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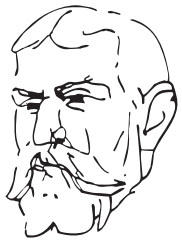

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CONTENTS

ORIGINAL ARTICLE

THE OVERWEIGHT AND OBESITY ROLE IN THE OCCURRENCE OF CHEMOTHERAPY-INDUCED HEPATOTOXIC REACTIONS IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

DOI: 10.36740/WLek202206114

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ABSTRACT

The aim: To investigate the frequency of development and nature of cytostatic-induced hepatotoxic reactions in patients with acute myeloid leukemia (AML) with overweight and obesity during remission induction chemotherapy (CT).

Materials and methods: We examined 25 patients with newly diagnosed acute leukemia (AL), of which 56% (14/25) were men, 44% (11/25) were women. Depending on the body mass index (BMI), patients were divided into groups: I (n=10) – patients with AML and BMI of 18.5-24.9 kg/m^2; II (n=15) – patients with AML and BMI ≥25.0 kg/m^2. The biochemical blood analysis was evaluated twice: before and on the 56th day of CT, which included alanine-, aspartate-aminotransferases, gamma-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), total protein and total bilirubin.

Results: In patients with AML and normal BMI, CT conduction increased the risk of GGT (RR=3.00; 95% CI=1.14-7.91; p<0.05) and ALP activity impairment (RR=2.67; 95% CI=0.98-7.22; p>0.05). The presence of overweight and obesity in patients with AML of group II led to significant risk of increase the GGT (RR=3.00; 95% CI=1.46-6.14; p<0.05) and ALP activity (RR=4.00; 95% CI=1.41-11.35; p<0.05) during CT. GGT and ALP activity in the blood serum of group II patients after CT exceeded the baseline data in 2.4 times (p<0.0001) and 1.6 times (p=0.0007), respectively.

Conclusions: The remission induction CT of AML is accompanied by the risk of cytostatic-induced liver injury. The presence of overweight, obesity and primary disorders of biochemical liver tests due to the oncohematological disease influence are the risk factors for hepatotoxic reactions development during CT.

KEY WORDS: acute myeloid leukemia, chemotherapy, overweight, obesity

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INTRODUCTION

Obesity is an important medical and social problem. Over the past three decades, the prevalence of obesity in the world has tripled and become an epidemic [1-4]. The pathogenetic basis of diseases associated with obesity is dyslipidemia and insulin resistance. Hyperinsulinemia with obesity-associated insulin resistance increases the risk of acute leukemia occurrence and reduces the chemotherapy (CT) effectiveness [5, 6]. Chronic systemic inflammation is also considered to be one of the important pathogenetic mechanisms of development and progression of oncological diseases in patients with obesity [7].

At the same time, overweight and obesity promote xenobiotic metabolism violation, which can lead to an increased risk of hepatotoxicity [5, 8-10]. However, data from individual studies of cytostatic-induced liver injury are conflicting. In some retrospective studies conducted in a limited number of patients, the toxicity of intensive CT was assessed in overweight and obese patients [8, 11-18], which did not show increased toxicity and deterioration of treatment outcomes in adult patients. However, the Crysandt M [4] study demonstrated that increased body mass index (BMI) is a negative prognostic factor for incidence of de novo acute myeloid leukemia (AML) and overall survival for patients younger than 65 years with the presence of cytogenetic mutations FLT3, NPM1 or CEBPA, which was characterized by a decreased long-term survival in 5-7% (3-year OS 39.9% vs. 47.3%; 10-year OS 28.7% vs. 33.8%, P=0.0002). Deterioration of the CT results in patients with acute leukemia (AL) with overweight and obesity may be associated with a decreased of the cytostatic therapeutic doses, done to prevent their toxic effects, especially in patients with body surface area greater than 2 m^2 [13].

Therefore, the incidence and nature of liver injury in patients with de novo AML and under the influence of CT need to be studied in detail, which is of particular importance for the prediction and prevention of cytostatic-induced hepatotoxic reactions.

THE AIM

To investigate the frequency of development and nature of cytostatic-induced hepatotoxic reactions in patients with acute myeloid leukemia (AML) with overweight and obesity during remission induction chemotherapy (CT).

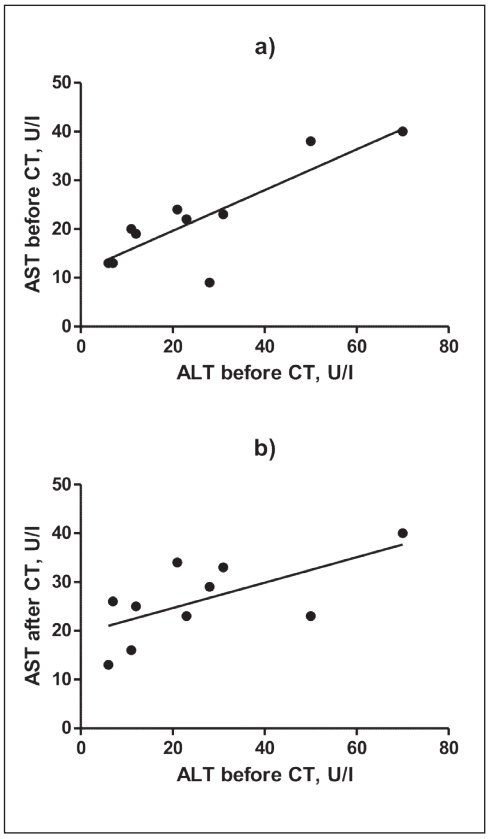

Fig.1. Direct correlation in patients of I group: a) between the ALT and AST activity before CT; b) between ALT activity before CT and AST after CT.

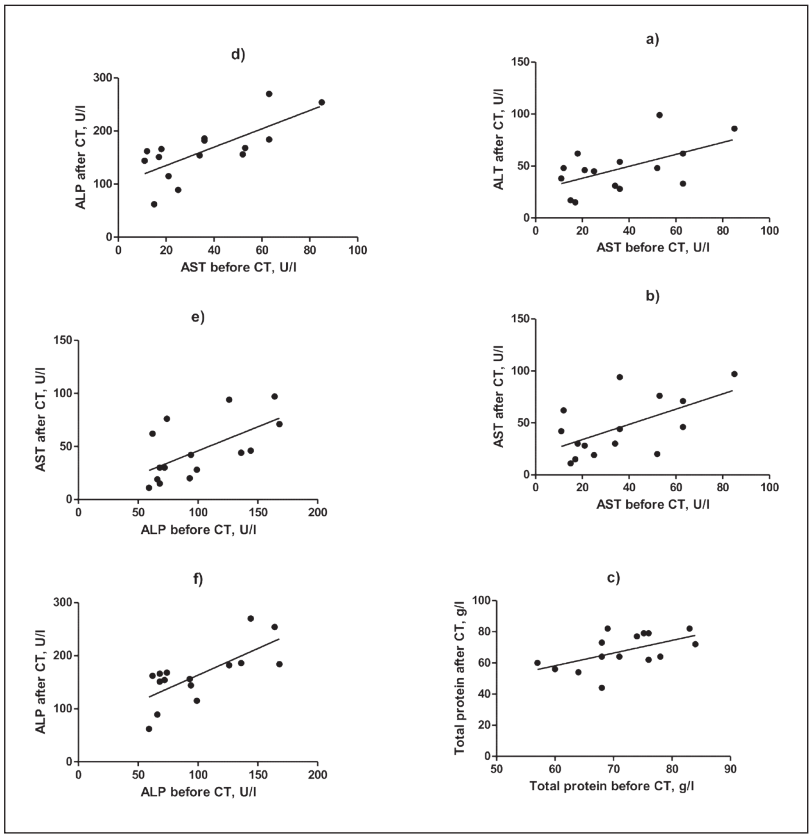

Fig. 2. Direct correlation in patients of II group: a) between the ALT activity before CT and AST after CT; b) between AST activity before and after CT; c) between the total protein content before and after CT; d) between AST activity before CT and ALP after CT e) between ALP activity before CT and AST after CT; f) between AST activity before and after CT.

MATERIALS AND METHODS

We examined 25 patients with newly diagnosed AML, who were treated in the hematology department of PE "Poltava Regional Clinical Hospital n.a. M.V. Sklifosovsky of Poltava Regional Council" since 2015 till 2019. The cohort consisted of 56% (14/25) males and 44% (11/45) females. The general patient's condition by ECOG was I-II, and according to Karnovsky performance status scale – 60-80%. The study included 25 patients with AML, classified by FAB criteria. AML variants M0, M1, M2 were determined in 40% (10/25) of patients, M3 – in 8% (2/25), M4 and M5 – in 52% (13/25) patients.) The body mass index (BMI) was calculated for all of them initially according to formula: BMI = weight (kg) / height (m^2). Adults, the patient's BMI was assessed: BMI in the range of 18.5-24.9 kg/m^2 was considered normal, and ≥25.0 kg/m^2 – overweight. Depending on the BMI, patients were further divided into groups: I (n=10) – AML patients with BMI 18.5-24.9 kg/m^2; II (n=15) – AML patients with BMI ≥25.0 kg/m^2;

All patients received CT in accordance with the Ministry of Health of Ukraine guidelines № 647 from 30 Jul 2010. Patients with AML were treated with "7+3" or "5+2", which included cytarabine and anthracycline antibiotic (doxorubicin, idarubicin, mitoxantrone), promyelocytic (M3) AML variant – "7+3" or "5+2 " with transretinoic acid, myelomono- (M4) and monoblastic (M5) – "7+3" or " 5+2" with etoposide [19].

The biochemical blood analysis parameters of all patients were evaluated twice: before CT and on the 56th day: alanine (ALT), aspartate (AST) aminotransferases, gamma-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), total serum protein and total bilirubin. The severity of cytostatic-induced hepatotoxic reactions was assessed by Common Terminology Criteria for Adverse Events (CTCAE).

The control group consisted of 20 healthy individuals (9 (45%) women and 11 (55%) men, age 22-26 years.

Statistical data analysis was performed on a Pentium 4 personal computer using Excel spreadsheets Microsoft Office – 2000 (USA). The Shapiro-Wilk test was used to verify the data distribution normality. The study results were processed by the Student-Fisher variation statistics method. Under normal distribution conditions, tables of Student's critical distribution points according to criteria (t) and (p) were used. The average value for each variation series (M) and its error (m) were calculated. Nonparametric study results were calculated by Wilcoxon (W). The relationship between the studied parameters was evaluated using Pearson correlation analysis (r). Relative risk analysis was performed by calculating the risk ratio (RR) and its 95% confidence interval (CI). Used the formula: RR=A (C+D) / C(A+B), where A, B, C, D is the number of observations in the coupling table.

Table I. The biochemical blood analysis parameters in AML patients during CT

Parameters	Almost healthy	I (n=10)		II (n=15)	
		Before CT	After CT	Before CT	After CT
ALT, U/l	14.65±1.03 95% CI 12.50-16.80	25.90±6.46 95% CI 11.28-40.52	39.80±6.98 95% CI 24.01-55.59	33.93±4.40 95% CI 24.49-43.37	47.47±5.99 95% CI 34.61-60.32
p		p_1>0.05 p_2>0.05	p_3=0.01	p_1=0.03 p_2=0.003	p_3=0,0003
AST, U/l	18.75±0.83 95% CI 17.01-20.49	22.10±3.21 95% CI 14.83-29.37	26.20±2.59 95% CI 20.33-32.07	36.07±5.81 95% CI 23.61-48.52	45.67±7.28 95% CI 30.05-61.28
p		p_1>0.05 p_2>0.05	p_3=0.03	p_1>0.05 p_2=0.02	p_3=0.004
Total protein, g/l	14.65±1.03 95% CI 12.50-16.80	69.08±2.84 95% CI 62.65-75.51	69.37±1.37 95% CI 66.28-72.46	71.41±1.99 CI95% 67.14-75.69	67.47±2.94 CI95% 61.16-73.77
p		p_1>0.05 p_2>0.05	p_3>0.05	p_1>0.05 p_2>0.05	p_3>0.05
GGT, U/l	21.10±0.47 95% CI 20.11-22.09	41.90±4.01 95% CI 32.82-50.98	71.40±14.50 95% CI 38.60-104.2	44.27±3.87 95% CI 35.96-52.57	107.5±25.79 95% CI 52.23-162.8
p		p_1=0.007 p_2=0.005	p_3=0.005	p_1<0.0001 p_2=0.0007	p_3=0.0007
ALP, U/l	61.35±4.31 95% CI 52.34-70.36	109.7±17.19 95% CI 70.82-148.6	211.4±25.17 95% CI 154.5-268.3	99.53±9.88 95% CI 78.34-120.7	162.9±13.75 95% CI 133.4-192.4
p		p_1=0.009 p_2>0.05	p_3=0.002	p_1=0.0007 p_2=0.004	p_3=0.0001
Total bilirubin, µmol/l	9.80±0.63 95% CI 8.48-11.12	11.13±1.46 95% CI 7.82-14.43	15.12±1.31 95% CI 12.16-18.08	14.19±2.07 95% CI 9.74-18.64	17.21±3.17 95% CI 10.40-24.01
p		p_1=0.01 p_2>0.05	p_3=0.009	p_1>0.05 p_2>0.05	p_3>0.05

Note: p_1 – the significant difference between the pre- and post-CT values in group I and II; p_2 – the significant difference between parameters in groups I and II before CT and almost healthy; p_3 – the significant difference between parameters in groups I and II after CT and almost healthy.

Table II. The incidence and relative risk of cytostatic-induced hepatotoxic reactions in AML patients

Parameters	I (n=10)		II (n=15)	
	Before CT (number of patients, %)	After CT (number of patients, %)	Before CT (number of patients, %)	After CT (number of patients, %)
ALT, U/l	2 (20%)	4 (40%)	7 (46.7%)	9 (60%)
RR (95% CI)	RR=2.00; 95% CI=0.46-8.56; p>0.05		RR=1.28; 95% CI=0.65-2.54; p>0.05	
AST, U/l	0	0	5 (33.3%)	8 (53.3%)
RR (95% CI)	-		RR=1.60; 95% CI=0.67-3.77; p>0.05	
Total protein, g/l	2 (20%)	1 (10%)	2 (13.3%)	8 (53.3%)
RR (95% CI)	RR=0.5; CI=0,05-4.67; p>0.05		RR=4.00; 95% CI=1.01-15.81; p<0.05	
GGT, U/l	3 (30%)	9 (90%)	5 (33.3%)	15 (100%)
RR (95% CI)	RR=3.00; 95% CI=1.14-7.91; p<0.05		RR=3.00; 95% CI=1.46-6.14; p<0.05	
ALP, U/l	3 (30%)	8 (80%)	3 (20%)	12 (80%)
RR (95% CI)	RR=2.67; 95% CI=0.98-7.22; p>0.05		RR=4.00; 95% CI=1.41-11.35; p<0.05	
Total bilirubin, µmol/l	0	1 (10%)	3 (20%)	5 (33.3%)
RR (95% CI)	-		RR=1.67; 95% CI=0.48-5.76; p>0.05	

Note: p – relative risk significant difference

RESULTS

The liver injury was detected in 60% (6/10) of patients of group I with AML and normal BMI during the initial examination (Table II), of whom 1 patient had mixed syndrome, 1 patient – cytolytic and 3 – cholestatic syndromes, isolated decrease in the total protein content in the blood serum was observed in 2 patients.

The presence of overweight and obesity in patients with AML of group II contributed to an increase frequency of hepatotoxic reactions. At baseline the liver injury was detected in 73.3% (11/15) of group I patients (Table II), of whom cytolytic syndrome was recorded in 27.3% (3/11) of patients, cholestatic – in 18.2% (2/11), mixed syndrome – in 45.5% (5/11), isolated serum total protein decrease – in 9.1% (1/11) of patients. The biochemical blood analysis parameters before CT in all patients with AML were increased within the limits of grade I by CTCAE. Thus, the development of liver injury was observed against the

AML background, regardless of BMI, which is due to the oncohematological disease influence.

The ALT, AST, ALP activity, total protein and total bilirubin content in the blood serum in patients with AML and normal BMI did not significantly differ from almost healthy individuals at baseline (p>0.05) (Table I). However, the GGT activity in patients of group I was 2 times higher than normal (p=0.005) (Table I).

In the presence of overweight and obesity in patients of group II before CT, the ALT activity in the blood serum was 2.3-fold higher (p=0.003), AST – 1.9-fold (p=0.02), GGT – 2.1-fold (p=0.0007), ALP – 1.6-fold higher (p=0.004) compared with almost healthy individuals (Table I).

The frequency and severity of liver injury in patients of groups I and II increased after two courses of CT and achieving clinical and hematological remission. Thus, on the 56th day, the biochemical liver tests violation was recorded in 90% (9/10) of patients with AML of group I (Table II), of which 4 patients had a mixed syndrome, 5 – cholestatic syndrome. The mixed syndrome detection in 1 patient was accompanied by an increased total bilirubin level and decreased serum total protein. The violations of biochemical liver tests in patients with AML and normal weight after CT did not exceed grade 1 according to CTCAE. There was a general tendency to increase the risk of hepatotoxic reactions development in patients with AML and normal BMI under the cytostatic drugs influence (RR=1.28; CI=0.81-2.02; p>0.05) (Table II).

On the 56th day of observation in patients of group I, the ALT and AST activity of in the blood serum exceeded the normal range in 2.7 (p=0.01) and 1.4 times (p=0.03) respectively (Table I).

Two courses of CT, which contained a combination of cytarabine and anthracycline antibiotic, increased the risk of GGT activity impair (RR=3.00; 95% CI=1.14-7.91; p<0.05) and ALP impair (RR=2.67; 95% CI=0.98-7.22; p>0.05) in the blood serum of patients with AML and normal BMI (Table II). Thus, the GGT and ALP activity in the blood serum of group I patients after remission induction CT exceeded the baseline parameters by 1.7 times (p=0.007) and 1.9 times (p=0.009) respectively (Table I).

The total bilirubin level in AML patients of group I after CT was 1.3-fold higher (p=0.01) compared with the baseline and 1.5-fold higher (p=0.01) compared with normal (Table I).

It is important that the use of cytarabine and anthracycline antibiotic combination in patients of group I with AML and normal BMI did not lead to the hypoproteinemia (Table II).

The biochemical liver parameters during the initial examination were of particular importance to predict the growth of hepatotoxic reactions during CT. A direct correlation was recorded between ALT and AST activity at baseline (r=+0.65; p=0.04 by Pearson) (Fig. 1, a) and ALT activity during the initial examination and AST activity after CT (r=+0.84; p=0.002 by Pearson) (Fig. 1, b). From our point of view, the AML progression affects the primary liver injury, and also creates the preconditions for the development of cytostatic-induced hepatotoxic reactions in patients with normal BMI.

The overweight and obesity were among the risk factors for the cytostatic-induced hepatotoxic reactions development in patients with AML. After two courses of remission induction CT, the biochemical liver tests violations were recorded in 100% (15/15) of group II patients with overweight and obesity (Table II), of which cholestatic syndrome was detected in 20% (3/15) of patients and mixed syndrome – in 80% (12/15) of patients. The GGT activity increased to grade 2 according to CTCAE in 1 patient after CT, other indicators of liver tests during the second examination were within the CTCAE grade I toxicity. Therefore, patients with AML of group II with overweight and obesity showed a significant increase in the risk of hepatotoxic reactions during CT (RR=1.36; 95% CI=1.00-1.85; p<0.05) (Table II). The increased risk of the mixed liver injury development was detected in this category of patients under the influence of cytostatic drugs, namely cytarabine and anthracycline antibiotics (RR=2.4; 95% CI=1.12-5.13; p<0.05).

The ALT activity in the blood serum of overweight patients with AML of group II after CT exceeded the baseline parameter in 1.4 times (p=0.03) and almost healthy individuals in 3.2 times (p=0.003), AST activity increased in 2.4 times (p=0.004) compared with norm (Table I).

CT led to a significant risk of increased GGT activity (RR=3.00; 95% CI=1.46-6.14; p<0.05) and ALP activity (RR=4.00; 95% CI=1.41-11.35, p<0.05) in the blood serum in patients of group II (Table II). The GGT activity in the blood serum in patients of group II after CT exceeded the baseline in 2.4 times (p<0.0001) and almost healthy individuals – 5.1 times (p=0.0007) (Table I). The ALP activity in the blood serum of overweight and obese patients after CT increased in 1.6 times (p=0.0007) compared with the parameter before CT and in 2.6 times (p=0.0001) compared with norm (Table I).

The remission induction CT, which contained cytarabine and anthracycline antibiotic, led to a significant increase in the risk of hypoproteinemia development in patients with AML of group II (RR=4.00; 95% CI=1.01-15.81; p<0.05) (Table II). However, the average values of the total protein level in the blood serum in patients of group II after CT did not differ from those before CT and almost healthy individuals (p>0.05 according to t and W criteria). At the same time in patients of group II the total bilirubin content in the blood serum did not significantly increase after CT (p>0.05) (Table I).

The importance of biochemical liver tests primary violation in the prediction of cytostatic-induced liver injury was confirmed in overweight and obese patients with AML. This opinion was confirmed by a direct correlation between the AST activity before CT and ALT after (r=+0.56; p=0.03 by Pearson) (Fig. 2; a), AST (r=+0.59; p=0.02 by Pearson) (Fig. 2; b) and ALP after two CT courses (r=+0.73; p=0.002 by Pearson) (Fig. 2; d), as well as between the ALP activity before CT and AST activity after CT (r=+0.61; p=0.02 by Pearson) (Fig. 2; e). At the same time, the direct correlation

was observed between the total protein content before and after CT (r=+0.55; p=0.03 by Pearson) (Fig. 2; c). Increased ALP activity during the initial examination of overweight and obese AML patients poses a significant risk of cytostatic-induced hepatotoxic reactions development. This opinion was confirmed by a strong direct correlation between ALP activity before and after CT in patients of group II (r=+ 0.72; p=0.002 by Pearson) (Fig. 2; f).

DISCUSSION

During the initial examination of AML patients, we found that the manifestation of oncohematological disease leads to biochemical liver tests violation. Should be noted, that in patients with overweight and obesity, primary liver injury is more common than in patients with a normal body mass index. It can be concluded that the presence of severe intoxication syndrome, liver tissue infiltration by tumor cells are the main pathogenetic mechanisms of liver injury in the onset of AL. However, the presence of overweight and obesity potentiates the development of liver injury with the AL progression, which was confirmed by the higher frequency and severity of biochemical liver tests violations in this category of patients compared with patients with normal BMI patients.

Remission induction in patients with AML is accompanied by a general tendency to biochemical liver tests changes, regardless of the presence of additional risk factors. It should be noted that in patients with normal BMI on the background of induction chemotherapy there was a high risk of following changes development: increased GGT activity and total serum bilirubin level. And in the presence of overweight and obesity – increased GGT, ALP activity and decreased serum total protein level.

In addition, AML patients with overweight and obesity during CT developed hepatotoxic reactions of mixed type, the probability of which depended on the presence of primary liver injury before the start of specific treatment, which coincides with other studies [6, 14]. Therefore, patients with oncohematological profile who have abnormal liver biochemical tests at the initial examination are at increased risk of developing cytostatic-induced hepatotoxic reactions. This fact must be taken into account for supportive care therapy.

An additional risk factor for chemotherapy-induced hepatotoxicity is overweight and obesity. Given that reducing the dose of cytostatic drugs will reduce the CT effectiveness, patients with overweight and obesity need to undergo specific treatment with strict adherence to doses and regimens of drugs administration [5, 8, 13, 14]. Patients of this category need to be carefully monitored for biochemical blood test changes during CT. The individual approach for supportive treatment should be developed.

CONCLUSIONS

Primary biochemical liver tests changes in patients with AML, regardless of BMI, are associated, first of all, with the influence of oncohematological disease, which may be based on several pathogenetic factors from intoxication to tumor liver tissue infiltration.

There is an increased risk of cytostatic-induced hepatotoxic reactions in patients with AML during remission induction CT. The overweight and obesity presence is a risk factor for liver injury development in the dynamics of acute leukemia treatment.

In patients with AML, regardless of BMI, induction CT was associated with a risk of increased GGT and ALP activity. However, in patients with normal BMI, GGT and ALP activity increase was associated with hyperbilirubinemia, and in overweight and obese patients – with hypoproteinemia development. Moreover, the increased ALT activity after CT compared with the baseline data was observed in AML patients with high BMI.

It should be noted that the level of biochemical blood analysis parameters after CT was primarily influenced by their baseline level, which can be used to predict the cytostatic-induced hepatotoxic reactions and determine the category of patients in need of cytostatic-induced liver injury drug prevention.

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