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Grydguk T.I.
SHEE «Ivano-Frankivsk National Medical University» 2 Halytska str., Ivano-Frankivsk, 76018.

Correspondence:
Grydguk T.I.
SHEE «Ivano-Frankivsk National Medical University» 2 Halytska str., Ivano-Frankivsk, 76018.

Differential access to treating of drug-induced hepatotoxicity in patients with chronic Lymphocytic Leukemia

Grydguk T.I.

Abstract
In this article abilities of differential administration of hepatoprotective medications are observed regarding a type of drug-induced liver injury during chemotherapy in patients with chronic lymphocytic leukemia. The type of drug-induced liver injury was determined depending on the grade of increasing of aminotransferase and alkaline phosphatase levels. Effectiveness of arginine glutamate at presence of cytolitic type of drug-induced liver injury and ursosan at presence of cholestatic type of drug-induced liver injury was studied. It was determined that including of these medicines in basic therapy of drug-induced liver injury promotes normalization of biochemical indexes that characterize functional state of liver parenchyma and enables to provide chemotherapy courses of chronic lymphocytic leukemia completely.

Keywords: chronic lymphocytic leukemia, drug-induced liver injuries, chemotherapy, hepatoprotective medicines.

1. Introduction
Numerous data about hepatotoxic effect of various medicine solutions enable to conclude that drug-induced liver injuries (DILI) are one of important problems of modern hepatology. Occurrence of hepatotoxicity during chemotherapy use in patients suffering from chronic lymphocytic leukemia (CLL) necessitates using of certain treatment measures directed to both prevention and treatment of this complication [1, 2]. However the question of diagnostics tactics optimization and treatment of drug-induced liver injury at CLL presence because of chemotherapy remains unexplored.
Till modern days choose of medicine for treatment of toxic liver injuries remains a subject of debate due to complexity and variety that led to the hepatotoxicity development [3]. Results of numerous experimental and clinical researches demonstrate a considerable therapeutic effect of correction of drug-induced hepatotoxicity using groups of hepatoprotective medications [4, 5]. But even in case of accompanying hepatoprotective medicines administration during providing of chemotherapy the type (DILI) is not counted that serves as a restriction in achieving of maximal clinical effect [1, 6, 7]. Therefore necessity of diagnostics ways and treatment of patients suffering from DILI with CLL perfection is urgent and та highly necessary. Assistance algorithm for such patients should contain concrete steps with appropriate medicines administration.

Aim: to evaluate effectiveness and tolerance of ursodeoxycholic acid (ursosan) and L-arginine-L-glutamate (arginine glutamate) drugs for pharmacological therapy of cholestatic and hepatocellular DILI types in patients with CLL during providing of chemotherapy.

2. Materials and Methods: In clinical research 32 patients with cholestatic type and 36 patients with hepatocellular type of DILI that developed during the chemotherapy of CLL. Patients got inpatient treatment in department of haematology in Ivano-Frankivsk Regional Clinical Hospital. Among them were 40 (58, 82%) men and 28 (41, 18%) women aged from 38 to 72. Average age of patients was (56, 4±2, 62) years.
CLL diagnosis was verified according to clinical care protocols in Haematology approved by MoH of Ukraine Order №647 from 30.07.2010. DILI diagnosis was made according to standardized diagnostics and treatment of the digestive system protocols (MoH of Ukraine Order № 271 from 13.06.2005).

Negative results of screening viral hepatitis markers researches allowed exclude viral genesis of disease.

We decided to use for pharmacological treatment of DILI a differential a differentiated approach in choosing of hepatoprotective therapy in patients with CLL depending on DILI type. So in case of cholestatic type of DILI we used ursodeoxycholic acid drug (UDCA) – ursosan. On propose of cytolysis syndrome correction at presence of hepatocellular type of DILI we used L-arginine-L-glutamate drug with trade name glutargin (arginine glutamate).

For realization of work aim all patients were divided into four groups: patients with cholestatic type of DILI that got UDCA drug dosage: 10 mg per 1 kg of body weight per day as a part of traditional basic therapy during 1,5 month entered the group I (n=17); the group II contained 15 patients with 3 cholestatic type of DILI that got only basic treatment; into group III (n=19) we included patients with hepatocellular type of DILI that at presence of basic treatment got arginine glutamate intravenous drop-by-drop 10 ml of 40% solution in 200 ml of isotonic sodium chloride solution during 10 days with the next switchover to tablet form dosed with 1 tablet (0,75 g) 3 times per day during 30 days; patients with hepatocellular type of DILI being treated traditionally entered the group IV (n=17). All groups were randomized by patients´ age, gender, severity of DILI and CLL course.

Effectiveness of performed treatment was evaluated regarding dynamics of biochemical indexes and possibility of providing a full chemotherapy course. Type of DILI was determined depending on alanine aminotransferase (ALAT) and alkaline phosphatase (ALP) level increasing grade [8].

Statistical evaluation of received results was provided on personal computer using a computer program STATISTIKA-6 and set of statistical functions of «Microsoft Excel».

3. Received results and discussion on them: Considering those biochemical indexes, according to which type of DILI is determined we came to a decision to monitor the dynamics of average values of ALAT and ALP during the treatment with hepatoprotective medicines (schema 1).

Schema 1: Dynamics of average ALAT and dosage form values in groups during the treatment

	Control, n=15	**Group I, n=17 (basic therapy+ursosan)**		**Group II, n=15 (basic therapy)**		**Group III, n=19 (basic therapy + glutargine)**		**Group IV, n=17 (basic therapy)**	
		Before treatment	**After treatment**	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**
ALAT, mmol/L h	0,41±0,03	0,72±0,04 p<0,001	0,57±0,03 p<0,01	0,7±0,03 p<0,001	0,63±0,01 p<0,001	1,64±0,03 p<0,001	0,66±0,07 p<0,01	1,62±0,05 p<0,001	1,28±0,09 p<0,001
		p_{1-3}<0,001		p_{2-4}<0,001		p_{2-3}<0,001		p_{1-4}<0,001	
			p_1<0,01		p_1<0,05		p_1<0,001		p_1<0,01
Dosage form, nmol/sec•h	1174±114,5	3115±125 p<0,001	1650±145 p<0,05	3005±105 p<0,001	2320±154 p<0,001	1468±121 p>0,05	1250±118 p>0,05	1425±116 p>0,05	1310±82 p>0,05
		p_{1-3}<0,001		p_{2-4}<0,001		p_{2-3}<0,001		p_{1-4}<0,001	
			p_1<0,001		p_1<0,01		p_1>0,05		p_1>0,05

Notes: p – difference probability comparatively to control group indexes; p_{1-3} – difference probability between patients of groups I and III; p_{1-4} – difference probability between patients of groups I and IV; p_{2-3} – difference probability between patients of groups II and III; p_{2-4} – difference probability between patients of groups II and IV; p_1 – difference probability between indexes before and after treatment.

Scheme 2: Dynamics of lipid peroxidation system and endogen intoxication indicators in groups during the treatment

	Control, n=15	**Group I, n=17 (basic therapy+ursosan)**		**Group II, n=15 (basic therapy)**		**Group III, n=19 (basic therapy + glutargine)**		**Group IV, n=17 (basic therapy)**	
		Before treatment	**After treatment**	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**
MDA, nmol/ml	2,56±0,16	5,78±0,14 p<0,001	3,75±0,15***• p<0,001	5,75±0,12 p<0,001;	4,7±0,16*** p<0,001	6,56±0,17 p<0,001	3,25±0,12***• p<0,01	6,48±0,14 p<0,001	4,9±0,33*** p<0,001
Δ, %			Δ-35,12		Δ-18,26		Δ-50,46		Δ-24,38
MMP, RVU.	0,23±0,021	0,38±0,02 p<0,001	0,321±0,015* p<0,01	0,37±0,02 p<0,001	0,355±0,03 p<0,01	0,45±0,015 p<0,001	0,32±0,015***• p<0,01	0,23±0,021	0,392±0,01 p<0,001
Δ, %			Δ-15,53		Δ-4,05		Δ-28,9		Δ-8,84

Notes:

1. P – reliability of changes compared to indicators of control group,
2. * – reliability of difference of indicators before treatment: *- p<0,05, **- p<0,01, *** - p<0,001,

• – reliability of difference of indicators after basic therapy and hepatoprotectors treatment (p<0, 05).

Comparing indexes of biochemical research it was found that in patients with hepatocellular type of DILI credibly higher activity levels in blood plasma: ALAT ((1,64±0,03) mmol/L h in patients from group III and (1,62±0,05) mmol/L h in patients from group IV) compared to patients with cholestatic type of DILI, in which ALAT levels were (0,72±0,04) mmol/L h in patients from group I and (0,7±0,03) mmol/L h in patients from group II. In patients with cholestatic type of DILI Alat concentration influenced by ursosan treatment decreased in 20,83 % – from (0,72±0,04) to

(0,57±0,03) mmol/L (p<0,01) and under influence of basic therapy it decreased in 10 % – from (0,7±0,03) to (0,63±0,01) mmol/L (p<0,05). In patients of group III with hepatocellular type of DILI that received arginine glutamate, Alat concentration decreased in 59,76% from (1,64±0,03) to (0,66±0,07) mmol/L (p<0,001), and under influence of basic therapy it reduced in 20,99% from (1,62±0,05) to (1,28±0,09) mmol/L (p_1<0,01). So usage of arginine glutamate and ursosan decreases significantly Alat level as one of the cytolytic syndrome markers in CLL patients.

Concentration of alkaline phosphatase in blood plasma exceeded normative values in patients with cholestatic type of DILI (p<0,001). It is to be noted that in patients with cholestasis average level of this marker was more than twice higher compared to 3 referent normative values and was equal to (3115±125) nmol/sec•h in patients of group I and to (3005±105) nmol/sec•h in patients of group II that credibly differed from average ALP concentration in pateints of groups III and IV (schema 1). Addition of ursosan to the basic therapy promoted elimination of cholestasis syndrome most that was signified by credible decreasing of alkaline phosphatase concentration in 1,9 time compared to start index in patients of group I reaching (1650±145) nmol/sec•h (p<0,001). In patients of group II ALP concentration reduced compared to start index in 1, 4 times (p<0, 01) and was after basic therapy finish (2320±154) nmol/sec•h however remained higher than analogical index of patients group that received UDCA. So hepatoprotector therapy with ursosan usage results significant decreasing of ALP concentration and normalization of this index in 88, 24% patients of group I.

Drug-induced liver injuries are accompanied by increase of lipid peroxidation processes, decreasing of body antioxidant reserves and occurring of endogen intoxication syndrome. Correction of mentioned pathologic changes has leading place in therapy of DILI.

So malondialdehyde (MDA) level in blood serum of the patients from group I exceeded before treatment analogical level in apparently healthy people in 2,26 times (p<0,001), and after provided therapy course in 1,46 times (p<0,001). Namely under influence of Ursosan treatment credible decreasing of this indicator in 35, 12% (p<0,001) was observed. In group II of patients that got only basic therapy this indicator contained (4,7±0,16) nmol/ml at the moment of treatment finish that was less than reference values in 18,26%, but in the same time it exceeded in 1,8 times norm value (p<0,001) and in 1,25 times analogical value in patients of group I (p<0,05). Concentration of MDA in examined patients of group III after provided Glutargine therapy decreased in 50, 46%, namely to (3, 25±0, 12) nmol/ml comparatively to reference value (p<0,001). In group IV of patients that got only basic therapy this value decreased to (4, 9±0, 33) nmol/ml, namely in 24, 38% comparatively to reference value (p<0,001), but remained above norm in 1, 91 times (p<0,001) on the average.

Mid-molecular peptides (MMP) level in blood as indicator of «syndrome of metabolic intoxycation» decreased after treatment of all groups. Under the influence of UDCA MMP concentration decreased from (0, 38±0, 02) to (0,321±0,015) RVU (p<0, 05). In the same time in patients of group II MMP concentration decreased to a lesser extent: from (0, 37±0, 02) to (0,355±0, 03) RVU (p>0, 05) under the influence of basic therapy. Analogical tendency was observed also in patients with hepatocellular type of DILI. We noticed that in patients of group IV MMP level after basic therapy course was (0,392±0, 01) RVU, namely it decreased only in 8, 84% (p>0, 05) comparatively to its level before treatment: (0, 43±0, 03) RVU. In patients of group III MMP level in the process of glutargine treatment decreased in 28, 9% (p<0,001) and was (0, 32±0,015) RVU that is reliable lower than level of this value after treatment of patients of group IV (p<0, 05). So it is found that in groups of patients that got additionally Ursosan or Glutargine in the treatment complex antioxidant effect of these hepatoprotectors realized completely and clearly expressed positive dynamics of metabolic homeostasis was observed.

Moreover we determined correlation between patients in groups that needed correction of CTX regimens (schema 3).

Schema 3: Correction necessity of chemotherapy regimens in groups of patients

	Group I, n=17		Group II, n=15		Group III, n=19		Group IV, n=17	
	n	%	n	%	n	%	n	%
Deferment of CTX courses	-		2	13,33	-		3	17,65
Decreasing of CTX doses	2	11,76	3	20,0	3	15,79	4	23,53
Full CTX	15	88,24	10	66,67	16	84,21	10	58,82

Note: n – number of people in group.

It is seen in the schema 3 that in group I of patients that received ursosan, it was necessary only for 2 (11, 76%) patients to reduce CTX dose; and in group III, to whose treatment complex arginine glutamate was included, this concerned only 3 (17, 65%) patients. However 2 (11,76%) patients of group II and 3 (17,65%) patients of group IV, that received only basic treatment needed to stop and deferment CTX courses due to hepatotoxicity and side effects, 3 (20%) patients of group II and 4 (23,53%) patients of group IV needed decreasing of CTX dose.

4. Conclusions

Results of provided studies indicated that administration of UDCA (ursosan) and L-arginine-L-glutamate (arginine glutamate) drugs increases much therapeutic effect of basic treatment of patients with на DILI.

Usage of ursosan at presence of cholestatic type of DILI and arginine glutamate at presence of hepatocellular type of DILI in patients with chronic lymphocytic leukemia allows reaching decreasing of biochemical markers (ALAT, ALP) level and providing planned chemotherapy without protocol deviations.

Including of Ursosan and Glutargine in complex therapy of DILI promotes practically full normalization of values that characterize activity of lipid peroxidation and metabolic intoxication processes.

Side effects during medicines usage were not discovered, all patients tolerated treatment well.

5. References

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