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Chronic lymphocytic leukemia – clinical course, prognostic parameters, prognostic markers

The pathogenic mechanisms of the hematologic malignancies

In order to maintain the stability of internal parameters of the body there is a necessity of constant cooperation of a large number of mechanisms and factors regulating the immune response. Hematopoiesis is a complex process differentiating all blood cell types from the hematopoietic stem cells (HSC – hematopoietic stem cells). This process is an excellent model for studying the molecular mechanisms that control the fate of cells. The comprehensive analysis of the research is crucial for the development of new treatment techniques. Hematopoietic stem cells have a high capacity for self-renewal and differentiation into the various hematopoietic cell lines. The microenvironment made of inter alia fibroblasts, bone marrow stromal cells, adipocytes, macrophages, and extracellular matrix is necessary for proper hematopoiesis. Growth factors and cytokines produced by bone marrow stromal cells have an impact on the differentiation of HSC. The HSC receptors, by connecting with the surface growth factor, cause the activation and proliferation of the cells (Riegier et al., 2012; Krzakowski, Warzocha, 2013). Abnormal expression and transcription factor mutations, disturbances in the activity of cytokines, growth factors, and deregulation of epigenetic mechanisms of signal transduction are specific for tumor cells of the hematopoietic system (Figure 1) (Krzakowski, Warzocha, 2013). Bone marrow is the primary site of creation and development of blood cells. The multipotent progenitor cells of myeloid and lymphoid lineage are formed from HSC. The way of differentiation into the cells that perform adaptive and innate immune response mechanisms is subject to strict, multi-level control by direct and indirect factors which regulate the production of the cellular components of blood. Myeloid progenitor cell differentiates into a cell line represented by neutrophils, eosinophils, mast cells, basophils, monocytes, erythrocytes and megakaryocytes. The lymphoid lineage is divided into lines represented by cells targeted for T cells, B cells and NK cells (Doulatov et al., 2012).

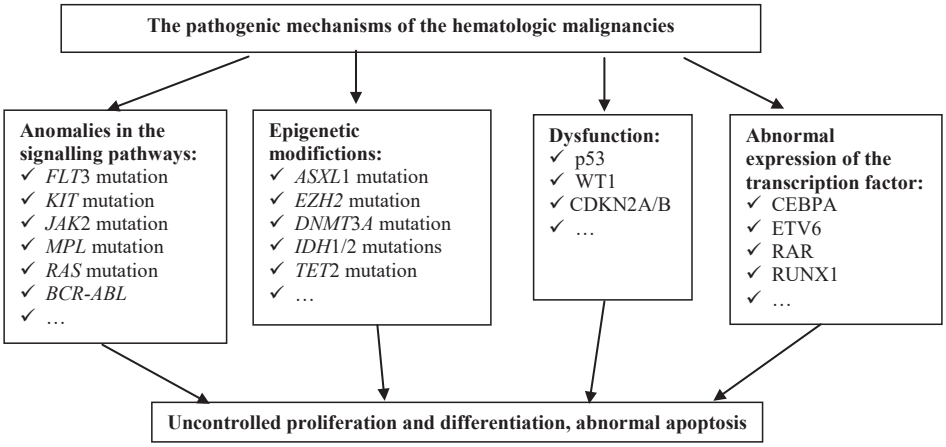

Fig. 1. The pathogenic mechanisms of the hematologic malignancies (Krzakowski M., Warzocha K., *Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych*, vol. II, 2013, p. 658)

Chronic lymphocytic leukemia – the definition, epidemiology, clinical view

Hematopoietic tumors are clonal diseases of hematopoietic stem cells or progenitor cells of the myeloid lineage. Chronic lymphocytic leukemia composes approximately 30% of all leukemia among adults. The essence of the disease is the accumulation and expansion of malignant cells in blood, bone marrow, lymph nodes, liver and spleen. The disease is accompanied by quantitative and qualitative disorders of B cells and T cells. The substantial majority of cells are found in the G0/G1 phase of the cell cycle (Chiorazzi et al., 2005; Hallek et al., 2008). Clinical course and prognosis of CLL is characterized by extremely high variability for individual patients. The survival time ranges from very short to several decades – similar to that of healthy people. Some patients during long-term observations do not require treatment as the disease is mild. While with others, it is a dynamic and aggressive progression of the disease symptoms. This heterogeneity has important implications for the selection of treatment strategies and survival time after diagnosis of the disease (Hallek et al., 2008). The clinical course is often asymptomatic, the diagnosis is often determined by chance on a base of blood count control and evaluation of blood smears. The incidence is 4 per 100,000 people per year, with the incidence growing rapidly with age. Only 14% of patients are less than 55 years old at the time of confirmation of the diagnosis of CLL (Eichhorst, Hallek, 2010). The average age at diagnosis is about 70 years. The diagnosis of CLL is established by the presence in the peripheral blood of ≥ 5,000 monoclonal B lymphocytes/μl for the duration of at least 3 months (Gribben, 2010). The usage of the analytical technique of flow cytometry allows for a qualitative and quantitative assessment of the physical and biological cells. The results obtained from cytometry provide complementary information

to classical hematology tests which allow one to make the required markings of phenotypical lymphocytes. In the case of CLL differentiation, the important matter is the expression of the typical surface markers: CD5, CD19, CD20 and CD23. Bone marrow biopsy is not the most important parameter for the diagnosis, although it is usually recommended prior to initiation of treatment with myelosuppressives, or in the case of diagnostic doubts (Bergmann, Wendtner, 2015). Leukemic cells in the blood smear have an appearance of mature cells. The characteristics of these cells are a narrow hem of the cytoplasm and a compact nucleus. There are also so-called Gumprecht's shadows; the fragments and residues of disintegrated cells (Dmoszyńska, Robak, 2008; Semanaj et al., 2014). In about 5–20% of CLL patients the transformation into aggressive lymphoma may be suspected. The appearance of Richter's syndrome it is usually associated with a very poor prognosis, short survival time and increased resistance to treatment. On the basis of symptoms and clinical changes amongst patients with chronic lymphocytic leukemia, such as fever, substantial and rapid weight loss, increasing organomegaly – enlarged lymph nodes, liver, spleen – night sweats, and elevated lactate dehydrogenase levels (LDH), the transformation into Richter's syndrome may be expected. The gold standard for diagnosis is the histopathological examination – lymph node biopsy (Adamowicz et al., 2008; Zhou, Wan, 2013). Risk factors associated with the development of Richter's transformation in patients with CLL are unfortunately unknown and unidentified. However, many reports in literature confirm that the activation of *C-MYC* gene, mutations in *NOTCH1*, *SF3B1*, *BIRC3* and tumor suppressor gene *TP53*, Epstein-Barr virus (EBV) infection, chromosomal aberrations of leukemia cells such as chromosome 12 trisomy, and chemotherapeutic agents used in the treatment of CLL may increase the risk of Richter's syndrome (Jain, O'Brien, 2012; Ghia, Hallek, 2014; Parikh et al., 2014). A common occurrence is the simultaneous recognition of a second tumor in patients with CLL. Melanoma, sarcoma and lung cancer are the usual coexisting types of cancer. Their treatment is very similar to the treatment in those that occur *de novo* (Adamowicz et al., 2008). In the standards of treatment, polychemotherapy with monoclonal antibodies is mainly used, but unfortunately does not provide long-term remission. Another strategy is allogeneic stem cell transplantation (allo-HSCT) (Eichhorst, Hallek, 2010). Unfortunately, the median age of diagnosis along with the high morbidity and mortality limits the ability to perform allogeneic stem cell transplantation to a small group of patients (Dmoszyńska, Robak, 2008). Before starting the optimal treatment program for patients with CLL, the clinical factors, hematological, immunophenotyping, biochemical and cytogenetics of potential prognostic should be marked. Before taking chemoimmunotherapy or allo-HSCT, certain examinations must be performed, such as virological evaluation of HBV (hepatitis B virus), HCV (hepatitis C virus), CMV (Cytomegalovirus) and HIV (human immunodeficiency virus) and radiological examinations – ultrasound of the abdomen and pelvis, and X-ray of chest. These tests are performed with the intention of establishing the aggravating factors that can affect the response to the treatment

(Elhefni, 2013). Differential diagnosis of CLL compared with other lymphomas having immunophenotypical and cytogenetic abnormalities are shown in Table 1.

Tab. 1. Immunophenotypic and genetic features of other B-cell lymphomas that may be confused with CLL (Gribben J.G., 2010, *How I treat CLL up front*, Blood 14, 115(2), 187–197)

Neoplasm	sIg	cIg	CD5	CD10	CD23	CD43	Cyclin D1	Bcl-6 protein*	Genetic abnormality (%)	IgVh genes
CLL	+	–/+	+	–	+	+	–	–	del 13q(50); del 11q(20); trisomy 12(20); del 17p(10)	50% unmutated
LPL	+	+	–	–	–	–/+	–	–	t(9;14)-*PAX5R*	mutated
MCL	+	–	+	–	–	+	+	–	t(11;14)-*BCL1R*	unmutated (rarely mutated)
FL	+	–	–	+	–/+	–	–	+	t(14;18)-*BCL2R*	mutated, ongoing
Extraodal and nodal MZL	+	–/+	–	–	–/+	–/+	–	–	trisomy 3; t(11;18)-*API2/MLT*; t(1;14)-*BCL10R*	mutated, ongoing
Splenic MZL	+	–/+	–	–	–	–	–	–	del7q21-32(40)	50% mutated

LPL indicates lymphoplasmacytic lymphoma; MCL – mantle cell lymphoma; FL – follicle center lymphoma; MZL – marginal zone lymphoma

+, more than 90% positive; –/+, less than 50% positive; and –, less than 10% positive

* Residual GC may be + in MZL, MCL

The clinical course and prognostic factors

The clinical (e.g. age, sex, co-morbidities) and biological (e.g. aberrations and genetic mutations) parameters in patients with CLL are inhomogeneous. The most important phenomena underlying the pathogenesis of CLL is the inhibition of programmed cell death. To assess the severity of CLL, two standards developed in 1970 are used interchangeably – classifications by Rai and Binet. They take into account both clinical and laboratory parameters. One of the first and the most important achievements of the supplementary classification scheme by Binet/Rai was the development of the molecular cytogenetic technique FISH – fluorescence in situ hybridization. This method allows to routinely detect genetic aberrations in CLL cells (Mertens, Stilgenbauer, 2014). Clinical stage CLL evaluated on the basis of the classification of Rai and Binet is the basis of the guidelines for the decision of whether to start treatment. Both of these systems are essential for the assessment of prognosis and are widely used in clinical practice. The Rai classification system is more popular in North America, while the Binet classification system is more popular in Europe. The disadvantage of these classification systems is their failure to take into account disease progression or response to treatment (Parker, 2011). Classification by Rai and Binet is presented in Table 2. The system presented

by Rai takes into account the laboratory parameters such as lymphocytosis in peripheral blood and bone marrow and the number of platelets and red blood cells in a given stage. Classification of Binet is based on the class of lymphatic areas, the concentration of hemoglobin and the number of thrombocytes. Lymphatic areas are groups of lymph nodes: cervical, axillary and inguinal, as well as splenic and liver. Both systems include the median survival time (Sagatys, Zhang, 2012).

Tab. 2. Rai classification and Binet staging systems for CLL (Gribben J.G., 2010, *How I treat CLL up front*, Blood 14, 115(2), 187–197)

System		Clinical features	Median survival, y
Rai stage (simplified 3-staged)			
	0 (low risk)	Lymphocytosis in blood and marrow only	>10
	I and II (intermediate risk)	Lymphadenopathy, splenomegaly +/- hematomegaly	7
	III and IV (high risk)	Anemia, thrombocytopenia	0.75–4
Binet group			
	A	Fewer than 3 areas of lymphadenopathy; no anemia or thrombocytopenia	12
	B	More than 3 involved node areas; no anemia or thrombocytopenia	7
	C	Hemoglobin < 100g/L; plates <100x10g/L	2–4

In everyday clinical practice there is a recommended number of methods and techniques to be the most optimal for the diagnosis of CLL. Biochemical parameters are easy to determine and allow for the assessment of activity and severity of disease in individual patients. Important markers of the proliferative activity and risk of progression in the serum of patients with CLL are inter alia, β-2-microglobulin (β-2-M), the level of soluble CD23 receptor (sCD23) and thymidine kinase (TK) (Cramer, Hallek, 2011). β-2-microglobulin is a 12kD protein associated with histocompatibility antigens, as a component of MHC class I molecules (Lisowska--Myjak, 2010). B-2-microglobulin is identified as a reliable prognostic marker for estimating survival time without treatment (TFS; treatment-free survival) and overall survival (OS) in patients with CLL. The simultaneous analysis of the level of this protein with the glomerular filtration rate is a clinically important parameter (Delgado et al., 2009). TK activity in patients with CLL reflects the proliferative potential of the malignant clone, and is a valuable addition to the diagnosis of CLL. Mutations of the immunoglobulin heavy chain variable genes (*IGVH*) and ZAP-70 expression is closely related to the high activity of thymidine kinase (Konoplev et al., 2010; Magnac et al., 2013). The stage of development of chronic lymphocytic leukemia and the forecasting of overall survival correlates with the level of sCD23. CD23 is a transmembrane glycoprotein on the surface of B cells with low affinity for immunoglobulin E (IgE). CD23 protein is unstable, and it is present in its soluble form in the serum. In CLL patients, the level of sCD23 is significantly higher than

in patients suffering from other diseases of the lymphatic system and healthy individuals. Doubling the level of sCD23 correlates with advanced stages of the disease and increases the risk of a more aggressive course of CLL. The concentration of sCD23 in the plasma is determined by ELISA (Meuleman et al., 2008; Kaaks et al., 2015). Markers of immunophenotype – ZAP-70, CD38 *IGVH* genes mutations, chromosomal aberrations characteristic of leukemia cells, are clinically significant in new clinical practices. ZAP-70 is a cytoplasmic protein tyrosine kinase (PTK), which was originally identified in T cells. ZAP-70 plays a key role in the maturation of T cells and its presence has not been observed in normal B cells. ZAP-70 may be a stronger risk factor for aggressive CLL than the lack of somatic hypermutation *IGVH*. There is no other mutation in the *IGVH* gene which correlates with a worse prognosis and a more aggressive course of the disease. The importance of ZAP-70 expressions as a prognostic factor is the confirmation of the need of evaluation in the routine diagnosis of patients with CLL. Based on the evaluation of ZAP-70 expression, it is possible to distinguish a group of patients with a worse prognosis at an early stage of the clinical disease. The expression of ZAP-70 can be determined by flow cytometry or immunocytochemistry technique (Burger, Chiorazzi, 2013). Numerous scientific reports suggest a relationship between clinical CLL and the activity of pro-apoptotic signaling pathway phosphatidylinositol 3-kinase – PI3K. Cytokine signals from the microenvironment affect the regulation of differentiation and maturation of B lymphocytes. The activity of PI3K is also connected to the negative selection of autoreactive B cells (Lafarge et al., 2014). Glycoprotein CD38 is a membrane antigen presented on cells derived mainly from the lymphoid lineage. Membrane expression of CD38 is an important prognostic factor and proliferation index in the diagnosis of CLL. Research on the functions of CD38 may help to explore the pathogenesis of CLL and be a suggestion in choosing therapy strategies in individual cases. There is a correlation between CD38 expression and the weakening of response to pharmacological treatment and shorter overall survival time (Malavasi et al., 2011). Simultaneous determination and analysis of factors such as TK, ZAP-70 and CD38 in the early phases of the disease makes it possible to start the cancer therapy and indicates the need for further study of their role in regulating the survival of B-CLL cells (Rivkina et al., 2011).

In literature, there is a constant verification of the usefulness of new prognostic markers. Regulatory T cells (Treg) are currently the subject of research into the pathogenesis and progression of chronic lymphocytic leukemia. The number of Treg cells in the peripheral blood of CLL patients is much higher compared to that of the control samples, and is dependent on the stage of the disease, high levels of LDH, β-2-microglobulin, and CD38 expression. Many authors also indicate the potential role of Treg cells in the pathogenesis of autoimmune cytopenias accompanying CLL. The current knowledge of manipulation of Treg cells may represent a future strategy for the treatment of patients with CLL (Andrzejczak et al., 2011; Arefi et al., 2015).

In recent years, there has been increased attention on the role of molecules of the TNF superfamily in the regulation of cell survival of B-CLL. Proinflammatory cytokines play a special role in the pathogenesis of CLL. In patients with CLL a significant increase in the level of TNF-α in blood serum has been observed. The coupling of elevated levels of cytokines in the serum of patients and anemia in patients with CLL, may suggest a role of TNF in the progression of chronic lymphocytic leukemia. Many authors indicate a close relationship between concentrations of TNF-α in patients with CLL with unfavorable prognostic markers, such as high expression of the antigen CD38 or ZAP-70 protein in leukemic cells. The results of the studies may provide a basis for the use of specific inhibitors of TNF-α because of the control of proliferation of leukemic cells. TNF-α is a factor engaging in the process of cell differentiation and may optionally be used as a predictor of overall survival (Singer et al, 2011; Wasik-Szczepanek, 2012).

Selective inhibitors of nuclear export (SINE)

Adjusting the nuclear-cytoplasmic transport plays an important role in maintaining cellular homeostasis. Exportin 1 XPO is responsible for the transport of more than 200 proteins – mainly suppressor proteins (TSP – tumor suppressor proteins), and growth regulators, including p53, p21, FOXO, PI3K/Akt, Wnt/β-catenin and NF-kB. It is characterized by the overexpression in other hematological malignancies. Small molecule selective inhibitors of nuclear export have been designed to specifically inhibit XPO 1. Exportin XPO 1 was first identified in the early 90s. From experiments it has been shown that the high expression correlated with progression of the clinical course of chronic lymphocytic B-cell leukemia. Overexpression of Mcl-1 prolongs the survival of CLL cells exposed to a variety of apoptosis-inducing stimuli. Mcl-1 is a protein belonging to the Bcl-2 family and acts anti-apoptically. Mechanisms of action and clinical significance of SINE have been analyzed, inter alia, in chronic lymphocytic leukemia. On the basis of preclinical studies, it was found that the lower SINE *MCL-1* in CLL cells produced an influence on the regulation of signal transduction pathways and metabolic pathways in CLL inhibit growth and induce apoptosis of CLL cells, which usually do not respond to conventional therapies. In the search for new therapeutic solutions, drugs that selectively inhibit nuclear exportins are now arousing interest (Lapalombella et al., 2012; Das et al., 2015).

According to the analysis of bibliographic data, chronic lymphocytic leukemia is clinically heterogeneous and in most cases an incurable disease, which is why a breakthrough in the effectiveness of the treatment is very important and awaited. Monoclonal antibodies have contributed to substantial progress in the treatment of chronic lymphocytic leukemia. In some cases the use of the therapeutic strategy can result in long-term remission, while in other patients there has been observed a high resistance to the applied therapy, and an aggressive course of disease progression. Due to the high probability of Richter's transformation, special attention is required

from clinicians. Early detection and diagnosis of a second cancer plays a key role in achieving therapeutic success. In recent years, rapid development of test methods, more accurate understanding of the biology of the disease, careful evaluation of clinical experience and numerous scientific papers on the pathogenesis of chronic lymphocytic leukemia have enabled thorough knowledge of many new factors which influence the development and course of the disease.

The diagnosis of cancer is a very difficult and sudden situation that affects a hierarchy of values and aims. Cancer influences rhythm of life, reduces physical activity, worsens mental wellbeing and causes many negative emotions such as: aggression, fear, regret, frustration, uncertainty or shame. Changes occur slowly and simultaneously in various areas of life. There are many factors that have an influence on physical, mental and emotional state of a patient and his family members. A long battle with life-threatening disease is connected with changes in a family system and personal and social life. Cancer may affect the family in a destructive way or, on the contrary, it can motivate to take action. Encouraging the patient to deal with the disease and to treat it in a proper way is very important. The majority of cases confront the family with the necessity of solving emotional and financial problems. The pharmacological help along with psychological assistance, discipline and following doctor's instructions lead to the improvement of treatment outcomes and to the decrease of undesirable effects. Targeting psychological help and undertaking psychological activities supporting patients during each step of therapy, as well as improving knowledge of psychological mechanisms of behaviour play vital role in the disease course.

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Chronic lymphocytic leukemia – clinical course, prognostic parameters, prognostic markers

Abstract

An increase in the number of patients diagnosed with cancer and death caused by malignant tumors has been observed in the world in recent years. The process of tumor formation is very complex and multistage. The pathogenesis of hematopoietic system diseases is mostly associated with anomalies in the signaling pathways, genetic and epigenetic modifications. The gene mutations responsible for DNA methylation and acetylation and methylation of histone proteins play an important role in the formation of hematologic malignancies. Disorders of the basic stages of hematopoiesis may result in uncontrolled proliferation and differentiation, and tumor initiation. Disorders of DNA repair mechanisms, as well as cell cycle deregulation may increase the risk of hematological malignancies. The basic division of hematologic malignancies are by their morphological traits, cytochemical and immunophenotyping of

cells. New reports of specific genetic and molecular disorders may become therapeutic targets and be used to monitor the remission and progression of diseases. Chronic lymphocytic leukemia (CLL) represents about 30% of adult leukemia and is a disease of the elderly people. CLL is usually diagnosed between 60 and 70 years of age, with a male to female ratio of 2:1. The disease occurs more frequently in Caucasians than in the Black and Asians population. The clinical course of the disease usually presents as a chronic condition and is very diverse. The deregulation of the immune system is manifested by reduced resistance, and the possibility of the emergence of autoimmune processes depends on the degree of development of the cancer. In most cases the therapeutic goal is to achieve complete remission and overall survival. Mutations of the immunoglobulin heavy chain variable genes (*IGVH*), blood biochemical markers, antigen CD38 and ZAP-70 expression and chromosomal abnormalities are amongst the most important prognostic parameters in CLL. The main objective of this review is to attempt to summarize the current information on clinical symptoms identified by genetic abnormalities and prognostic markers among patients with chronic lymphocytic leukemia.

Key words: pathogenesis of CLL, prognostic factors, chromosomal abnormalities

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