MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA

„NICOLAE TESTEMITANU" STATE UNIVERSITY OF MEDICINE AND PHARMACY

Musteata Vasile

CLINICAL FEATURES, DIAGNOSIS AND TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

(methodical guidelines for students)

Chisinau, 2021

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CONTENTS

LIST OF ABBREVIATIONS

CLL– chronic lymphocytic leukemia

CD – cluster of differentiation

ECOG – The Eastern Cooperative OncologyGroup

WHO – Word Health Organization

FISH – fluorescence in situ hybridization

IGHV – Ig heavy chain variable gene

BCRIs – B-cell receptor inhibitors

BTKIs – Bruton tyrosine kinase inhibitors

alloHSCT – allogeneic hematopoietic stem-cell transplantation

CLB – chlorambucil

BR – Bendamustine + Rituximab

FCR – Fludarabine + Cyclophosphamide + Rituximab

CIT – chemoimmunotherapy

PFS – progression-free survival

CHRONIC LYMPHOCYTIC LEUKEMIA

Definition

Chronic lymphocytic leukemia (CLL) is a monoclonal neoplasm characterized by the proliferation and accumulation of the apparently mature and immunologically incompetent lymphocytes in the bone marrow, lymph nodes, liver, spleen and peripheral blood. CLL is not homogeneous according to the morphological, immunophenotyping, cytogenetic, clinical and hematological patterns, response to treatment and prognosis. In 95-98% of cases the leukemia cells originate from B lymphoid progenitor cells and in 2-5% - from T lymphoid progenitor cells.

Preface

These methodical guidelines comprise the basic topics necessary for medical students to make the diagnosis of CLL, as well as elaborate treatment principles and personalized treatment strategies. The methodical guidelines constitute an effort to make the subject issues on CLL available, thus being perceived by the students. The major objective is to support the students of the Faculties of Medicine and Public Health. There have been defined the notions that will allow enriching the knowledge related to this field , as well as will provide useful data at all steps of knowledge assessment. An appropriate attention will be paid to the clinical activity of the students at the patient's bed, when carrying out practical skills, tests and clinical cases on the given subject. In order to achieve a better understanding of the subject issues presented in this methodical guidelines, we opted for using graphical materials (tables, figures, and diagrams), images, clinical cases and control tests.

Duration of the seminar

The seminar lasts 5 hours.

The aim of the seminar

To study the epidemiological patterns, etiology, pathogenesis, clinical features, laboratory tests and health careoptions applied for diagnosing CLL, synthesisof treatment principles and personalized strategies.

Objectives of the seminar

1. To build-up knowledge on the epidemiology, etiologyand pathogenesis of CLL;
2. To developknowledge on the clinical, hematological, morphological, immunophenotyping and cytogenetic features of CLL;
3. To acquire practical skills in CLL diagnosis;
4. To build-up knowledge ondifferential diagnosis of CLL;
5. To develop general principles and personalized strategies of CLL treatment.

The seminar will be proceeded

1. On Hematology Discipline, at "Nicolae Testemitanu" SUMPh, in groups of students, by using study modules.
2. Within the Hematology units at the Hematology Department of the PMSI Institute of Oncology of the Republic of Moldova.
3. Within the Hematology centres at the Consulting Diagnostic Centre of the PMSI Institute of Oncology of the Republic of Moldova.

Methods and materials used for the seminar

Teaching methods to be used

Teaching methods and procedure, involved in the effective learning and achievement of the suggested objectives, are as following:

- presentation of the subject by formulation of definitions, description, explanation and demonstration;
- joint interactive discussion;
- problem-solving cases;
- data summarizing and synthesizing.

Various forms of independent, frontal, group, interactive activities are used at the seminars.

Methods of evaluation

- questioning on the study issue;
- problem-solving situations;
- analysis of clinical cases;
- single choice and multiple choice tests;
- individual work;
- assessment of practical skills;
- taking exam.

Materials used at the seminar

Teaching materials such as tables, schemes, algorithms, digital images, international guidelines are used for broader learning of CLL. Power Point presentations are alsoappliedduringthe seminars.

Questions for students' self-training

1. Epidemiology and etiology of CLL.
2. Pathogenesis of CLL.
3. Clinical classification and staging of CLL.
4. Clinical features of CLL.
5. Clinical types of CLL.
6. Diagnosis of CLL, including the value of immunophenotyping.
7. Hematological patterns of CLL.
8. The value of the bone marrow biopsy in CLL.
9. Differential diagnosis of CLL.
10. Principles and options of treatment of CLL.
11. Evolution and prognosis of CLL.

Epidemiology of chronic lymphocytic leukemia

Regarding the structure of leukemia morbidity, LLC ranks second after acute leukemia [1,2,3,5,8]. LLC has notbeen reported in children. Approximately 70% of patients are aged between 50-70

years [2,3,4,6,7,8]. The average age at time of diagnosis is 55 years. CLL is more common in males. Global CLL incidence is not geographically homogeneous. This type of leukemia is quite common in European countries, Canada, USA, and rarely registered in East and South-East Asia (India, Japan) [1,3,7,8]. The incidence of CLL in the USA is 1.3-2.2, Norway - 1.2, Poland - 1.0, Japan - 0.08 per 100000 inhabitants. In Europe, the incidence rate for all subtypes of leukaemia is 7.2 per 100,000, of which 34% of cases are CLL, reporting approximately 12,500 new CLL cases per year. Each year, CLL is responsible for approximately 6000 deaths across Europe [9].The incidence of this leukemia in the Republic of Moldova is 1.2 per 100000 inhabitants. According tothe morbidity data on malignant tumours, described in 1973-1977 across 11 US states, the incidence of CLL in white males was 5.2, in white females - 2.6, in Chinese people (both genders) - 1.0 and in Japanese - 0.2 [2,3,4,5,7,8]. These data prove the role of ethnic groups and indicate the importance of genetic factors in the development of CLL [3,7]. These above mentioned data can be evidenced by the occurrence of CLL cases among people from the same family.

Etiology of chronic lymphocytic leukemia

The etiology of CLL is not definitely studied. The ionizing radiation, alkylating agents and leukemogenic chemicals involved in the etiopathogenesis of other leukemias do not relate to CLL triggering factors [2,3,4,5]. The most important factor is the genetic predisposition.

Pathogenesis of chronic lymphocytic leukemia

The progressive accumulation of CD5-positive B cells is the mainfeature of CLL pathogenesis due to a failure in programmed cell death or apoptosis *(Figure 1).* Neoplastic CLL B cells are antigen-experienced, expressing CD23, CD25, CD27, CD69, CD71, ROR1 and CD20 [9,10]. The immunoglobulin heavy chain variable region

(IGHV) gene is mutated in half of the cases, and unmutated in the rest of cases. The immunoglobulin gene repository in CLL shows biased (non-random) VH usage compared to normal B cells. This restricted VH usage relates to the degree of somatic hypermutation.

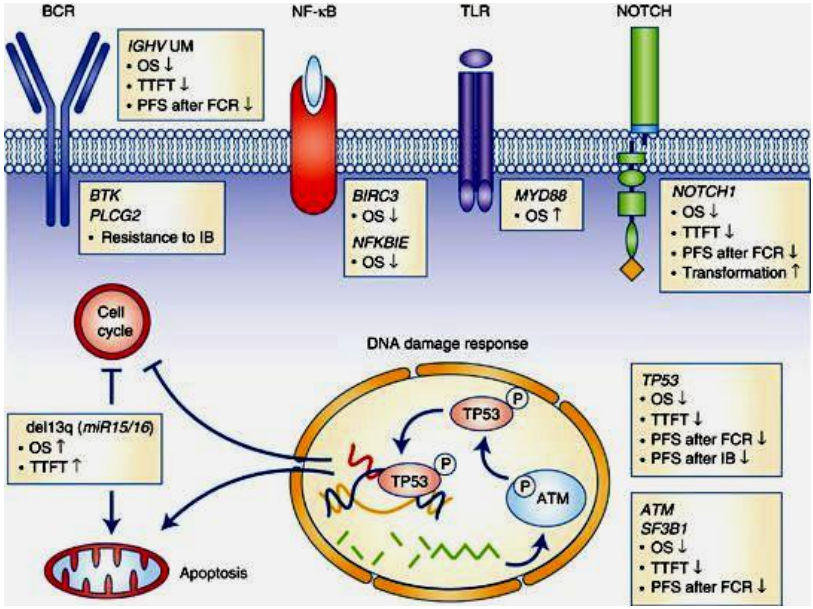

Figure 1. **Pathogenesis of CLL**
[British Journal of Cancer 2016, 114: 849–854]

The pathogenesis of CLL involvesaclose relationship of B cells, through the B-cell antigen receptor (BCR), microenvironment and T cells [9,10]. Normal B cells have the ability to proliferate in response to antigens, where single B cells will proliferate extensively in a very short period of time to create the primary and secondary immune response. CLL cells use the BCR signaling pathway to rapidly proliferate. Furthermore, normal B cells that are self-reactingare deleted or anergized to prevent autoimmunity. In CLL, many of the antigens to which the CLL cell respond provide evidence of beingself-antigens. Thereafter, normal B cells have to be removed (apoptosed)

when the antigen they are responding to has been cleared with a very small proportion becoming long-lived memory cells. All of these features are part of the CLL cell biology, which is proliferative when given the correct signals, however, this may lead to autoimmunity, showing dysfunctional apoptotic mechanisms (ubiquitous expression of BCL-2) [3,4,9,10]. This type of abnormalities causes the accumulation of mature CLL B cells. Nevertheless, all CLL cases are preceded by a subclinical phase consisting of a high number of polyclonal B cells that would be subsequently selected and expanded upon the influence of some genetic events. This would give rise to a monoclonal B-cell lymphocytosis (MBL)-like picture. The accumulation of genetic alterations might lead to transformation of a small proportion of MBL clones to CLL. Genetic drivers of this effect are the deletion of miR15 and miR16 in chromosome 13q14, trisomy 12 and MYD88 mutations. Over time, other mutations appear, including those involving TP53, ATM, NOTCH1 and SF3B1. Finally, in the most advanced cases, C-MYC and CDKN2A mutations can also occur. Through a selection process, a minute clone harbouring these genetic lesions can overcome other clones and become predominant.

Clinical classification and staging of chronic lymphocytic leukemia

The clinical picture of CLL depends on the extent degree of the tumor process at the time of diagnosis [3,8]. There are two classifications that reflect the clinical stages of CLL [1,2,9,10]. Staging is important in determining the prognosis of the disease and assessing the results of treatment. One of them was proposed in 1977 by J. Binettogether with the co-authors and is mainly used in Europe *(Table 1).* The second classification was published earlier in 1975 by K. Raiet.al. and is mostly applicable in the U.S.A. *(Table 2).*

Table 1. **CLL staging according to J. Binet classification**

Stage	Criteria	Median survival (years)
A	Hemoglobin value more than 10.0 g/dL, platelet count more than 100.0 x 103/μL, lymph node enlargement in 1-2 anatomical areas	> 10
B	Hemoglobin value more than 10.0 g/dL, platelet count more than 100.0 x 103/μL, lymph node enlargement in 3 and more anatomical areas	>6
C	Hemoglobin value less than 10.0 g/dL, platelet count less than 100.0 x 103/μL in association withlymph node enlargement in 1 and more anatomical areas, regardless of the internal organs involvement	≈ 6,5

Clinical features, types and complications of chronic lymphocytic leukemia

Approximately 25% of stage A cases evolve asymptomatically (when the leukocytes count is below 30 x 103/μL) and are occasionally detected by a routine haematological examination. General symptoms occurin stage B and C: asthenia, profuse sweating, exaggerated physical weakness, loss of working capacity and weight loss.The main objective clinical signs are lymphadenopathy, splenomegaly and hepatomegaly. The enlarged lymph nodes are painless, soft, mobile, symmetrical andvarious in size (0.5-5 cm) [3,4,10,11]. Both superficial and deep lymph nodes (hyllary, mediastinal and abdominal) may be involved. The splenomegaly is frequently revealed (in 90% of cases), being rarely within the normal ranges. The hepatomegaly is also common (in 50% of cases). Tonsils hyperplasia is found in 70% of patients (1,2,3,10).

Table 2. **CLL staging according to K. Rai classification**

Stage / Risk group	Criteria	Prognosis	Median survival (years)
0 / low	Lymphocytosis > 5,0 x 103/μL in the peripheral blood and >40% in the bone marrow	Favorable	> 10
I / intermediary	Lymphocytosis + lymph node enlargement	Intermediary	> 8
II / intermediate	Lymphocytosis + splenomegaly and (or) hepatomegaly, regardless of the lymph node enlargement	Intermediary	> 6
III / high	Lymphocytosis + hemoglobin value < 11.0 g/dL, regardless of the lymph node enlargement and organ involvement	Unfavorable	1.5-2
IV / high	Lymphocytosis + platelet count < 100.0 x 103/μL, regardless of the anemia, lymph node enlargement and organ involvement	Unfavorable	

In stage C, the somatic decompensation of patients occurs. The lymph nodes are considerably enlarged, severe anemia develops, and patients experience weight loss up to cachexia. The disease may shift into diffuse large B-cell non-Hodgkin's lymphoma, with the rapid growth of a hard lymph node group Richter). Hemorrhagic syndrome of thrombocytopenic origin may develop. The blast crisis occurs in very few cases in the last stage [1,3,7,8].

LLC has a variable clinical evolution, which determines the development of different disease types: benign, classic type with constant progression, tumoral, splenic, osteomedullary, T-cell and prolymphocytetypes [3,4,7].

CLL-related complications:

1. Infectious: bacterial and viral complications due to immunedeficiency and neutropenia (acute pneumonia, acute otitis, abscesses, sepsis, Herpes Zoster, etc.);

2. Bone marrow failure;

3. Autoimmune: autoimmune hemolytic anemia, autoimmune thrombocytopenia, autoimmune neutropenia;

4. Conversion to prolymphocytic leukemia;

5. Occurrence of secondary solid tumors: melanoma, bronchopulmonary cancer, colorectal cancer, etc.

Diagnosis of chronic lymphocytic leukemia. The value of immunophenotyping

According to the International Workshop on CLL (IWCLL), the diagnosis of CLL is confirmed by the following parameters [9,10]:

- Presence of monoclonal B lymphocytes >5 x 103/μL in peripheral blood, lasting for at least 3 months;
- Evidence on population clonality (flow cytometric analysis of kappa (κ) andlambda (λ) light chain ratio);
- Immunophenotype characteristics: SmIg weak, CD5+, CD19+, CD20, CD23+.

Based on immunophenotypic characteristics and giving one point to eachone of the following: CD5+, CD23+, FMC7 weak, SmIg (κ/λstaining) weak and CD79b weak, Matutes and Catovsky showed that patients with a 4–5 scoring are nearly always diagnosed with CLL, while cases with a score <3 are extremely unlikely to be diagnosed with CLL. Evidence of CD38 and ZAP70 may be required for prognosis assessment. Molecular analysis for detecting Ig heavy chain variable (IGHV) gene mutation status may be also recommended. Cytogenetic examinations (preferably FISH) are useful for the detection of del (17p-), del (11q-), +12, del (13q-), TP53 mutation. Nevertheless, cytogenetic examination may be delayed in patients who do not require treatment at diagnosis [12].

Bone marrow aspiration shows an increased rate of lymphocytes (over 30%) that is helpful in early diagnosed cases.

Lymph node biopsy is needed in cases of CLL transformation into diffuse large cell non-Hodgkin's lymphoma (Richter syndrome) or Hodgkin's lymphoma [12].

Computed tomography scan and magnetic resonance imaging are not commonly recommended in asymptomatic patients. Computed tomography scan may be recommended in symptomatic patients, namely in pulmonary symptomatic patients, in order to exclude pulmonary infiltration or pleural effusion by CLL. Magnetic resonance imaging, chest x-ray, or abdominal ultrasound may be considered as alternatives if computed tomography is contraindicated or if the scan is not available [11].

Hematological patterns of chronic lymphocytic leukemia

Leukocytosis occurs due to lymphocytosis, which is the main symptom of the disease. The absolute number of lymphocytes increases over 10 x 103/μL. In most cases the leukocyte count varies between 20 x 103/μL and 200 x 103/ μL, rarely exceeding 500 x 103/μL [3,4,11]. Lymphocytes in CLL are small, with condensed nucleus chromatin and a very narrow cytoplasm. Gumpreht shadows (semi-destroyed lymphocytes) are also detected. There is also a population of larger lymphocytes with more dispersed chromatin, sometimes with nucleoli (<10%), called prolymphocytes. The rate of these lymphocytes may increase significantly in the advanced stages [6,7,12]. Anemia is common in advanced CLL, indicating stage C of the disease when hemoglobin drops below 10 g/dL [3,7,8,11]. Anemia deepens progressively due to the nodular dislocation and acute hemolysis. Erythrocytes are normocytic and normochromic. Reticulocytes are usually within the normal limits, however they increase in caseof hemolysis. The sudden onset of a severe anemic syndrome is usually the consequence of the autoimmune haemolysis. In order to assess the autoimmune origin of anemia, a direct Coombs test is performed. Like anemia, thrombocytopenia is a sign of advanced disease, characterizing stage C of CLL, when the number of platelets

drops below 100 x 103/μL. It is commonly due to the dislocation of megakaryocytes by lymphocytic infiltration of the bone marrow. Thrombocytopenia is probably of autoimmune origin in cases when the platelets count is rapidly corrected, whereas the megakaryocytes are normal or increased in the bone marrow [3,6,11,12].

The value of bone marrow biopsy in chronic lymphocytic leukemia

Bone marrow biopsy can be useful in cases with complexity of diagnosis, as well as to provide relevant information on the origin of cytopenias (i.e. bone marrow failure due to leukemic infiltration versus "peripheral mechanisms" such as hypersplenism or autoimmunity). The bone marrow displays a variable degree of infiltration by the disease and, compared to follicular lymphoma, there is no paratrabecular infiltration [9,10]. Four infiltration types have been described: nodular, interstitial, mixed (nodular+interstitial) and diffuse.

Nodular type: the presence of nodules formed by mature lymphocytes, the nodules being larger than physiological lymphoid follicles.

Interstitial type: lymphocyte infiltration between closely spaced normal bone marrow cells.

Mixed: combination of nodular and interstitial types.

Diffuse: lymphocytes form an extremely dense reticulation/ webbing/tracery, which almost completely replaces hematopoietic tissue and adipocytes.

While in early clinical phase nodular and interstitial patterns predominate, in advanced phase a diffuse infiltration is a norm. Generally, bone marrow biopsy and immunohistochemistry test are not required, if flow cytometry is performed. The marrow biopsy may be considered as a baseline parameter to assess treatment response.

Differential diagnosis of chronic lymphocytic leukemia

In stage A, the differential diagnosis of CLL should be performed with infectious mononucleosis and infectious lymphocytosis [6,7,8,12]. In patients with infectious mononucleosis, the lymphocytes are large with less condensed chromatin and a well-marked cytoplasm, usually basophilic.

In patients with asymptomatic infectious lymphocytosis, changes in the blood count are not stable and tend to regress.

In stage B and C, the differential diagnosis is made with indolent small-cell non-Hodgkin's lymphoma with leukemic conversion and hairy-cell leukemia.

In indolent non-Hodgkin's lymphomas with leukemic conversion, the primary tumor focus is commonly detectable, from which the neoplastic process spreads to the other anatomical areas, not being generalized at the onset of the disease. The disease is characterized by the absence of a correlation between leukocytosis and lymphocytosis, and tumor sites comparatively larger than the leukocyte count. In patients with non-Hodgkin's lymphomas, the percentage of lymphocytes in the blood count often does not correspond to that in the bone marrow aspirate. After successful treatment of non-Hodgkin's lymphomas, blood leukocytosis usually disappears, which is not seen in CLL cases. Differential diagnosis is assessed by immunophenotyping, cytogenetic and molecular tests [6,9,10].

The main clinical symptom of hairy-cell leukemia is splenomegaly. Lymphadenopathy is a very rare and insignificant manifestation. Infectious complications develop frequently due to the presence of neutropenia. Pancytopenia with lymphocytosis is reported in complete blood count. Tumor lymphocytes have special morphological features. The nucleus of these lymphoid cells has less compact chromatin than the lymphocytes in the classicCLL type. The cells are larger with a well-marked cytoplasm. The hairy extensions outset from the cytoplasm. Cytochemically, these cells are characterized by a positive reaction to acid phosphatase, which is not inhibited by

sodium tartrate. The diagnosis is definitively proved by the bone marrow biopsy and immunophenotyping [1,3,6,8].

Principles and updated options of treatment of chronic lymphocytic leukemia

Since most CLL cases remain incurable, the treatment is aimed to improve quality of life and to increasethe survival rate. In daily life, important treatment end points, such as response rate, MRD status or progression-free-survival, may be more relevant for young and/or fit patients than in older patients and/or patients with relevant comorbidities.

Treatment of early stage disease (Binet stage A and B without active disease; Rai 0, I and II without active disease)

The standard treatment of patients with early inactive disease is a watch-and-wait strategy (I, A, B). Blood cell counts and clinical examinations should be carried out every 3-12 months after the first year, when 3-monthly intervals should be applied for all patients.

Treatment of advanced stage disease (Binet stage A and B with active disease or Binet stage C; Rai 0-II with active disease or Rai III-IV)

For first-line therapy, different treatment strategies are available *(Figure 2);* continuous treatment with BTKIs such as ibrutinib until progression or time-limited therapy with ChT backbone and CD20 antibodies. The United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved the combination of venetoclax plus obinutuzumab as first-line therapy for CLL.CIT-free regimen is an alternative third option. The treatment decision should include an assessment of IGHV and TP53 status, as well as patient-related factors such as concomitant medication, comorbidities, preferences, drug availability and potential of treatment adherence. Therapy until progression with ibrutinib alone or in combination with CD20 antibodies has yielded a longer PFS when compared with fixed duration CIT (FCR, BR, chlorambucil plus obinutuzumab) in phase III randomised trials [11,17].

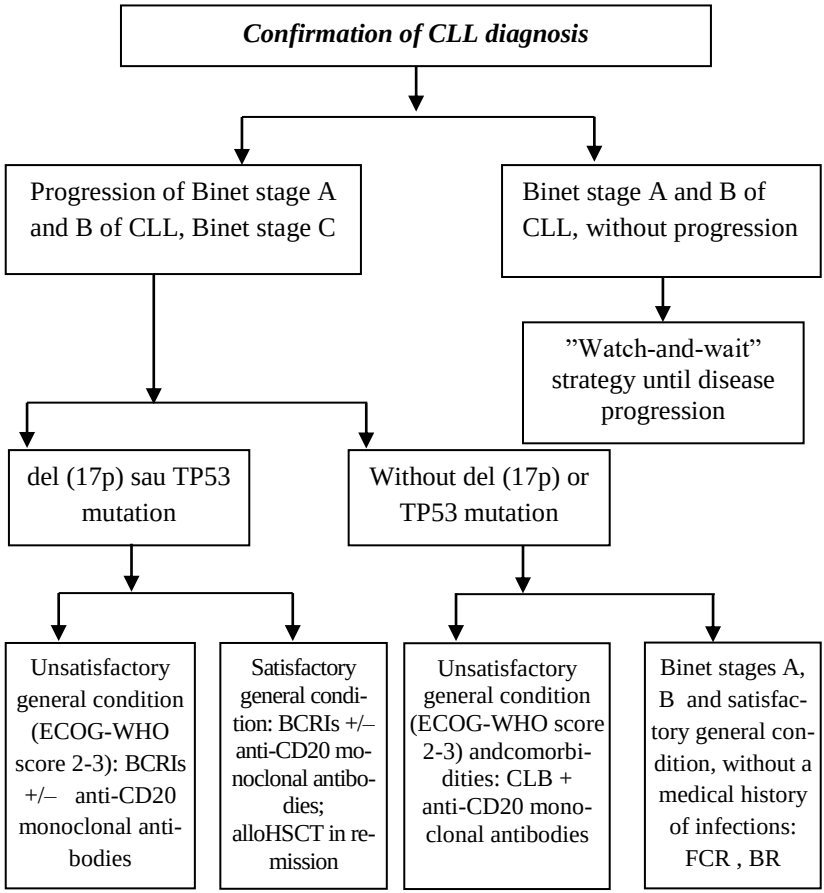

Figure 2. **Algorithm for the treatment of newly-diagnosed chronic lymphocytic leukemia**

Treatment of relapse and refractory disease

As in first-line therapy, treatment of relapses should be started in symptomatic patients and not simply at the time of its re-occurrence *(Figure 3)* [13]. Many patients with recurrent but asymptomatic CLL can be followed up without therapy for an extended period of time. Even the cessation of a continuous BTKIs (ibrutinib or others) or idelalisib or venetoclax administration (for example due to the side-effects) does not necessarily require an immediate alter-

native treatment, especially if recurrent CLL. In case of rapid progression of targeted drugs, an immediate change in therapy is recommended. In case of symptomatic relapse within 3 years after a fixed-duration therapy or therapeutic non-response, the treatment approach should be changed, regardless of the type of first-line therapy (CIT or novel therapies).One of the two following treatment options should be considered [14,15,16]:

- Venetoclax plus rituximab for 24 months;
- Ibrutinib or acalabrutinib or other BTKis (if available) as continuous therapy.

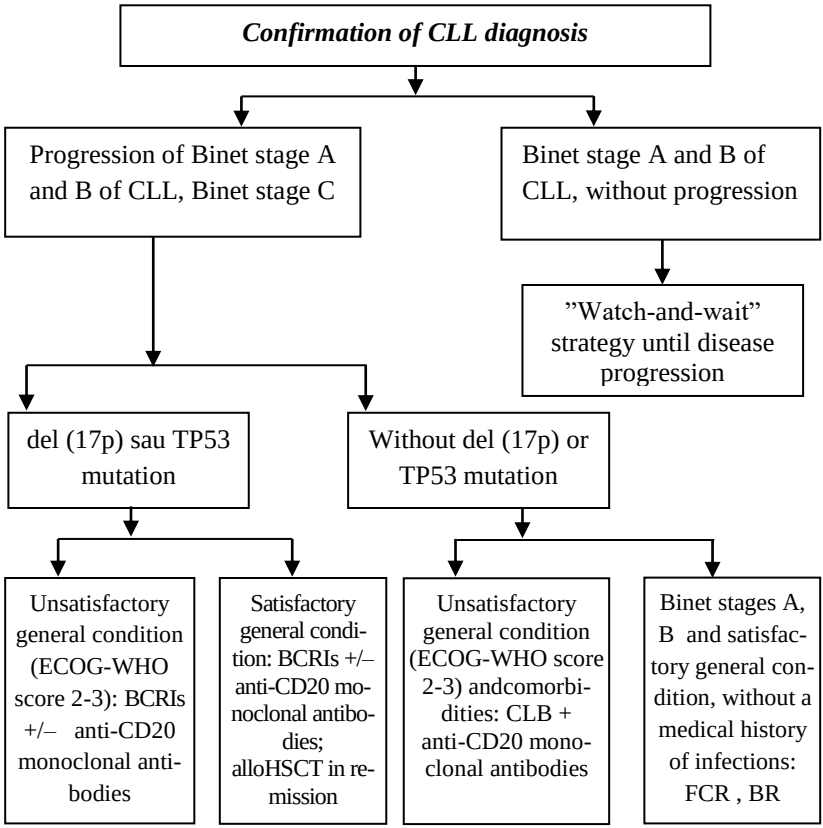

Figure 2. **Algorithm for the treatment of newly-diagnosed chronic lymphocytic leukemia**

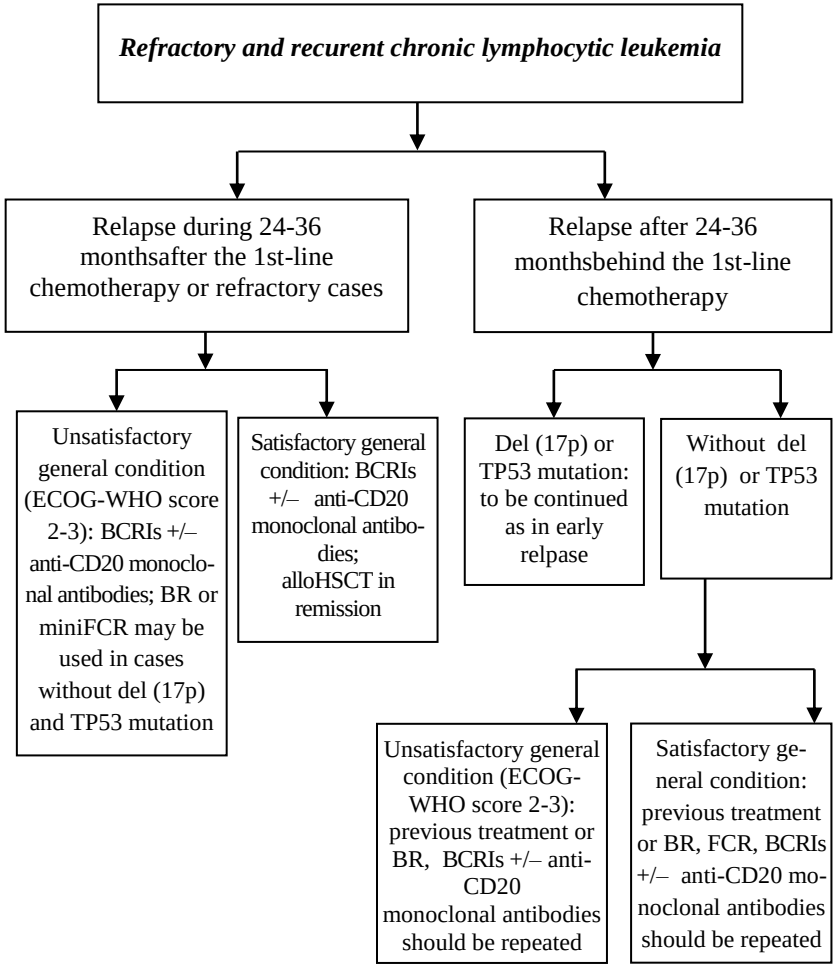

Figure 3. **Algorithm for the treatment of recurrent and refractory chronic lymphocytic leukemia**

Treatment of CLL complications.

The treatment of patients with autoimmune cytopaenias should be peformed according to the recommendations of the International Workshop on CLL guidelines [13] and ofthe ESMO guidelines consensus conference on malignant lymphoma [18]. Most patients with autoimmune cytopaenias, specifically those with warm auto-antibodies, respond to high-dose corticosteroids. For patients not responding to corticosteroids, rituximab alone or in combination with cyclophosphamide and dexamethasone might be a reasonable treatment option, as well as BR.

Infectious complications are common in CLL patients. The use of prophylactic Ig replacement therapy does not exert an impact on the overall survival [19], being recommended only in patients with severe hypogammaglobulinaemia, as well as in recurrent or severe infections. Antibiotic and antiviral prophylaxis should mainly be used in cases with recurrent infections and/or high risk of developing infections (for example, pneumocystis prophylaxis with co-trimoxazole during treatment with CIT based on purine analogues or idelalisib).

Life-long observation and follow-up is recommended for all CLL patients. In asymptomatic patients, the follow-up should include a blood cell count and the palpation of lymph nodes, liver and spleen every 3-12 months depending on the dynamics of the disease [11]. CLL patients have a two- to sevenfold increased risk of developing secondary malignancies (commonly solid cancers, but also secondary myelodysplastic syndromes, acute myeloblastic leukaemia).

Evolution and prognosis

The average lifespan of patients with CLL varies from 3.5 to 6 years. Survival continues to increase in chronic lymphocytic leukaemia and may reach 15 years in low- and intermediate risk groups.

The markers of the unfavorable prognosis are:

- Generalized stages (C and III-IV) according to K. Rai and J. Binet classifications;

- Male gender;
- Doubling the number of lymphocytes within the last 12 months;
- Diffuse and mixed infiltration of the bone marrow (according to histological examination);
- Increase of prolymphocytes number in the blood count;
- Insufficient response to chemotherapy;
- High level of β 2-microglobulins;
- High expression of Ki67, p27;
- Presence of mutations in the p53 tumor suppressor gene.

Favorable prognostic factors:

– IGHV mutated mutational status (<98% homology to germ-line conformation),
– CD38 <30%, ZAP70 <20%,
– Del (13q-) as the only one anomaly.

Unfavorable prognostic factors:

– IGHV unmutated mutational status (> 98% homology to germ-line conformation),
– CD38 ≥ 30%, ZAP70 ≥ 20%,
– del (11q-), del (17q-).

Clinical case studies

Clinical case 1

An 18-year-old man complains of malaise, fatigue, headache, dyspnea on physical exertion for over one month. The overall condition aggravated last week. He developed high fever 39, sore throat, nose and gums bleeding.

Physical exam: Skin paleness. Petechiae and bruises on the skin and mucous. On palpation, enlarged peripheral lymph nodes up to 5 cm are detected. Nose and gum bleeding. Hyperemia of the pharynx. Lungs: vesicular murmur. Rhythmic heart sounds. Blood pressure– 120/75 mm Hg. Soft and painless abdomen. The liver is palpable + 3 cm below the costal margin. The spleen is palpable + 7 cm below the costal margin.

Peripheral blood count: Hb – 72 g/l, RBC– 2,4x1012/l, WBC – 132x109/l, reticulocytes – 80‰, PLT – solitary, unseg. – 6%, segm.- 20%, lymph.- 74%, erithrocyte sedimentation rate – 84 mm/h, Ht – 39%.

Biochemical test: all parameters are within the reference range.

Abdominal ultrasound: Splenomegaly: 20x11 cm, homogeneous structure. Hepatomegaly: RL 17 cm, LL 11 cm, diffuse changes.

1. What diagnosis would you determine?
2. Could you develop the investigation plan?
3. How would you perform the differential diagnosis?
4. Could you develop the treatment plan?

Clinical case 2

A 78-year-old woman presents general malaise and fatigue. She was treated for acute viral infection by a therapist. The peripheral blood count exhibited certain changes, thus she was referred to a hematologist.

Physical exam: Normal skin color. Skin hemorrhages are not detectable. All groups of the peripheral lymph nodes are palpable up to 1 cm. In the lungs: vesicular murmur. Rhythmic heart sounds. Blood pressure – 120/75 mm Hg. The spleen and the liver are palpabe at the costal margin.

Peripheral blood count: Hb112 g/l, RBC – 3,7x1012/l, WBC – 52,0x109/l, reticulocytes - 3‰, PLT – 130,0 x109/l, unseg.- 1%, segm.- 8%, lymph.- 81%, monocytes – 4%, erithrocyte sedimentation rate – 14 mm/h, Ht – 45%.

Biochemical test: LDH 587 U/H, other parameters are within the reference range.

Bone marrowaspiration: hypercellular, lymphocytes - 96%.A low number of megakaryocytes.

Immunophenotyping of the peripheral blood: CD5+, CD20+, CD23+.

Abdominal ultrasound: Splenomegaly: 14.5x8 cm, homogeneous structure. Liver: RL 14 cm, LL 7 cm, diffuse changes.

1. What diagnosis would you determine?
2. How would you perform the differential diagnosis?
3. Could you develop the treatment plan?

Control tests

S In chronic lymphocytic leukemia, the morphological substrate of the tumor contains:

A. Blast cells
B. Granulocytes
C. Mostly mature lymphocytes
D. Lymphoblasts
E. Plasmacytes
Correct answer: 120 – **C**

S The autoimmune hemolytic anemia associated with autoimmune thrombocytopenia commonly complicates:

A. Acute lymphoblastic leukemia
B. Chronic myeloid leukemia
C. Acute promyelocytic leukemia
D. Chronic lymphocytic leukemia
E. Chronic monocytic leukemia
Correct answer: 121 – **D**

S The following clinical features are true for the diagnosis of hairy cell leukemia:

A. Generalized lymph nodes enlargement and splenomegaly
B. Generalized lymph nodes enlargement and pancytopenia
C. Splenomegaly and hyperleukocytosis
D. Hepatosplenomegaly and hyperleukocytosis
E. Splenomegaly and pancytopenia
Correct answer: 122 – **E**

S In chronic lymphocytic leukemia, the first-line therapeutic option is as following:

A. Chlorambucil
B. Cyclophosphamide
C. Melphalan
D. Busulfan
E. Vincristine
Correct answer: 123 – **A**

S The Gumprecht shadows in the blood smear of the CLL patient show:

A. Functional platelets disorder
B. Fragility of lymphoid cells
C. Marked hypersplenism
D. Intravascular hemolysis
E. None of the above mentioned signs
Correct answer: 131 – **B**

S Terminal phase of chronic lymphocytic leukemia is manifested by:

A. Sarcomatization
B. Blast crisis
C. Hypoplastic anemia
D. Chronic myeloid leukemia
E. Leukopenia
Correct answer: 132 – **A**

S Chronic lymphocytic leukemia develops commonly in:

A. Females
B. Children
C. Young patients
D. Persons aging over 45, predominantly in males
E. Adolescents
Correct answer: 134 – **D**

S In chronic lymphocytice leukemia mutation occurs in:

A. Stem cell
B. Lymphoid cell precursor
C. Lymphoid B-cell precursor, which is differentiated up to the stage of plasmacyte
D. It is a systemic disease, which results from the disturbance of hematopoieticcells differentiation
E. Malignant transformation takes place in blast cells of the bone marrow
Correct answer: 135 – **B**

S The advanced stage of chronic lymphocytic leukemia is characterized by:

A. the satisfactory patient's overall condition;
B. frequent development of sarcomatization;
C. non-palpable liver and spleen;
D. normal range of peripheral blood smear analysis;
E. not increasedlymph nodes
Correct answer: 95 – **B**

S Which of the following statements on the advanced stage of chronic lymphocytic leukemia is true:

A. in very few cases blast crisis occurs;
B. somatic patients are compensated;
C. lack of tumor enlargement on the examination of patients;
D. bone marrow aspiration is within the normal range;
E. it is very rarely complicated by intercurrent infections and autoimmune processes
Correct answer: 96 – **A**

S In the initial stage of chronic lymphocytic leukemia the following preparations are used:

A. Leucheranul
B. Cyclophosphamide
C. specific treatment is not administered
D. Vincristine
E. Fludarabine
Correct answer: 97 – **C**

S The stage of clinical hematological manifestations of chronic lymphocytic leukaemia is characterized by:

A. enlargement of peripheral lymph nodes, as well as an enlarged liver and spleen;
B. weight loss up to cachexia;
C. somatic patient are compensated;
D. peripheral blood analysis reveals leukopenia;
E. blast cells are frequently detected
Correct answer: 98 – **A**

S Chronic lymphocytic leukemia is frequently complicated by:

A. autoimmune hemolytic anemia and autoimmune thrombocytopenia;
B. infarcts in the spleen;
C. thrombosis at the level of small vessels;
D. neuroleukemia
E. blast crisis
Correct answer: 99 – *A*

S In the early stage of chronic lymphocytic leukemia:

A. Lymph nodes are notenlarged, while the liver and spleen are not palpable
B. Marked splenomegaly
C. Bones and liver are frequently involved
D. Neuroleukemiadevelops
E. Marked hepatomegaly
Correct answer: 136 – **A**

S In the early stage of chronic lymphocytic leukemia the peripheral blood analysis reveals:

A. Blast cells
B. Leukopenia
C. Leukocytosis up to 200.0 – 300.0 x 109/l
D. Myeloma cells
E. Leukocytosis up to 30.0 x 109/l and lymphocytosis 70–90%
Correct answer: 137 – **E**

S In the advanced stage of chronic lymphocytic leukemia, the peripheral blood examination reveals:

A. Leukopenia
B. Myeloma cells
C. Blast cells
D. Leukocytosis up to 500.0 – 600.0 x 109/l and lymphocytosis 90%
E. Lymphopenia
Correct answer: 138 – **D**

S The developed stage of chronic lymphocytic leukemia is characterized by:

A. Central nervous system involvement
B. Frequent involvement of flat bones
C. Peripheral lymph nodes enlargement, the liver and spleen are palpable
D. Isolated involvement of the liver
E. Marked skin itching
Correct answer: 139 – **C**

C Which of the following statements on the diagnosis of chronic lymphocytic leukemia are true:

A. Infectious complications frequently occur
B. The first-line treatment includesMelphalan
C. Leukocytosis is caused by absolute lymphocytosis
D. Polyclonal character of lymphoid infiltration
E. The cause of anemia is always autoimmune hemolysis
Correct answer: 260 – **A, C**

C Chronic lymphocytic leukemia is a tumor of hematopoietic system, originating from:

A. Stem cell
B. Lymphoid B-cell precursor
C. Lymphoid T-cell precursor
D. Myeloid cell precursor
E. Blast cell
Correct answer: 261 – **B, C**

C The causes of anemia in chronic lymphocytic leukemia are as following:

A. Iron deficiency
B. Vitamin B12-deficiency
C. Autoimmune hemolysis
D. Bleeding
E. Bone marrow involvement
Correct answer: 262 – **C, E**

C Chronic lymphocytic leukemia is:

A. B-cell lymphocytic leukemia in 94 – 95% of cases
B. Neoplasia with morphological substrate composed of blast cells
C. T-cell lymphocytic leukemia in 5 – 6% of cases
D. A systemic disease
E. A disease, which affects mostly young persons
Correct answer: 276 – **A, C**

C Chronic lymphocytic leukemia is characterized by:

A. Domination of blast cells in the peripheral blood count
B. Frequent involvement of the gastrointestinal tract
C. Peripheral lymph nodes enlargement
D. It develops and progresses rapidly
E. Liver and spleen involvement
Correct answer: 278 – **C, E**

C The developed stage of chronic lymphocytic leukemia is characterized by:

A. Generalized lymph nodes enlargement
B. Richter syndrome
C. Splenomegaly
D. Frequent infectious complications
E. Central nervous system involvement
Correct answer: 362 – **A, C, D**

C Infectious complications in chronic lymphocytic leukemia are caused by:

A. Marked neutropenia
B. Hypersplenism
C. It occurs concomitantly with Richter syndrome
D. Immune deficiency
E. Long-lasting treatment with glucocorticoids
Correct answer: 363 – **A, D, E**

C In chronic lymphocytic leukemia the prognosis depends on:

A. The disease phase
B. The extent of lymphoid infiltrate in the bone marrow
C. Patient age

D. Gender
E. Tumor mass at time of diagnosticconfirmation
Correct answer: 364 – **A, B, E**

C The following statements are true for the diagnosis of chronic lymphocytic leukemia:
A. Sarcomatous growth does not develop
B. It affects persons over 45 , predominantly males
C. Leukocyte count may reach the values of several hundred thousands
D. The morphological substrate is composed of mature lymphocytes
E. Splenectomy is widely practicable
Correct answer: 378 – **B, C, D**

C The terminal stage of chronic lymphocytic leukemia is manifested by:
A. Body weight loss up to cachexia
B. The lymph nodes, liver and the spleen are considerably enlarged
C. The patient's satisfactory performance status
D. Blast crisis develops frequently
E. Progressive anemia and thrombocytopenia
Correct answer: 379 – **A, B, E**

C Chronic lymphocytic leukemia is characterized by:
A. Leukopenia associated with lymphopenia
B. Detection of Gumprecht shadows (damaged lymphocyte nuclei)
C. Lymphocytosis up to 90%
D. The leukocyte count may reach the values of 500.0 – 600.0 x 109/lin the advanced stage
E. Vascular complications: cerebral, mesenteric and venous thrombosis
Correct answer: 380 – **B, C, D**

C In hairy cell leukemia the indications for splenectomy are:
A. Marked cytopenia
B. Frequent infectious complications

C. Autoimmune complications
D. Massive splenomegaly
E. Generalized lymph nodes enlargement
Correct answer: 460 – **A, B, C, D**

C Chronic lymphocytic leukemia has the following clinical types:
A. Benign type
B. Classic type with continuous progression
C. Tumor type
D. Hairy cell leukemia
E. Reticular type
Correct answer: 476 – **A, B, C, D**

C The treatment of chronic lymphocytic leukemia includes:
A. Busulphan
B. Radiotherapy
C. Chemotherapy (medicine of choice is chlorambucil)
D. Glucocorticoids
E. Splenectomy in cases of hypersplenism and recurrent auto-immune complications
Correct answer: 475 – **B, C, D, E**

C The following drugs are administered in chronic lymphocytic leukemia:
A. Leucheran;
B. Prednisolone;
C. L-asparaginase;
D. Cytosar;
E. Myelosan
Correct answer: 254 – **A, B**

C The following drugs are administered in the treatment of chronic lymphocytic leukemia:
A. Myleran;
B. Hydroxyurea;
C. Glevec;
D. Fludarabin;
E. Mabthera
Correct answer: 255 – **D, E**

C In chronic lymphocytic leukemia splenectomy is indicated:

A. in the initial stage of the disease;
B. in relapsing autoimmune complications;
C. in the stage of clinico- hematological manifestations;
D. in case of hypersplenism;
E. in the stage of sarcomatisation
Correct answer: 256 – **B, D**

C Chronic lymphocytic leukemia develops the following most common complications:

A. the DIC syndrome;
B. thrombosis-relatedcomplications;
C. the neurologic syndrome;
D. infectious complications;
E. autoimmune complications
Correct answer: 257 – **D, E**

C Chronic lymphocytic leukemia commonly leads to the following complications:

A. infectious complications;
B. viral infections;
C. autoimmune thrombocytopenia;
D. neuroleukemia;
E. autoimmune hemolytic anemia
Correct answer: 444 – **A, B, C, E**

C Which of the following statements confirms the diagnosis of chronic lymphocytic leukaemiain the initial stage:

A. The satisfactory patient's overall condition;
B. The leukocyte count does not exceed 30.0x109/l;
C. The lymph nodes are not enlarged;
D. The liver and spleen are not palpable;
E. Lower hemoglobin and platelet counts
Correct answer: 445 – **A, B, C, D**

C Which of the following criteria confirms the diagnosis of chronic lymphocytic leukemia in the advanced stage:

A. enlargement of the peripheral lymph nodes;
B. enlarged liver and spleen;

C. leukocytosis in the analysis of peripheral blood;
D. thrombosis often develops;
E. lymphocytosis up to 80-90%
Correct answer: 446 – **A, B, C, E**

C Which of the following factors argues for the diagnosis of the initial stage of chronic lymphocytic leukemia :
A. the count of leukocytes does not exceed 30.0•109/l;
B. the lymph nodes are not enlarged;
C. the liver and spleen are not palpable;
D. high platelet count;
E. lymphocytosis 70-90%
Correct answer: 447 – **A, B, C, E**

C The treatment of chronic lymphocytic leukemia includes:
A. phlebotomy;
B. chemotherapy;
C. radiotherapy;
D. corticosteroids;
E. splenectomy
Correct answer: 449 – **B, C, D, E**

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str. Ștefan cel Mare și Sfânt, 194