2. Barone N, Safran T, Vorstenbosch J, Davison PG, Cugno S, Murphy AM. Current Advances in Hypertrophic Scar and Keloid Management. Semin Plast Surg. 2021; 35(3):145–152. doi:10.1055/s–0041–1731461.
3. Belfry KD, Deibel SH, Kolla NJ. Time of Day Matters: An Exploratory Assessment of Chronotype in a Forensic Psychiatric Hospital. Front Psychiatry. 2020; 11:550597. Published 2020 Dec 18. doi:10.3389/fpsyt.2020.550597.
4. Cardinali DP, Brown GM, Pandi-Perumal SR. Chronotherapy. Handb Clin Neurol. 2021;179:357–370. doi:10.1016/B978–0–12–819975–6.00023–6.
5. Gauglitz GG. Management of keloids and hypertrophic scars: current and emerging options. Clin Cosmet Investig Dermatol. 2013 Apr 24;6:103–14. doi: 10.2147/CCID.S35252. PMID: 23637546; PMCID: PMC3639020.
6. Montaruli A, Castelli L, Mulè A, Scurati R, Esposito F, Galasso L, et al. Biological Rhythm and Chronotype: New Perspectives in Health. Biomolecules. 2021; 11(4):487. https://doi.org/10.3390/biom11040487.
7. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound Healing: A Cellular Perspective. Physiol Rev. 2019;99(1):665–706. doi:10.1152/physrev.00067.2017.
8. Roveda E, Montaruli A, Galasso L, Pesenti C, Bruno E, Pasanisi P, et al. Rest–activity Circadian Rhythm and Sleep Quality in Patients with Binge Eating Disorder. Chronobiol. Int. 2018;35:198–207. doi: 10.1080/07420528.2017.1392549.
9. Roy T, Chavez J, R Reid R. Skin Deep: Perception of Scars After Cranial Vault Reconstruction. Cleft Palate Craniofac J. 2021;58(11):1376–1381. doi:10.1177/1055665620984349.
10. Yang S, Luo YJ, Luo C. Network Meta-Analysis of Different Clinical Commonly Used Drugs for the Treatment of Hypertrophic Scar and Keloid. Front Med (Lausanne). 2021;8:691628. Published 2021 Sep 9. doi:10.3389/fmed.2021.691628.

Стаття надійшла 3.04.2021 р.

DOI 10.26724/2079-8334-2022-2-80-146-150
UDC (616.36:616.155.392)-056.5

I.M. Skrypnyk, G.S. Maslova, T.V. Lymanets
Poltava State Medical University, Poltava

OVERWEIGHT AND OBESITY AS RISK FACTORS FOR CHEMOTHERAPY-INDUCED HEPATOTOXICITY IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

e-mail: maslovaas1708@gmail.com

Obesity is one of the proven risk factors for all types of tumors and is one of the reasons for reducing the effectiveness of specific chemotherapy and the development of chemotherapy-induced injury of liver. This article presents the results of functional liver state monitoring in patients with acute lymphoblastic leukemia during remission induction chemotherapy, taking into account the overweight and obesity. High toxicity of acute lymphoblastic leukemia chemotherapy regimens with a general tendency to hypoproteinemia development has been demonstrated. The overweight and obesity potentiate cytostatic-induced liver injury in patients with acute lymphoblastic leukemia with maximum risk in case of primary liver injury due to tumor exposure.

Key words: acute lymphoblastic leukemia, obesity, chemotherapy, L-asparaginase, liver injury.

І.М. Скрипник, Г.С. Маслова, Т.В. Лиманець

НАДЛИШКОВА ВАГА ТА ОЖИРІННЯ ЯК ФАКТОР РИЗИКУ ЦИТОСТАТИК ІНДУКОВАНИХ УРАЖЕНЬ ПЕЧІНКИ У ХВОРИХ НА ГОСТРУ ЛІМФОБЛАСТНУ ЛЕЙКЕМІЮ

Ожиріння належить до доведених факторів ризику розвитку всіх видів пухлин, а також є однією із причин зниження ефективності специфічної хіміотерапії, а також розвитку хіміотерапевтично індукованих уражень печінки. У даній статті наведені результати спостереження за функціональним станом печінки у хворих на гостру лімфобластну лейкемію у динаміці індукції ремісії з урахуванням надмірної ваги і ожиріння. Продемонстровано високу токсичність схем хіміотерапії гострих лімфобластних лейкемій із загальною тенденцією розвитку гіпопротеїнемії. Надмірна вага і ожиріння потенціюють розвиток цитостатикіндукованих уражень печінки у хворих на гостру лімфлбластну лейкемію із максимальним ризиком за умов первинних уражень печінки, зумовлених впливом пухлини.

Ключові слова: гостра лімфобластна лейкемія, ожиріння, хіміотерапія, L-аспарагіназа, ураження печінки.

The study is a fragment of the research project "Improvement of diagnostic methods, treatment and prophylaxis of internal organs drug induced lesions", state registration No 0121U113862.

In recent decades, there has been a global trend toward increasing the number of overweight and obese people. According to modern research, obesity is associated with an increased incidence of leukaemias in adults [2, 3, 6, 7]. Obesity has not been shown to affect the risk of developing acute lymphoblastic leukemia (ALL) in children. However, the presence of obesity leads to aggravation in overall and relapse-free survival in patients with ALL, both adults and children [3, 6, 12, 14]. It has been proven that children with obesity and ALL have a 50 % increased risk of recurrence compared to children with normal body weight [7].

An important mechanism of carcinogenesis in obese patients is chronic inflammation [9]. Adipocytes are able to produce proinflammatory cytokines such as interleukin (IL)-1b, IL-6, IL-7 and tumor necrosis factor, which leads to systemic inflammation and potentiates tumor development. Thus, high levels of IL-7 are observed in patients with T-cell ALL and are associated with resistance to glucocorticoids and cytostatics [6].

The optimal dose of chemotherapeutic drugs, included in the treatment regimens of cancer patients, is justified and confirmed by the results of randomized clinical trials. Strict adherence to doses and regimens of cytostatics can ensure the achievement of clinical and hematological remission, reduce the risk of early and late relapse in patients with ALL [11, 12]. In adult patients, the calculation of the chemotherapy (CT) doses is based on the body surface area (BSA). Numerous studies have shown convincing evidence of the impact of reducing the standard dose on the overall and relapse-free survival of cancer patients. During CT in obese patients in 40 % of cases, the calculation of the cytostatic dose is not based on actual weight. In this category of patients, physicians continue to use ideal body weight or adjusted body weight, namely 2.0 m^2, when assessing BSA, which is a significant risk factor for failing to respond to specific treatment. This tactic is due to the high probability of cytostatic-induced injury, which may be a limiting factor for CT [9, 10, 13, 15]. From this point of view, it is especially important to determine the risk factors for liver injury in the dynamics of specific therapy, separating the impact of oncohematological disease, obesity and the action of cytostatic drugs.

The purpose of the study was to assess the frequency and character of liver injury during remission induction chemotherapy in acute lymphoblastic leukemia patients with overweight and obesity.

Materials and methods. We examined 20 patients with newly diagnosed acute leukemia (AL), 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 55 % (11/20) males and 44 % (9/20) females. The general patient's condition by ECOG was I-II, and according to Karnofsky performance status scale – 60-80 %. The study included 20 patients with ALL L1, L2 variants according to the FAB classification [4, 8]. The BMI was calculated for all of them initially by the formula: BMI = weight (kg) / height (m^2). According to the European Guidelines for Obesity Management in 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 with ALL were further divided into groups:

I (n=10) – ALL patients with BMI 18.5–24.9 kg/m^2;

II (n=10) – ALL patients with BMI ≥25.0 kg/m^2.

All patients received CT in accordance with the Ministry of Health of Ukraine guidelines No. 647 from 30 Jul 2010. Patients with ALL underwent CT according to protocols GMALL 04/89 (D. Hoelzer) or BFM, the first remission induction phase (prednisolone, doxorubicin, vincristine, L-asparaginase) and the second remission induction phase (cyclophosphamide, cytarabine, 6-mercaptopurine) [4, 8].

The biochemical blood test parameters of all patients were evaluated twice: before CT and on the 56^{th} day: alanine (ALT), asparagine (AST) aminotransferases, gammaglutamyltranspeptidase (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.

Results of the study and their discussion. Against the background of a detailed clinical picture in ALL patients with overweight and obesity increased frequency and severity of cytostatic-induced hepatotoxic reactions was observed.

At baseline the liver injury was detected in 60 % (6/10) of patients of group I with ALL and normal BMI (2 people had a mixed syndrome, 2 – cholestatic, 1 – cytolytic syndrome, and in 1 patient a decreased total protein in the blood serum was noticed) (Table 2). Before CT in patients of group I, the activity of ALT in the blood serum was 2.4-fold higher (p=0.04), AST – 1.7-fold (p=0.01), GGT – 2-fold (p=0.002)

and ALP – 1.8-fold (p=0.002) higher compared to the norm (table 1). The total protein and total bilirubin contents in the blood serum of group I patients did not significantly differ from almost healthy individuals (p>0.05).

Table 1

The biochemical blood analysis parameters in ALL patients during CT

Parameters	Almost healthy	I (n=10)		II (n=10)	
		Before CT	After CT	Before CT	After CT
ALT, U/l	14.65±1.03 95 % CI 12.50–16.80	35.60±7.66 95 % CI 18.27–52.93	71.71±18.19 95 % CI 30.56–112.9	48.70±9.47 95 % CI 27.27–70.13	91.90±22.44 95 % CI 41.13–142.7
p		p_1>0.05 p_2=0.04	p_3=0.009	p_1>0.05 p_2=0.03	p_3=0.002
AST, U/l	18.75±0.83 95% CI 17.01–20.49	32.96±5.12 95 % CI 21.37–44.55	32.50±5.28 95 % CI 20.56–44.44	43.10±8.63 95 % CI 23.58–62.62	47.10±20.96 95 % CI 17.03–94.51
p		p_1>0.05 p_2=0.01	p_3=0.01	p_1>0.05 p_2=0.02	p_3=0.03
Total protein, g/l	14.65±1.03 95% CI 12.50–16.80	71.11±2.06 95 % CI 66.44–75.78	62.72±3.79 95 % CI 54.13–71.31	71.49±2.27 95 % CI 66.35–76.63	61.69±2.21 95 % CI 56.69–66.69
p		p_1=0.04 p_2>0.05	p_3=0.04	p_1=0.009 p_2>0.05	p_3=0.01
GGT, U/l	21.10±0.47 95 % CI 20.11–22.09	42.20±4.10 95 % CI 32.92–51.48	102.6±21.23 95 % CI 54.57–150.6	77.90±22.59 95 % CI 26.81–129.0	132.8±20.96 95 % CI 85.39–180.2
p		p_1=0.01 p_2=0.002	p_3=0.005	p_1>0.05 p_2=0.003	p_3=0.002
ALP, U/l .	61.35±4.31 95 % CI 52.34–70.36	109.1±16.56 95 % CI 97.82–173.4	142.8±18.23 95 % CI 101.6–184.0	111.9±12.20 95 % CI 84.30–139.5	205.3±56.64 95 % CI 77.17–333.4
p		p_1>0.05 p_2=0.002	p_3=0.002	p_1>0.05 p_2=0.02	p_3=0.003
Total bilirubin, µmol/l	9.80±0.63 95 % CI 8.48–11.12	8.23±1.72 95 % CI 4.34–12.12	15.63±3.85 95 % CI 6.92–24.34	14.68±2.15 95 % CI 9.81–19.55	21.02±5.61 95 % CI 8.32–33.72
p		p_1=0.04 p_2>0.05	p_3>0.05	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.

The liver injury was detected in 40% (4/10) of overweight and obese ALL patients of group II at initial examination (3 of them had cytolytic syndrome, 1 – mixed) (table 2).

Table 2

The incidence and relative risk of cytostatic-induced hepatotoxic reactions in ALL patients

Parameters	I (n=10)		II (n=10)	
	Before CT (number of patients, %)	After CT (number of patients, %)	Before CT (number of patients, %)	After CT (number of patients, %)
ALT, U/l	3 (30 %)	7 (70 %)	4 (40 %)	6 (60 %)
RR (95 % CI)	RR=2.33; 95 % CI=0.83–6.54; p>0.05		RR=1.00; 95 % CI=0.48–2.05; p>0.05	
AST, U/l	1 (10 %)	1 (10 %)	4 (40 %)	2 (20 %)
RR (95 % CI)	–		RR=0.50; 95 % CI=0.11–2.14; p>0.05	
Total protein, g/l	1 (10 %)	5 (50 %)	2 (20 %)	6 (60 %)
RR (95 % CI)	RR=5.00; 95 % CI=0.70–35.49; p>0.05		RR=3.00; 95 % CI=0.78–11.44; p>0.05	
GGT, U/l	2 (20 %)	9 (90 %)	7 (70 %)	9 (90 %)
RR (95 % CI)	RR=4.50; 95 % CI=1.28–15.81; p<0.05		RR=1.28; 95 % CI=0.81–2.03; p>0.05	
ALP, U/l	3 (30 %)	4 (40 %)	3 (30 %)	5 (50 %)
RR (95 % CI)	RR=1.33; 95 % CI=0.39–4.48; p>0.05		RR=1.67; 95 % CI=0.54–5.17; p>0.05	
Total bilirubin, µmol/l	1 (10 %)	3 (30 %)	1 (10 %)	4 (40 %)
RR (95 % CI)	RR=3.00; CI=0.37–24.17; p>0.05		RR=4.00; 95 % CI=0.53–29.8; p>0.05	

Note: p – relative risk significant difference

The total protein and total bilirubin contents in the blood serum of group II patients did not significantly differ from almost healthy individuals (p> 0.05). However, the ALT, AST, GGT and ALP

activity in the blood serum of these patients before CT was 3.3-fold higher (p=0.02), 2.3-fold (p=0.02), 3.7-fold (p=0.003) and 1.8-fold (p=0.02) higher, respectively, compared with the norm.

After the first and second phases of remission induction CT in group I liver injury was recorded in 90 % (9/10) of patients (7 people had a mixed syndrome, 2 – cholestatic syndrome), and 55.6 % (5/9) of them revealed a decreased serum total protein level. The overall risk of liver injury associated with CT in patients of group I did not significantly increase (RR=1.50; 95 % SI=0.87-2.59; p>0.05). All indices were within the grade I toxicity limits according to CTCAE.

The ALT, AST and ALP activity in the blood serum of group I patients after CT exceeded the norm by 4.9 times (p=0.009), by 1.7 times (p=0.01) and by 2.3 times (p=0.002) respectively, without significant changes compared to baseline (p>0.05).

However, after remission induction CT in patients of group I decreased level of serum total protein was revealed: 1.13-fold lower (p=0.04) compared with the initial examination and 1.2-fold lower (p=0.04) compared with almost healthy. The risk of hypoproteinemia development during CT depended on the primary level of serum total protein in patients with ALL and normal BMI. There was a direct correlation between the serum total protein before and after induction CT in patients of group I (r=+0.8; p=0.005 by Pearson).

Induction CT in patients of group I with ALL and normal BMI is the risk factor for increased GGT activity (RR=4.50; 95% SI=1.28-15.81; p<0.05). On the 56th day, the serum GGT activity in patients of group I increased 2.4 times (p=0.005) compared with the baseline and in 4.8 times (p=0.005) compared with almost healthy individuals. Simultaneously, the total serum bilirubin content increased in 1.9 times (p=0.04) after induction CT in patients of group I compared with the initial examination. The risk of hyperbilirubinemia development during CT depended on the primary level of total serum bilirubin in patients with ALL and normal BMI. There was a direct correlation between the total bilirubin in the blood serum before and after CT in patients of group I (r=+0.66; p=0.04 by Pearson).

The overweight and obesity presence in patients with ALL of group II contributed to an increase in the frequency of the hepatotoxic reaction and their severity according to CTCAE. After CT, liver injury was detected in 9 (90 %) patients of group II (2 of them had the cytolytic syndrome, 5 – mixed syndrome, and 2 – had cholestatic syndrome). CT was a risk factor for cytostatic-induced hepatotoxic reactions in patients with overweight and obesity (RR=2.25; 95 % SI=1.02-4.94; p<0.05). In addition, after CT in 3 patients of group II, ALT activity was recorded at the level of grade II by CTCAE, other indicators did not exceed grade I toxicity by CTCAE.

On the 56th day of treatment in patients of group II, the ALT, AST, GGT and APL activity exceeded the norm by 6.3 times (p=0.003), by 2.5 times (p=0.03), by 6.3 times (p=0.002) and by 3.3 times (p=0.003), respectively, without significant differences compared to the baseline data.

It is important that the ALL induction CT was accompanied by a decrease in serum total protein in 1.18 times (p=0.009) compared with the initial examination and 1.18 times (p=0.01) compared with almost healthy individuals. In patients of group II after remission induction treatment an association of increased GGT activity and hypoproteinemia development was revealed, which is confirmed by the inverse correlation between GGT activity and the total protein content in the blood serum (r=-0.71; p=0.01 by Pearson).

There were no significant changes in the total serum bilirubin on the 56th day of treatment in patients of group II compared with the baseline (p>0.05). However, there was a direct correlation between the ALP activity and the total serum bilirubin in patients with ALL of group II after CT (r=+0.69; p=0.02 by Pearson).

Thus, the detailed clinical picture of ALL was associated with an increased risk of impaired biochemical liver tests in patients with normal BMI, as well as against the background of overweight and obesity. We can explain this fact by the influence of oncohematological disease, namely intoxication, tumor infiltration of the liver tissue. Our results coincide with the data of other researchers, which confirm the high risk injury of the body organs and systems due to cancer progression, including the manifesto of ALL [6, 10, 13, 15].

Remission induction CT of ALL have high toxicity, which is confirmed by the increased frequency and severity of biochemical liver tests violations. We have revealed a high risk of increased GGT activity in patients with ALL with normal BMI and an increased overall risk of hepatotoxic reactions in overweight and obese patients. Our results are consistent with the data of other researchers, which confirms the increased risk of CT complications in cancer patients who are overweight and obese [2, 3, 9, 11, 12, 14].

The pecularity of chemotherapy-induced liver injury in ALL patients is the hypoproteinemia development. This is due to the action of L-asparaginase, which disrupts protein metabolism, reducing the

availability of asparagine and glutamine for tumor cells. The main antitumor effect of L-asparaginase leads in parallel to the formation of hypoproteinemia [1, 5]. It is important that the level of biochemical liver tests after cytostatic therapy primarily depended on their baseline value, which must be taken into account for supportive therapy in this category of patients.

Conclusions

1. Remission induction CT in ALL patients of group I decreased level of serum total protein was revealed: 1.13-fold lower (p=0.04) compared with the initial examination and 1.2-fold lower (p=0.04) compared with almost healthy.

2. The increased GGT activity after two induction CT cycles in patients of group I with ALL was a risk factor for liver injury (RR=4.50; 95 % SI=1.28-15.81; p<0.05), the serum GGT activity in patients increased in 2.4 times (p=0.005) compared with the baseline and in 4.8 times (p=0.005) compared with almost healthy individuals.

3. The overweight and obesity potentiate the cytostatic-induced hepatotoxic reactions in ALL patients (RR=2.25; 95 % SI=1.02-4.94; p<0.05), this was confirmed by the ALT, AST, GGT and APL activity, that exceeded the norm in 6.3 times (p=0.003), 2.5 times (p=0.03), 6.3 times (p=0.002) and 3.3 times (p=0.003), respectively, without significant differences compared to the baseline data.

References

1. Alachkar H, Fulton N, Sanford B, Malnassy G, Mutonga M, Larson RA, et al. Expression and polymorphism (rs4880) of mitochondrial superoxide dismutase (SOD2) and asparaginase induced hepatotoxicity in adult patients with acute lymphoblastic leukemia. Pharmacogenomics Journal. 2017;17(3):274–9. doi: 10.1038/tpj.2016.7

2. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003; 348(17):1625–38.

3. Castillo JJ, Reagan JL, Ingham RR, Furman M, Dalia S, Merhi B, et al. Obesity but not overweight increases the incidence and mortality of leukemia in adults: a meta-analysis of prospective cohort studies. Leuk Res. 2012; 36(7):868–75. doi: 10.1016/j.leukres.2011.12.020

4. Chiaretti S, Zini G, Bassan R. Diagnosis and subclassification of acute lymphoblastic leukemia. Mediterr J Hematol Infect Dis. 2014;6:e2014073.

5. De Santo C, Booth S, Vardon A, Cousins A, Tubb V, Perry T, et al. The arginine metabolome in acute lymphoblastic leukemia can be targeted by the pegylated-recombinant arginase I BCT-100. Int J Cancer. 2018;142(7):1490–502. doi: 10.1002/ijc.31170.

6. Griggs JJ, Mangu PB, Anderson H, Balaban EP, Dignam JJ, Hryniuk WM, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2012;30(13):1553–61. doi: 10.1200/JCO.2011.39.9436.

7. Ehsanipour EA, Sheng X, Behan JW, Wang X, Butturini A, Avramis VI, et al. Adipocytes cause leukemia cell resistance to L-Asparaginase via release of glutamine. Cancer Res. 2013;73(10):2998–3006. doi: 10.1158/0008-5472.CAN-12-4402.

8. Hoelzer D, Bassan R, Dombret H, Fielding A, Ribera JM, Buske C, et al. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5): 69–82. doi: 10.1093/annonc/mdw025.

9. Lin A , Othus M, McQuary A, Chi M, Estey E. Influence of obesity on efficacy and toxicity of induction chemotherapy in patients with newly diagnosed acute myeloid leukemia. Leuk Lymphoma. 2013;54(3):541–6. doi: 10.3109/10428194.2012.717278

10. Maslova G, Skrypnyk I, Lymanets T. The role of arginine/citrulline cycle disorders in the liver injury pathogenesis in acute myeloid leukemia patients with concomitant obesity. Annals of Oncology journal.2020 (31), S4: S655–656. DOI:10.1016/j.annonc.2020.08.022

11. Orgel E, Mueske NM, Sposto R, Gilsanz V, Freyer DR, Mittelman SD. Limitations of body mass index to assess body composition due to sarcopenic obesity during leukemia therapy. Leuk Lymphoma. 2018;59(1):138–45. doi: 10.3109/10428194.2015.1136741.

12. Orgel E, Sea JL, Mittelman SD. Mechanisms by Which Obesity Impacts Survival from Acute Lymphoblastic Leukemia. J Natl Cancer Inst Monogr. 2019; 2019(54):152–6. doi: 10.1093/jncimonographs/lgz020

13. Skrypnyk I, Maslova G. The Overweight role in the occurrence of hepatotoxic reactions during chemotherapy of acute leukemia. Sharing the future of digestive health. UEG Week. 2018; Abstr. of the 26 UEGW (October, 20-24, 2018); Vienna, Austria. 2018; 401–2. DOI:10.1016/S0618-8278(19)30842-4

14. Sheng X, Mittelman SD. The role of adipose tissue and obesity in causing treatment resistance of acute lymphoblastic leukemia. Front Pediatr. 2014; 2:53. doi: 10.3389/fped.2014.00053

15. Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy – associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg. 2007; 94(3):274–86. doi: 10.1002/bjs.5719.

Стаття надійшла 12.05.2021 р.