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Evaluation of the prognostic and predictive value of free light chains in patients with chronic lymphocytic leukemia – preliminary results

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Abstract

Introduction: κ and λ serum free light chains (sFLCs) are produced during physiological lymphopoesis by plasmocytes and B lymphocytes in a constant ratio related to heavy chains. The measurement of sFLC plays an important role in the diagnosis and monitoring of patients with multiple myeloma (MM). The first reports suggested that sFLC disturbances might have prognostic value also in patients with chronic lymphocytic leukemia (CLL). Aim of the study: The aim of the study was to evaluate the relationship between sFLC concentration and recognized prognostic factors and clinical course of CLL. Materials and methods: The sFLC concentration was measured using a latex-enhanced immunoassay in 59 patients with newly diagnosed CLL. The relationship between sFLC concentration and time to start of the treatment (TFT), the response rate to therapy (ORR) and overall survival (OS) was assessed. Results: A significant correlation was found between sFLC κ concentration and the clinical stage of leukemia according to Rai classification, β-2 microglobulin concentration, LDH activity, CD38 expression, as well as between sFLC λ level and β-2 microglobulin concentration and platelet count (PLT). There was also a correlation between the values of summated κ and λ and the clinical stage of disease according to Rai classification, β-2 microglobulin concentration, CD38 expression, white blood cells count (WBC), lymphocyte count (ALC) and hemoglobin (Hgb) concentration. The κ/λ ratio (FCLR) values were significantly different in the CD38+ and CD38- population. Summary: Simple and reproducible clonality index, which constitutes the sFLC concentration assessment, can be an attractive, potential prognostic marker in patients with CLL, however further studies are needed on a larger group of patients especially in relation to the predictive value of sFLC.

Keywords:
chronic lymphocytic leukemia, free light chains, prognostic factors

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by excessive proliferation and accumulation of monoclonal B lymphocytes with CD5+/CD19+/CD23+ phenotype in the bone marrow, peripheral blood, lymph nodes, and also, in some patients with aggressive disease, non-lymphatic organs, resulting in a reduction in the number of normal immunocompetent cells [1, 2].

Specific to CLL is heterogeneity in clinical course, prognosis and response to the treatment. The start of treatment is determined individually for each patient and depends on the clinical symptoms of advanced or progressive disease. About one third of patients have mild course of CLL and long survival, without the need for treatment. In the remaining patients, the disease is more aggressive and despite therapy can lead to death even within a few years from the diagnosis [3].

Due to such a variable clinical course, there is a need for reliable prognostic factors that would allow for precise determination of prognosis, and thus selection of the optimal time and method of treatment. For many years, the most important prognostic factor was the clinical stage assessed according to the Rai's or Binet's classification, but their main disadvantage is the inability to select the patients in early clinical stages in whom the aggressive course of the disease might be predicted with high probability [4, 5].

Many parameters with prognostic value such as: absolute lymphocytes count in peripheral blood, doubling time of lymphocytosis, character of bone marrow infiltration by leukemic lymphocytes, concentration of soluble CD23 and β-2 microglobulin antigen, thymidine kinase and lactate dehydrogenase (LDH), expression of CD38, ZAP-70 [4], CD69 [6] have been described in CLL. The mutational status of a variable part of immunoglobulin heavy chain (IgVH) and cytogenetic abnormalities, particularly del17p and del11q are considered to have the not only prognostic but also predictive value. A considerable disadvantage is the high cost of laboratory assays [3, 4, 7, 8]. There is still a need to look for new prognostic and predictive factors that are simple to determine and that would allow for the choice of optimal therapy. The first reports indicated that such a value might have the serum level of free light chains (sFLCs) [9].

During physiological lymphopoiesis, sFLCs are produced by plasmocytes and B lymphocytes in excess of heavy chains, and their presence can be detected in small amounts in the serum. In a normal, polyclonal response to antigen, the amounts of sFLC κ and λ produced from sFLCs are similar. In plasma cell dyscrasias, excessive proliferation of one cell clone and production of monoclonal protein, result in overproduction of one type of sFLC and κ/λ ratio (sFLCR) alteration [10, 11]. sFLC evaluation is used in the diagnostics and treatment monitoring in patients with plasmocytoma, amyloidosis, monoclonal gammopathy of undetermined importance, light chain diseases, Waldenstrom's macroglobulinemia [12, 13, 14].

The production of monoclonal protein was also found in patients with non-Hodgkin lymphomas (NHL) and CLL. However, laboratory methods used as a standard in plasma cell dyscrasias, such as protein

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Table I. Clinical and laboratory characteristics of the study group

Age	Md (years) ± SD (min.-max.)	64.4 ± 9.5 (44–85)
Sex	female	31
	man	28
Clinical stage according to the Rai classification	early (0-I)	37
	advanced (II-IV)	22
CD38 (cut-off point 30%)	positive	16
	negative	43
ZAP-70 (cut-off point 20%)	positive	18
	negative	41
Cytogenetic aberrations	del17p	9/25
	del11q	11/25
WBC (G/l)	M ± SD (min.-max.)	29.4 ± 20.1 (6.5–133.9)
ALC (G/l)	M ± SD (min.-max.)	23.6 ± 19.4 (5.1–110.7)
Hgb (g/dl)	M ± SD (min.-max.)	13.2 ± 1.3 (9.0–15.4)
PLT (G/l)	M ± SD (min.-max.)	191.0 ± 60.0 (58.0–395.0)
β-2 microglobulin (mg/l)	M ± SD (min.-max.)	3.7 ± 2.8 (1.1–17.0)
LDH (U/l)	M ± SD (min.-max.)	402.5 ± 123.5 (272.0–897.0)
CD 69	M ± SD (min.-max.)	25.3 ± 18.8 (1.1–75.9)

Md – median, M – medium, SD – standard deviation, LDH – lactate dehydrogenase

electrophoresis and immofixation, determination of Bence-Jones protein concentration in urine, here very often give negative results. It was the introduction of the nephelometric method of quantitative determination of sFLCs into the haematological diagnostics that allowed for assessing monoclonal protein concentration and disturbances as well as its prognostic and predictive value in NHL and CLL [11].

Materials and Methods

Patients and samples

Peripheral blood samples were taken from 59 patients diagnosed with CLL at the Department of Haematooncology and Bone Marrow Transplantation in Lublin in 2009-2010. CLL diagnosis was established according IWCLL criteria [15].

Blood samples were taken at CLL diagnosis, before the start of any anti-leukemic treatment. Exclusion criteria were as follows: severe concomitant diseases (renal failure, amyloidosis, monoclonal gammapathy of unknown etiology, connective tissue diseases, autoimmune diseases, concomitant cancer, heart failure, liver failure, respiratory distress, the symptoms of infection or allergic diseases at the time of testing, transfusions of blood products in the last year, taking drugs that affect the function of the immune system.

In all the patients, the prognostic factors were evaluated. Clinical characteristics of the study group and prognostic factors are presented in table I.

Patients follow-up

Patients underwent clinical follow-up to assess the relation between sFLC concentration at CLL diagnosis on primary endpoints such as time to first treatment (TFT), overall response rate (ORR) to therapy and overall survival (OS). Evaluation of responses to anticancer therapy was made based on criteria of response to the treatment according to the criteria of International Workshop on Chronic Lymphocytic Leukemia (IWCLL) [15].

Blood preparation

Peripheral blood samples were collected into tubes without anticoagulant, and then within 2 hours centrifuged for 10 minutes at 1600 x g at room temperature (Eppendorf 5810R, Germany). The prepared sera were stored at –80 ° C until further analysis.

Assessment of sFLC concentration

The sFLC were measured using a latex-enhanced immunoassay (Freelite; The Binding Site, Birmingham, UK) on a Cobas Integra 400 plus analyzer (Roche Diagnostics, Mannheim, Germany). Normal ranges were 3.3-19.4 mg/l for κ sFLC, 5.7-26.3 mg/l for λ sFLC and 0.26-1.65 for κ/λ ratio (sFLCR). The analysis was performed according to the manufacturer's instructions. To further dissect the potential predictive value of sFLC, the κ and λ FLC concentrations were summed to produce a new variable, summed κ and λ. Based on literature data [11] the cut-off point was set at 66.6 mg/l.

Ethics statement

This study was approved by the Ethics Committee of the Medical University of Lublin. Written informed consent was obtained from all patients.

Statistical analysis

The obtained results were subjected to statistical analysis based on Statistica 12.0 computer software (StatSoft, USA). The Shapiro-Wilk test was used to assess the variables. Due to the fact that no features of the normal distribution were found, further statistical analyzes were conducted on the basis of non-parametric tests. Non-parametric tests were used in statistical analyzes: Mann-Whitney U test (for 2-category variables), Kruskall-Wallis test (for more than 2-category variables), Spearman's rank correlation test for studying dependencies between variables, and analysis Kaplan-Meier experience. In all analyzes, the significance level $p < 0.05$ was assumed as critical.

Results

sFLC and sFCLR values

The mean sFLC κ concentration in the study group was 48.6 ± 69.5 mg/l (min. 8.4 mg/l, max. 409,5 mg/l), sFLC λ 17.5 ± 16.0 mg/l (min. 3.5 mg/l, max. 107.8 mg/l), summed κ and λ 66.1 ± 78.2 mg/l (min. 14.8 mg/l, max. 465.7 mg/l), while sFLCR 3.6 ± 4.4 (at least 0.39, max. 24.9). Elevated sFLC κ values were found in 64.4% (n = 38), sFLC λ in 13.6% (n = 8), summed κ and λ in 25.4% (n = 15) and sFLCR in 51.8% (n = 29) patients.

Correlations between sFLC and sFLCR values and complete blood count (CBC) parameters

Statistically significant negative correlation was found between between sFLC λ and PLT count ($p = 0.04$). There was also a correlation between summed κ and λ WBC, ALC and Hgb concentration (table II).

Correlations between sFLC and sFCLR values and prognostic factors

sFLC κ concentration was significantly higher in patients with a high clinical stage of disease according to the Rai classification as compared to the lower stages. In addition, a positive correlation was found between sFLC κ concentration and β-2 microglobulin concentration, LDH activity and CD38 expression. For sFLC λ, only the correlation between their level and the β-2 microglobulin concentration was statistically significant. There was a correlation between summed κ and λ and the clinical stage of disease according to Rai classification, β-2 microglobulin concentration and CD38 expression (table III and IV).

Correlations between sFLCs, sFLCR and primary endpoints

The average follow-up time was 72.5 ± 25.2 months (min. 8 months, max. 129 months). 10 patients died during the follow-up.
At the time of data analysis, 49% (n = 29) patients enrolled in the study completed the first-line therapy. Mean TFT was 18.5 ± 24.6 months (at least 0 months, max 85 months). The following treatment regimens were used in the study group: chlorambucil in combination with prednisone (n = 12), fludarabine in combination with cyclophosphamide +/- rituximab (n = 9), bendamustine +/-rituximab

Table II. Correlations between sFLC, FLCR, summated κ and λ values and complete blood count (CBC) parameters

	sFLC κ (mg/dl)		sFLC λ (mg/dl)		summated κ and λ(mg/dl)		FCLR	
	rho	p	rho	p	rho	p	rho	p
WBC (G/l)	0.11	0.41	0.20	0.13	0.28	0.03	-0.07	0.59
ALC (G/l)	0.11	0.412	0.13	0.34	0.26	0.04	-0.05	0.71
Hgb (g/dl)	-0.21	0.110	-0.21	0.12	-0.32	0.01	-0.02	0.85
PLT (G/l)	0.01	0.922	-0.27	0.04	-0.08	0.56	0.14	0.29

rho – Pearson's correlation coefficient, p – probability

Table III. Correlations between sFLC, FLCR, summated κ and λ values and β-2 microglobulin values, LDH activity and CD 69 expression

	sFLC κ		sFLC λ		summated κ and λ		FCLR	
	rho	p	rho	p	rho	rho	rho	p
β-2 microglobulin	0.54	0.00002	0.37	0.005	0.69	0.0000001	0.25	0.06
LDH	0.26	0.05	-0.02	0.86	0.22	0.11	0.23	0.09
CD 69	0.08	0.52	0.19	0.14	0.18	0.17	-0.10	0.47

rho – Pearson's correlation coefficient, p – probability

Table IV. Correlations between sFLC, FLCR, summated κ and λ values and stage of the disease according to the Rai classification,expression ZAP-70, CD 38 and cytogenetic risk

Stage of disease according to the Rai classification								
	sFLC κ ± SD (mg/dl)	**p**	**sFLC λ ± SD (mg/dl)**	**p**	**summated κ and λ ± SD (mg/dl)**	**p**	**FCLR ± SD**	**p**
early	27,2 ± 26.22	0.01	14.2 ± 6.9	0.63	41.4 ± 27.4	0.005	2.2 ± 2.1	0.09
advanced	83.2 ± 100.7		23.2 ± 24.0		106.4 ± 113.5		5.1 ± 6.3	
ZAP-70								
	sFLC κ ± SD (mg/dl)	**p**	**sFLC λ ± SD (mg/dl)**	**p**	**summated κ and λ ± SD (mg/dl)**	**p**	**FCLR ± SD**	**p**
positive	57.8 ± 66.9	0.59	18.1 ± 11.0	0.31	75.9 ± 69.0	0.06	4.7 ± 6.6	0.95
negative	44.5 ± 71.0		17.2 ± 17.9		61.8 ± 82.3		2.8 ± 2.8	
CD 38								
	sFLC κ ± SD (mg/dl)	**p**	**sFLC λ ± SD (mg/dl)**	**p**	**summated κ and λ ± SD (mg/dl)**	**p**	**FCLR ± SD**	**p**
positive	91.6 ± 74.2	0.0002	16.6 ± 13.3	0.57	108.2 ± 82.4	0.001	7.3 ± 6.8	0.00001
negative	32.6 ± 61.1		17.8 ± 17.1		50.4 ± 71.4		1.9 ± 1.4	
cytogenetic risk								
	sFLC κ ± SD (mg/dl)	**p**	**sFLC λ ± SD (mg/dl)**	**p**	**summated κ and λ ± SD (mg/dl)**	**p**	**FCLR ± SD**	**p**
without del11q or del 17p	70.6 ± 120.8	0.80	18.9 ± 14.3	0.89	89.5 ± 141.8	0.93	2.7 ± 2.1	0.80
del11q or/and del 17p	50.6 ± 60.3		19.4 ± 14.5		70.0 ± 66.4		3.2 ± 4.1	

SD – standard deviation, p – probability

(n = 5), CHOP/CVP (n = 3). The response to the applied treatment was obtained in 50% of patients. No significant relationships between sFLC κ and λ as well as sFLCR and ORR were found. There was no statistically significant correlation between the elevated concentrations of sFLC, sFLCR and summed κ and λ and TFT and OS, however, in patients with normal and elevated sFLC λ, Kaplan-Meier curves clearly differed (Fig. 1).

Discussion

Abnormalities in the secretion of sFLC have been previously reported in patients with B-cell NHL, including CLL [9]. Witzig et al. [16] analyzed the expression of sFLC in a population of 492 patients with newly diagnosed B and T-cell lymphomas. They showed that the expression of sFLC and abnormal sFLCR most often (79% of respondents, including 50% monoclonal, 29% polyclonal) were reported in the lymphoplasmacytic lymphoma (LPL) population, mantle cell lymphoma (68% of patients, 24% monoclonal; 44 % polyclonal),

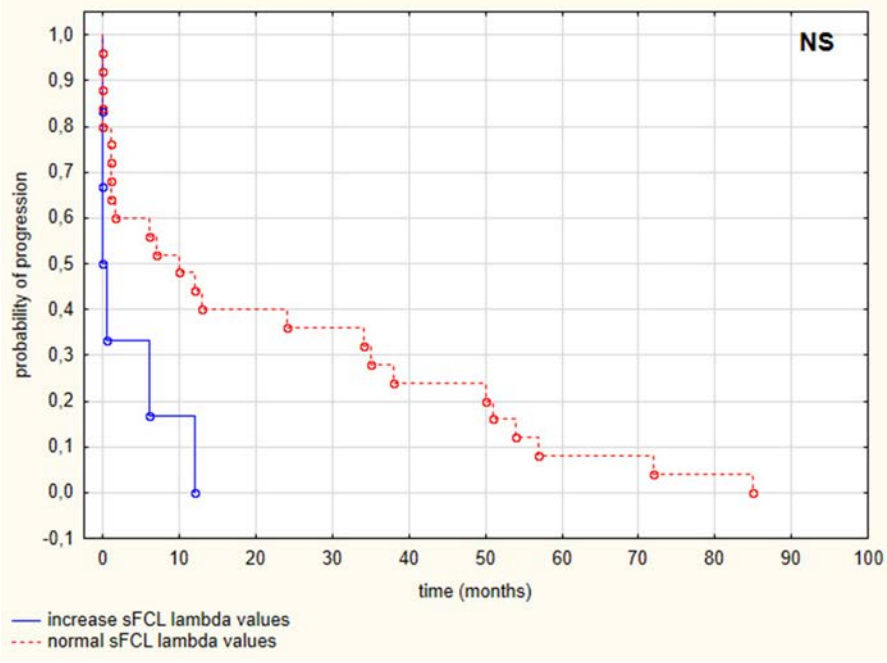

Fig. 1. Correlation between the elevated concentrations of sFLC λ and TFT

Burkitt/high-grade lymphoma (67% of patients, 50% monoclonal, 27% polyclonal). The authors showed that high expression of sFLC (both polyclonal and monoclonal) correlated with shorter overall survival (OS) and time to first treatment (TFT). Interestingly enough, also in patients with follicular lymphoma (FL), where sFLC expression disorders were described least frequently (15% of respondents, 4% monoclonal, 11% polyclonal), significant relationship between their concentration and OS was noted, and in the population of patients with a more advanced stage of the disease (stage 3 according to the Ann-Arbor classification) there was a connection with EFS. They hypothesized that it could have been associated with co-morbidities and other unfavorable prognostic factors [16]. M-protein was also found in patients with CLL. Rochester et al. showed M-protein in the serum of 18 patients, indicating that sFLC assessment was superior to electrophoresis and immunofixation, since in 6 of 8 CLL patients, M-protein was only detectable by the FLC assay) [17].

There are suggestions that analysis of CLL patients with sFLC assays may also provide additional information regarding outcome. In our study, there was no significant correlation between sFLC κ and sFLCR concentration and parameters of the whole blood count, however, in the patients with elevated sFLC λ, the number of platelets was lower and the concentration of β-2 microglobulin was higher that might be associated with higher tumor burden. Statistical analysis confirmed also a significantly higher sFLC κ concentration in patients with advanced stage of disease according to Rai's classification. Additionally, higher sFLC κ concentration was found in patients with high β-2 microglobulin concentration, high LDH activity and CD38-positive elevated sFLC λ. Morabito et al. developed a new prognostic factor – summed κ and λ. They noticed that this parameter is significantly higher in the sick population who had the required treatment. On the basis of the multivariate analysis performed, a relationship between the clinical evaluation and the cytogenetic risk, ZAP-70 expression was presented, as well [11]. The results of our study confirmed these observations, since summed κ and λ values correlated positively with WBC and ALC values, while negative correlation was demonstrated for Hgb concentration. The relationship between and the summed κ and λ values and the clinical stage of disease according to Rai classification, β-2 microglobulin concentration and CD38 expression was also established.

Attempts to find correlations between the level of sFLC expression and selected prognostic factors in patients with CLL were carried out by Pratt et al. [18] in the group of 259 patients (181 untreated and 78 who had received treatment). The authors identified sFLC concentration as one of the independent prognostic factors beside IgVH mutational status, β-2 microglobulin concentration and ZAP-70 expression. Pertiago et al. [19] also demonstrated the relationship between sFLC levels and the mutational status of IgVH and primary endpoints such as OS and TFT. Ruchlemer et al. [20] found a relationship between sFLCκ concentration and the clinical stage of the disease according to Rai's classification as well as between low FLCR and worse outcome for the treatment. However, they did not confirm the relationship between sFLC or FLCR and prognostic factors such as ZAP-70 and CD38 expression, cytogenetic aberrations, peripheral blood leukocytosis and LDH activity [20].

On opposite, Yegin et al. [21] noted the relationship between abnormal sFLC and FLCR and LDH activity, hemoglobin concentration, platelet, leukocyte, and lymphocyte counts [21]. The relationship between overexpression of CD-38 antigen and increased sFLC concentration, might indicate that they are markers of excessive stimulation of B lymphocytes. The relationship between abnormal FLCR and ZAP-70, expression, cytogenetics aberrations, TFT in a multivariate model was demonstrated in a large group of 446 patients [11].

We found no differences in sFLC level between the patients with adverse cytogenetic aberrations (del17p and/or del11q) and/or high ZAP-70 expression and the population with standard cytogenetic risk and/or low ZAP-70 expression. However, it should be noted that this assessment, could be unreliable due to the small size of the group. Therefore, further research is needed in concerning this subject.

Our results suggest that higher sFLC κ expression in patients with unfavorable prognostic factors such as clinical stage according to Rai, β-2 microglobulin concentration, LDH activity and CD38 expression could be helpful in selecting the population of patients with progressive form of the disease.

An important element in the assessment of the prognostic value of the studied factor is an attempt to assess its impact on the primary endpoints. Literature data confirmed the relationship between sFLC concentration and FLCR disorders and both OS and TFT. Pratt et al. [18] showed that high concentration of sFLC was an independent factor, associated with increased mortality in the studied population, regardless of the cause of death. Also, if only CLL-related deaths were taken into account, the elevated concentration of sFLC was associated with a shorter OS. TFT was statistically significantly longer in the group of patients with lower sFLC levels [18]. Also, Morabito et al. [11] unambiguously confirmed the relationship between abnormal FLC κ and λ concentration and TFT. These studies are in line with the results of Maurer et al. [22] who found that sFLC and FLCR can be considered as independent prognostic factors and translate into OS and TFT, regardless of whether secretion of sFLC was polyclonal or monoclonal. In this study, higher sFLC levels were found in older patients, with elevated creatinine levels that could also contribute to shorter OS [22].

Our own research does not confirm the relationship between sFLC, summed κ and λ and sFCLR and primary endpoints such as OS, TFT and ORR. However, it should be emphasized that CLL is an extremely heterogeneous disease and very often at the time of the diagnosis does not show clinical symptoms, and in the case of patients who do not perform regular check-ups, the diagnosis can be made even a few years after the first disturbances in peripheral blood morphology. The sFLC and FLCR determinations were made at the time of the diagnosis, therefore a meaningful determination of OS and TFT length in this group of patients is difficult. Also, the ORR assessment in such a small group of patients could not be reliable, especially considering the number of different treatment regimens that are used in everyday clinical practice and the necessity to reduce doses of cytostatics in older patients with numerous comorbidities. It would be interesting to evaluate predictive value of sFLC in larger group of patients treated with new agents, such as BCR or Bcl-2 inhibitors.

Despite the fact that many prognostic factors have been identified so far, their role in prognosing the course of the disease and anti-cancer therapy is very often still unclear. The introduction of new molecular and cytogenetic markers to everyday clinical practice is

very often impossible due to the high cost-effectiveness and the need to have adequate laboratory facilities. That is why it is important to look for new, cheaper markers that will allow to optimize the treatment choice [23]. Taking into account the results of our research and the literature on the subject presented above, it can be concluded that the evaluation of sFLC expression, summed κ and λ levels and sFLCR disorders in patients with CLL may be an important element that supplements the diagnostic procedure. It would be interesting to assess the predictive value of these parameters in relation to ORR, carried out in a larger and more homogeneous group of patients.

Authors' contributions/ Wkład autorów

The order of the authors reflects their participation in preparation of the manuscript.

Conflict of interest/ Konflikt interesu

There are no conflicts of interests.

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Ethics/Etyka

The work descibed in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to biomedical journals.

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