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FEATURES OF L-ARGININE-CITRULLINE CYCLE FUNCTIONING IN PATIENTS WITH MULTIPLE MYELOMA WITH CONCOMITANT CORONARY HEART DISEASE

Background. Disorders of the L-arginine-citrulline cycle affect the functioning of the cardiovascular system. Cancer-induced augmentation of arginase activity stimulates the biotransformation of L-arginine to form polyamines, which causes NO deficiency and increases the risk of endothelial dysfunction in the category of high-risk patients for developing cytostatic-induced cardiotoxicity. **The aim** was to investigate features of L-arginine-citrulline cycle functioning in patients with multiple myeloma (MM) and concomitant coronary artery disease (CAD) during chemotherapy (CT). **Materials and Methods.** 42 patients with MM progression were examined and divided into 2 groups: group I (n = 20) — patients without CAD and group II (n = 22) — patients with CAD. The concentrations of L-arginine and citrulline and the activity of arginase in the blood serum of the patients were measured before and after the 1st and 5th courses of chemotherapy. **Results.** Before chemotherapy, in patients of both groups, the blood serum level of L-arginine decreased, while the activity of arginase and the level of citrulline increased compared to healthy individuals. In patients of group II, the level of citrulline was higher than in patients of group I. After the 5th course of chemotherapy, L-arginine content in patients of both groups increased and citrulline levels decreased compared to the initial examination. **Conclusions.** The progression of MM was accompanied by a decrease in the blood serum content of L-arginine along with an increase in the arginase activity in the blood serum compared to practically healthy individuals. An increase in the cumulative dose of cytostatics during CT in the MM patients with concomitant CAD led to a decrease in the content of L-arginine in the blood serum with a simultaneous increase in the content of citrulline compared to corresponding levels in MM patients without concomitant CAD.

Keywords: nitric oxide, NO synthase, L-arginine, lipid peroxidation, multiple myeloma, coronary artery disease, arginase.

Disorders of the L-arginine-citrulline cycle affect the functioning of the cardiovascular system (CVS) and play an important role in the pathogenesis of coronary heart disease (CHD) [1]. Arginine is an essential amino acid in children, and a partially essential amino acid in adults, which is involved in the synthesis of nitric oxide (NO), polyamines, creatine, and amino acids and the ammonia neutralization in the urea cycle. The main sources of arginine in the human body are food,

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protein metabolism, and the endogenous synthesis in the small intestine and kidneys. Arginine is synthesized from ornithine, which in turn is produced by glutamate [2—4]

It should be noted that it is the oxidation of L-arginine that produces NO and citrulline, the latter of which can again act as a substrate for the resynthesis of L-arginine. This sequence of reactions forms the arginine-citrulline cycle. NO synthesis is regulated by NO synthases, which catalyze the formation of NO from L-arginine. The place of NO formation depends on the type and location of the NO synthase. Three main isoforms of this enzyme have been described in the literature: neuronal NO synthase (nNOS) expressed in neurons, skeletal muscle, and pancreas, endothelial NO synthase (eNOS) expressed in endothelial cells, and inducible NO synthase (iNOS), expressed in macrophages [5]. Therefore, the activation of macrophages leads to the hyperproduction of iNOS with the potentiation of the aggressive free radical generation. This mechanism may be protective, but it is considered the leading one in the damage of organs and systems in the setting of oncohematological diseases and under the influence of cytostatic drugs [5—8].

Simultaneously, NO is the key endothelial vasodilation agent. Therefore, L-arginine as a substrate for NO synthesis plays an important role in endothelial protection [3, 9]. In cancer, activation of iNOS and lipid peroxidation processes is observed, which is accompanied by depletion of L-arginine stores [10].

L-arginine preparations are widely used in clinical practice to reduce the severity of endothelial dysfunction, mainly in the setting of cardiovascular disease (CVD). Thus, according to Zharinova et al. [11], the addition of L-arginine to standard therapy in patients with coronary artery disease (CAD) leads to an improvement in NO synthesis in the endothelium and a significant decrease in the titer of autoantibodies to eNOS, which contributed to a significant improvement in the functional state of the endothelium and a decrease in platelet aggregation and an increase in the volumetric blood flow rate in tissues. At the same time, the use of L-arginine in patients with acute leukemia during the administration of chemotherapy (CT) reduces the risk of cytostatic-induced cardiotoxic effects and improves the quality of life of patients [12].

Another important pathway for the metabolic transformation of L-arginine is the arginase pathway. Arginase catalyzes the biotransformation of L-arginine to form polyamines including putrescine, spermidine, and spermine. From a clinical point of view, it is important that arginase determines the availability of L-arginine for the synthesis of NO, amino acids, and polyamines. Animal experiments have shown that NO synthase competes with arginase for L-arginine. In other words, NOS directs the catabolism of L-arginine toward the formation of NO, the main vasodilator, while arginase stimulates the biotransformation of L-arginine to form polyamines. Polyamines, in turn, act as regulators of cell growth and proliferation. In tumor cells, arginase activity increases tenfold, causing acceleration of L-arginine catabolism with the formation of stimulating polyamines, which causes NO deficiency and endothelial dysfunction [2, 3, 9].

According to Matsuzaki et al. [13], patients with multiple myeloma (MM) have abnormalities in the amino acid balance of blood plasma with a significant decrease in the levels of histidine and L-arginine. Thus, patients with MM progression have an increased risk of endothelial dysfunction. The likelihood of severe endothelial dysfunction increases significantly in patients with concomitant CVS diseases, primarily CAD. According to current data, low levels of L-arginine may also reduce the effectiveness of bortezomib-containing CT regimens by protecting tumor cells from the cytotoxic effects of proteasome inhibitors [14].

Thus, the study of L-arginine-citrulline cycle parameters in patients with MM is of particular importance for the prediction of cytostatic-induced cardiotoxicity, especially in the presence of concomitant CAD.

The aim of our study was to investigate the features of the L-arginine-citrulline cycle in patients with multiple myeloma and concomitant coronary artery disease during chemotherapy.

Materials and Methods

The study examined 42 patients with MM progression who were treated in the Hematology department of the Poltava Regional Clinical Hospital named after M.V. Sklifosovsky from 2021 to 2023. The ratio of men to women was 50%/50%, and the average age was 62.05 ± 9.75 years. All patients were diagnosed with MM by the standards for the management of oncohematological patients with MM in accordance with Order of the Ministry of Health of Ukraine dated 02.11.2015 No. 710 [15] and the clinical guidelines of the European Society for Medical Oncology [16]. The study included patients whose general condition according to ECOG corresponded to I—II, according to the Karnowski index of 60%—80%.

In 22 (52.4%) patients, the concomitant CHD was detected as stable angina pectoris of FC I—II. The diagnosis of CHD was confirmed in accordance with the order of the Ministry of Health of Ukraine dated December 23, 2021 No. 2857 [17].

All patients were divided into group I (n = 20) — MM patients without concomitant diseases of CVS and group II (n = 22) — MM patients with concomitant CAD.

The control group consisted of 20 practically healthy individuals with an average age of 25 ± ± 1.6 years.

According to the Durie and Salmon (1975) classification, in group I, stage IIA was detected in 3 (15%) patients, stage III in 11 (55%), and stage IIIA in 6 (30%) patients. In group II, stage IIIA was in 19 (86.4%) and stage IIIA in 3 (13.6%) patients.

All patients with MM progression were prescribed bortezomib-containing chemotherapy regimens: VRD (bortezomib, lenalidomide, dexamethasone), VD (bortezomib, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), VTD (bortezomib, thalidomide, dexamethasone), and VMP (bortezomib, melphalan, prednisone). In group I, 17 (85%) patients received the VRD regimen, 1 (5%) VCD, 1 (5%) VTD, and 1 (5%) VD. In group II, 14 (63.7%) patients received the VRD regimen, 3 (13.6%) received VD, 3 (13.6%) received VMP, and 2 (9.1%) received VCD.

Patients of both groups were examined 4 times: before and after the 1st and 5th courses of chemotherapy. The concentration of L-arginine in the blood serum was determined by the Sakaguchi reaction [18], and the activity of arginase in the blood serum by the method of Khramov, which is a modified method of Chinard [19]. The concentration of citrulline in the blood serum was studied using the method of Boyde and Rahmatullah [20]. The determination of the concentrations of L-arginine and citrulline and the activity of arginase in the blood serum was done using a PV1251 spectrophotometer.

The statistical processing of the results was performed using the statistical program GraphPad Prism version 8.0.1 (GraphPad Software, Inc., USA), which allows for parametric and nonparametric statistical analysis. In the case of normal distribution of data, the results were presented as M ± SD. The reliability of differences was calculated using Student's *t*-test. In the case of a distribution that differed from the normal one, results were presented as median (X) and interquartile range (IQR), and the paired nonparametric methods of Wilcoxon and Mann —Whitney rank tests were used. Differences at $p < 0.05$ were considered statistically significant [21].

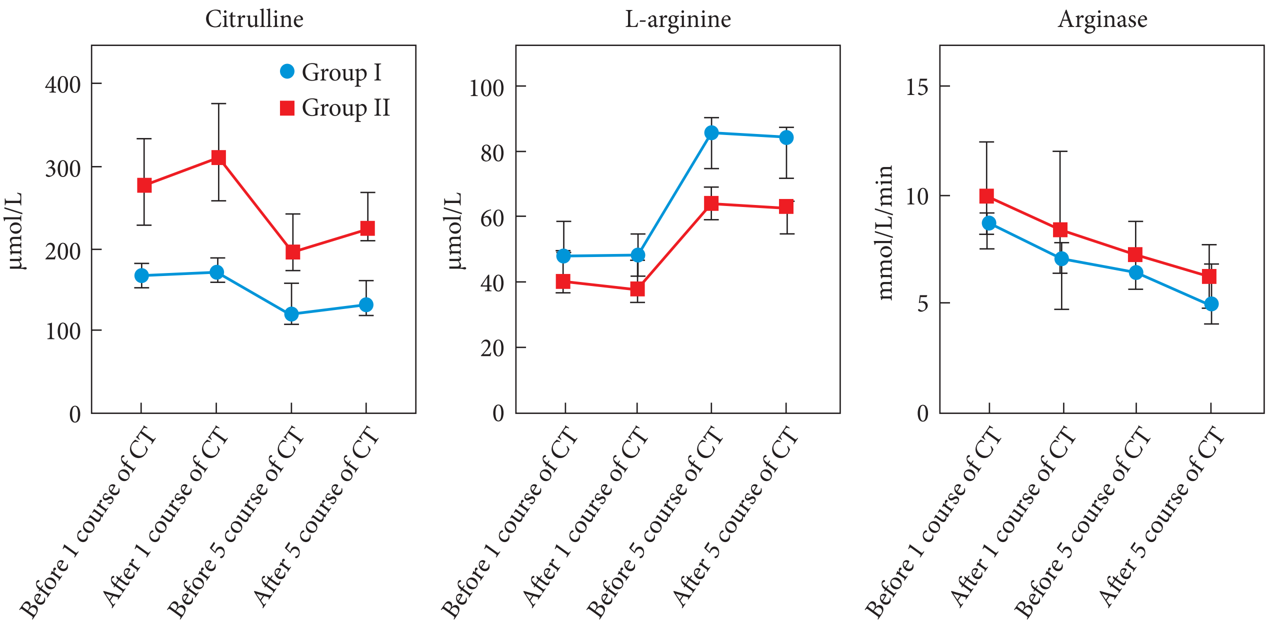
Results

Before the start of chemotherapy, the level of L-arginine in blood serum in patients of groups I

Main indicators of the L-arginine-citrulline cycle components during the initial examination (X; IQR)

Indicator	Group I (n = 20)	Group II (n = 22)	Practically healthy individuals (n = 20)
L-arginine, μmol/L	48.24; 36.54—58.87	40.58; 37.54—49.9	95.07; 82.15—104.9
p	$p_1 < 0.0001$	$p_2 = 0.31$	
Arginase, mmol/L/min	8.75; 8.22—9.2	9.19; 8.32—10.4	3.3; 0.99—4.18
p	$p_3 < 0.0001$	$p_4 = 0.12$	
Citrulline, μmol/L	167.9; 151.3—183.5	277.1; 229.3—334.6	54.11; 49.08—64.49
p	$p_5 < 0.0001$	$p_6 < 0.0001$	

Notes: p_1 — L-arginine levels in patients of groups I and II compared to healthy individuals; p_2 — comparison between L-arginine levels in patients of groups I and II, p_3 — arginase activity levels in patients of groups I and II compared to healthy individuals, p_4 — comparison between arginase activity levels in patients of groups I and II, p_5 — citrulline levels in patients of groups I and II compared to healthy individuals, p_6 — comparison between citrulline levels in patients of groups I and II.



Changes in the L-arginine-cirtulline cycle components in the blood serum of patients with MM during CT

and II decreased by 2 ($p_1 < 0.0001$) and 2.1 ($p_1 < 0.0001$) times compared to the practically healthy individuals (Table) with no difference between the groups ($p_2 = 0.31$). The activity of arginase in patients of groups I and II increased by 2.9 ($p_3 < 0.0001$) and 3.25 ($p_3 < 0.0001$) times, respectively, compared to the practically healthy individuals (Table) with no difference between the groups ($p_4 = 0.12$). Thus, it can be assumed that the increase in the arginase activity with a predominance of L-arginine biotransformation with the formation of polyamines is primarily influenced by the progression of MM. At the same time, the level of serum citrulline in patients of groups I and II was 2.9 times ($p_5 < 0.0001$) and 3.8 times ($p_5 < 0.0001$) higher than normal, respectively (Table). In patients of group II (MM + CAD), the level of citrulline was 1.7 times higher ($p_6 < 0.0001$) than in patients of group I indicating the presence of endothelial dysfunction in patients with the concomitant CAD.

In patients of groups I and II, the level of L-arginine after the first course of CT decreased by 1.1 ($p = 0.01$) and 1.07 ($p = 0.02$) times, respectively, without a significant difference between the groups, indicating its increased consumption during the administration of cytostatics. It should be noted that before the 5th course of CT in patients of groups I and II, the level of L-arginine increased by 1.7 ($p < 0.0001$) and 1.4 ($p < 0.0001$) times, respectively, compared to the initial examination (Figure). At the same time, in patients with concomitant CAD, the level of serum L-arginine decreased by 1.3 ($p < 0.0001$) times compared to patients without concomitant CVD (Figure). Similar dynamics of changes in the L-arginine content in patients of groups I and II was observed after the 5th course of CT: the level of L-arginine increased by 1.7 times ($p < 0.0001$) and 1.4 times ($p < 0.0001$), respectively, compared to the initial examination values. The level of L-arginine in patients with concomitant CAD was 1.3 ($p < 0.0001$) times lower than in patients with MM without concomitant CVD (Figure).

At the same time, in patients of groups I and II, arginase activity progressively decreased along with the administration of cytostatic drugs. Thus, arginase activity decreased by 1.2 and 1.2 times after the first CT course, by 1.3 and 1.4 times before the 5th course, and by 1.6 and 1.6 times after the 5th course as compared to the initial examination (Figure) without significant difference between the groups.

In patients of groups I and II, the level of citrulline after the first course of CT insignificantly increased by 1.05 times and 1.13 times, respectively, compared to the initial examination, indicating an increase in lipid peroxidation (LPO) activity with the participation of iNOS. At the same time, in patients of group II, the level of citrulline was 1.8 times higher ($p < 0.0001$) compared to patients of group I. In patients of groups I and II, the level of citrulline before the 5th course of CT decreased by 1.3 times ($p < 0.0001$) and 1.4 times ($p = 0.0002$), respectively, compared to the initial examination and was 1.5 times higher in patients of group II ($p < 0.0001$) compared to patients of group I. After the 5th course of CT, citrulline levels decreased by 1.2 times ($p < 0.0001$) and ($p = 0.004$) in patients of groups I and II, respectively, compared to the initial examination values. At the same time, in patients of group II, citrulline levels were 1.6 times ($p < 0.0001$) higher than in patients of group I, which indirectly indicates the predominance of intensification of LPO in patients with MM + CAD in the dynamics of CT (Figure).

Discussion

The study found that MM progression is accompanied by changes in the L-arginine-citrulline cycle, which were represented by a decrease in the content of L-arginine in the blood serum along with a simultaneous increase in the arginase activity. These changes represent a cancer-related pathway of L-arginine metabolism, which leads to an increase in the synthesis of polyamines [2, 5] Our data are in accordance with the data of other authors [22, 23]. By the obtained data, a decrease in the concentration of L-arginine in the serum of MM patients with high cardiovascular risk may be the cause of eNOS deficiency and the formation of cytostatic-induced cardiotoxicity during the accumulation of a cumulative dose of cytostatic drugs. In addition, according to experimental studies [14], low levels of L-arginine can affect the progression of MM and play a protective role for tumor cells, thereby reducing the effectiveness of CT, in particular proteasome inhibitors [14].

At the same time, the progression of oncohematological diseases, including MM, is accompanied by an increase in macrophage activity, which causes the hyperproduction of iNOS [5—7]. During the initial examination before the appointment of CT, we recorded an increase in the concentration of citrulline in the blood serum of patients. This fact confirms the activation of the iNOS pathway of L-arginine metabolism in the course of MM progression. According to studies [24, 25], the side effects of CT may also be due to the activation of the production of reactive oxygen species due to the increased activity of iNOS. In our study, a single course of CT in MM patients was accompanied by an increased citrulline content in the blood serum, which can indirectly reflect the iNOS activity.

In the background of CAD, a decreased expression of eNOS is an important component of endothelial dysfunction [26]. From this point of view, a decreased content of L-arginine in the blood serum in MM + CAD patients is of particular importance. According to the results of our study, each course of CT in MM patients was accompanied by a decrease in serum L-arginine levels, which created a prerequisite for the occurrence of cytostatic-induced malfunction of the CVS in patients, especially those with concomitant CAD.

Thus, the level of serum L-arginine in patients with MM and concomitant CAD may serve as a predictor of cardiotoxic events.

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Informed consent was obtained from all individual participants involved in the study. The research was approved by the Medical Ethical Committee of the Poltava State Medical University. All procedures performed in study were in accordance with the guidelines of the Declaration of Helsinki of 2000.

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ОСОБЛИВОСТІ ФУНКЦІОНУВАННЯ L-АРГІНІН-ЦИТРУЛІНОВОГО ЦИКЛУ У ХВОРИХ НА МНОЖИННУ МІЄЛОМУ ІЗ СУПУТНЬОЮ ІШЕМІЧНОЮ ХВОРОБОЮ СЕРЦЯ

Стан питання. Порушення L-аргінін-цитрулінового циклу впливає на функціонування серцево-судинної системи. Збільшення активності аргінази, що виникає на фоні онкопатології, зумовлює прискорення катаболізму L-аргініну з утворенням стимулюючих поліамінів, що викликає дефіцит NO та збільшує ризик розвитку ендотеліальної дисфункції у пацієнтів високого ризику щодо розвитку кардіотоксичності, індукованої цитостатиками. **Мета.** Дослідити особливості функціонування L-аргінін-цитруліного циклу у хворих на множинну мієлому із супутньою ішемічною хворобою серця в динаміці хіміотерапії. **Матеріали та методи**. Обстежено 42 пацієнта із прогресією множинної мієломи. У 22 (52,4%) пацієнтів виявлено супутню ішемічну хворобу серця. У залежності від наявності супутньої ішемічної хвороби серця пацієнти були розподілені на групи: I група (n = 20) — хворі на множинну мієлому без супутніх захворювань серцево-судинної системи та II група (n = 22) — хворі на множинну мієлому із супутньою ішемічною хворобою серця. Хворих обох груп обстежено 4 рази: перед початком та після завершення 1-го та 5-го курсів хіміотерапії. Досліджували концентрацію L-аргініну, цитруліну та активність аргінази в сироватці крові. **Результати**. Перед початком хіміотерапії в пацієнтів обох груп вміст L-аргініну в сироватці крові був достовірно нижчим, а вміст цитроліну й активність аргінази вищими, ніж у здорових людей. У пацієнтів II групи вміст цитруліну був вищим, ніж у пацієнтів I групи. Після 5-го курсу хіміотерапії у пацієнтів обох груп вміст L-аргініну в сироватці крові підвищувався, а вміст цитруліну — знижувався в порівнянні з первинним обстеженням. **Висновки**. Прогресія множинної мієломи супроводжувалася зниженням вмісту L-аргініну і підвищенням активності аргінази в сироватці крові порівняно з практично здоровими особами. Підвищення кумулятивної дози цитостатиків впродовж 5 курсів у хворих на множинну мієлому із супутньою ішемічною хворобою серця приводить до зниження вмісту L-аргініну в сироватці крові з одночасним зростанням вмісту цитруліну у порівнянні з хворими множинну мієлому без супутньої ішемічної хвороби серця.

Ключові слова: оксид азоту, NO синтаза, L-аргінін, множинна мієлома, ішемічна хвороба серця, аргіназа.