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THE ROLE OF L-ORNITHINE-L-ASPARTATE IN PROPHYLAXIS OF CYTOSTATIC-INDUCED LIVER INJURY IN PATIENTS WITH MULTIPLE MYELOMA

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The paper presents the findings of our studies on the assessment of the effectiveness of L-ornithine-L-aspartate in the prophylactic of chemotherapy-induced liver injury in patients with multiple myeloma. 24 patients with multiple myeloma were examined (11 females and 13 males, ages 46–78). The condition assessment was conducted twice: before chemotherapy and after 3 courses of chemotherapy. Patients were analyzed for the following biochemical parameters: the activity of alanine and asparagine aminotransferases, gamma-glutamyltranspeptidase, alkaline phosphatase, total bilirubin, total protein, creatinine, urea, total blood calcium level. Depending on the inclusion of L-ornithine-L-aspartate as an adjuvant treatment, patients were divided into 2 groups: group I (n=12) – patients with multiple myeloma, who underwent onl□ h□m□th□r□□□; gr□u□ □□(n=12) – patients with multiple myeloma, who during chemotherapy received L-ornithine-L-aspartate at a dose of 10 g/day intravenously for 10 days, then 5 g 2 twice a day for 20 days. Group III (n=20) the control group, included 20 practically healthy persons. It was established, that application of L-ornithine-L-aspartate as an adjuvant treatment in patients with multiple myeloma that undergo chemotherapy provides the effective prophylactic of pathological alterations in liver and kidney functional state.

Keywords: chemotherapy, hepatotoxicity, nephrotoxicity, adjuvant therapy.

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РОЛЬ L-ОРНІТИНУ-L-АСПАРТАТУ У ПРОФІЛАКТИЦІ ЦИТОСТАТИК-ІНДУКОВАНИХ УРАЖЕНЬ ПЕЧІНКИ У ХВОРИХ НА МНОЖИННУ МІЄЛОМУ

У статті наведені результати власних досліджень по оцінці ефективності L-орнітин-L-аспартату у профілактиці хіміотерапевтично-індукованих уражень печінки у хворих на множинну мієлому. Обстежено 24 пацієнти із множинною мієломою (11 жінок і 13 чоловіків, віком від 46 до 78 років). Оцінку стану пацієнтів проводили двічі: до хіміотерапії (ХТ) і після трьох курсів специфічної терапії. Оцінювали показники біохімічного аналізу крові: активність аланінової, аспарагінової амінотрансфераз, гамаглутамілтранспетидази, лужної фосфатази, загального білірубіну, загального білку, креатиніну, сечовини, рівень кальцію крові. В залежності від включення до складу терапії супроводу L-орнітин-L-аспартату пацієнти були розподілені на 2 групи: I група (n=12) – хворі на ММ, котрі отримували ХТ; II група (n=12) – хворі на ММ, які на тлі ХТ отримували L-орнітин-L-аспартат в дозі 10 г/добу внутрішньовенно впродовж 10 днів, потім 5 г 2 рази на день 20 днів. III (n=20) контрольну групу склали 20 практично здорових осіб. Доведено, що застосування L-орнітин-L-аспартату сприяє ефективній профілактиці порушень функціонального стану печінки та нирок у хворих на множинну мієлому при проведенні ХТ.

Ключові слова: хіміотерапія, гепатотоксичність, нефротоксичність, супровідна терапія.

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Multiple myeloma (MM) is a chronic lymphoproliferative disorder that is characterized by malignant proliferation of clonal plasma cells that produce monoclonal immunoglobulin. MM is the second most common oncohematological disorder after Non-Hodgkin lymphoma [4]. The incidence of MM is approximately 50 cases per million population per year [12].

The liver injury in patients with oncohematological disorders can be caused by the detrimental effect of oncohematological disorder itself, by the medications, by the progression of the preexisting liver disease, or by the reactivation of infections as hepatitis B virus or hepatitis C virus [7].

It is important to mention, that the major pathogenic mechanism of liver injury in patients with MM is related to the infiltration of the liver tissue by the plasma cells. In most cases plasma cells cause diffuse sinusoidal infiltration or formation of a plasmacytoma, also liver damage can be caused by the deposition of immunoglobulin light chains or amyloid that is associated with the higher risk of thrombosis [5, 10].

In patients with MM, the clinical manifestations of liver injury include hepatomegaly, nonobstructive jaundice, ascites, or extrahepatic biliary obstruction [3]. According to Perez-Soler et al, in postmortem studies, the diffuse liver infiltration by plasma cells was present in 10 out of 21 patients with MM [8]. Thomas et al, reviewed the autopsy results of 64 patients with MM, where they have assessed the clinical manifestations of MM in concerning of histological abnormalities. Hepatomegaly was present in 58 % of patients, splenomegaly in 25 %, and exudative ascites in 14.1 %. In 40 % of cases, diffuse hepatic infiltration has been described. According to the authors, hepatic infiltration can be divided into 2 types: plasmacytoma and diffuse sinusoidal infiltration. It is important to mention, that only in 9.4 % of patients with the normal histological picture has been determined [11].

It is necessary to mention that chemotherapy-induced liver injury can develop even in patients with the normal functional state of the liver tissue during the initial examination [10].

Cytostatic-induced hepatotoxicity can be characterized as an ability to disrupt the normal histological structure of the liver with the development of hepatic dysfunction. Important to mention, that liver tissue can adapt to certain drugs through the development of tolerance to the medication. The intake of drugs to which the tolerance has developed can be associated with only mild elevation of aminotransferases without any relevant clinical symptoms [9].

Modern therapeutic options in the treatment of MM include combinations of proteasome inhibitors bortezomib and carfilzomib, thalidomide and its analogue lenalidomide, cyclophosphamide, dexamethasone, and doxorubicin. Most of these agents are contraindicated for liver dysfunction and require dose adjustment in patients with abnormal liver function tests [10]. Thus, currently, the prophylaxis of cytostatic-induced liver injury in patients with MM had emerged as a particularly important problem. In this category of patients inclusion of L-ornithine-L-aspartate to adjuvant therapy during CT can provide a beneficial effect on liver functional state and can prevent potential cytostatic-induced liver injury [2].

The purpose of the study was to assess the effectiveness of L-ornithine-L-aspartate in the prophylaxis of chemotherapy-induced liver injury in patients with multiple myeloma.

Materials and methods. 24 patients with MM were studied. All patients were treated in the Hematology Department of M.V. Sklifosovsky Poltava Regional Clinical Hospital during the 2018–2021 years. 11 (46 %) females and 13 (54 %) males, ages 46–78. All patients were diagnosed with MM, indications for CT were determined, CT was appointed accordingly to the standards of treatment of patients with oncohematological diseases with acute and chronic hemoblastosis, according to the order № 647 of the Ministry of Health of Ukraine since 30.07.2010 [1], European Society for Medical oncology [6]. According to Durie, Salmon classification for patients with MM, in 11 (45.8 %) patients were diagnosed II (A) stage, II (B) – in 1 (4.2 %), III (A) – in 8 (33.3 %), III (B) stage – in 4 (16.7 %) patients. Patients with ECOG performance status I–II, and Karnofsky Performance Status – 60-80 % were enrolled. The examinations were conducted twice: before CT and after 3 courses of CT. Patients were analyzed for the following biochemical parameters: the activity of alanine (ALT) and asparagine (AST) aminotransferases, gamma-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), total bilirubin, total protein, creatinine, urea, total blood calcium level.

All patients received CT according to current standards, specifically, the following combinations with bortezomib and thalidomide were used: VTD (bortezomib, thalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), VRD (lenalidomide, bortezomib, dexamethasone), Cycle-Thal (cyclophosphamide, thalidomide). Depending on the inclusion of L-ornithine-L-aspartate as an adjuvant treatment, patients were divided into groups:

– Group I (n=12) – patients with MM, who underwent only CT.

– Group II (n=12) – patients, who during chemotherapy received L-ornithine-L-aspartate at a dose of 10 g/day intravenously for 10 days, then 5 g 2 twice a day for 20 days.

– Group III (n=20) – the control group, that included 20 practically healthy persons (9 (45 %) females and 11 (55 %) males, ages 22–26).

The liver and kidney function tests were assessed according to Common Terminology Criteria for Adverse Events, Version 4.02. Viral hepatitis B and C were excluded in all patients prior to the study.

Ethical norms have been adhered: all enrolled patients were fully informed about the research and informed consents were obtained before the study.

GraphPad Prism version 5.00 (GraphPad Software, Inc., San Diego, CA, USA) was applied for statistical analysis software. Normally, distributed data were expressed as mean ± standard deviation. Students' t criteria were used for normally distributed data. Non-parametric Wilcoxon-Mann-Whitney test was used for the analysis of unevenly distributed data. Spearman's rank correlation coefficients were used to assess the correlations between the results. The risk ratio (RR) was calculated with a 95 % confidence interval. The following formula was applied: RR=A(C+D) / C(A+B), where A, B, C, D – incidence rate at which the outcome develops in the cohort. For studies comparing prevalence between two groups, p value of < 0.05 was considered statistically significant.

Results of the study and their discussuion. On the initial examination in patients with MM abnormal biochemical liver markers were detected in 33.3 % (4/12) of patients in group I and in 25 % (3/12) of patients in group II. In patients of group, I increased activity of ALT was detected in 25 % (3/12), AST – in 16.6 % (2/12), GGT – in 25 % (3/12), total bilirubin – in 8.3 % (1/12) of patients. Similar findings were observed in patients of group II, increased activity of ALT was discovered in 8.3 % (1/12), GGT – in 16.6 % (2/12), total bilirubin – in 16.6 % (2/12) of patients. Abnormal biochemical liver function tests in patients of group I and group II before CT were within I grade according to CTCAE.

The activity of GGT in blood serum in patients of group I and group II were in 1.96 times (p=0.0025) and in 1.73 times (p=0.0024) respectively higher as compared to the control group. (table 1).

Table 1

Biochemichal values in patients of the I group before and after treatment, M±m

Values	I (n=12)		III (n=20)
	V1	V2	
Blood protein level, g/l	89.32±16.20 * 95%CI 79.02-99.61	76.16± 12.84 95%CI 68.00- 84.32	73.10±5.17 95%CI 70.68-75.52
Creatinine, mmol/l	114.2±50.71 95%CI 81.98-146.4	111.2± 80.38 & 95%CI 60.17- 162.3	59.00±6.43 # 95%CI 55.99-62.01
ALT, U/l	37.83±19.09 95%CI 25.71-49.96	42.09±14.64 & 95%CI 32.79- 51.40	14.65±4.60 # 95%CI 12.50-16.80
AST, U/l	26.75±12.40 95%CI 18.87-34.63	29.28± 8.79 95%CI 23.68- 34.87	18.75±3.71 # 95%CI 17.01-20.49
GGT, U/l	41.42±10.73 * 95%CI 34.60-48.24	75.75±27.84 & 95%CI 58.06-93.44	21.10±2.12 # 95%CI 20.11-22.09
ALP, U/l	55.75± 14.53* 95%CI 46.52- 64.98	110.0± 38.21 95%CI 85.72- 134.3	61.35±19.25 # 95%CI 52.34-70.36
Bilirubin, µmol/l	11.00±5.01 95%CI 7.82-14.18	10.72± 4.05 95%CI 8.14- 13.29	9.80±2.82 95%CI 8.48-11.12
Urea, µmol/l	8.27±4.04 95%CI 5.70-10.85	8.32± 5,31& 95%CI 4.94- 11.70	4.09±1.25 # 95%CI 3.50-4.67
Blood calcium, µmol/l	2.50±0.44 95%CI 2.21-2.78	2.39± 0.16 & 95%CI 4.13- 7.16	2.26±0.06 # 95%CI 2.23-2.29

Note: V1 – the first examination, V2 – the second examination, * - statistically significant diffrence between V1 and V2 values in patients of the I group (p<0,05), &- statistically significant diffrence between V1 values in patients of the I group and the III group (p<0,05), # - statistically significant diffrence between V2 values in patients of the I group and the III group (p<0,05).

Simultaneously in patients of group I and group II activity of ALT was in 2.58 times (p=0.0087) and in 1.55 times (p=0.0309) higher than normal. Accordingly, the progression of MM is accompanied by abnormalities in liver function tests, that are characterized by a cytolytic pattern of liver injury.

Also, progression of MM is often accompanied by kidney injury. Before CT the creatinine level was elevated in 16.6 % (2/12) of patients in group I and in 25 % (3/12) of patients in group II. Increased urea level was detected in 33,3 % (4/12) of patients in group I and in 33.3 % (4/12) patients in the II group. Abnormal renal tests in patients of group I and group II before CT were within I-II grade according to CTCAE. The mean blood creatinine level in patients of the I and II group were in 1.94 times (p=0.0005) and in 2.23 times (p=0.0025) higher compared to the control group. At the same time, urea concentration in patients of group I and group II was in 2.02 times (p=0.0034) and 2.52 times (p=0.0034) higher than normal.

Hypercalcemia was observed in 25 % (3/12) of patients in group I and in 16.6 % (2/12) of patients in group II. The progression of MM was associated with an increase in blood calcium level in patients of group I and group II in 1.1 times (p=0.00376) and 1.14 times (p=0.0498) respectively compared to the control group (table 2).

Table 2

Biochemichal values in patients of the I group before and after treatment, M±m

Values	II (n=12)		III (n=20)
	V1	V2	
Blood protein level, g/l	81.56±19.37 * 95%CI 64.65-77.68	69.93± 5.81 95%CI 66.24- 73.63	73.10±5.17 95%CI 70.68-75.52
Creatinine, mmol/l	131.3±98,84 * 95%CI 68.47-194.1	83.33± 20,93 & 95%CI 70.04- 96.63	59.00±6.43 # 95%CI 55.99-62.01
ALT, U/l	22.67±10.85 95%CI 15.77-29.56	21.25± 5.24 & 95%CI 17.92- 24.58	14.65±4.60 # 95%CI 12.50-16.80
AST, U/l	20.92±4.52 95%CI 18.04-23.79	19.58± 2.87 95%CI 17.76- 21.41	18.75±3.71 95%CI 17.01-20.49
GGT, U/l	36.58±12.28 95%CI 28.78-44.39	36.25±8.29 & 95%CI 30.98-41.52	21.10±2.12 # 95%CI 20.11-22.09
ALP, U/l	52.33± 18.04 95%CI 40.87- 63.79	67.08± 21.01 95%CI 53.74- 80.43	57.30±10.11 95%CI 50.07-64.53
Bilirubin, µmol/l	11.81±7.72 95%CI 6.90-16.71	10.65± 3.88 95%CI 8.18- 13.12	9.80±2.81 95%CI 8.48-11.12
Urea, µmol/l	10.30±9.62 95%CI 4.18-16.42	6.71± 3.07 & 95%CI 4.76- 8.67	4.09±1.25 # 95%CI 3.53-4.67
Blood calcium, µmol/l	2.58±0.60 95%CI 2.20-2.97	2.35± 0.13 & 95%CI 2.27- 2.44	2.26±0.06 # 95%CI 2.23-2.29

Note: V1 – the first examination, V2 – the second examination, * - statistically significant diffrence between V1 and V2 values in patients of the II group (p<0,05), & – statistically significant diffrence between V1 values in patients of the II group and the III group (p<0.05), # - statistically significant diffrence between V2 values in patients of the II group and the III group (p<0.05).

Thus, the initial examination, before CT, in patients with MM the initial moderate liver injury was diagnosed, which was characterized predominantly by hepatocellular pattern and was associated with an increase in GGT and ALT level in patients of both groups as compared to practically healthy persons. At the same time, in patients of group I and group II the elevation of creatinine and urea blood levels were determined, which can be a sign of kidney dysfunction. The elevation of hepatic biochemical markers before CT can be considered as a risk factor of secondary chemotherapy-induced hepatotoxicity. Kidney injury can be considered as a risk factor of cytostatic-induced nephrotoxicity, that in turn potentiate hepatotoxic reactions. Considering, that liver dysfunction can potentiate renal dysfunction, patients with MM that undergo CT, are at risk of severe hepatotoxic and nephrotoxic reactions, that can lead to a hepatorenal syndrome. Also, the elevation of blood calcium level can be considered as an additional risk factor of cytostatic-induced nephrotoxicity.

After the third course of CT in patients of group I, that underwent CT without inclusion of L-ornithine-L-aspartate for adjuvant treatment, abnormal liver function tests were determined in 75 % (9/12) of patients, increase in ALT was observed in 16.6 % (2/12) of patients, AST – in 8.3 % (1/12), GGT – in 75 % (9/12), ALP – in 16.6 % (2/13), total bilirubin – in 15.4 % (2/13). Thus, in patients with MM of group I, CT was associated with an increased risk of hepatotoxic reactions as compared to the initial examination. (RR=2.25: 95 % CI 0.95–5.34; $p>0.05$). The mean values of ALT in blood serum in patients of group I after CT were in 2.87 times ($p=0.001$), AST – in 1.56 times ($p=0.0057$), GGT – in 3.59 ($p=0.0025$), ALP – 1.79 times ($p=0.001$) higher respectively as compared to practically healthy persons.

In patients of group II, that received L-ornithine-L-aspartate for adjuvant treatment, abnormal liver function tests were determined in 1 (8.3 %) patient, which is characterized by increased GGT level. Thus, patients with MM of group II, that received L-ornithine-L-aspartate during CT, had a lower risk of cytostatic-induced hepatotoxic reactions (RR=0.11: 95 % CI 0.02–0.74; $p<0.05$). In all patients of both group I and group II the alterations in liver enzymes did not exceed the I grade according to CTCAE.

In patients of group II, that received L-ornithine-L-aspartate as an adjuvant treatment, on the second examination the activity of ALT was in 1.45 times ($p=0.028$), GGT – in 1.72 times ($p=0.0025$) higher as compared to the control group. Moreover, exactly in patients of group II the abnormalities in liver enzyme tests were significantly lower as compared to group I, specifically the activity of ALT was in 1,98 times ($p=0.0051$), AST – in 1.49 times ($p=0.0085$), GGT – in 2.09 times ($p=0.0005$), ALP – in 1.64 times ($p=0.0049$) lower compared to group I.

In patients of group I elevation of creatinine level was observed in 16.6 % (2/12) of patients, increase urea level – in 33.3 % (4/12) of patients, therefore CT was associated with increased incidence of kidney injury. At the same time the blood creatinine, urea and calcium levels maintained elevated, specifically creatinine was in 1.88 times ($p=0.0025$), urea in 2.03 times ($p=0.0096$), calcium in 1.05 times ($p=0.0309$) higher as compared to the control group. The decrease in creatinine level can be explained by the efficacy of CT. CT cause a decrease in total tumour mass which in turn provides a positive impact on kidney functional capacity. Also, improvement in the renal functional state can be explained by the positive impact of L-ornithine-L-aspartate on renal tissue.

In all patients of group II blood creatinine level did not exceed the upper limit of normal (ULN). An increase in urea above the ULN was detected in 25 % (3/12) of patients of group II. Elevation of blood creatinine and urea levels did not exceed grade I according to CTCAE. Simultaneously in patients of group II blood creatinine level was in 1.41 times ($p=0.0032$), urea level – by 1.64 times ($p=0.021$), calcium level – by 1.04 times ($p=0.028$) higher as compared to the control group. At the same time, in patients of group II, that received L-ornithine-L-aspartate as an adjuvant treatment, after the 3 courses of CT blood creatinine level was by 1.58 times ($p=0.0137$) lower as compared to creatinine level on initial examination.

On initial examination 33.3 % of patients in group I and 25 % of patients in group II had liver injury, that was characterized by abnormal biochemical liver markers. Preexisting liver injury can be explained by detrimental effect of MM itself. In MM liver injury is caused primarily by plasma cell infiltation of the liver or by massive deposition of immunoglobulin light chains in the liver tissue [5, 10]. The similar results were observed by Thomas et al, in their study in most cases in patients with MM they determined the elevation of liver enzymes. Moreover, the elevation of the liver enzymes was associated with plasma cell infiltration of the liver tissue [11]. According to the novel clinical investigations, liver injury in patients with MM can serve as a marker of a poor prognosis and is associated with a lower frequency of achieving a full response during the treatment [5].

Currently, for patients with MM the only treatment option is CT. However, most cytostatic drugs used in the treatment of MM have a significant hepatotoxicity and nephrotoxicity. In our study, after the third course of CT in patients of group I abnormal liver function tests were determined in 75 % patients. Increase

in incidence of abnormal liver function tests were caused by hepatotoxic effect of CT agents. The hepatotoxic effect of the cytostatic drugs can be explained by their metabolism through the liver. This feature becomes of primary importance in the assessment of the risk of cytostatic-induced hepatotoxic reactions [5]. Moreover, cytostatic drugs can cause a hepatotoxic effect indirectly, through the reactivation of viral hepatitis or cytomegalovirus infection [10]. The hepatotoxicity of CT agents become a major concern, because in the high-risk category of patients that have liver dysfunction, the liver adaptive capacity can be impaired. Low adaptive liver capacity causes increase in incidence cytostatic-induced hepatotoxic reactions, which in turn causes the necessity to decrease the therapeutic dosage of a chemotherapeutic agent. In most cases, exactly the hepatotoxic effect of a cytostatic agent is the cause of CT discontinuation [5].

Therefore, the prophylaxis of chemotherapy-induced injuries, primarily of liver injury, emerges as an important issue in patients that undergo CT. Effective prophylactic can significantly increase the efficacy of CT in this category of patients. Nowadays, L-ornithine-L-aspartate, is regarded as one of the optimal medications for adjuvant treatment in patients with MM that undergo CT, due to the positive impact on liver and kidney tissue, which allows to reduce the risk of hepatotoxic and nephrotoxic reactions [2]. In our study in patients that received L-ornithine-L-aspartate for adjuvant treatment, the abnormalities in liver enzyme tests were significantly lower as compared to group I. At the same time, the absence of hypercalcemia on the second examination can be explained by the effect of CT itself, which provided the beneficial impact through a decrease in a total tumour mass.

Conclusions

1. On initial examination in patients with MM abnormal biochemical liver markers were detected in 33.3 % (4/12) of patients in group I and in 25 % (3/12) of patients in group II, that were characterized predominantly by hepatocellular pattern.

2. Progression of MM is often accompanied by kidney injury. Before CT the creatinine level was elevated in 16.6 % (2/12) of patients in group I and in 25 % (3/12) of patients in group II. The mean blood creatinine level in patients of the I and II group were by 1.94 times ($p=0.0005$) and by 2.23 times ($p=0.0025$) higher compared to the control group.

3. CT was associated with development of functional liver injury. Abnormal liver function tests were determined in 75 % (9/12) of patients that underwent CT. In patients with MM of group I, CT was associated with an increased risk of hepatotoxic reactions as compared to the initial examination. (RR=2.25: 95 % CI 0.95–5.34; $p>0.05$).

4. In patients of group II, that received L-ornithine-L-aspartate for adjuvant treatment, abnormal liver function tests were determined in 1 (8.3 %) patient, which is characterized by increased GGT level. Thus, patients with MM of group II, that received L-ornithine-L-aspartate during CT, had a lower risk of cytostatic-induced hepatotoxic reactions (RR=0.11: 95 % CI 0.02–0.74; $p<0.05$). Thus, it is possible to conclude that application of L-ornithine-L-aspartate as an adjuvant treatment in patients with MM that undergo CT, provides the effective prophylactic of pathological alterations in liver and kidney functional state.

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