Original Article

An Overview About Management Of Chronic Lymphocytic Leukemia

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Abstract

Background: Lymphoid neoplasms are broadly categorized into precursor lymphoid neoplasms and mature B-cell, T-cell, or natural killer (NK) cell neoplasms. Chronic lymphocytic leukaemia (CLL) is a malignancy of CD5+ B cells that is characterized by the accumulation of small, mature-appearing lymphocytes in the blood, marrow and lymphoisd tissues. Not all patients with CLL require treatment at the time of diagnosis, and most patients can undergo active surveillance for many years before treatment is needed. Indications for treatment are detailed in the 2008 iwCLL guidelines and are mainly based on 3 elements: symptoms, complete blood cell count, and physical examination findings. Response assessment is detailed in the iwCLL 2008 guidelines,22 although their timing and validity may be challenged by the advent of the new biological agents. Response should be assessed 2 to 3 months after the completion of therapy and should be based on complete blood cell count, physical examination findings, and bone marrow biopsy. Of interest, the clinical benefit of complete remission (CR) with incomplete bone marrow recovery seems to be comparable to that of CR. If criteria for CR are met but the bone marrow includes lymphocytic nodules, the recommended term is nodular partial remission, the prognosis of which is more similar to that of partial remission. Fit patients are good candidates for chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab. Patients who experience relapse from 24 to 36 months after frontline chemoimmunotherapy can be safely rechallenged with the same regimen, their median PFS after salvage therapy is only 21 months; even more disappointing outcomes are observed with the use of salvage FCR in high-risk patients. Treatments with antibodies such as rituximab and ofatumumab have been explored as consolidation strategies to prolong response duration, with moderate success.

Keywords: Chronic Lymphocytic Leukemia

INTRODUCTION

Introduction

Lymphoid neoplasms are broadly categorized into precursor lymphoid neoplasms and mature B-cell, T-cell, or natural killer (NK) cell neoplasms (***Swerdlow et al., 2016)***. Mature B-, T-/NK neoplasms can be further segregated into disorders likely to exhibit primary manifestations in blood and bone marrow (i.e. chronic leukemias) compared with mature neoplasms that predominate in extramedullary sites but may involve blood or bone marrow more typically as a secondary event (B-, T-/NK-lymphomas). Chronic lymphoproliferative neoplasms represent clonal proliferations of morphologically and immunophenotypically mature B or T cells characterized by a low proliferation rate and prolonged cell survival ***(1)***.

Chronic lymphocytic leukemia is the most common adult leukemia in the Western World, accounting for nearly 25% of all leukemias and 1.3% of all cancers ***(2)***

A genetic predisposition for CLL is suggested by family studies, with a higher prevalence of disease observed among relatives of patients with sporadic CLL ***(3)***.

Genetic factors contribute to disease susceptibility; among patients who are registered in the CLL Research Consortium, 9% of patients have a relative with CLL. In addition, first-degree relatives of patients with CLL have an 8.5-fold increased risk of developing this disease **(4),** and the concordance of CLL is higher among monozygotic twins than among dizygotic twins **(5).**

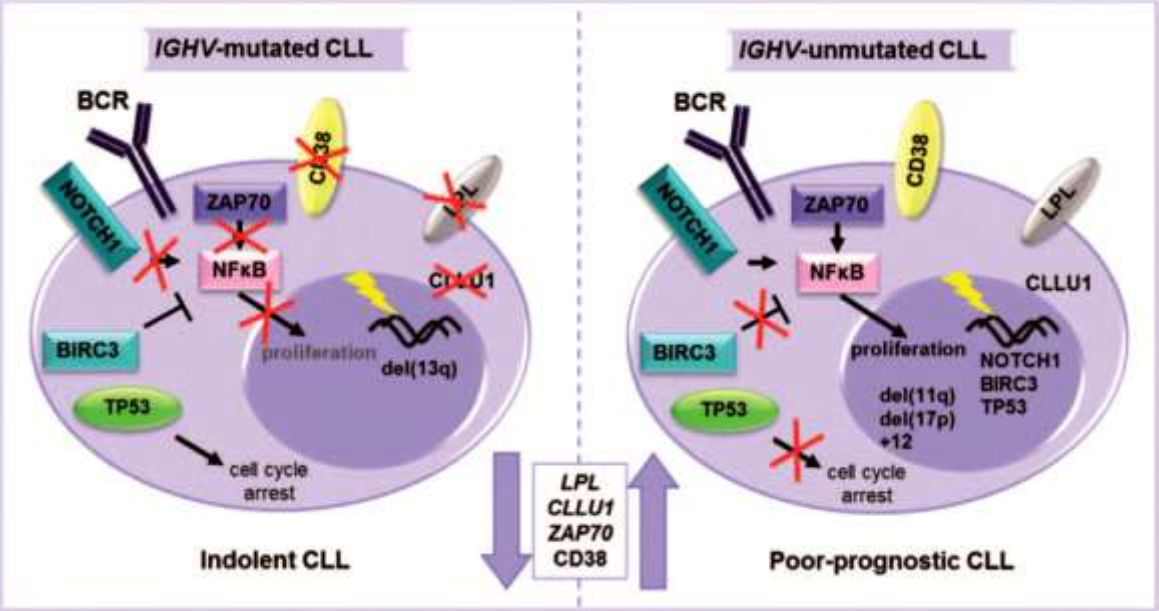


Figure (1) : Different molecular mechanisms driving IGHV -mutated and unmutated CLL. **(IGHV)** Ig heavy-chain variable-region gene, (BCR) B cell receptor, **(ZAP-70)** ζ-associated protein of 70 kD, **(NF-kB)** nuclear factor kB, **(LPL)** lipoprotein lipase, **(CLLU1)** CLL upregulated gene 1, **(BIRC3)** baculoviral inhibitor of apoptosis, **(IAP)** repeat–containing 3 protein, **(SF3B1)** splicing factor 3B sub-unit 1, **(NOTCH1)** neurogenic locus notch homolog protein 1. ***(6)***

Most often, patients with CLL are asymptomatic at the time of diagnosis and become aware of the disease following the detection of lymphocytosis in a routine blood count. However, CLL can have a range of clinical presentations; some patients feel well and are fully active, but a minority have disease-related symptoms. The usual symptoms of CLL include fatigue, involuntary weight loss, excessive night sweats, abdominal fullness with early satiety and increased frequency of infections, which might be associated with hypogammaglobulinaemia. Some patients can present with symptoms of an autoimmune cytopenia (for example, autoimmune haemolytic anaemia or immune thrombocytopenic purpura). Patients can also have or develop enlarged lymph nodes, hepatomegaly and splenomegaly, which are palpable on physical examination. Enlarged lymph nodes can be easily palpable at three sites: the cervical, axillary and inguino-femoral regions ***(7).***

General Symptoms:

Over 25% of patients are asymptomatic at diagnosis. Such patients are detected due to discovery of non tender lymphadenopathy or an unexplained absolute lymphocytosis, or may present with an exacerbation of another underlying medical condition ***(8).***

Some patients may have only mild symptoms of reduced exercise tolerance, fatigue or malaise, while others may present with more severe symptoms as weight loss, recurrent infections, bleeding and/or symptomatic anemia. However, night sweats and fevers (the so called B symptoms) are uncommon and evaluation for complicating infectious diseases should be done ***(9).***

Lymphadenopathy:

Nearly 80% of all patients have non-tender lymphadenopathy at diagnosis. The lymph nodes are usually discrete and freely mobile ***(10).*** Enlargement of cervical and supraclavicular nodes occur more commonly than axillary or inguinal lymphadenopathy ***(11).***

Extranodal Involvement:

Hepatosplenomegaly

Approximately 50% of CLL patients present with mild to moderate anemia and thrombocytopenia. However, in CLL such cytopenias are more commonly secondary to extensive marrow involvement with CLL and/or intermittent expression of auto-antibodies. Hepatomegaly occurs less frequently than splenomegaly ***(12).***

Organ infiltration

Organ infiltration with leukemic cells is frequently detected at autopsy but is not commonly symptomatic. However, it may become symptomatic when it develops in certain locations such as in the retro-orbit, pericardium or lung parenchyma ***(13).***

The gastrointestinal tract may be infiltrated by leukemic cells causing mucosal thickening, ulceration and bleeding may occur. Small bowel affection often causes diarrhea and intestinal malabsorption which induces megalobalstic anemia due to folate malabsorption ***(14).***

Treatment

Indications for Treatment:

Not all patients with CLL require treatment at the time of diagnosis, and most patients can undergo active surveillance for many years before treatment is needed. Indications for treatment are detailed in the 2008 iwCLL guidelines and are mainly based on 3 elements: symptoms, complete blood cell count, and physical examination findings ***(15)***

Constitutional symptoms, defined as persistent and unexplained fever (temperature >38oC) and/or weight loss (>10% of the baseline weight over the course of less than 6 months) and/or severe night sweats, can represent a first indication for treatment. Progressive lymphocytosis, hemoglobin level less than 10 g/dL, or platelet count less than 100 × 109/L represents another indication for treatment; of interest, rather than the absolute number of lymphocytes, it is the lymphocyte doubling time that is noted in the guidelines (rapid doubling is <6 months). In addition, in presence of anemia and/or thrombocytopenia, an autoimmune etiology must always be ruled out, and only refractory autoimmune hemolytic anemia (AIHA) and/or immune thrombocytopenia (ITP) would prompt CLL-specific therapy initiation. Finally, treatment is recommended in the presence of progressive and/or symptomatic lymphadenopathy (>10 cm) and/or hepatosplenomegaly ***(16).***

Assessment of Response:

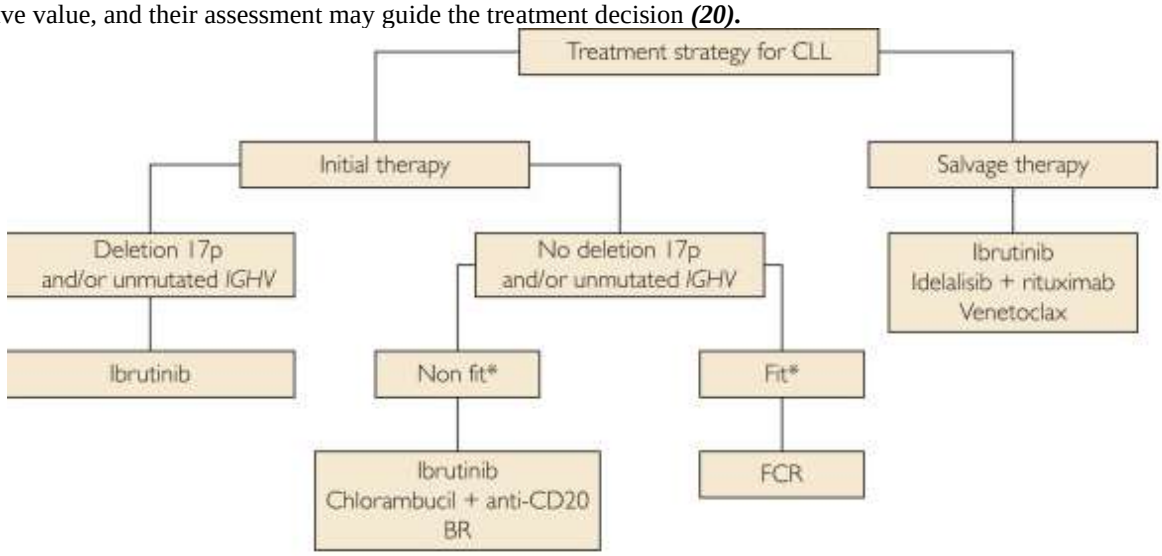
Response assessment is detailed in the iwCLL 2008 guidelines, although their timing and validity may be challenged by the advent of the new biological agents ***(17).*** Response should be assessed 2 to 3 months after the completion of therapy and should be based on complete blood cell count, physical examination findings, and bone marrow biopsy

Of interest, the clinical benefit of complete remission (CR) with incomplete bone marrow recovery seems to be comparable to that of CR. If criteria for CR are met but the bone marrow includes lymphocytic nodules, the recommended term is *nodular partial remission*, the prognosis of which is more similar to that of partial remission ***(18).***

Over the past several years, the eradication of MRD, measured by flow cytometry with a sensitivity of less than 0.01%, has increasingly gained importance. In particular, achievement of negative MRD status after chemoimmunotherapy has been prospectively associated with prolonged survival, with retrospective evidence that early eradication may prompt treatment discontinuation. However, similar data have not yet been obtained with newer agents such as ibrutinib, idelalisib, and venetoclax, and MRD monitoring and achievement is not recommended by standard guidelines ***(19).***

Treatment strategy:

A treatment strategy flow chart is proposed in the Figure1 . Some of the prognostic factors outlined previously, such as deletion 17p (or TP53 mutation), IGHV mutation status, and complex cytogenetics have increasingly been shown to have predictive value, and their assessment may guide the treatment decision ***(20).***



Fit is defined in the United States as patients younger than 65 years and with a good performance status and in Europe as patients with a creatinine clearance of 70 mL/min or greater and a comorbidity index of rating scale score of 6 or less. **BR** = bendamustine and rituximab;; FCR = fludarabine, cyclophosphamide, and rituximab ***(21).***

Figure(2): Treatment strategy flow chart for chronic lymphocytic leukemia

Initial Therapy:

Fit patients are good candidates for chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (**FCR**) ***(22)***. Frontline treatment with is associated with a response rate of 90% to 95% and a CR rate of 40% to 75%. Typically, 6 cycles are given, and early discontinuation based on achievement of MRD eradication has not yet been prospectively proven effective. Prolonged myelosuppression, early and late infections, and second cancers still remain the main concerns with the

use of this regimen ***(23).***

For patients with deletion 17p or *TP53* mutation, the long-term results with chemoimmunotherapy are suboptimal. For these patients, ibrutinib, an oral selective and irreversible inhibitor of the Bruton tyrosine kinase (BTK), is the current standard treatment. Bruton tyrosine kinase is a kinase in the B-cell receptor signaling pathway and is required for normal B-cell function and development. Ibrutinib also disrupts the interaction between the CLL clone and the bone marrow microenvironment, inducing further apoptosis ***(24***).

Ibrutinib produced high response rates (84%-97%) but CR rates of only 12% to 23%, with most patients achieving either a partial remission (mostly because of persistent bone marrow disease) or a partial remission with a lymphocytosis (likely as a consequence of its mechanism of action, aimed at blocking the interaction between CLL cells and their niche. Ibrutinib is associated with adverse effects, the most prominent being hypertension, atrial fibrillation, musculoskeletal pain, diarrhea, bleeding, and drug-drug interaction ***(25***).

In a clinical trial of frontline therapy in older patients with CLL, ibrutinib was superior to chlorambucil in terms of response rate, survival, and toxicity. Ibrutinib is an appropriate frontline regimen for patients who are not eligible for chemoimmunotherapy based on clinical fitness and is the recommended regimen in the presence of deletion 17p/*TP53* mutation ***(26)***

In frail patients, treatment can still be administered because most patients tolerate it well. For this population, frontline treatment can be given with a combination of chlorambucil and an anti-CD20 monoclonal antibody; with the use of rituximab, the overall response rate (ORR) is 82% to 84%, and median PFS is 24 to 35 months ***(27)***

Patients who experience relapse from 24 to 36 months after frontline chemoimmunotherapy can be safely rechallenged with the same regimen, their median PFS after salvage therapy is only 21 months; even more disappointing outcomes are observed with the use of salvage FCR in high-risk patients ***(28)***.

Short-lasting responses are observed with ofatumumab, an agent approved for patients who experience relapse after chemoimmunotherapy or whose CLL is refractory to such treatment ***(29).***

The use of ibrutinib as salvage therapy has considerably changed the management and prognosis of patients with relapsed CLL ***(Brown et al., 2018).30***

The most common options for patients who experience relapse after chemoimmunotherapy and/or ibrutinib are idelalisib (in combination with rituximab) and venetoclax. Idelalisib is a potent and selective inhibitor of PI3K-δ, a kinase downstream in the B-cell receptor signaling pathway; this pathway is constitutively activated in CLL cells. Venetoclax is a BH3 mimetic targeting BCL2, a protein overexpressed in CLL. In a study of patients with relapse/refractory CLL treated with venetoclax**.** When combined with rituximab, venetoclax prolonged PFS compared with chemoimmunotherapy (bendamustine and rituximab) in a phase 3 trial of patients with relapsed/refractory CLL ***(31).***

Whole-exome sequencing of 6 patients with CLL who had development of resistance to ibrutinib revealed mutations acquired in BTK at the binding site of ibrutinib (C481) with a cysteine to serine mutation, and several different mutations in phospholipase Cγ2, the kinase immediately downstream of BTK. Mechanisms of resistance to idelalisib and venetoclax have not yet been described, but potential pathways may include up-regulation of either PIK3CD or an alternative class 1A PI3K for the former and up-regulation of alternative antiapoptotic BCL2 family members, such as BCL-XL, BCL-W, MCL1, and BCL2A1 for the latter ***(32).***

Maintenance Therapy

Treatments with antibodies such as rituximab and ofatumumab have been explored as consolidation strategies to prolong response duration, with moderate success ***(33).*** Lenalidomide is an oral immunomodulatory drug with activity in both treatment-naive and relapsed CLL ***(34).***

Role of Stem Cell Transplant

The advent of novel biological agents able to produce durable responses in high-risk patients is changing the treatment paradigm in CLL, considerably decreasing the number of patients evaluated for stem cell transplant (SCT). However, in absence of long-term follow-up data, allogeneic SCT should still be considered in fit patients with relapsed/refractory CLL and deletion 17p/*TP53* mutation once remission is achieved with therapy. In fact, with the use of reduced-intensity conditioning regimens, early mortality has significantly decreased, but 5-year survival remains no higher than 60%, mostly because of non–disease-related mortality related to acute and chronic graft-vs-host disease (***35***).

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