

Watch and Wait – Actualities in the Treatment of Chronic Lymphocytic Leukemia

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ABSTRACT

In Western countries, chronic lymphocytic leukemia (CLL) is one of the most diagnosed leukemia types among elderly patients. CLL is described as an indolent lymphoproliferative disorder, characterized by the presence of a high number of small, mature B-cells in the peripheral blood smear, with a particular immunophenotype (CD5, CD19, CD23 positive and CD20 dim positive) and accumulation in the bone marrow and lymphoid tissue (e.g., lymph nodes, spleen). The experience of the past decades showed that CLL is clinically very heterogeneous; while some patients present a chronic clinical evolution, with a prolonged survival, in which the treatment can be delayed, others suffer from a more aggressive form, which must be treated early and is associated with many relapses. This observation led to several genomic studies that have mapped the genetic modifications involved in the disease conformations, including del(13q14), del(11q), or trisomy 12. On the other hand, certain genetic mutations such as del(17p13)–p53, NOTCH1 mutation, or ZAP70/CD38 increased expression are associated with worse clinical outcome. In order to apply the right treatment strategy, the Rai and Binet staging systems should be considered, which are based on clinical and laboratory assessment, on genetic mutations that may influence the resistance to chemotherapy, as well as the patient's age and comorbidities. The aim of this manuscript was to present the therapeutic approaches of CLL, in order to attempt to answer the following question: to treat, or not to treat? This clinical update focuses on the managements of CLL patients in the 21st century.

Keywords: chronic lymphocytic leukemia, treatment, stem cell transplantation, conservatory therapy

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a frequent form of leukemic malignancy among adults in developed countries. The incidence was reported around 4 to 6 cases per 100,000 persons per year in Europe and in the United States. The incidence increases with age, most of the patients being diagnosed after the age of 65. A lower incidence of CLL is maintained in Asian individuals, however.

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TABLE 1. The Rai staging system

Stage	Characteristics	Median survival
0	lymphocytosis ($>5 \times 10^9$ B lymphocytes/L) in the blood and bone marrow aspirate, with atypical lymphocytes	>150 months
I	stage 0 + lymphadenopathies	101 months
II	stage 0 + splenomegaly and/or hepatomegaly associated with or without lymphadenopathies	71 months
III	anemia, with serum hemoglobin level <11 g/dL	19 months
IV	thrombocytopenia, platelet count $<100,000/\text{mm}^3$	19 months

TABLE 2. The BINET staging system (lymphoid areas include the laterocervical, axillary, inguinal lymph nodes, liver, and spleen)

Stage	Characteristics
A	lymphocytosis ($>5 \times 10^9$ B lymphocytes/L) and 2 lymphoid areas affected
B	lymphocytosis ($>5 \times 10^9$ B lymphocytes/L) and 3 or more lymphoid area affected
C	anemia (Hb <10 g/dL) and/or thrombocytopenia (Plt $<100,000/\text{mm}^3$) independent of the number of lymphoid area affected

TABLE 3. Chronic Lymphocytic Leukemia–International prognostic Index (CLL-IPI)

Category	Overall survival (at 5 years)	Clinical approach
Low risk	93.2 %	„Watch and wait”
Intermediate risk	79.3 %	Treat in case of symptoms
High risk	63.3 %	Treatment indication, only if the disease is active (symptomatic)
Very high risk	23.3 %	If it is possible, treat with novel agent or enroll in clinical trials

Despite affecting older age subjects, in the last years, CLL was found more frequently in younger individuals, less than 55 years of age. Based on the gender distribution, males get sick more often compared to women (male : female ratio 1.5–2 : 1).^{1,2} CLL is a chronic lymphoproliferative disease, accounting for one third of adult leukemia cases and one quarter of non-Hodgkin lymphomas (NHL).³ According to the WHO classification (World Health Organization, 2008), CLL is an indolent lymphoproliferative disorder, composed by small, mature, monomorphic, monoclonal B-cells accumulating in peripheral blood, bone marrow, and lymphoid organs.⁴ The monoclonal character of these cells is based on the particular immunophenotype that includes specific cellular surface markers (CD5 – T-cell antigen; CD19, CD23, and CD20 as B-cell antigens). On the other hand, the WHO states that the difference between CLL and small lymphocytic lymphoma (SLL) is only in the leukemic appearance.⁵

DIAGNOSIS OF CLL

The positive diagnosis of CLL is based on blood smears, full blood cell count, and immunophenotyping from peripheral blood.⁵

According to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL),^{6,7} updated by the National Cancer Institute-Working Group (NCI-WG) guidelines,^{7,8} CLL diagnosis is based on the presence of documented lymphocytosis ($\geq 5 \times 10^9$ B lymphocytes/L) in the peripheral blood in the last 3 months; and secondly, flow cytometry showing a specific immunophenotypic outline: CD5 and CD23 expression with a low-level expression of CD20, CD79b, and surface immunoglobulin, as well as clonal light chain restriction (either kappa or lambda).

During the analysis of the peripheral blood smear, the leukemia cells present as healthy, mature, small lymphocytes with little cytoplasm and a dense nucleus with aggregated chromatin, without recognizable nucleoli.^{5,6}

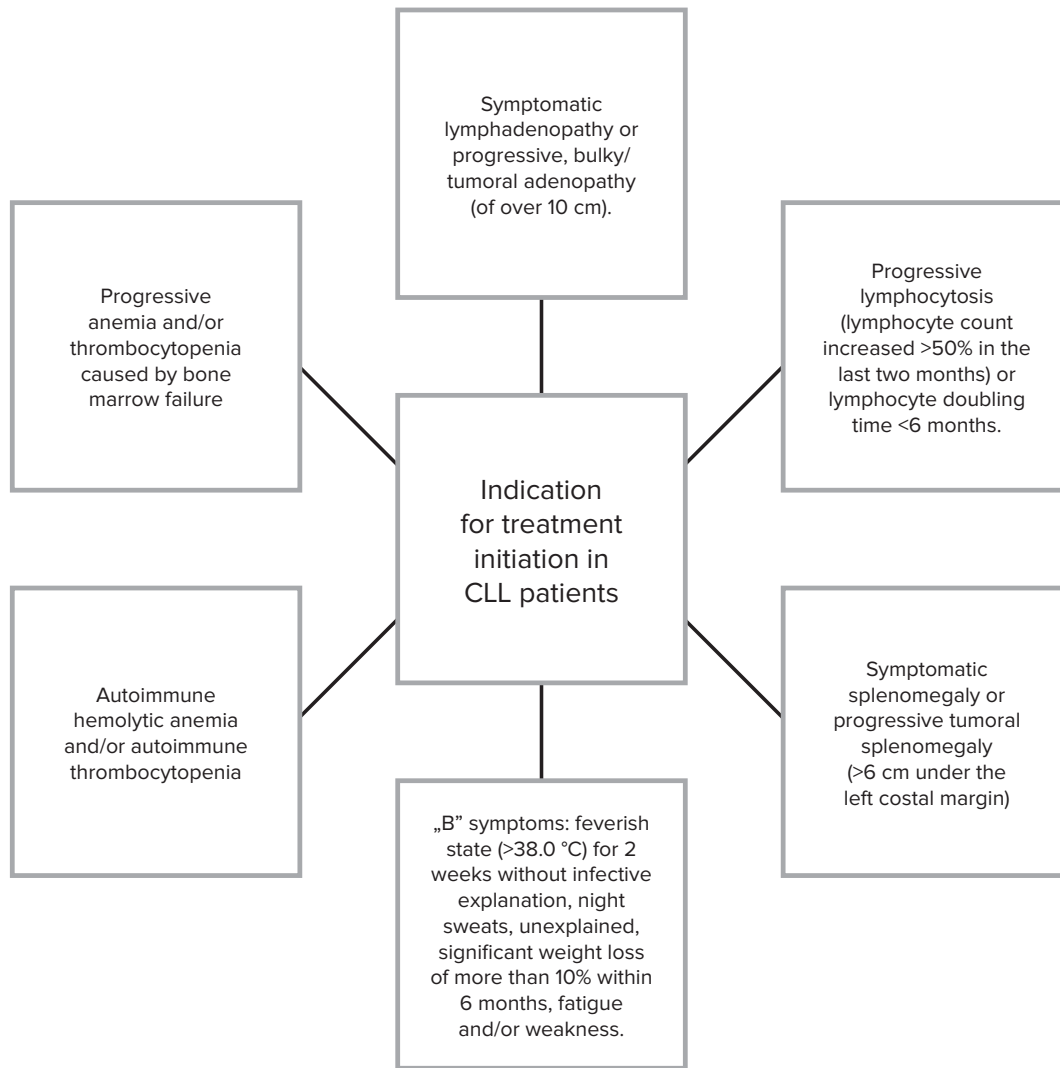


FIGURE 1. Indications for treatment in CLL according to the International Workshop on Chronic Lymphocytic Leukemia Guidelines

Hallek *et al.* and Scarfo *et al.* mention two clinical entities: small lymphocytic lymphoma and monoclonal B-cell lymphocytosis, which must be distinguished from CLL by assessing the signs and symptoms and the count of B lymphocytes in the peripheral blood. The diagnosis of lymphocytic lymphoma involves the presence of less than 5×10^9 B lymphocytes/L in the peripheral blood and is clinically characterized by lymphadenopathies and/or enlarged spleen and liver, without bone marrow infiltration-related cytopenia, requiring, in some cases, histopathologic examination from a lymph node. Monoclonal B-cell lymphocytosis is confirmed by a B-lymphocytes blood count under 5×10^9 /L, in the absence of lymphadenopathies, hepatosplenomegaly, disorder-related cytopenia, or B symptoms.^{5,7}

STAGING AND RISK STRATIFICATION OF CLL

In current clinical practice, the RAI and BINET staging systems are available for defining disease prognosis and indication for treatment in CLL patients.^{9,10}

The RAI staging system includes 4 stages that present the median survival according to the laboratory and clinical features of the disease, and it allows classification of patients into three risk categories (Table 1). Low-risk patients present RAI stage 0, intermediate risk includes stages I and II, while high-risk patients include stages III and IV, with anemia and/or thrombocytopenia.⁹

The BINET staging system categorized patients into 3 classes, according to the B-lymphocyte count and the number of affected lymphoid regions, and the hemoglobin and platelet count (Table 2).¹⁰

The disadvantage of the two staging systems is that they allow the identification of only three prognostic subgroups. However, in the last two decades, genetic studies have isolated several genomic and chromosomal modifications in patients with CLL that present prognostic value irrespective of the clinical stage. In consequence, an international consortium of study groups has developed a relevant prognostic score — the Chronic Lymphocytic Leukemia-International Prognostic Index (CLL-IPI). In this staging system, five independent prognostic factors were included: age, clinical stage, serum β 2-microglobulin levels, IGHV mutational status, and del(17p) and/or TP53 mutation.^{5,7,11}

THERAPEUTIC GUIDELINES — INDICATION FOR TREATMENT

The two main questions to be answered before commencing a proper patient management in CLL are “When?” and “How?”.¹² The International Workshop on Chronic Lymphocytic Leukemia clearly defined the signs and/or symptoms of active disease that has indication for prompt treatment initiation (Figure 1).^{6,7,11}

PROPER SELECTION OF TREATMENT REGIMENS

When faced with a diagnosis of CLL, the clinician should assess the proper timing and method, either in monotherapy or with combination drug regimens, for initiating the therapeutic management of such patients. Therefore, several parameters should be evaluated, which include (1) the fitness of the patient (age, comorbidity, performance status, comorbidity index of rating scale – CIRS, renal function); (2) the stage of the disease (RAI and BINET); (3) disorder-related symptoms; (4) gene mutations [del (17p) and/or TP53 mutation]; (5) previous treatment, as well as the presence of relapse or refractory disease to the last administered treatment regimens.^{5,7,11}

Considering the 5 parameters previously listed, there are different possible treatment modalities.

The “Watch and wait” conduct

Delayed treatment initiation can be applied in case of CLL patients with RAI stage 0 to I and BINET stage A and B, irrespective of the gene mutations and fitness.

First-line therapy

In fit patients (“go go”), with normal organ and kidney function, with a creatinine clearance of >70 mL/minute,

with a CIRS of ≤ 6 , the current procedure is to apply standard combination chemotherapy with fludarabine, cyclophosphamide and CD20 monoclonal antibody – rituximab (FCR). Two comprehensive studies have shown an outstanding response rate with this scheme, with an overall response rate of 90% and a rate of complete response of 40%.^{12,13} But the toxicity of this combination may lead to a greater incidence of grade 3 or 4 neutropenia and bacterial or viral infections within the first 2 years after treatment.^{14,15} Unfortunately, there is no suitable data on methods for toxicity reduction and the only way is to reduce the treatment cycles during minimal residual disease (MRD).¹⁶ An alternative treatment may be the combination of bendamustine + rituximab (BR).¹⁶ At the same time, a randomized GCLLSG trial (2013) showed that the BR combination presents a better clinical tolerance, but the clinical remission rate and progression-free survival were shown to be inferior to that of the FCR combination.¹⁸

In unfit patients, (“slow go”), with damaged organ functions (creatinine clearance less than 70 mL/minute) and several relevant comorbidities (CIRS score >6), the therapeutic method of choice is the chlorambucil (alkylating agent) and anti-CD20 antibody combination. In 2014, Gode *et al.*, used the chlorambucil + obinutuzumab (anti-CD20 antibody) scheme and were able to prove a higher clinical response rate compared to chlorambucil monotherapy and a longer progression-free survival; however, the authors did not study the side effect profile of this regimen.¹⁹ In 2013, Hillmen *et al.* reported similar results with the use of chlorambucil and ofatumumab combination.²⁰ According to Foon *et al.* (2009), the FCR-lite regimen consists in reducing the doses of fludarabine, cyclophosphamide and rituximab down to the patient’s tolerability.²¹

High-risk patients, with del(17p) and/or TP53 mutations present a negative, reserved prognosis, but the recommendations are not clear about the standard therapy, which underlines the importance of patient enrollment in clinical experiments with novel drugs.

Currently, new kinase inhibitors (ibrutinib and idelalisib) are approved by the Food and Drug Administration and the European Medicines Agency as the main treatment line in patients with 17p deletion and/or TP53 mutation.^{5,7}

Ibrutinib is an inhibitor of Bruton-tirosine kinase, linked irreversibly to B-cell receptor, which acts on this pathway by inducing apoptosis and blocking the proliferation process. Its adverse effects include coagulopathies (manifested with bleeding), gastrointestinal effects (e.g., diarrhea), and also CYP3A4 interactions, thus indicating careful administration in association with other inducers

of inhibitors of cytochrome p450. Also, it had also been proven useful in relapsed/refractory CLL.^{22–24}

Idelalisib is a phosphoinositide 3-kinase (PI3K) inhibitor, with oral administration, and as side effects it causes hepatic cytolysis, lung involvement, and colitis with diarrhea.^{25,26} This drug presents first-line indication in patients with del(17p), and, on the other hand, it can be associated with anti-CD20 monoclonal antibody (rituximab) for relapsed or refractory CLL.²⁷

Second-line therapies (for relapsed and refractory CLL)

This category of patients is a gray zone too. But the recommendations are the same for patients who have received a first-option immunochemotherapy combination (such as FCR) and they relapse after more than 24 to 36 months.¹² On the other hand, if the relapse occurs within 24–36 months after the end of the treatment, or the subjects are refractory to the fludarabine-based combination (with non-progressive or progressive disease or patients who relapse within 6 months after the end of treatment), the option of clinical trial enrollment should be taken into account. In such cases, there are several possibilities of treatment. The use of alemtuzumab and fludarabine combination has been shown by Elter *et al.* (2011) to reach a response rate of more than 80% and a clinical remission in 30% of cases.²⁸ The anti-CD20 monoclonal antibody in association with corticosteroids were proposed by Castro *et al.* (2008), by administering rituximab in days 1, 8, and 15, with high doses of methylprednisolone (1 g/m²) over a 4-week period.²⁹ Ibrutinib and idelalisib (without or with rituximab) have also been proved as indication in this patient category,^{23,27} ofatumumab is a second-generation anti-CD20 monoclonal antibody that binds to a different epitope of the CD20 surface marker. It shows a tardive dissociation, which leads to a better, more efficient complement-dependent cytotoxicity. This effect is superior compared to rituximab. In double-refractory (resistant to fludarabine + alemtuzumab) CLL patients, ofatumumab is a suggested treatment possibility.³⁰

Allogeneic stem cell transplantation

Sutton *et al.*, Montserrat *et al.*, and Magni *et al.* have shown that autologous stem cell transplantation dose not present a superior, significant effect on the general survival rates and on the progression-free survival, in comparison to standard immunochemotherapy schemes (e.g., fludarabine, cyclophosphamide, and rituximab regimen).^{31–33}

In young CLL patients with refractory disease, with or without genetic abnormalities (17p deletion and/or TP53 mutation), allogeneic stem cell transplantation should be taken into consideration.³⁴ This statement is encouraged by the fact that although new pharmacological agents (tyrosine-kinase inhibitors and new-generation monoclonal antibodies) have reformed the treatment modalities in CLL, there has yet to be sufficient information on their long-term efficacy and safety. As a final thought, in these patients, after the right novel agent has been chosen and has led to an optimal response, there are two options for furthering the treatment. The first option consists in performing allogeneic stem cell transplantation in order to conserve the clinical response, and the second option is to delay the cell therapy and to continue the initiated treatment with the novel drug.

OUTLOOK ON THE FUTURE OF CLL TREATMENT

Over the last two decades, there have been multiple developments that triggered a change in the therapeutic management of CLL. Due to several genetic investigations, clinicians are mapping the genetic background, which has led to a better understanding of why this indolent lymphoproliferative disease presents a slow progression in some patients (with a longer period of inactivity of the disease), while other patients should be treated shortly after diagnosis, by initiating proper therapeutic measures.

CONCLUSIONS

Comprehensive clinical studies have generated new personalized guidelines, which indicate “when” and “how” to treat patients with chronic lymphocytic leukemia. Novel pharmacological agents have significantly improved clinical outcomes in high-risk, relapsed, or refractory CLL. At the same time, there are still unanswered questions regarding the safety and long-term efficacy of such novel therapies, which require further clinical studies that may be able to provide clear answers.

CONFLICT OF INTEREST

Nothing to declare.

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