is constantly growing [*Tajiri K., Shimizu Y., 2008*].

Currently, liver injury ranging from subclinical forms to fulminant liver failure has been described for approximately 1000 drugs [*Kliaritskaia I.L. et al., 2016*]. From the millions of known chemicals more than 63 thousand are widely used, of which about 55 thousand compounds are drugs that represent danger to humans [*Chalasani N.P. et al.*, 2014]. In recent years, there has been a clear trend to an increase in the number of drug-induced liver injury, caused by the constant expansion of the pharmaceutical market. So, in Japan for 30-year period 11-fold growth of drug hepatotoxicity was stated [*Chen M. et al., 2015*].

In clinical practice, the diagnosis of drug-induced liver injury is formed unreasonably rarely, since it is very difficult to estimate the true prevalence. This is due to: on the one hand, frequent cases of concealment of side effects of drugs by doctors; on the other hand, insufficient awareness of their clinical manifestations [*Kliaritskaia I.L., Maksimova E.V, 2012*].

Clinical manifestations of drug-induced liver injury can range from the absence or presence of mild symptoms with minor abnormalities in laboratory tests (most often in the form of a slight increase in aminotransferase levels) to severe cytolytic and cholestatic syndromes with jaundice and even the development of acute liver failure with hepatic coma and death [*Mohankumar N. et al., 2015*]. With a mild course of the disease, in case of discontinuation of the drug, a rapid reverse development of the process occurs.

Advances in modern chemotherapy have made it possible to cure many oncological diseases that were previously considered fatal [*Danan G., Teschke R., 2016*]. Effectiveness of treatment increase was achieved due to the intensification of chemotherapy modes. However, polychemotherapy negative point is the side effects of anticancer drugs [*Kliaritskaia I.L., Maksimova E.V, 2010*], due to the low selectivity of most cytostatics, which is a serious limitation in receiving the maximum therapeutic effect [*Bahirwani R., Reddy K.R., 2014*]. Anticancer chemotherapy drugs are the leaders in terms of frequency and severity of hepatotoxic diseases reactions caused by them [*Ortega-Alonso A. et al., 2016*].

Drug-induced liver injury is one of the most serious problems in hepatology. This is due to the fact that potential hepatotoxicity is possible when using all drugs administered in the curative doses, the clinical course and outcomes of drug-induced liver injuryare unpredictable [*Stine J.G., Lewis J.H., 2016*]. The leading positions in the frequency and severity of hepatotoxic reactions caused by them are considered to be antitumor chemotherapy drugs, in particular cytostatics. Side effects of anticancer drugs maintain a sufficiently high therapeutic dose due to the low selectivity of most cytostatics, the specifics of the antitumor effect of these drugs, as well as necessary [*Baykova I.E., Nikitin I.G., 2009*].

Diagnosis of drug-induced liver injury in most cases is difficult, since the clinical manifestations of the drug-induced liver injury are various and essentially they don't differ from those ones as for other diseases. Prevention of drug-induced liver injury is complex and unresolved problem [*Maksimova E.V., Kliaritskaia I.L, 2015*]. In most cases of acute drug-induced liver injury, the abolition of the "causative" drug is a sufficient condition for the reverse development of pathological changes [*Dara L et al., 2016*]. However, in the case of chemotherapy for cancer patients, the abolition of hepatotoxic drug is impossible without creating an immediate or delayed threat to the patient's life [*Andrade R et al, 2009*].

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Until now, drug choice defining in drug-induced liver injury treatment remains the subject of study due to complexity and diversity of the pathogenetic mechanisms that led to hepatotoxicity development. In addition, even in cases of therapy administration companied with hepatoprotectors during chemotherapy, the type of developed drug-induced liver injury is not taken into account, which may serve as a limitation in achieving the maximum therapeutic effect [*Fontana R.J., 2014*].

Based on all of the above, numerous data on the hepatotoxic effect of various drugs allow us to conclude that drug-induced liver injury is one of the most important problems not only for gastroenterologists, hepatologists, but also for doctors of other specialties. In developed countries, drug-induced liver injury is the leading cause of liver failure and the most common indication for liver transplantation [*Reuben A. et al., 2010*].

Thus, the problem of hepatotoxicity today is characterized by a lack of accurate diagnostic methods, the lack of a unified point of view on the nature, intensity and duration of treatment.

All of the above determines the relevance of the problem of further studying the features of the occurrence of drug-induced liver injury in cancer patients during chemotherapy. In addition, promising are the development of methods for the prevention, diagnosis, monitoring of side effects during chemotherapy, as well as treatment methods to reduce the toxic effect of cytostatics on the body with sufficient efficiency, which could be widely used in clinical practice.

In this regard, the main goal of the study was defined as the development of optimal schemes for the prevention and treatment of drug-induced liver injury by identifying risk factors and studying the characteristics of toxic liver damage with various chemotherapy regimens in the group of patients with breast cancer and ovarian cancer.

Objective: to develop optimal schemes for the prevention and treatment of drug-induced liver injury by identifying risk factors and studying the characteristics of this injury with various chemotherapy regimens in patients with breast cancer and ovarian cancer.

Material and methods

The study included 291 patients (screening group) aged 39 to 68 years who underwent chemotherapy courses for breast cancer (n=157) and ovarian cancer (n=134). All patients were on the stationary treatment at the Clinical Oncological Dispensary.

The diagnosis of drug-induced liver injury was based on laboratory data (alanine aminotransferase and/or alkaline phosphatase increase above 2 norms) and the exclusion of other etiologies of liver diseases (viral, autoimmune, hereditary, as well as alcoholic and non-alcoholic fatty liver disease). Chemotherapy hepatotoxicity was assessed using the Shaposhnikov scale (according to the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and bilirubin in the blood) (table 1). The degree of hepatic encephalopathy was determined using a critical flicker frequency test. The type of drug-induced liver injury was determined depending on the degree of increase in the level of ALT and alkaline phosphatase.

The degree of hepatotoxicity was assessed in points: 0 degree = 0-3 points; I degree = 3-8 points; II degree = 9-14 points; III degree = 15-20 points; IV degree = 21-25 points.

The general condition of patients was assessed according to the WHO-ECOG scale, and the quality of life - according to the EORTC - QLQ - C 30 questionnaire.

Results and iscussion.

When studying the incidence of side effects during chemotherapy in patients with breast cancer and ovarian cancer (in the screening group), it was found that hematological complications, in partic-

Table 1

Hepatotoxicity scale according to A.V. Shaposhnikov

Indicator	Points at different regards to the norm (its exceeding at times)			
Alanine aminotransferase	1 p. (1.25-2.5)	3 p. (>2.5-5)	6 p. (>5-10)	9 p. (>10)
Alkaline phosphatase	1 p. (1.25-2.5)	2 p. (>2.5-5)	3 p. (>5-10)	4 p. (>10)
Bilirubin	1 p. (>1-1.5)	4 p. (>1.5-2.5)	8 p. (>2.5-5)	12 p. (>5)

ular, anemia and leukopenia, are the most common undesirable side effects and do not statistically differ in groups of patients with breast cancer and ovarian cancer . The patients were also worried about complaints from the gastrointestinal tract: most of all they paid attention to nausea: its manifestations were more often noted by patients with ovarian cancer (63.43% of cases) compared with patients with breast cancer (47.13% of cases).

Most often, among the changes in biochemical parameters, there was an increase in the level of transaminases (ALT, AST): in 64.93% of patients in the ovarian cancer group and in 61.78% of patients in the breast cancer group, as well as in the level of alkaline phosphatase: in 41.40% and in 40.30% patients in the breast cancer and ovarian cancer groups, respectively.

According to the abdominal ultrasound, diffuse changes in the liver were registered in more than half of the studied patients: in 56.69% in the Breast cancer group and in 57.46% in the ovarian cancer group, respectively. Also, with a fairly high frequency, there was an increase in liver echogenicity (27.39% in the breast cancer group versus 26.12% in the ovarian cancer group).

Thus, it was found that the most common side effects of chemotherapy are leukopenia and anemia. Side effects from the liver are quite common, while side effects in the form of an increase in the level of ALT, AST are the second most common after hematological side effects, and in the ovarian cancer group they are somewhat more common than in the breast cancer group.

A further study included patients in whom chemotherapy was accompanied by an increase in the level of ALT and/or alkaline phosphatase more than 2 norms: 78 patients with breast cancer and 53 patients with ovarian cancer.

Depending on the current chemotherapy regimen, the groups were divided into subgroups: the breast cancer group into the Cyclophosphamide +Methotrexate+Fluorouracil (CMF) subgroup (n=27), in which the patients received treatment according to the CMF regimen (cyclophosphamide, methotrexate, fluorouracil), the AC subgroup (n=26) received treatment according to the scheme AC (doxorubicin, cyclophosphamide), Epirubicin+Cyclophosphamide+5-fluorouracil (ECF) subgroup (n=25) - treatment according to the ECF scheme (epirubicin, cyclophosphamide, fluorouracil), and the ovarian cancer group - into the following subgroups: TP subgroup (n=26) - treatment according to the TP scheme (paclitaxel, cisplatin), subgroup CC (n=27) – treatment according to the CC regimen (carboplatin, cyclophosphamide).

The study revealed that three-component chemotherapy regimens for breast cancer in more than half of the patients (51.85% for the CMF regimen and 52% for the EFC regimen) led to the fact that patients were unable to work (grade 2 on the WHO scale-ECOG), while on the two-component chemotherapy regimen of breast cancer AC 2nd degree of general condition was detected in a third (34.62% of patients), and in the regimens of chemotherapy ovarian cancer, disability was noted in 23.08% of patients on the TP regimen and in 29.63% of patients on the CC regimen.

When assessing the quality of life, it was revealed that at the beginning of the observation in all the studied groups there was a decrease in the quality of life indicators to an average value of 68.09 ± 0.83% in the group of patients with breast cancer and to an average value of 77.34 ± 0.67% in the group of patients with ovarian cancer. It was found that three-component chemotherapy regimens used for the treatment of breast cancer (CMF and EFC) cause a significantly more significant decrease in quality-of-life (65.37±1.59% in patients on the CMF regimen and 66.89±1.00% in patients on EFC regimen) compared with the two-component chemotherapy regimen for breast cancer (72.07±1.3%; $p=0.002$), as well as compared with chemotherapy regimens used for patients with ovarian cancer (79.68±0.97% in the TP regimen; $p<0.001$; 75.07±0.71% in CC mode; $p<0.001$).

An analysis of the components of the integral indicator of quality-of-life showed that the decrease in quality-of-life (according to the EORTC - QLQ - C 30 questionnaire) occurred mainly due to a decrease in the number of points scored (by 1-2 points) on a scale of general condition and quality of life, a scale of emotional functioning, a symptomatic scale fatigue, as well as a scale of physical condition.

When analyzing the mental state of patients with breast cancer and ovarian cancer, it was found that the most patients complained about the feeling

of anxiety (65.65%) and the feeling of depression (61.83%). There were no significant differences in the frequency of complaints of tension, anxiety, irritation and depression in the groups.

When analyzing the average values of biochemical parameters by groups, depending on the CT regimen for breast cancer and ovarian cancer, it was found that the average level of bilirubin in AC regimens was 1.89 times, and in CMF regimen 1.77 times higher than the average bilirubin levels in regimens chemotherapy of ovarian cancer (TP and CC). The highest average ALT level was registered in CMF (2.96±0.16 *mmol/l*), EFC (2.78±0.10 *mmol/l*) and CC (2.40±0.13 *mmol/l*) regimens. The highest average level of AP was observed in the AC mode (500.61±36.90 *U/L*), and GGTP - in the TP mode (114.44±5.52 *U/L*).

When conducting a test for the critical flicker frequency (CFF), it was revealed that hepatic encephalopathy (HE) was registered in 81.9% of cases, which emphasizes the importance of the test for the CFF in gynecological cancer patients. Most often, HE of the 1st degree was recorded (in 49.52% of patients), the second most common was minimal hepatic encephalopathy - it was observed in 26.67 % of patients.

The degree of hepatotoxicity was higher in patients with breast cancer, especially with diabetes (grade 2 in 73.1% and 62.9% of patients in groups 3 and 4, respectively, $p < 0.05$). In the group of patients with ovarian cancer 2, the degree of hepatotoxicity was not registered in any of the studied patients. And in the group of patients with breast cancer, all patients developed hepatotoxicity of either 1 or 2 degrees, which indicates a greater toxicity of chemotherapy regimens used or treatment of breast cancer.

Also, during the study, analysis was made about which chemotherapy course first caused HT development in patients from breast cancer and ovarian cancer groups (table 2)

Occurrence frequency development of hepatotoxicity on the regimen and course number of chemotherapy was revealed. As it can be seen from data presented in Table 2, the CMF and EFC chemotherapy modes were the first to cause hepatotoxicity development: for example, in 37.1 % in the CMF group and in 36 % in the EFC one, its progress was observed during only the second cycles of chemotherapy at these courses, and even chemotherapy on CMF regimen in 18.5 % of patients and on EFC one in 24 % of patients with breast cancer contributed to drug-induced liver injury development. In patients from TP group, on the contrary, conducting at least three chemotherapy courses according to this regimen only led to hepatotoxicity development, and most often drug-induced liver injury (in 34.6% of patients) was observed already during its sixth course. Obtained information allowed us to conclude that three-component chemotherapy modes including cyclophosphamide in the protocol, used when treating breast cancer, lead to hepatotoxicity progress earlier than other regimens, which requires more careful monitoring of these groups patients and more frequent checking of biochemical parameters before administering chemotherapy, and during its application.

For drug correction of drug-induced liver injury, a differentiated approach was used, which consisted in determining the type of drug-induced liver injury and prescribing an appropriate hepatoprotector. So, in the cholestatic type of drug-induced liver injury, patients were prescribed ursodeoxycholic acid (UDCA) at dosage of

Table 2

Occurrence hepatotoxicity frequency in patients with breast cancer and ovarin cancer, depending on the mode and the number of chemotherapy courses (according to their number)

Chemotherapy course	Chemotherapy mode									
	Breast cancer (n=78)						Ovarian cancer (n=53)			
	CMF (n=27)		AC (n=26)		EFC (n=25)		TP (n=26)		CC (n=27)	
	n	%	n	%	n	%	n	%	n	%
1st	5	18.5	2	7.7	6	24.0	0	0	1	3.7
2nd	10	37.1	3	11.6	9	36.0	0	0	5	18.5
3rd	7	25.9	5	19.2	5	20.0	4	15.4	7	25.9
4th	2	7.4	7	26.9	3	12.0	6	23.1	6	22.2
5th	2	7.4	7	26.9	1	4.0	7	26.9	5	18.5
6th	1	3.7	2	7.7	1	4.0	9	34.6	3	11.2

Notes: *CMF - Cyclophosphamide + Methotrexate+ Fluorouracil, AC - Doxorubicin (also known as Adriamycin) + Cyclophosphamide, EFC - Epirubicin + Cyclophosphamide + 5-fluorouracil,TP - Paclitaxel + Cisplatin, CC - Carboplatin + Cyclophosphamide*

23 *mg/kg/day* for 8 weeks, with the cytolytic type - S-adenosylmethionine (SAMe) 400 *mg* x 3 times a day for 8 weeks. In the control group, patients received only standard therapy for the underlying disease.

A comparative analysis of the effectiveness of the chosen strategies in the group of oncological patients was carried out before treatment by UDCA and SAMe, on 4th and 8th weeks according to the severity of clinical manifestations of drug-induced liver injury; change in quality-of-life according to the EORTC - QLQ - C 30 questionnaire; change in the degree of hepatotoxicity (according to the Shaposhnikov scale); dynamics of biochemical parameters (ALT and alkaline phosphatase); dynamics of the degree of hepatic encephalopathy (according to the test for the critical frequency of flashing); the possibility of conducting full course of chemotherapy.

The symptoms of astheno-vegetative syndrome tended to decrease (at week 4) and almost completely disappeared by the end of treatment (at week 8) in the group of patients who received, in addition to chemotherapy, additional therapy with hepatoprotectors (UDCA and SAMe), compared with the control group. A similar trend was observed in relation to dyspeptic syndrome. The feeling of anxiety and depression by the end of the study almost did not bother the patients in I and II groups.

Accompanying therapy with hepatoprotectors during chemotherapy in patients with breast cancer and ovarian cancer did not lead to normalization of quality-of-life in the study groups, but there was a statistically significant increase in quality-of-life in groups taking additional hepatoprotectors (86.64±0.91% versus 72.02±1 .13%, $p<0.001$ - in I group 85.27±0.83% versus 70.17±1.30%, $p<0.001$ - in II group at 8 and 0 weeks, respectively) compared with the control group, in which no significant differences were found between the quality-of-life index at 8 and 0 weeks of the study.

After 8 weeks of therapy with accompanying hepatoprotectors, none of the studied patients in I and II groups had grade 2 hepatotoxicity compared with the control group, in which the majority of patients retained grade 2 hepatotoxicity detected at study week 0. In groups 1 and 2, by the end of the study, in most cases, the absence of hepatotoxicity was determined (in 57.14% of patients in I group and in 59.38% of patients in II group, respectively).

The use of UDCA and SAMe as an accompanying therapy significantly reduces the level of ALT as one of the main components of the hepatotoxicity scale and allows reaching a normal level of ALT by the 8th week of treatment in 77.14% in I group and in 71.87% in the II group. A significant decrease in the level of alkaline phosphatase and normalization of this indicator was observed in 85.71% of patients in I group and in 87.50% in II group.

According to the results of the critical flicker frequency test, the majority of patients in all groups had grade 1 HE (51.52% in I group and 53.13% and 51.43% in II and III groups, respectively). After treatment, 48.57% of patients in I group and 50.00% of II grouphad normal results of the critical flicker frequency test, which indicates the absence of HE. In addition, none of the studied patients of I and II groups had grade 2 HE by the end of therapy. 91.43% of patients in II group and 93.74% of patients in II group were able to complete chemotherapy in full against 66.67% of patients in the control group ($p<0.05$). Thus, the UDCA and S-adenosylmethionine proved to be effective means for the medical correction of drug-induced liver injury in oncogynecological patients, having a positive effect on the quality of life of patients and contributing to a more rapid elimination of symptoms of astheno-vegetative, dyspeptic and pain syndromes; leads to a decrease in the degree of hepatotoxicity of chemotherapy, as well as to a decrease in the degree of HE. Hepatoprotective therapy during chemotherapy helps to improve the mental state of patients, which is expressed in a decrease in the frequency of occurrence of feel-

Table 3

The need to correct the chemotherapy regimen by groups in patients with breast cancer and overine cancer

	UDCA group (n=35)		SAMe group (n=32)		Control group (n=33)	
	n	%	n	%	n	%
Postponement of chemotherapy courses	1	2.86	1	3.13	3	9.09
Dose reduction of chemotherapy drugs	2	5.71	1	3.13	8	24.24
Chemotherapy in full	32	91.43	30	93.74	22	66.67

ings of anxiety and depression.

In addition, we determined the proportion of patients in groups who needed to change the chemotherapy regimen, cancel the course of chemotherapy, or need to reduce the dose of chemotherapy drugs (Table 3).

In I group, which received UDCA preparations as an accompanying therapy, only one patient (2.86%) had to delay the course of chemotherapy, 2 (5.71%) patients needed to reduce the doses of chemotherapy drugs. In II group, who received SAMe as a hepatoprotector, 1 (3.13%) patient had to interrupt the course of chemotherapy and 1 (3.13%) patient had to reduce the dose of chemotherapy drugs, while in the control group, which did not take additional hepatoprotectors, in 3 (9.09%) patients chemotherapy had to be interrupted and postponed due to hepatotoxicity and side effects, and 8 (24.24%) patients needed to reduce the doses of chemotherapy drugs.

Thus, the use of S-adenosylmethionine in the hepatocellular type of drug-induced liver injury and UDCA preparations in the cholestatic type of drug-induced liver injury for 8 weeks as an accompanying therapy in patients with breast cancer and ovarian cancer makes it possible to achieve a rapid decrease in the level of biochemical parameters (ALT, alkaline phosphatase) and conduct planned chemotherapy without deviations from protocol.

Conclusion

UDCA preparations and SAMe proved to be effective means for the medical correction of drug-induced liver injury in oncogynecological patients, having a positive effect on the quality of life of patients and contributing to a more rapid elimination of symptoms of asthenic-vegetative, dyspeptic and pain syndromes.

Therapy accompanied by hepatoprotectors (UDCA preparations and SAMe) leads to a decrease in the degree of hepatotoxicity of chemotherapy, as well as to a decrease in the degree of hepatic encephalopathy.

The use of SAMe in the hepatocellular type of drug-induced liver injury and UDCA preparations in the cholestatic type of liver injury for 8 weeks as an accompanying therapy in patients with breast cancer and ovarian cancer makes it possible to achieve a rapid decrease in the level of biochemical parameters (ALT, alkaline phosphatase) and to carry out the planned chemotherapy without deviations from the protocol.

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