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ORIGINAL ARTICLE

EXPRESSION PROFILE OF IMMUNOPHENOTYPIC MARKER MOLECULES ON B-LYMPHOCYTES IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AT THE STAGES OF IMMUNOCHEMOTHERAPY

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ABSTRACT

Purpose of the study. To study the expression of immunophenotypic marker molecules on B-lymphocytes of patients with chronic lymphocytic leukemia at the stages of immunochemotherapy while monitoring minimal residual disease.
Patients and methods. 20 patients with CLL were examined, who in the period 2019–2022 underwent 6 courses of immunochemotherapy (ICT) in the RB/FCR mode at the National Medical Research Centre for Oncology, Rostov-on-Don. Before, after 3, 6 courses of ICT, bone marrow immunophenotyping was performed by flow cytometry. The data is evaluated in Statistica 13.0.
Results. Before treatment, 3 groups of patients were identified depending on the expression of prognostic markers (CD38, ZAP-70, CD11c, CD25, FMC7). I (2 people) – without expression of CD38, ZAP-70, CD11c, CD25, FMC7 on tumor B-lymphocytes. II (14 people) – with variable expression of CD25, CD38 (0.4–47.6 % and 0.0–57.5 %, respectively), lack of expression of ZAP-70, CD11c, FMC7. III (4 people) – with high expression of CD38 (57.5–69.2 %), ZAP-70 (36.6–48.3 %), CD11c (20.0–96.5 %), CD25 (64.9–92.7 %), FMC7 (13.6–88.6 %). After the 3rd course of ICT, the minimum residual disease (MRD): 0 % in group I, 0.48 ± 0.13 % in group II, 33.5 ± 7.84 % in group III. After the 6th course of ICT MRD: 0 % in group I, 0.42 ± 0.09 % in group II, 33.2 ± 8.07 % in group III. The expression of immunophenotypic markers in groups II and III remained unchanged after 3, 6 courses of ICT. According to the criteria for assessing the response to therapy (IWCLL, 2018), patients of groups I, II after the 6th course of ICT have complete remission, 3 patients of group III have partial remission, 1 patient has stabilization of the process. Preliminary data have been obtained indicating that the absence or increased expression of CD38, CD25, ZAP-70, CD11c, FMC7 on B-lymphocytes of CLL patients before treatment may predetermine the hematological response to therapy according to RB/FCR regimens.
Conclusion. Initially, increased expression of all prognostic antigens simultaneously: CD38, CD25, ZAP-70, CD11c, FMC7 on the tumor population of B-lymphocytes in patients with CLL is associated with an unsatisfactory response to treatment, which seems promising from the point of view of studying the effect of the analyzed marker molecules on achieving a hematological response at the stages of immunochemotherapy.

Keywords:
chronic lymphocytic leukemia, flow cytometry, minimal residual disease, immunophenotypic markers, immunochemotherapy

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ПРОФИЛЬ ЭКСПРЕССИИ ИММУНОФЕНОТИПИЧЕСКИХ МАРКЕРНЫХ МОЛЕКУЛ НА В-ЛИМФОЦИТАХ У БОЛЬНЫХ ХРОНИЧЕСКИМ ЛИМФОЛЕЙКОЗОМ НА ЭТАПАХ ИММУНОХИМИОТЕРАПИИ

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РЕЗЮМЕ

Цель исследования. Изучить экспрессию иммунофенотипических маркерных молекул на В-лимфоцитах больных хроническим лимфолейкозом на этапах иммунохимиотерапии при мониторинге минимальной остаточной болезни.
Пациенты и методы. Обследованы 20 больных ХЛЛ, которым в период 2019–2022 гг. проведено 6 курсов иммунохимиотерапии (ИХТ) в режиме RB/FCR в НМИЦ онкологии г. Ростова-на-Дону. До лечения, после 3, 6 курсов ИХТ выполнялось иммунофенотипирование костного мозга методом проточной цитофлюориметрии. Данные оценены в Statistica 13.0.
Результаты. До лечения в зависимости от экспрессии прогностических маркеров (CD38, ZAP-70, CD11c, CD25, FMC7) выделены 3 группы больных. I (2 чел.) – без экспрессии CD38, ZAP-70, CD11c, CD25, FMC7 на опухолевых В-лимфоцитах. II (14 чел.) – с вариабельной экспрессией CD25, CD38 (0,4–47,6 % и 0,0–57,5 %, соответственно), отсутствием экспрессии ZAP-70, CD11c, FMC7. III (4 чел.) – с высокой экспрессией CD38 (57,5–69,2 %), ZAP-70 (36,6–48,3 %), CD11c (20,0–96,5 %), CD25 (64,9–92,7 %), FMC7 (13,6–88,6 %). После 3 курса ИХТ минимальная остаточная болезнь (МОБ): в I группе 0 %, во II-й 0,48 ± 0,13 %, в III-й 33,5 ± 7,84 %. После 6 курса ИХТ МОБ: в I группе 0 %, во II-й 0,42 ± 0,09 %, в III-й 33,2 ± 8,07 %. Экспрессия иммунофенотипических маркеров в II, III группах без изменений после 3,6 курсов ИХТ. Согласно критериям оценки ответа на терапию (IWCLL, 2018 г.) у пациентов I, II групп после 6 курса ИХТ полная ремиссия, у 3-х пациентов III группы частичная ремиссия, у 1 больного стабилизация процесса. Получены предварительные данные, указывающие на то, что отсутствие или повышенный уровень экспрессии CD38, CD25, ZAP-70, CD11c, FMC7 на В-лимфоцитах больных ХЛЛ до лечения могут предопределять гематологический ответ на терапию по схемам RB/FCR.
Заключение. Исходно повышенная экспрессия одновременно всех прогностических антигенов: CD38, CD25, ZAP-70, CD11c, FMC7 на опухолевой популяции В-лимфоцитов больных ХЛЛ ассоциируется с неудовлетворительным ответом на лечение, что представляется перспективным с точки зрения изучения влияния анализируемых маркерных молекул на достижение гематологического ответа на этапах иммунохимиотерапии.

Ключевые слова:
хронический лимфолейкоз, проточная цитометрия, минимальная остаточная болезнь, иммунофенотипические маркеры, иммунохимиотерапия

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RELEVANCE

Chronic lymphocytic leukemia (CLL) is a tumor of lymphoid tissue from mature (peripheral) B cells, characterized by damage to the bone marrow and lymph nodes. People over the age of 50 get sick, mostly. CLL is detected randomly, progresses slowly and often proceeds without pronounced symptoms for a long time [1; 2]. According to a number of studies [3; 4], CLL is classified as an extremely heterogeneous disease, the nature of the course of which varies from indolent to aggressive, and the prognosis in the same patient can change significantly over time [5]. Tumor B lymphocytes in CLL express antigens – CD19, CD5, CD23, CD20 (weak), CD22 (weak), CD43 [6; 7].

The assessment of the response to therapy is carried out according to the updated criteria of the International Working Group on CLL (IWCLL, 2018), according to which complete remission, partial remission, stabilization or progression of the disease is established. Parameters characterizing tumor mass (lymphadenopathy, hepatomegaly, splenomegaly, blood lymphocyte level, bone marrow infiltration, constitutional symptoms) and indicators characterizing bone marrow function (platelet, hemoglobin, neutrophil levels) are evaluated [8]. The most important stage in the final assessment of the effect of immunochemotherapy used in the treatment of CLL is the determination of minimal residual disease (MRD), which IWCLL is also included in the criteria for evaluating the response to therapy [8]. Minimal residual disease is characterized by the presence of a population of tumor cells in patients in complete remission, which cannot be detected by cytological method, but can be determined by highly sensitive methods of PCR and multicolored flow cytometry. Most prognostic schemes are based on the assessment of MRD in the blood and/or bone marrow, which allows us to reliably confirm MRD-negative complete remission. Thus, the content of the residual population of CLL cells in the blood or bone marrow above 1 % foreshadows an early relapse and may serve as a basis for changing therapy. The MRD content in the range from 0.90 % to 0.01 % characterizes a group of patients with a median disease progression-free survival (IBD) of about 3 years, which gives reason to consider the possibility of maintenance therapy. MRD values below 0.01 % indicate a high probability of long-term remission (> 5 years) [9; 10]. Gabor Kovacs et al. [11] analyzed the prognostic significance of MRD in comparison with the clinical response to therapy. It has been shown that achieving MRD negativity is as important as the clinical response to evaluate the effectiveness of therapy.

In the last decade, an improved understanding of the pathogenesis of CLL and the active introduction of the flow cytometry method into clinical practice has made it possible to use the expression of a number of immunophenotypic markers as prognostic indicators. In particular, activation antigens CD38 and CD25, ZAP70 protein, myelomonocytic antigens CD11c and CD11b, FMC7 (antigen of mature B-lymphocytes), absence of CD23 antigen or its weak expression on the surface of lymphocytes, etc. [10]. It was also found that CD38 expression on more than 20 % of CD19+/CD5+ cells is associated with a poor prognosis, and patients with immunophenotypically immature CD38+ CLL respond poorly to long-term multimode chemotherapy and, therefore, have a short life expectancy [12]. In almost 50 % of CLL patients, the expression of CD25 activation antigen on lymphoid cells is noted, which is considered a marker of tumor lymphocytes in hairy cell leukemia and is associated with an unfavorable prognosis of the disease [12]. The expression of ZAP-70 ≥ 20 % on tumor B-lymphocytes is considered as a risk factor for the progression and development of Richter syndrome [12]. In 26.7 % of patients with CLL, expression of the myelomonocytic antigen CD11c is observed, which is associated with a short doubling time of the number of lymphocytes in peripheral blood (< 12 months) [13]. The absence of CD23 antigen or its weak expression on the surface of lymphocytes, along with the simultaneous detection of positive expression by FMC7 (antigen of mature B-lymphocytes), is also associated with a poor prognosis [14].

Analysis of the literature data shows that the search for markers that allow predicting the course of the tumor process and the response of CLL patients to therapy at the stages of diagnosis and monitoring of MRD does not lose its relevance.

Purpose of the study: to study the expression profile of immunophenotypic marker molecules on B-lymphocytes in patients with chronic lymphocytic leukemia at the stages of immunochemotherapy while monitoring minimal residual disease.

PATIENTS AND METHODS

The study included 20 patients (13 men, 7 women), median age 66.4 ± 1.9 years with chronic lymphocytic leukemia (CLL) in stage C according to Binet, who had not previously received specific therapy. In the period from 2019 to 2022, 6 courses of antitumor drug therapy in RB or FCR mode were conducted in the Department of Oncogematology National Medical Research Centre for Oncology in Rostov-on-Don. At the stages before, after 3 and 6 courses of ICT, bone marrow immunophenotyping was performed by 10-color flow cytometry (Navios 10/3, Beckman Coulter, USA). The studies were carried out in native bone marrow cells in a solution of anticoagulant K2 EDTA. The study of the primary immunophenotype of B lymphocytes and prognostic marker molecules was performed using a panel of monoclonal antibodies labeled with various fluorochromes: CD45 (PB), CD19 (ECD, PC7), CD5 (PC7, APC), CD10 (PE), CD11c (PE), CD20 (PC7), CD22 (PE), CD23 (PE), CD25 (PC5), CD38 (FITC, PC7), CD43 (APC-A750), and FMC7 (FITC), ZAP-70 (PE), CD3 (PC7), kappa (FITC), lambda (PE). MRD was evaluated, taking into account that the residual population of CLL cells in the bone marrow < 0.01 % (0 %) is estimated as MRD negative status [9]. The results of flow cytometry were analyzed using the Kaluza v2.1 software (Beckman Coulter, USA). The collection of clinical information, biological material, sample preparation, quality control of biological samples, storage, as well as compliance with legal norms and rules related to patient confidentiality were carried out according to the developed algorithms of actions of departments of research and clinical groups National Medical Research Centre for Oncology [15]. The data obtained are evaluated in the Statistica 13.0 program, the results are presented taking into account the average values (M), the errors of the averages (m).

RESEARCH RESULTS AND DISCUSSION

Prior to treatment (MRD day 0), according to the results of flow cytofluorometry, all patients showed high expression of markers characteristic of CLL– CD5, CD23, CD20, CD22, CD43 (Fig. 1). Depending on the expression profile of prognostic markers such as CD38, ZAP-70, CD11c, CD25, FMC7, 3 groups of patients were identified (Table 1). Group I (2 people) was characterized by the absence of expression of CD38, ZAP-70, CD11c and CD25 markers, the level of FMC7 expression did not exceed 0.2 %. In group II (14 people), variable expression of CD25 and CD38 was noted, respectively 0.4 % – 47.6 % and 0.0 % – 57.5 %, the absence of expression of ZAP-70, CD11c, FMC7 was not more than 1.6 %. In group III (4 people), high expression of all studied prognostic markers was found: CD38 (57.5 % – 69.2 %), ZAP-70 (36,6 % – 48,3 %), CD11c (20.0 % – 96.5 %), CD25 (64.9 % – 92.7 %), FMC7 (13.6 % – 88.6 %) (Fig. 1, 2). There were no differences in age and gender between the groups.

After 3 courses of ICT, a decrease in the number of tumor B-lymphocytes was noted in all groups, but with varying degrees of intensity. Thus, patients of group I had MRD – negative status: no CLL cells were detected in the bone marrow (Table 2). In group II, a significant decrease in the amount of MRD (0.48 ± 0.13 %) was noted in comparison with the data before treatment (86.2 ± 1.43) ($p < 0.05$), at this stage attention was paid a decrease in CD38 expression on CLL cells to < 3 %, the expression of other prognostic markers remained unchanged in comparison with the level before treatment. In group III, after 3 courses of ICT, the residual population of CLL cells (MRD) averaged 33.5 ± 7.84 %, while the expression profile of all prognostic markers detected at the onset of the disease remained unchanged.

After 6 courses of ICT, attention was drawn to the absence of statistically significant differences in MRD values in all 3 groups in comparison with the data after 3 courses of ICT. The amount of MRD in group I was 0 %, in group II – 0.42 ± 0.09 %, in group III – 33.2 ± 8.07 % (Table 2). The expression profile of prognostic markers remained unchanged: the absence of expression in group I, variable CD25 expression, decreased CD38 expression after the 3rd course of ICT and the absence of ZAP expression-70, CD11c and FMC7 in group II, high expression of all analyzed markers – CD25, CD38, ZAP-70, CD11c and FMC7 in group III. The lack of dynamics in the values of MRD and expression of immunophenotypic markers after 6 courses of ICT may be the basis for evaluating the effect of treatment by IFT already at intermediate stages, that is, after the 4th and/or 5th courses of therapy in order to revise treatment regimens, which in our opinion requires further research.

At the same time, the differences in the expression profile of marker molecules on B-lymphocytes

established by us before the start of ICT in patients with CLL are of undoubted interest. Thus, a number of authors are conducting studies to assess the effect of CD38, ZAP-70, CD11c, CD25, FMC7 expression on the results of specific therapy, but these data are contradictory. It is known that in CLL, the positivity of CD38, which is a transmembrane glycoprotein, is a poor prognostic marker associated with resistance to treatment [16; 17]. It is assumed that CD38 expression of more than 20 % is associated with damage to the lymph nodes, liver, as well as with the aggressive course of the disease [17]. According to other data, CD38 positivity in the late stages is associated with eventless and overall survival, and in the early stages is a poor prognostic factor for overall survival [17].

According to our data, patients of group II (remission) had initially high levels of expression of 2 markers – CD38 and CD25. After ICT, there was a significant decrease in CD38 expression. And in group III (stabilization), the outcome showed high expression of all markers – CD38, ZAP-70, CD11c CD25, FMC7 and no change in the expression profile after treatment.

The results of the study of FMC7 expression are consistent with the literature data. It was shown that patients with FMC7 expression below 30 % needed treatment more often, in contrast to patients with expression over 30 % [18]. In our study, on the contrary, the absence of FMC7 expression was noted in groups I and II of patients with a positive response to RB and FCR treatment, while in group III there was a high expression of FMC7, which is consistent with the data of Choi Y. et al. (2021), who received similar results to ours [19].

Further, CD11c positivity is defined as aberrant expression in CLL [20; 21]. Clinical data and prognostic significance of CD11c in CLL are limited. A study by Umit E. G. (2017) revealed a significant relationship between CD11c positivity (≥ 20 %) and time to treatment [22]. According to our data, CD11c positivity was noted in group III patients and varies from 20.0 to 96.5 %.

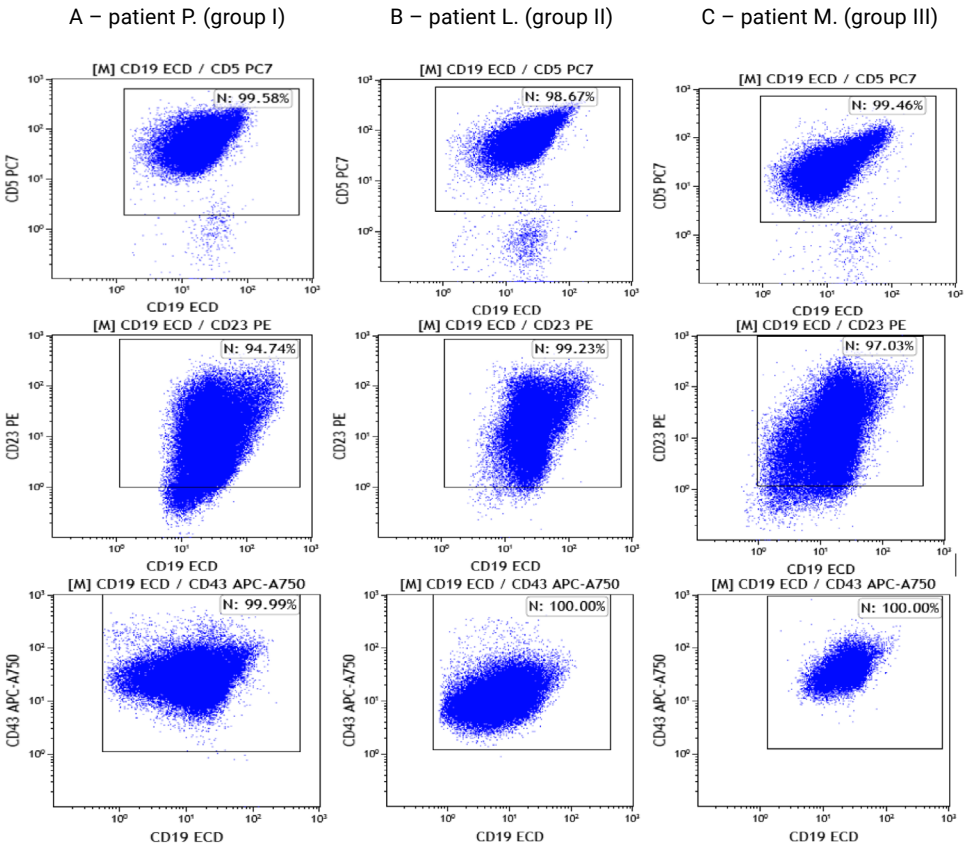

Fig. 1. Results of immunophenotyping of the bone marrow of patients with CLL by flow cytometry before treatment. Dot graphs of B-CLL-specific coexpression of CD molecules. The population of tumor B-lymphocytes is highlighted in blue: A – patient P. (group I), B – patient L. (group II), C – patient M. (group III).

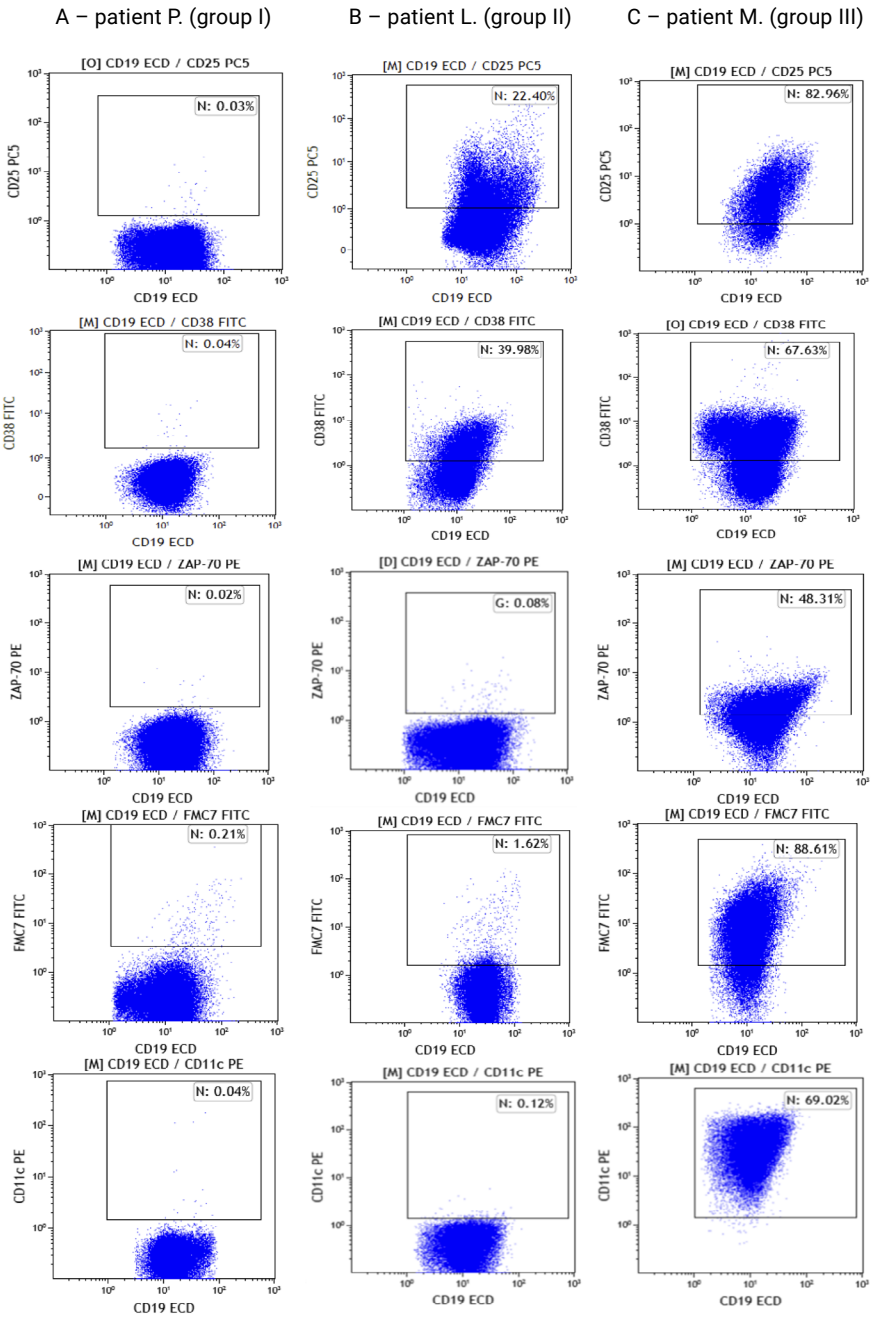

Fig. 2. Results of immunophenotyping of the bone marrow of patients with CLL by flow cytometry before treatment. Dot graphs of the expression of prognostic marker molecules. The population of tumor B-lymphocytes is highlighted in blue: A – patient P. (group I), B – patient L. (group II), C – patient M. (group III).

Table 1. Expression of CD38, ZAP-70, CD11c, CD25, FMC7 on B-lymphocytes before treatment in the bone marrow of CLL patients

Patients groups	CD38, %	ZAP-70, %	CD11c, %	CD25, %	FMC7, %
I (*n* = 2)	0	0	0	0	0–0.2
II (*n* = 14)	0–57.5	0	0	0.4–47.6	0–1.6
III (*n* = 4)	57.5–69.2	36.6–48.3	20.0–96.5	69.4–92.7	13.6–88.6

Table 2. Quantitative characteristics of MRD in the bone marrow of CLL patients at the stages of ICT

Patients groups	Quantitative characterization of MRD at the stages of examination (% of the total residual population of CLL nucleated cells)		
	Day 0 (M ± m)	After 3 ICT courses (M ± m)	After 6 ICT courses (M ± m)
I (*n* = 2)	72.4 ± 1.21	0*,**	0*,**
II (*n* = 14)	86.2 ± 1.43	0.48 ± 0.13*,**	0.42 ± 0.09*,**
III (*n* = 4)	90.1 ± 1.60	33.5 ± 7.84*,**	33.2 ± 8.07*,**

Note: NC – nucleated cells, * – statistically significant differences from MRD "day 0" in its group ($p < 0.05$), ** – statistically significant differences from MRD I and II/III groups ($p < 0.05$).

The expression of the CD25 antigen (the α-chain of the IL-2 surface receptor) reflects the activated state of the tumor lymphocyte. Shvidel L. et al. (2012) found no evidence that this parameter alone can be used as a predictor of overall survival or time to first treatment [23]. In our studies, the increased expression of CD25 on tumor B lymphocytes in group III, along with CD38, ZAP-70, CD11c, FMC7, was accompanied by an unsatisfactory response to therapy.

Thus, preliminary data were obtained indicating that the absence or increased expression of prognostic markers CD38, CD25, ZAP-70, CD11c, FMC7 on B-lymphocytes in patients at the stage of diagnosis of CLL may predetermine the hematological response to therapy according to RB or FCR schemes.

CONCLUSION

Initially, increased expression of all prognostic antigens simultaneously: CD38, CD25, ZAP-70, CD11c, FMC7 on the tumor population of B-lymphocytes in patients with CLL is associated with an unsatisfactory response to treatment, which seems promising from the point of view of studying the effect of the analyzed marker molecules on achieving a hematological response at the stages of immunochemotherapy.

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