Current concepts in diagnosis and treatment of chronic lymphocytic leukemia

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Chronic lymphocytic leukemia (CLL) is the most commonly diagnosed type of leukemia in Western Europe and North America, and represents about 30% of all leukemias in adults. Chronic lymphocytic leukemia is a disease of the elderly, who are often in poorer general health and burdened with multiple comorbidities. These factors affect the decision making when choosing an appropriate method of treatment.

In recent years there has been significant progress in the treatment of chronic lymphocytic leukemia, first due to the introduction of immunochemotherapy with monoclonal antibodies and latterly small molecules, like tyrosine kinase inhibitors targeting B-cell receptor signaling. This article discusses the current diagnostic principles, the most important prognostic factors and therapeutic options, available in first-line treatment and in refractory/resistant disease, including high-risk CLL, both for patients with good and those with poor performance status. It also presents important novel molecules which have been evaluated in clinical trials.

Key words: chronic lymphocytic leukemia, clinical symptoms, diagnosis, prognostic factors, treatment.

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Introduction

Chronic lymphocytic leukemia (CLL) is the type of leukemia most commonly diagnosed in Western Europe and North America, with an incidence rate of 4.2/100,000 [1]. Chronic lymphocytic leukemia is a disease of the elderly; the median age at diagnosis is 67–72 years [2], and approximately 70% of patients are over 65 years old. The only known risk factor is a family history of this disease. For relatives of CLL patients, the risk increases by a factor of 2.5–7.5 [3].

Onset of the disease is usually asymptomatic; only abnormalities in whole blood count such as leukocytosis with lymphocytosis are found. In more advanced stages, lymphadenopathy, hepatomegaly/splenomegaly, recurrent infections, weakness, pallor, hemorrhagic diathesis and general symptoms such as fever, weight loss and night sweats are observed. Nowadays, due to more frequent routine blood counts, more and more cases of CLL are diagnosed at an early, asymptomatic stage.

Principles of chronic lymphocytic leukemia diagnosis

The basic criterion for CLL diagnosis is an absolute number of peripheral blood B cells greater than 5.0 G/l, lasting more than three months; clonality should be confirmed by flow cytometry (κ or λ light chains) [4]. Chronic lymphocytic leukemia is characterized by a specific immunophenotype. In addition to the typical markers of B lymphocytes (CD19, CD20, CD23), 95% of patients with leukemia exhibit the cell surface antigen CD5 [5, 6]. In most cases, the immunophenotyping of peripheral blood lymphocytes by flow cytometry allows the establishment of a diagnosis, and distinguishes CLL from other B-cell lymphomas. In the differential diagnosis, one should take into account other indolent lymphomas (marginal zone lymphoma, hairy cell leukemia) and mantle cell lymphoma (MCL). In cases of doubt, methods which are helpful include histopathology and cytogenetic evaluation (FISH – fluorescent in situ hybridization) (for example, t(11;14) translocation, typical of MCL).

Bone marrow examination is not required to establish the diagnosis of CLL [4]. It is recommended in patients with cytopenias to differentiate between autoimmune cytopenias and the replacement of normal bone marrow cells by leukemic cells [4]. Bone marrow assessment should be performed before the start of therapy, especially myelosuppressive ones [1, 4, 7], and repeated in the case of persistent cytopenias after the treatment. Marrow biopsy is only recommended in clinical trials to confirm complete remission, but in practice it is optional and depends on the discretion of the physician [4].

Lymph node biopsy is indicated only in case of suspicion of transformation into a more aggressive type of lymphoma (Richter's syndrome). Tests performed at diagnosis of CLL are shown in Table 1.

Table 1. Tests to establish the diagnosis of chronic lymphocytic leukemia [4]

Test	Indications
Complete blood count and white blood cells smear	Always
Immunophenotyping of peripheral blood lymphocytes	Always
Bone marrow biopsy (aspiration, trephine biopsy)	Not necessary for a diagnosis. Recommended only to differentiate autoimmune cytopenia from cytopenia resulting from replacement of normal bone marrow pattern by leukemic cells.
Lymph node biopsy	Not necessary for diagnosis. Recommended only in cases of suspected Richter's transformation.
Cytogenetic evaluation	Only in the case of diagnostic problems, e.g., translocation of t(11:14), typical of mantle cell lymphoma.

The significance of prognostic factors in chronic lymphocytic leukemia

A characteristic feature of CLL is its heterogeneous clinical course [8]. Some patients do not require treatment for many years, if ever, whilst for others treatment is necessary soon after diagnosis. Staging of the disease is based on the Binet classification system introduced in 1975 [9] and the Rai staging system presented in 1981 [10] (Table 2).

However, both systems have limited value in determining the clinical course of the disease in individual cases, and in the identification of progressive CLL, especially in the early stages of disease.

Apart from the stage of the disease, clinical parameters (age, sex, comorbidities) and laboratory parameters (β2-microglobulin, lactate dehydrogenase, thymidine kinase, soluble CD23 receptor, lymphocyte doubling time, the type of marrow infiltration by leukemic lymphocytes) have significant prognostic value [5, 11–16].

Over the past several years, a group of so-called new prognostic factors has been developed. This group includes the mutational status of immunoglobulin heavy chain variable region (*IGVH*) genes [17–19], the expression of ZAP-70 protein in CLL cells [20–22], the expression of CD38 antigen on leukemic cells [23, 24] and cytogenetic abnormalities.

Cytogenetic abnormalities have the most important practical significance, especially deletions of 11q and 17p [25]. The presence of 11q deletion correlates with significant lymphadenopathy and rapid progression of the disease [26], while 17p deletion is associated with short survival time and lack of response to treatment with alkylating agents and purine analogs [25]. Results of the CLL8 trial showed that adding rituximab to FC (fludarabine and cyclophosphamide) chemotherapy makes the prognosis of patients with 11q deletion similar to those without the deletion [27]. Unfortunately, this has no significant effect on improving the prognosis of patients with the 17p deletion. The 17p deletion occurs at diagnosis in about 5–7% of all CLL patients, and its frequency increases significantly with the progression of the disease. For patients in whom

Table 2. Chronic lymphocytic leukemia staging systems by Rai et al. [10] and Binet et al. [9]. Median survival time based on updated data [11]

Stage	Parameter	Median overall survival
Rai classification		**Modified Rai classification**
0	absolute lymphocytosis > 5 G/l	> 10 years/**low risk**
I	absolute lymphocytosis > 5 G/l + lymphadenopathy	> 8 years/**intermediate risk**
II	absolute lymphocytosis > 5 G/l + splenomegaly or hepatomegaly +/– lymphadenopathy	> 8 years/**intermediate risk**
III	absolute lymphocytosis > 5 G/l + hemoglobin < 11 g/l +/– lymphadenopathy, +/– splenomegaly or hepatomegaly	6.5 years/**high risk**
IV	absolute lymphocytosis > 5 G/l + PLT < 100 G/l +/– lymphadenopathy, +/– splenomegaly or hepatomegaly +/– hemoglobin < 11 g/l	6.5 years/**high risk**
Binet classification		
A	involvement of < 3 lymphoid tissue areas	> 10 years
B	involvement of ≥ 3 lymphoid tissue areas	> 8 years
C	hemoglobin < 10 g/dl and/or PLT < 100 G/l	6.5 years

therapy overcoming the resistance may be applied, an assessment of the 17p deletion should be undertaken before each line of treatment, keeping in mind that the presence of 17p deletion alone without signs of CLL progression is not an indication for treatment.

The most recent prognostic factors, assessed by whole genome sequencing, include *NOTCH1*, *SF3B1* and *BIRC-3*mutations. At present, determination of these mutations is not recommended in clinical practice.

Initial clinical evaluation

Initial clinical evaluation of a patient with diagnosis of CLL should include:

- detailed physical examination including lymph nodes, liver and spleen assessment,
- determination of the clinical stage (according to Rai or Binet classification),
- finding out the cause of cytopenia (autoimmune, bone marrow infiltration by leukemic cells, hypersplenism, other), if present at diagnosis.

Laboratory tests recommended at CLL diagnosis include [7]:

- whole blood count with white blood cell smear,
- reticulocyte count,
- direct antiglobulin test (DAT, Coombs test),
- routine biochemical assessment of renal and hepatic function,
- serum immunoglobulins concentration (IgG, IgA, IgM).

For patients with a normal total IgG level experiencing recurrent infections, consider an assessment of IgG subclasses IgG1, IgG2, IgG3, IgG4, if possible.

In clinical practice, there are no recommendations for computed tomography (CT) scanning in patients with early asymptomatic stages of CLL or for monitoring of patients after the treatment completion [7], while CT is necessary to assess the tumor burden as well as the response to the therapy in clinical trials. In routine practice, CT scanning may be indicated in patients treated with intensive chemoimmunotherapy [7]. Positron emission tomography (PET) is not applicable in patients with CLL, except in cases of Richter's transformation.

Patients should undergo the following tests before the start of intensive chemotherapy or immunotherapy:

- cytogenetic evaluation (17p and 11q deletions by FISH),
- virological tests: hepatitis B and C viruses (HBV, HCV), cytomegalovirus (CMV), human immunodeficiency virus (HIV).

The most serious complication of therapy with alemtuzumab is the reactivation of a cytomegalovirus infection.

Immunotherapy with rituximab and other anti-CD20 monoclonal antibodies might be associated with reactivation of HBV infection.

Indications for treatment of chronic lymphocytic leukemia

In most cases, establishing the diagnosis of CLL does not indicate the need for the initiation of therapy. Treatment is not recommended for patients with CLL in early stages. Only patients with active disease require therapy. Generally accepted indications for CLL treatment according to the IWCLL (International Workshop on Chronic Lymphocytic Leukemia) [4] are shown in Table 3. One has to remember that a high number of lymphocytes alone, without signs of leukostasis, should not be an indication to start treatment.

Assessment of response to therapy

The current criteria for the response to therapy (by IWCLL) were published by Hallek *et al.* in 2008 [4]. Complete remission (CR) requires the fulfillment of all of the following criteria, assessed at least two months after completion of the therapy: absence of lymphadenopathy (lymph node size < 1.5 cm, evaluated in clinical trials, using a CT scan and in clinical practice, using a physical examination); the absence of hepato- and splenomegaly; peripheral blood lymphocyte count < 4000/µl; the percentage of lymphocytes in the bone marrow < 30%, with normal cellularity, without B lymphocyte clusters; peripheral blood parameters: neutrophils > 1.5 G/l, PLT count > 100 G/l, Hgb > 11 g/dl.

In clinical trials, complete remission should be determined on the basis of CT scans and bone marrow assessment. According to recent recommendations [1], assessment of patients' response in clinical trials should include the assessment of MRD using four-color cytometry or ASO-PCR (allele-specific oligonucleotide polymerase chain reaction). Both complete and partial remission should be referred to as MDR+ or MDR–. Minimal residual disease assessment is not currently recommended in the clinical practice.

In the patients fulfilling the criteria of complete remission (as confirmed by bone marrow examination), with the persistence of anemia, thrombocytopenia or neutropenia (related to treatment toxicity), the response is defined as CR with incomplete marrow recovery [4].

Table 3. Indications for CLL treatment according to IWCLL [4]

Advanced clinical stage of the disease (Rai 3 or 4, Binet C)
A significant or progressive lymphadenopathy (longest dimension > 10 cm) or splenomegaly (> 6 cm below the costal margin)
Cytopenia due to disease progression or autoimmune disorders (lack of response to corticosteroids or other standard treatments)
General symptoms (weight loss, fever, fatigue, infection)
Lymphocyte doubling time of < 6 months, or an increase of > 50% in less than two months (for patients with lymphocytosis < 30 G/l, should not be the only indication for treatment)
Richter's transformation

Patients' assignment to the appropriate treatment regimen

The choice of an appropriate treatment for patients with CLL depends primarily on the expected tolerance of chemo-or immunochemotherapy, assessed on the basis of parameters such as:

- age,
- performance status according to ECOG (Eastern Cooperative Oncology Group) scale or Karnofsky index,
- comorbidities,
- creatinine clearance (≥ 70 ml/min).

The decision on whether a patient can receive intensive treatment is in many cases difficult, particularly in elderly patients. In the assessment of comorbidities in patients with cancer, appropriate scales may be helpful, such as the CIRS (Cumulative Illness Rating Scale) used by the German CLL Study Group (GCLLSG) [28].

The method of treatment is also dependent on whether it is:

- first- or subsequent-line therapy,
- high-risk CLL, defined by the presence of 17p deletion/TP53 mutation (in untreated and treated patients, with indications for treatment) or resistance/relapse within two years after immunochemotherapy [29].

First-line treatment

First-line treatment for patients in good general condition without significant comorbidities

The first-line treatment recommended for CLL patients in good general condition with no significant comorbidities, and without a 17p deletion, is immunochemotherapy with purine analogues (fludarabine or cladribine), cyclophosphamide and anti-CD20 monoclonal antibody – rituximab (FCR or CCR regimens). The results of CLL8 trail of the GCLLSG showed that FCR immunochemotherapy prolongs the overall survival in patients with CLL [27].

The results of the CLL3 trial, conducted by the PALG (Polish Adult Leukemia Study Group), demonstrated similar efficacy and safety of FC (fludarabine, cyclophosphamide) and CC (cladribine, cyclophosphamide) regimens in the first-line treatment of CLL [30]. According to the GCLLSG, eligibility criteria for FCR (fludarabine, cyclophosphamide, rituximab) immunochemotherapy are:

- creatinine clearance ≥ 70 ml/min and
- CIRS score ≤ 6 [31].

Patients not fulfilling the above criteria should be treated using less toxic regimens.

It is recommended to give patients 6 cycles of FCR immunochemotherapy, as this increases the probability of the eradication of minimal residual disease (MRD), which is an independent predictor of longer progression-free survival (PFS) and longer overall survival (OS) [32]. It is necessary to carefully monitor any adverse effects, and a patient must exhibit good tolerance in order to complete six cycles of treatment. The results of CLL10 study of the GCLLSG showed no benefit in PFS in patients aged ≥ 65 years treated with FCR over BR (bendamustine, rituximab) protocol [33]. Thus, taking into account higher hematological toxicity of FCR, BR protocol might be considered as first line therapy in fit, elderly patients with CLL.

Patients in worse general condition, with comorbidities

The drug used for many years in CLL treatment, and still recommended for elderly patients burdened with numerous comorbidities, is chlorambucil.

Advantages of using chlorambucil are the convenient oral route of administration, the relatively good patient tolerance

and the inexpensive cost of therapy. However, a complete response can be achieved only in 5–10% of patients.

Higher response rates and longer progression-free survival could be achieved when chlorambucil is combined with rituximab as it was demonstrated in two phase II clinical studies [34,35]. More recently, the results of multicenter randomized phase III study conducted by GCLLSG (CLL11) showed that immunochemotherapy with chlorambucil combined with rituximab or obinutuzumab (the new, type 2, glycoengineered anti-CD20 antibody) improves overall survival comparing to chlorambucil in CLL patients not qualified to FCR due to comorbidities or impaired renal function. Immunochemotherapy with obinutuzumab is more efficient in terms of higher responses rates, longer PFS and more frequent eradication of MRD as compared to rituximab and chlorambucil [36,37]. In COMPLEMENT-1 trail, ofatumumab (a type 1 humanized anti-CD20 antibody) combined with chlorambucil was also proved to be more effective than chlorambucil monotherapy, inducing higher response rates and longer PFS in patients with CLL inappropriate for fludarabine-based therapy due to advanced age and/or comorbidities [38]. Current ESMO [39] and NCCCN [40] guidelines recommend chlorambucil in combination with anti-CD20 antibodies (rituximab, obinutuzumab, ofatumumab) as a standard first line therapy in CLL patients that due to comorbidities are not candidates to intensive immunochemotherapy .

Other treatment options include bendamustine in monotherapy or in combination with rituximab (BR regimen) [41-43], FCR-Lite [44], Q-Lite [45] regimens or reduced doses of purine analogs [46].

Treatment of relapsed disease

Indications to initiate treatment in relapsed CLL are the same as for the first-line therapy. The choice of regimen for the second- and subsequent-line therapy depends, as in the case of first-line therapy, on the patient's performance status and comorbidities. The type of first-line therapy, its toxicity, and the duration of the response should also be taken into account. Regardless of the method of therapy, if a response lasting at least 24 – 36 months was achieved, the regimen used in the first line should be repeated [2]. In patients with a good performance status, without the 17p deletion/TP53 mutation, and for whom first-line treatment purine analogs or immunochemotherapy were used, the FCR/CCR or BR regimens should be used. Patients who received alkylating agents as a first-line treatment, and their general condition allows the use of intensive immu-

nochemotherapy, may benefit from the FCR regimen (on the basis of the results of the REACH study) [47]. Recently two new small molecules, tyrosine kinase inhibitors (TKI) blocking B-cell receptor (BCR) signaling have been approved for the treatment of patients with CLL who received at least one prior therapy. Ibrutinib that is irreversible inhibitor of Bruton's kinase, was shown to be more effective than ofatumumab in the patients with relapsed CLL by inducing higher response rates as well as longer PFS and OS in the RESONATE trail [48]. Idelalisib is a selective and reversible inhibitor of phosphatidylinositide 3-kinase (PI3K). In patients with relapsed CLL, idelalisib in combination with rituximab was proved to induce higher response rates and longer both PFS and OS comparing to rituximab monotherapy [49]. Both ibrutinib and idelalisib are well tolerated in long-term therapy and they could be used in elderly patients with coexistent conditions. Alternatives for less fit patients are: BR [50], FCR-lite, corticosteroids at high doses (high dose methylprednisolone, HDMP) +/– rituximab [51] or rituximab, cyclophosphamide and dexamethasone (the RCD regimen); the latter is especially recommended for patients with autoimmune cytopenias [52,53]. Patients with relapsed CLL are encouraged to participate in clinical trials, if possible.

Treatment of high-risk chronic lymphocytic leukemia

BCR inhibitors are considered nowadays the most effective conventional treatment for CLL patients with 17p deletion/TP53 mutation however their efficacy is still inferior comparing to the patients without these abnormalities. Ibrutinib and idelalisib + rituximab are recommended treatment for the CLL patients with 17p deletion/TP53 mutation both in first, as well as in the subsequent lines of therapy [39]. Also in patients with refractory CLL or with relapse within 24–36 months from the start of initial therapy BCR inhibitors are recommended [39]. An alternative for the high risk patients is alemtuzumab +/– corticosteroids [54], or fludarabine (FluCam) [55]. Nowadays, alemtuzumab is only available within a compassionate use program of Sanofi. In patients with a good performance status responding to the therapy, allogeneic hematopoietic cell transplantation (alloHSCT) may be considered. The indications for and timing of alloHSCT are under discussion after the introduction of small molecules into CLL therapy. This procedure needs to be taken under consideration in fit CLL patients failing to several lines of therapy or in patients with high-risk CLL relapsing to one TKI and respond to the second regimen [39]. In less fit patients with relapse within 24 – 36 months after immunochemotherapy, with no del17p or TP53 mutation, protocols like BR or FCR-lite could be used. Also corticosteroids in high doses combined with rituximab might be considered in high-risk disease [56,57]. An improvement of the prognosis in patients with high-risk CLL still remains an unmet need, so patients are encouraged to participate in clinical trials with new molecules, such as BCL-2 antagonist, ABT-199 (venetoclax) that shows efficacy in patients with high-risk CLL (refractory to fludarabine or with 17p deletion) [58] or new BCR inhibitors or immunomodulatory agents.

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