

HOW TO IMPROVE QUALITY OF LIFE IN PATIENTS WITH ACUTE LEUKEMIA AND COMORBID ISCHEMIC HEART DISEASE TREATED WITH ANTHRACYCLINE-BASED INDUCTION CHEMOTHERAPY

I. Skrypnyk¹, G. Maslova¹, T. Lymanets^{1, *}, I. Gusachenko²

¹Ukrainian Medical Stomatological Academy, Poltava 36011, Ukraine

²M.V. Sklifosovsky Poltava Regional Clinical Hospital, Poltava 36011, Ukraine

Aim: To evaluate the quality of life (QoL) parameters in patients with acute leukemia (AL) during standard induction chemotherapy, depending on the presence of concomitant ischemic heart disease and to improve them by the prevention of anthracycline cardiotoxicity with L-arginine. **Materials and Methods:** A total of 147 adult AL patients (72 males and 75 females with the mean age 54.7 ± 9.3 years) were enrolled in the study. QoL assessment was performed at baseline and after induction chemotherapy using SF-36 questionnaire. Both physical and mental parameters were evaluated. **Results:** The QoL analysis of patients with AL at the time of initial diagnosis showed extremely low QoL level in all subgroups compared with healthy individuals. It should be noted that the level of patients' QoL after achieving remission remained significantly lower than those of practically healthy, which is primarily due to the need for further long-term treatment and, probably, the fear of the disease relapse development. It was found that the administration of L-arginine during induction chemotherapy in order to reduce the risk of anthracycline cardiotoxicity development has allowed improving the QoL in patients with concomitant ischemic heart disease. **Conclusion:** L-arginine decreases the risk of anthracycline-induced myocardial injury and improves QoL in AL patients.

Key Words: quality of life, acute leukemia, ischemic heart disease, induction chemotherapy.

DOI: 10.32471/exp-oncology.2312-8852.vol-41-no-4.13906

Over the past decades, the development of oncohematology and implementation of new chemotherapy (CT) regimens have significantly altered both early and long-term outcomes for acute leukemia (AL) patients, extend the duration and improve the quality of life (QoL) of these patients. Anthracycline antibiotics (AA) are effective chemotherapeutic agents that are included in most CT regimens. One of the major problems in the treatment with anthracyclines continues to be cardiotoxicity, the severity of which sometimes may limit the possibility of specific therapy continuation [1]. The cardiotoxic effect of AA can significantly impair the patients' QoL, resulting in severe discomfort associated with subjective feelings of patients, which sometimes forces them to independently give up treatment. The lack of cytostatic therapy in target doses and drug administration regimens reduces patients' chances of achieving clinical and hematologic remission, and respectively, long-term, disease-free survival.

AL in adults is associated with poor clinical prognosis and treatment outcomes, with only 26% of patients achieving 5-year survival after diagnosis of acute myeloid leukemia (AML) [2]. For patients with AL diagnosis, aggressive CT with AA inclusion and bone marrow transplantation remain to be the most effective treatment options that often require long hospitalization and are accompanied by the development of serious side

effects, including anthracycline cardiotoxicity (AC). The severe general condition of the patients, the separation from the usual environment, the loss of social status, the need for prolonged exhausting treatment, disability, the threat of death adversely affect the psycho-emotional state of patients, violate the system of values, lead to the destruction of many plans and loss of hope. Violation of the mental status of patients affects the course of the underlying disease, significantly worsens the prognosis of leukemia and achieving compliance between patient and doctor, which is essential for a positive outcome [3, 4]. Recently, QoL has become an increasingly important factor in evaluating the effectiveness of treatment, along with statistical parameters such as remission, disease-free survival and overall mortality [5–7]. In addition, understanding the patients' QoL can help to identify the level of their adaptation to the disease and determine the need for appointment of concomitant therapy both during and after the end of CT [2, 8–11].

Recently, in Ukraine rapidly increased the number of research on QoL of oncohematological patients. In the world of hematological science, QoL is used as one of the criteria for evaluating the effectiveness of different treatment programs, new medications and for individual monitoring of patient's condition [6, 10, 12].

AL is a severe somatic disease that, in combination with concomitant ischemic heart disease (IHD), as a risk factor for anthracycline myocardial injury, can significantly affect the physical, emotional and social components of the health and vital activity of patients, which, in our opinion, definitely necessary to take into account in the complex treatment of this type of syndrome [13]. The NO-donor — L-arginine significantly improves endothelial function in patients with IHD

Submitted: December 10, 2018.

*Correspondence: E-mail: tlymanets@gmail.com

Abbreviations used: AA – anthracycline antibiotics; AC – anthracycline cardiotoxicity; AL – acute leukemia; ALL – acute lymphoid leukemia; AML – acute myeloid leukemia; CT – chemotherapy; ECG – electrocardiography; IHD – ischemic heart disease; LVEF – left ventricular ejection fraction; QoL – quality of life; SF-36 – Short Form Medical Outcomes Study 36.

and decreases the risk of cardiac injury by AA [1]. Considering the mechanism of L-arginine cardioprotective effect, we think that its administration during induction courses of CT can improve QoL in AL patients with comorbid IHD by preventing the AC development.

The aim of the study was to evaluate the QoL parameters in patients with AL during standard induction CT, depending on the presence of concomitant IHD and to improve them by the prevention of AC with L-arginine.

MATERIALS AND METHODS

The study involved 147 patients with newly diagnosed AL, who achieved remission after two courses of induction CT. The cohort consisted of 72 (49%) males and 75 (51%) females, the mean age 54.7 ± 9.3 years, by Eastern Cooperative Oncology Group scale I–II, 60–80% by Karnovsky index. All patients were on inpatient treatment at the Hematological Department of the M.V. Sklifosovsky Poltava Regional Clinical Hospital. The recruitment period lasted since 2011 till 2017.

Patients presented primarily with AML 111 (75.5%). The AML according to FAB classification was M_{0-2} in 36 (32.4%) cases; M_3 — in 6 (5.4%); M_4 — in 38 (34.2%); M_5 — in 31 (28%) cases. Patients with AML received standard induction CT “7+3” or “5+2”. The M_3 -promyelocytic AML variant was additionally treated with tretinoin, the M_4 -myelomonoblastic and M_5 -monoblastic — with etoposide.

Acute lymphoid leukemia (ALL) represented 36 (24.5%) of the observations, with L_1 according to FAB classification identified in 23 (63.9%) of the cases and L_2 — in 13 (36.1%). ALL patients were treated with standard BFM regimen, containing prednisolone, vincristine, doxorubicin and asparaginase.

Depending on the IHD concomitant presence, the patients were divided into two groups: I ($n = 81$) — AL patients without concomitant cardiovascular diseases; II ($n = 66$) — AL patients with concomitant IHD. The AC prevention was realized by L-arginine hydrochloride 4.2% 100 ml intravenously the day before and in the days of AA infusion, followed by oral L-arginine aspartate 5 ml three times a day during one month. Due to ongoing prevention of anthracycline-induced myocardial injury patients in both groups were further divided into subgroups: IA ($n = 47$) and IIA ($n = 36$) — patients receiving CT without L-arginine; IB ($n = 34$) and IIB ($n = 30$) — patients with AL, who received CT and prophylaxis of AC by L-arginine. The control group consisted of 18 healthy individuals (10 men and 8 women, mean age 22.5 ± 2.1 years).

In a comparative aspect, the assessment of the patients' condition in all groups was performed twice: at baseline and after the 2nd course of induction CT, when remission was achieved and AA low cumulative doses <200 mg/m² equivalent to doxorubicin were reached. There were no clinically significant differences between the reached doses in the groups.

The study was approved by the local ethical committee and all patients had given a written consent before they were included in the study.

The cardiotoxic effect of AA was evaluated by echocardiography and Holter electrocardiography (ECG) monitoring and considered to be according to Common Terminology Criteria for Adverse Events 4.03 as reduction of left ventricular ejection fraction (LVEF) more than 10% of baseline and QTc , calculated by Bazett, prolongation exceeded 450 ms. Additionally, the episodes of “silent ischemia” were assessed on the basis of ST segment depression by 1 mm or more in the absence of typical pain syndrome.

To study the patients' QoL the Short Form Medical Outcomes Study 36 (SF-36) questionnaire was used, with the evaluation of physical and mental components of life quality. SF36v2 license QM038232 was provided by Optum.

The calculation and statistical analysis of the SF-36 questionnaire results was carried out using a computer program QualityMetric's Scoring Software 4.5 [14, 15]. Differences were regarded statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

According to Holter ECG monitoring there were no changes of ST segment and QTc interval in patients of both subgroups of group I without concomitant IHD. In the presence of comorbid IHD the short-term episodes of ST segment depression were diagnosed in 8 (22.2%) patients and 5 (16.7%) patients of subgroups IIA and IIB respectively that developed in conditions of increased physical activity and were not accompanied by a typical pain syndrome in clinic. According to echocardiography, the patients of all subgroups at the time of AL diagnosis had no signs of systolic dysfunction.

The QoL analysis of patients with AL at the time of initial diagnosis of leukemia, regardless of concomitant cardiovascular diseases, showed extremely low QoL levels in all subgroups. Before CT in patients, there were significantly lower rates for all the estimated parameters, including the scales for summary indicators of the physical and mental QoL components, compared with healthy respondents (Table). The physical status in patients of all subgroups was by 1.5 times lower ($p < 0.05$) vs normal values. The general indicator of mental status in comparison with practically healthy respondents in subgroup IA was by 1.9 times lower ($p < 0.05$); in subgroup IB — by 1.8 times ($p < 0.05$), in subgroup IIA — by 1.8 times ($p < 0.05$) and in subgroup IIB — by 1.9 times ($p < 0.05$) less than normal values (see Table). We did not find the dependence of the influence of concomitant IHD on the QoL level in the beginning of AL, which can be explained by the severity of the underlying disease and its rapid onset.

After induction CT all the patients were tested again. Cumulative AA doses equivalent to doxorubicin reached (174.07 ± 22.13) mg/m², (162.04 ± 24.65) mg/m², (179.20 ± 19.24) mg/m² and (166.49 ± 27.34) mg/m² in patients of groups IA, IIA, IB and IIB respectively ($p > 0.05$).

The Holter ECG monitoring has shown an increased number of painless myocardial ischemia periods in 29 (80.5%) patients of subgroup IIA vs 8 (22.2%)

Table. QoL in patients with AL, depending on the presence of concomitant IHD before and after two courses of induction CT in conditions of AC prevention

SF-36 scale	Practically healthy (n = 18)	IA (n=47)		IB (n=34)		IIA (n=36)		IIB (n=30)		
		Before CT	After induction CT	Before CT	After induction CT	Before CT	After induction CT	Before CT	After induction CT	
SF-36 V2 Norm-Based Scales										
Physical functioning	55.3 ± 2.8	37.9 ± 2.6*	46.6 ± 2.0*√	38.1 ± 2.4*	48.5 ± 1.3*√	34.5 ± 2.7*	41.7 ± 1.4*√#	36.4 ± 2.0*	41.9 ± 2.8*#	
Role physical	54.3 ± 1.2	30.4 ± 2.3*	42.9 ± 3.1*√	32.7 ± 2.6*	43.9 ± 2.0*√	32.1 ± 2.2*	37.2 ± 2.1*	34.2 ± 1.3*	41.7 ± 2.8*√	
Bodily pain	57.6 ± 3.7	39.4 ± 3.5*	46.6 ± 2.8*	39.9 ± 2.0*	52.1 ± 2.2√	39.4 ± 1.8*	44.2 ± 3.7*	38.6 ± 1.4*	44.7 ± 1.0*√#	
General health	57.9 ± 3.5	28.9 ± 1.8*	35.1 ± 1.1*√	29.4 ± 2.6*	37.1 ± 2.3*√	26.8 ± 2.2*	32.3 ± 1.1*√	29.3 ± 2.1*	33.1 ± 2.3*	
Vitality	60.4 ± 2.4	31.3 ± 1.4*	45.5 ± 2.8*√	32.9 ± 1.8*	45.97 ± 1.6*√	33.8 ± 1.3*	43.3 ± 3.0*√	30.6 ± 2.5*	42.1 ± 2.2*√	
Social functioning	51.1 ± 2.4	31.7 ± 2.8*	38.2 ± 1.7*	32.9 ± 2.3*	38.5 ± 1.8*	29.5 ± 2.4*	35.2 ± 2.7*	29.8 ± 2.7*	37.1 ± 2.9*	
Role emotional	49.9 ± 2.4	29.2 ± 3.7*	42.6 ± 2.1*√	30.8 ± 3.8*	43.4 ± 2.0*√	28.4 ± 2.6*	36.2 ± 3.8*	31.5 ± 3.0*	40.9 ± 3.1*√	
Mental health	53.8 ± 3.4	27.1 ± 3.1*	42.1 ± 2.1*√	28.1 ± 2.2*	42.9 ± 2.1*√	28.9 ± 3.3*	38.7 ± 2.1*√	27.5 ± 3.6*	35.9 ± 3.3*	
SF-36 V2 summary scores										
Physical component summary	57.5 ± 1.3	37.9 ± 2.6*	44.4 ± 3.0*	38.7 ± 1.8*	47.5 ± 1.1*√	36.4 ± 2.3*	40.8 ± 2.6*	37.9 ± 2.4*	42.5 ± 2.6*	
Mental component summary	51.6 ± 3.3	27.1 ± 2.8*	40.9 ± 2.2*√	28.6 ± 2.1*	40.7 ± 1.2*√	28.3 ± 2.4*	37.3 ± 2.8*√	27.6 ± 3.0*	37.6 ± 3.5*√	

Note: significant differences ($p < 0.05$); * – between practically healthy and in the groups; √ – between indicators before and after induction CT in every group; # – between indicators in groups I and II after CT in relevant subgroups.

before treatment; $p < 0.001$. *QTc* prolongation was noticed in 14 (38.8%) patients of subgroup IIA vs 7 (14.9%) of subgroup IA without IHD; $p < 0.05$. The presence of IHD was a risk factor for AC development, the manifestations of which are prolongation of *QTc* interval (OR = 3.636; 95% CI = 1.278–10.349; $p < 0.05$) and *QRS* voltage decrease (OR = 3.482; 95% CI = 1.270–9.549; $p < 0.05$). Echocardiography showed LVEF reduction more than 10% of baseline in 13 (36%) patients of subgroup IIA, without a significant difference vs subgroup IA. The echocardiography changes received in this study are consistent with the results of Sawaya *et al.* and Thakur *et al.* [16, 17].

It had been shown that when remission was achieved, the patient's general condition, clinical and laboratory data were getting better, however, the indicators of QoL, while improving, remained significantly lower than normal values. Our results are consistent with previously published data of Ukrainian researchers, who studied the QoL of patients with AL [5, 12]. In patients of subgroup IA without concomitant cardiovascular diseases, who did not receive AC prophylaxis, following indices significantly increased: their physical functioning rates by 1.2 times ($p < 0.05$); the role of physical problems in life limiting — by 1.4 times ($p < 0.05$); the general health — by 1.2 times ($p < 0.05$); vitality — by 1.5 times ($p < 0.05$); the role of emotional problems in life limiting — by 1.5 times ($p < 0.05$); mental health — by 1.6 times ($p < 0.05$). Regarding the summary indicators, statistically significant changes were recorded only in the improvement of the mental status by 1.5 times ($p < 0.05$); while the physical status of patients in subgroup IA did not change significantly (see Table).

When re-evaluating QoL in patients of subgroup IIA with concomitant IHD a similar pattern of change was revealed. Compared with the data before treatment, parameters of physical functioning improved by 1.2 times ($p < 0.05$); the general health — by 1.2 times ($p < 0.05$); the vitality — by 1.3 times ($p < 0.05$); the mental health — by 1.3 times ($p < 0.05$). On summary scales, a picture similar to the data of the subgroup IA was also noticed. Reliable improvement was achieved only in mental status by 1.3 times

($p < 0.05$) without statistically significant changes in physical QoL component (see Table).

It should be noted that the level of patients' QoL in subgroups IA and IIA after achieving remission remained significantly lower than that of practically healthy individuals, which is primarily due to the need for further long-term treatment and, probably, the fear of the disease relapse development. The presence of concomitant IHD did not significantly affect the QoL level. Although the lowest QoL rates after induction CT were observed in patients of subgroup IIA, a significant difference with the data of subgroup IA patients, who did not have concomitant cardiovascular diseases, was found only between the levels of physical functioning ($p < 0.05$) without statistically significant changes of the summary physical component (see Table).

The best QoL scores were obtained in patients of subgroup IB, who did not have concomitant cardiovascular diseases and received L-arginine. After induction CT in patients of this subgroup, the indicators of QoL improved in the following categories: physical functioning — by 1.3 times ($p < 0.05$), the role of physical problems in life limiting — by 1.3 times ($p < 0.05$), the bodily pain — by 1.3 times ($p < 0.05$), the general health — by 1.3 times ($p < 0.05$), the vitality — by 1.4 times ($p < 0.05$), the role of emotional problems in life limiting — by 1.4 times ($p < 0.05$), mental health — by 1.5 times ($p < 0.05$). There was an improvement both in the mental and physical summary components of QoL in patients of subgroup IB, compared with the baseline indicators. The mental status of these patients improved by 1.4 times ($p < 0.05$), physical — by 1.2 times ($p < 0.05$). It must be emphasized that the parameter of bodily pain in patients of subgroup IB, which improved by 1.3 times vs baseline level ($p < 0.05$), had no statistical difference vs practically healthy level.

L-arginine in patients of group IIB with AL and concomitant IHD has reduced the frequency of "silent ischemia", according to Holter ECG monitoring, by 40.5%; $p < 0.05$, *QTc* interval prolongation — by 28.8%; $p < 0.05$, and according to echocardiography, LVEF decrease more than 10% of baseline — by 22.7%; $p < 0.05$. The absence of L-arginine prophylaxis was a risk factor for AC: painless *ST* segment depression (OR = 6.214;

95% CI = 2.064–18.710; $p < 0.05$); QTc prolongation (OR = 5.727; 95% CI = 1.458–22.497; $p < 0.05$) and decreased LVEF more than 10% of baseline (OR = 3.674; 95% CI = 1.049–12.865; $p < 0.05$). There was no systolic dysfunction in patients of this group with concomitant IHD, who received L-arginine during induction CT.

The administration of L-arginine during induction CT in order to reduce the risk of AC development has allowed improving the QoL in patients of subgroup IIB with concomitant IHD. The bodily pain parameter improved by 1.1 times ($p < 0.05$), the role of physical problems in life-limiting activity — by 1.2 times ($p < 0.05$), the vitality — by 1.4 times ($p < 0.05$), the role of emotional problems — by 1.3 times ($p < 0.05$). The summary physical component of life quality in patients of subgroup IIB has not significantly changed. At the same time, the mental status of these patients improved by 1.4 times ($p < 0.05$), maintaining a statistically significant difference vs control group parameters.

CONCLUSIONS

Thus, AL plays a critical role in the QoL impairing in patients at the beginning of the disease before CT initiation. With a decrease in the symptoms of the underlying disease, there is progressive gradual improvement of the QoL indicators of these patients.

The presence of concomitant IHD and the high risk of anthracycline-induced myocardial injury significantly affect the QoL parameters in patients with AL in the dynamics of induction CT. The prophylactic administration of L-arginine during remission induction courses significantly reduces the risk of AC development and improves the QoL of patients with AL and comorbid IHD. QoL was evaluated with the help of the SF-36 questionnaire, which should be used in patients with AL of high cardiological risk group in order to assess the QoL during induction CT.

REFERENCES

1. Skrypnyk I, Maslova G, Lymanets T, *et al.* L-arginine is an effective medication for prevention of endothelial dysfunction, a predictor of anthracycline cardiotoxicity in patients with acute leukemia. *Exp Oncol* 2017; **39**: 308–11.
2. Korol E, Wang S, Johnson K, *et al.* Health-related quality of life of patients with acute myeloid leukemia: a systematic literature review. *Oncol Ther* 2017; **5**: 1–16.
3. Maslova GS. Assessment of anxiety and depressive disorders in patients with haemoblastosis and modern methods of their correction. *Svit Med Biol* 2009; **3**: 191–5 (in Ukrainian).
4. Skrypnyk IM, Maslova GS. Contemporary approaches to appraisal of physiological health status and quality of life of oncohaematological patients. Significance and place of antidepressants in complex treatment. *Crimean J Internal Dis* 2008; **1**: 92–5 (in Ukrainian).
5. Goryainova NV, Basova OV, Tretyak NM, *et al.* Quality of life of acute leukemia using different chemotherapy programs. *Ukr J Hematol Transfus* 2015; **38**: 114–25 (in Ukrainian).
6. Kryachok I, Tytorenko I. The study of quality of life in elderly patients with non-Hodgkin's lymphomas. *Ukr J Hematol Transfus* 2015; **38**: 195–204 (in Ukrainian).
7. Slovacek L, Slovackova B, Jebavy L. Global quality of life in patients who have undergone the hemapoietic stem cell transplantation: finding from transversal and retrospective study. *Exp Oncol* 2005; **27**: 238–42.
8. Efficace F, Novik A, Vignetti M. Health-related quality of life and symptom assessment in clinical research of patients with hematologic malignancies: where are we now and where do we go from here? *Haematologica* 2007; **92**: 1596–8.
9. Moller T, Adamsen L, Appel C. Health related quality of life and impact of infectious comorbidity in outpatient management of patients with acute leukemia. *Leuk Lymphoma* 2012; **53**: 1896–904.
10. Oliva EN, Nobile F, Alimena G. Quality of life in elderly patients with acute myeloid leukemia: patients may be more accurate than physicians. *Haematologica* 2011; **96**: 696–702.
11. Sekers MA, Stone RM, Zahrieh D, *et al.* Decision-making and quality of life in older adults with acute myeloid leukemia or advanced myelodysplastic syndrome. *Leukemia* 2004; **18**: 809–26.
12. Tretyak NM, Basova OV, Goryainova NV. Substantiation of the study of quality of life in patients with leukemia in Ukraine. *Ukr J Hematol Transfus* 2012; **36**: 278–85 (in Ukrainian).
13. Lymanets T, Skrypnyk I, Maslova G, *et al.* Quality of life in acute leukemia patients with comorbid ischemic heart disease. *Abstract Book of the 23rd EHA Congress*; 2018 Jun 14–17; Stockholm. *HemaSphere* **2** (S1); 2018: 452.
14. Amirjanova VN, Goryachov DV, Korshunov NI. SF-36 questionnaire population quality of life indices. *Rheumatol Sci Pract* 2008; **1**: 36–48 (in Russian).
15. Maruish ME. User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated, 2011. 330 p.
16. Sawaya H, Sebag A, Plana JC, *et al.* Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes and trastuzumab. *Circ Cardiovasc Imaging* 2012; **5**: 596–603.
17. Thakur A, Witteles RM. Cancer therapy-induced left ventricular dysfunction: interventions and prognosis. *J Cardiac Fail* 2014; **20**: 155–8.