Chronic lymphocytic leukaemia

Michael Hallek, Tait D Shanafelt, Barbara Eichhorst

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Department of Internal Medicine, Center of Integrated Oncology Köln Bonn, University Hospital of Cologne, Cologne, Germany (Prof M Hallek MD, B Eichhorst MD); **and Stanford University School of Medicine, Stanford, CA, USA** (Prof T D Shanafelt MD)

Correspondence to: Prof Michael Hallek, Department of Internal Medicine, Center of Integrated Oncology Köln Bonn, University Hospital of Cologne, 50937 Cologne, Germany **michael.hallek@uni-koeln.de**

Important advances in understanding the pathogenesis of chronic lymphocytic leukaemia in the past two decades have led to the development of new prognostic tools and novel targeted therapies that have improved clinical outcome. Chronic lymphocytic leukaemia is the most common type of leukaemia in developed countries, and the median age at diagnosis is 72 years. The criteria for initiating treatment rely on the Rai and Binet staging systems and on the presence of disease-related symptoms. For many patients with chronic lymphocytic leukaemia, treatment with chemotherapy and anti-CD20 monoclonal antibodies is the standard of care. The impressive efficacy of kinase inhibitors ibrutinib and idelalisib and the BCL-2 antagonist venetoclax have changed the standard of care in specific subsets of patients. In this Seminar, we review the recent progress in the management of chronic lymphocytic leukaemia and highlight new questions surrounding the optimal disease management.

Introduction

Chronic lymphocytic leukaemia has been one of the most dynamic fields of clinical research in the past two decades. Important advances in understanding the pathogenesis of this disease have led to the development of new prognostic and diagnostic tools. New drugs approved for treatment of chronic lymphocytic leukaemia are poised to dramatically change the management of this leukaemia and are improving clinical outcomes for patients.

With an age-adjusted incidence of 4–5 per 100 000 population, chronic lymphocytic leukaemia is the most common type of leukaemia in developed countries.[1,2] The median age at diagnosis is 72 years, and more men than women (2:1) are affected.[2]

Pathophysiology, risk factors, and genetics

Chronic lymphocytic leukaemia is characterised by the clonal proliferation and accumulation of mature and typically CD5-positive B-cells within the blood, bone marrow, lymph nodes, and spleen.[3] The primary leukaemogenic event could involve multipotent and self-renewing haematopoietic stem cells.[4]

A limited number of risk factors for chronic lymphocytic leukaemia have been identified.[5] Chronic lymphocytic leukaemia has one of the strongest inherited predispositions of haematological malignancies. About 10% of individuals who develop chronic lymphocytic leukaemia have a family history of the disease.[6] Living on a farm or exposure to herbicides and pesticides,[5] reduced recreational sun exposure, medical history of atopic health conditions,[5] exposure to hepatitis C virus, and common infections can be associated with an increased risk.[5,7]

Comprehensive genomic analyses of chronic lymphocytic leukaemia have led to a model of sequential genetic evolution in which leukaemic transformation in most patients is initiated by the loss or gain of chromosomal material (figure 1). Additional mutations or chromosome alterations acquired during the course of the disease render this leukaemia more aggressive and resistant to treatment.[8] The initiating chromosomal aberrations comprise deletion of chromosome 13q (del[13q]) in about 55% of cases, and acquisition of chromosome 12 (trisomy 12) in 10–20% of cases. Deletion of chromosome 11q (del[11q]) is seen in about 10% of cases and deletion of chromosome 17p (del[17p]) in about 5–8% of cases, but these aberrations are usually acquired at late stages of the disease. Del(13q) causes the loss of miRNAs (miR-15a and miR-16-1), which initiates leukaemogenesis.[9,10] Del(11q) causes the loss of the *ATM* gene, which encodes a DNA damage response kinase ATM.[11,12] Del(17p) typically deletes the tumour suppressor gene *TP53*. More than 80% of cases with a del(17p) also carry mutations in the remaining *TP53* allele, resulting in a functional disruption of the TP53 pathway.[13] *TP53* mutations and del(17p) are therefore collectively categorised as genetic *TP53* aberrations. Additional recurrent somatic gene mutations have been identified in *NOTCH1, XPO1, KLHL6, MYD88,* and *SF3B1*.[14,15]

The survival of chronic lymphocytic leukaemia cells also depends on a permissive microenvironment of cellular components. Macrophages, T cells, or stromal follicular dendritic cells stimulate crucial survival and pro-proliferative signalling pathways in leukaemic cells by secreting chemokines, cytokines, and angiogenic factors or by expressing distinct surface receptors or adhesion molecules.[16]

Search strategy and selection criteria

We searched PubMed for articles published until Dec 31, 2017, using the terms "chronic lymphocytic leukemia" or "CLL" in combination with the terms "epidemiology" or "therapy" or "diagnosis" or "pathogenesis" or "genetic". We largely selected articles published since Jan 1, 2012, but did not exclude commonly referenced and highly regarded older reports. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant for inclusion here. Reviews and book chapters are cited to provide more details and references than this Seminar could accommodate.

Clinical presentation, differential diagnosis, diagnostic evaluation, and prognosis

The most common presentation of chronic lymphocytic leukaemia is the incidental discovery of lymphocytosis on

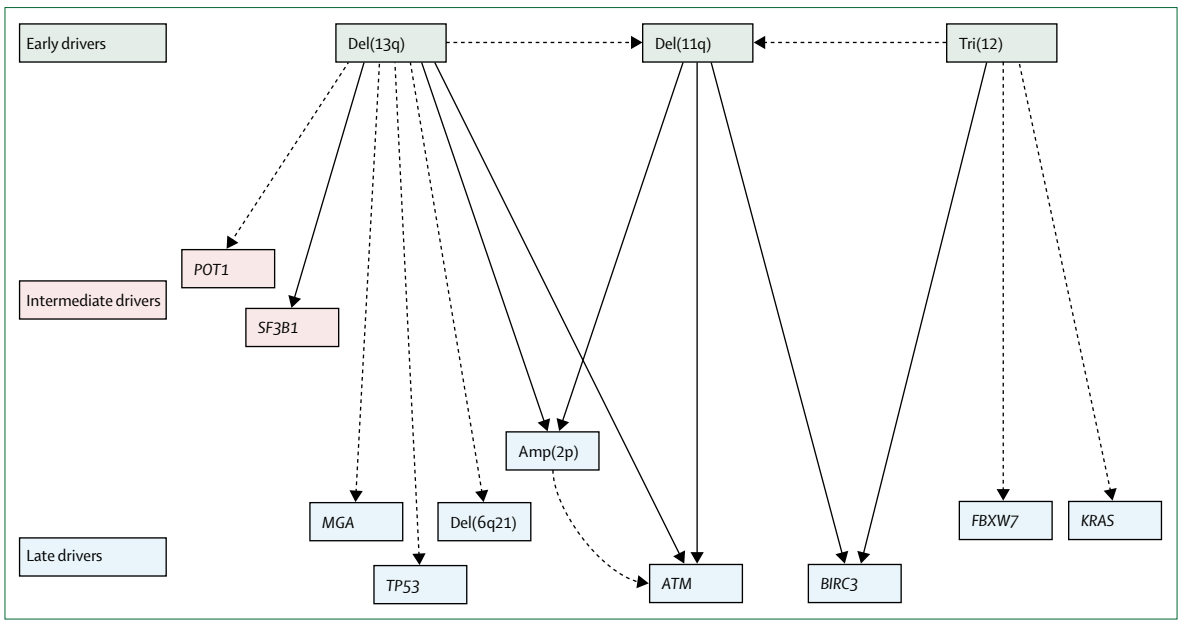

Figure 1: **Genetic drivers of chronic lymphocytic leukaemia**
Adapted from Landau et al (2015),[8] with permission of Springer Nature.

a complete blood count obtained for unrelated reasons. The second most common clinical presentation is lymphadenopathy, whereas B symptoms (fever, night sweats, weight loss, fatigue) or cytopenias (anaemia, thrombocytopenia, neutropenia) due to marrow infiltration present less frequently.

In the presence of an elevated B-cell count of at least 5000 B cells per µL peripheral blood, the diagnosis of chronic lymphocytic leukaemia is usually established by immunophenotyping.[17] Chronic lymphocytic leukaemia cells co-express CD5 and the B-cell surface antigens CD19, CD20, and CD23. The expression levels of surface immunoglobulin, CD19, CD20, and CD79b are characteristically low compared with normal B cells.[18,19] CD200 expression could also differentiate chronic lymphocytic leukaemia from other lymphomas.[20] Each clone of leukaemia cells expresses either κ or λ immunoglobulin light chains.[18]

The presence of such a clone with an absolute B-cell count of less than 5000 cells per µL blood and the absence of cytopenia, lymphadenopathy, hepatomegaly, or splenomegaly is designated monoclonal B-lymphocytosis, a precursor state to chronic lymphocytic leukaemia.[17,21,22] Monoclonal B-lymphocytosis progresses to frank chronic lymphocytic leukaemia at a rate of 1–2% per year[22] and is associated with an increased risk of infection and second malignancies.[23,24]

The diagnosis of small lymphocytic lymphoma requires the presence of lymphadenopathy due to a clonal B-cell population of chronic lymphocytic leukaemia phenotype and the absence of cytopenias caused by a clonal marrow infiltrate. Moreover, the number of B cells in the peripheral blood should not exceed 5000 cells per µL. The diagnosis of small lymphocytic lymphoma should be confirmed by histopathological assessment of a lymph node biopsy or other tissue whenever possible.[25]

Immunophenotyping of peripheral blood lymphocytes is used to distinguish clonal from reactive causes of lymphocytosis or lymphadenopathy and to distinguish chronic lymphocytic leukaemia from other low-grade non-Hodgkin lymphoma subtypes (table 1).[17] A lymph node biopsy should be done when immunophenotyping of peripheral blood lymphocytes does not definitively determine the diagnosis.[25]

Patients with an established diagnosis of chronic lymphocytic leukaemia should undergo risk stratification. The clinical staging systems for chronic lymphocytic leukaemia developed by Rai[26] and Binet[27] have formed the backbone of prognostication in clinical practice and trials in the past 40 years. These staging systems are based on a physical examination and standard laboratory tests and do not involve imaging studies.

In the past two decades, advances in understanding the genetic and molecular biology of chronic lymphocytic leukaemia has led to identification of markers associated with risk of progression and survival, providing prognostic information that is complementary to the classical staging systems.[8,28] In particular, *TP53* aberrations predict an aggressive disease course and refractoriness to chemoimmunotherapy.[29–31] The mutational status of the *IGHV* genes is also associated with survival, such that patients with unmutated *IGHV* genes have a more aggressive disease course than patients with mutated *IGHV* genes.[32,33] Other relevant

	sIg	CD5	CD23	CD79b	FMC7	CD20	CD22	CD103	CD200	CD25	CD11c	CD10	CD43	ROR1
Normal B lymphocytes	High	No	No	High	High	High	High	No	No	Low	Low	No	No	No
Chronic lymphocytic leukaemia	Low	High	High	Low	Low	Low	Low	No	Very high	Low	Low	No	Very high	High
Mantel cell lymphoma	High	High	No	High	Very high	Very high	High	No	Low	No	No	No	Very high	High
Lymphoplasmocytic lymphoma, immunocytoma	Very high	Low	Low	High	Low	High	High	No	No	Low	Low	No	Low	Not determined
Follicular lymphoma	Very high	No	No	High	Low	High	Low	No	No	No	No	Low	No	Low
Hairy cell leukaemia	Very high	No	No	Low	High	High	Very high	High	No	Very high	Very high	No	No	High
Marginal zone lymphoma	High	No	No	High	High	High	High	No	No	High	High	No	Low	Low

Table 1: **Differential diagnosis of chronic lymphocytic leukaemia using immunophenotyping to determine expression of surface markers on lymphoid cells**

prognostic parameters include expression of ZAP-70,[34,35] CD38,[35] and CD49d[36] and serum concentrations of thymidine kinase[37] and β_2-microglobulin.[38,39] Finally, mutations or deletions in genes such as *NOTCH1* and *SF3B1*[8,14,40] are associated with reduced survival. An international group of investigators did a comprehensive analysis[41] to develop a prognostic index for chronic lymphocytic leukaemia. Using data from 3472 treatment-naive patients participating in prospective, randomised clinical trials, five independent prognostic factors were identified: *TP53* deletion or mutation, or both, *IGHV* mutational status, serum β_2-microglobulin concentration, clinical stage, and age.[41] Using weighted grading of the independent factors, a prognostic index was derived that separated patients into four risk groups with significantly different overall survival at 5 years: low (93%), intermediate (79%), high (63%), and very high risk (23%; figure 2). This chronic lymphocytic leukaemia international prognostic index (CLL-IPI) has now been validated by several other groups[42–44] and is expected to improve patient counselling and the planning of clinical trials. Other risk scores have been proposed,[45–48] but none of them has been generally accepted. None of the scores (including the CLL-IPI) affects the decision of when to initiate therapy.

Indications for treatment

The criteria for initiating treatment[17] rely on the Rai and Binet staging systems and on the presence of symptoms caused by the disease. In general practice, most newly diagnosed patients present with asymptomatic, early-stage disease (Rai 0; Binet A); they should be monitored without therapy until disease progression. Findings from several randomised trials and a meta-analysis have shown that initiating treatment early does not result in any benefit and could cause harm.[49–52]

Patients with advanced disease (Rai stage III and IV; Binet stage C) and patients with symptomatic disease usually benefit from the initiation of treatment. Symptomatic or active disease is defined as follows: signs of progressive marrow failure (anaemia [haemoglobin concentration <11 g/dL for the Rai staging system and <10 g/dL for the Binet staging system] or thrombocytopenia [platelet count $<100\times10^9$ per L], or both); massive or progressive or symptomatic splenomegaly or lymphadenopathy; and autoimmune anaemia or thrombocytopenia, or both, not responding to corticosteroids. Other acceptable indications for treatment include disease-related symptoms such as unintentional weight loss (≥10% of body weight within the preceding 6 months), substantial fatigue, fevers of more than 38·0°C for at least 2 weeks without other evidence of infection, or night sweats for more than 1 month without evidence of infection. Alternative causes for B symptoms should be ruled out before starting an anti-leukaemic treatment.

Rapidly progressive lymphocytosis (a lymphocyte doubling time of less than 6 months) could also be an indication for treatment.[17] However, when lymphocyte doubling time is used as the sole criteria for treatment initiation, initial blood lymphocyte counts should be more than 30 000 cells per µl, and a careful clinical assessment should exclude other factors contributing to lymphocytosis or lymphadenopathy (eg, infections). Symptoms associated with leukocyte aggregates rarely occur in chronic lymphocytic leukaemia, even in patients with markedly increased leukocyte counts. The absolute lymphocyte count should therefore not be used as the sole indicator for treatment.

Therapeutic management of chronic lymphocytic leukaemia

Chlorambucil has been the standard treatment for chronic lymphocytic leukaemia for several decades.[53–55] In the 1990s, combinations of purine analogues (fludarabine) plus cyclophosphamide were found to improve the quality and duration of response in younger patients.[56–58] As a development of these drug combinations, the addition of the anti-CD20 monoclonal antibody rituximab to fludarabine plus cyclophosphamide (FCR) created the first treatment regimen that prolonged

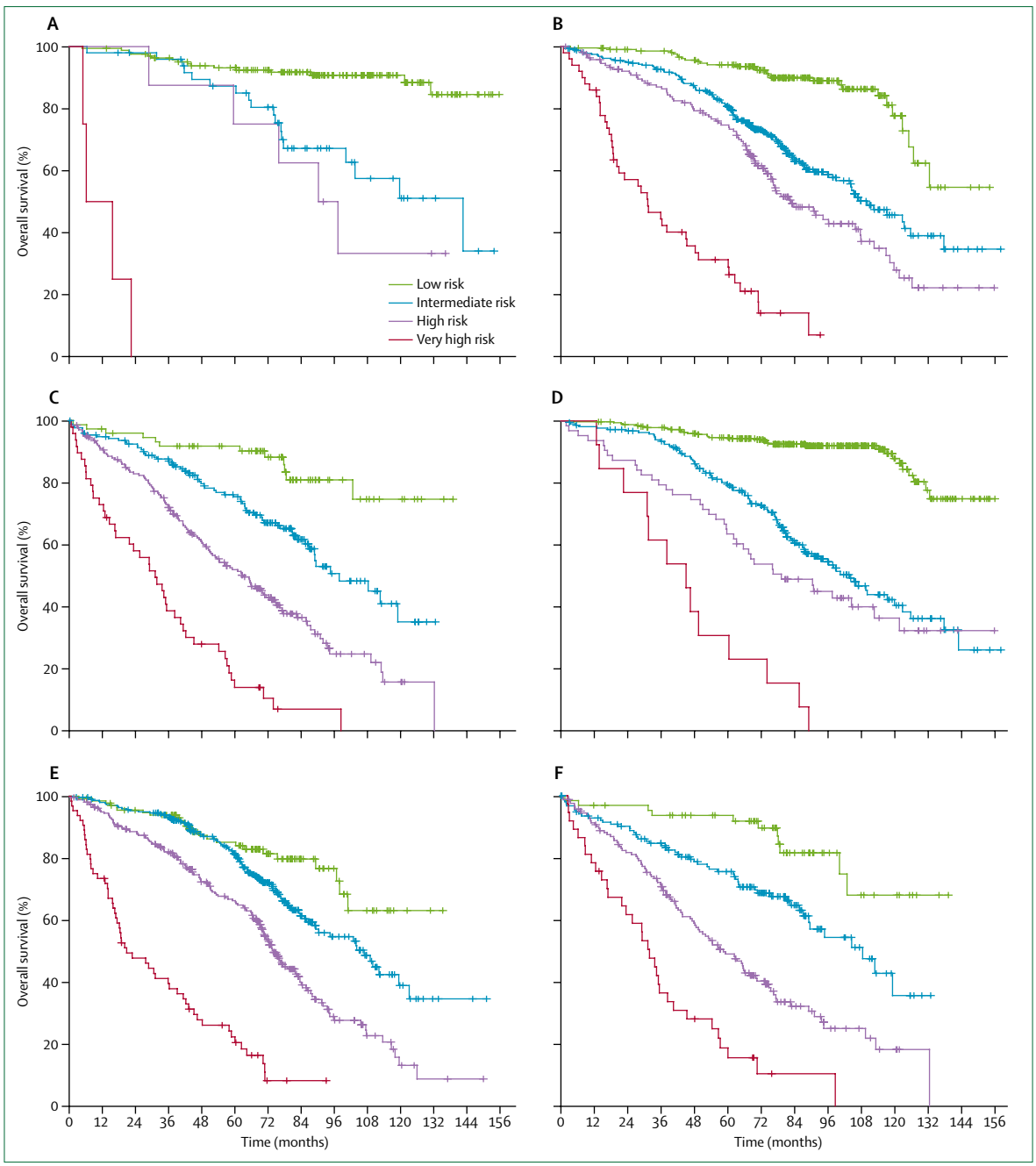

Figure 2: **Overall survival according to the CLL-IPI working group**
(A) Rai stage 0. (B) Rai stage I–II. (C) Rai stage III–IV. (D) Binet stage A. (E) Binet stage B. (F) Binet stage C. Adapted from the International CLL IPI working group (2016).[41]

overall survival for patients with chronic lymphocytic leukaemia.[59] Subsequently, the addition of anti-CD20 antibodies to chlorambucil also prolonged survival in elderly patients with comorbidities.[60,61] Chemoimmunotherapy using anti-CD20 monoclonal antibodies has thus become the standard treatment for most patients with chronic lymphocytic leukaemia, irrespective of age.

More recently, a growing understanding of the pathogenesis of chronic lymphocytic leukaemia has fostered essential for leukemic cell survival. Ibrutinib and idelalisib, two kinase inhibitors that target Bruton tyrosine kinase and phosphatidylinositol-3-kinase, respectively, have demonstrated efficacy and were recently approved. These drugs have specifically improved the care for patients with *TP53* aberration in the first-line setting.[62,63] Ibrutinib is recommended as a first-line therapy for all patients with a *TP53* aberration in the absence of a contraindication. Idelalisib in combination

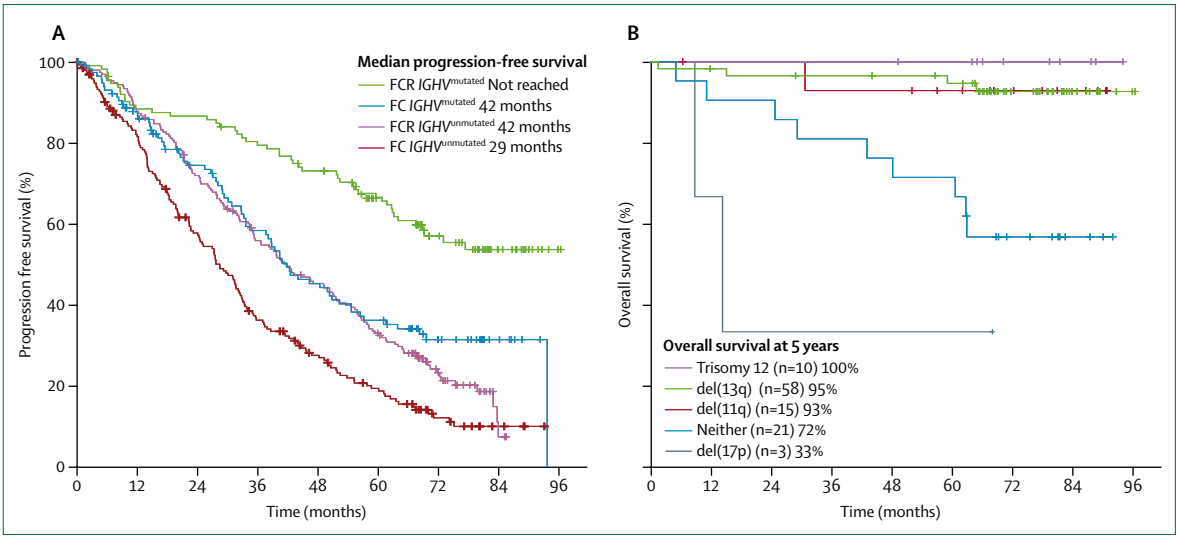

Figure 3: **Long-term benefit of fludarabine, cyclophosphamide, and rituximab (FCR) as first-line therapy for physically fit patients**
(A) Progression-free survival with FCR according to *IGHV* status in phase 3 study, including 817 patients for frontline therapy with a median observation time of 5·9 years.[69] (B) Overall survival with FCR for all patients with mutated *IGHV* status in phase 3 study, including 817 patients for frontline therapy with a median observation time of 5·9 years.[69]

with rituximab or the anti-CD20 monoclonal antibody ofatumumab is recommended for patients with *TP53* aberration who are not suitable for alternative first-line treatment options.

The BCL-2 antagonist venetoclax has an impressive therapeutic efficacy that seems to be independent of adverse prognostic parameters such as a *TP53* aberration or refractoriness to fludarabine.[64,65] Venetoclax was recently approved for treatment of patients with *TP53* aberration in relapse. In Europe, venetoclax is approved for patients with contraindications for kinase inhibitors as first-line treatment and for patients who do not respond to ibrutinib or idelalisib plus anti-CD20 antibody after chemoimmunotherapy.[65] On the basis of recent findings, the combination of venetoclax plus rituximab will also be approved in relapsed chronic lymphocytic leukaemia.[66]

First-line treatment of chronic lymphocytic leukaemia

Chemoimmunotherapy with FCR is recognised as the standard treatment for physically fit patients with chronic lymphocytic leukaemia.[59,67,68] Long-term follow-up results of the randomised CLL8 trial showed that 69% of patients treated with FCR were alive at the median observation time of 5·9 years compared with 62% of patients treated with fludarabine plus cyclophosphamide.[69] More importantly, in patients with mutated *IGHV* treated with FCR, the median progression-free survival had not been reached, and relapses were rarely observed after 9 years (figure 3). When analysing patients by risk category trisomy 12, del(13q), or del(11q), patients with mutated *IGHV* had an overall survival of more than 80% at 8 years (figure 3).[69] Results of follow-up investigations of patients treated with FCR in an American study showed that the 12·8-year progression-free survival was 80% for patients with mutated *IGHV* and who were negative for minimal residual disease (MRD) post-treatment. A plateau was seen on the progression-free survival curve in patients with mutated *IGHV*, with no relapses beyond 10·4 years in all 42 patients followed beyond this point.[70] Finally, in a multicentre, retrospective Italian study,[71] patients with chronic lymphocytic leukaemia and mutated *IGHV* but no del(17p) or del(11q) had a life expectancy of 91% at 5 years that was superimposable to a matched normal general population. These results show that that FCR can achieve durable remissions in a sizeable subgroup of patients.

Since 34% of patients who are treated with FCR have Common Toxicity Criteria grade 3–4 neutropenias, and 25% of patients have grade 3–4 infections,[59] attempts have been made to create equally potent but less toxic treatment regimens. These regimen used reduced doses of fludarabine and cyclophosphamide (FCR Lite)[72] or substituted fludarabine with pentostatin,[73–75] cladribine,[76] or bendamustine.[77–79] However, these alternative regimens appeared to be either less effective than FCR or had similar toxicity. Specifically, the German CLL Study Group compared FCR with the bendamustine plus rituximab regimen in the phase 3 CLL10 trial.[79] Severe grade 3–4 neutropenias (88% of patients treated with FCR *vs* 68% of patients with bendamustine plus rituximab) and severe grade 3–4 infections (40% *vs* 25%) were significantly higher with FCR than with bendamustine plus rituximab. However, patients treated with FCR achieved the longest median progression-free survival (54 months *vs* 43 months).

On the basis of this evidence, chemoimmunotherapy with FCR remains the first-line standard of care for

physically fit patients with chronic lymphocytic leukaemia without *TP53* aberration. For fit patients older than 65 years, bendamustine plus rituximab could be an alternative first-line therapy to decrease potential toxicity. Infection prophylaxis or haematopoietic growth factor support, or both, should be considered during treatment with FCR or bendamustine plus rituximab.[79]

Chlorambucil has long been the standard therapy for elderly patients and patients with comorbidities independent of age.[80–82] More potent drugs (eg, fludarabine and alemtuzumab) do not improve survival.[55,83–85] The CLL11 trial investigators assessed the addition of two different anti-CD20 monoclonal antibodies to chlorambucil versus chlorambucil alone in 781 elderly patients with coexisting medical conditions.[60,61] Overall and complete response rates with the addition of the novel anti-CD20 antibody obinutuzumab to chlorambucil (G-Clb; overall response 77%; complete response 22%) exceeded that of rituximab plus chlorambucil (R-Clb; 66%; 7%) and chlorambucil only (31%; no complete response). Notably, a substantial proportion of responding patients treated with obinutuzumab plus chlorambucil achieved MRD-negative remission in peripheral blood (38%) and bone marrow (20%). These responses improved progression-free survival with G-Clb relative to R-Clb (29·2 *vs* 15·4 months; p<0·0001).[60] G-Clb also improved the median overall survival relative to chlorambucil alone (p=0·0022).[60]

Compared with chlorambucil alone, ofatumumab plus chlorambucil (O-Clb) increased the overall response rate (69% with O-Clb *vs* 82% with chlorambucil; p<0·001) and complete response rate (1% *vs* 12%; p<0·001) and was associated with an improved median progression-free survival (13·1 months *vs* 22·4 months; p<0·0001) in treatment-naive patients.[86] 8% of patients who received ofatumumab achieved MRD negativity. Ofatumumab has not been compared with other anti-CD20 antibodies.

In a phase 3 trial of ibrutinib versus chlorambucil in elderly patients with comorbidities who had not received prior treatment,[87] the overall response rate was highest in patients receiving ibrutinib (86% with ibrutinib *vs* 35% with chlorambucil; p<0·001). Patients receiving ibrutinib also had superior progression-free survival (median not reached *vs* 18·9 months) and estimated overall survival at 24 months (98% *vs* 85%). On the basis of these results, ibrutinib was approved as a first-line therapy for chronic lymphocytic leukaemia.

Patients with a *TP53* aberration often have a very aggressive disease and respond poorly to chemoimmunotherapy.[13,88–91] The outcome for patients with *TP53* aberration improved with the introduction of ibrutinib, idelalisib, and venetoclax, which all act independently of the p53 pathway.[92–94] Both ibrutinib alone[95] and idelalisib combined with either rituximab[96] or ofatumumab[97] induced high response rates and promising progression-free survival and overall survival, independently of *TP53* aberration. Treatment outcomes achieved with ibrutinib and idelalisib were the best reported to date in patients with chronic lymphocytic leukaemia and *TP53* aberration.[63,95,96,98] Despite this progress, the presence of a *TP53* aberration in the leukaemic clone seems to retain its adverse prognostic effect, and treatment outcomes remain inferior with respect to the quality and duration of response compared with patients who do not have these genetic abnormalities.[62,63,95,96,98]

Given the rapidly increasing number of therapeutic options, choosing the optimal initial treatment for an individual with chronic lymphocytic leukaemia has become a task that requires experience and clinical judgment. Parameters that should be considered include fitness, age, comorbidities, and genetic status of *TP53*. We propose a guideline for first-line therapy on the basis of these parameters (table 2, table 3).[99,100] The use of kinase inhibitors should be guided by their safety profile and by considering the patient's comorbid health condition. For example, patients with increased bleeding risk due to comorbidity or medications should not receive first-line ibrutinib. The three-times increased risk of developing atrial fibrillation associated with ibrutinib therapy should also be taken into consideration, particularly in patients with a cardiac history.[101] Patients with a previous history of cytomegalovirus infection or pneumocystis pneumonia

	No *TP53* aberration	*TP53* aberration
Physically fit	Fludarabine plus cyclophosphamide plus rituximab (age ≤65 years); or bendamustine plus rituximab (age >65 years)	Ibrutinib or idelalisib plus rituximab or venetoclax (if ibrutinib therapy is not suitable because of comorbidities or comedication)
Physically unfit	Chlorambucil plus obinutuzumab; or chlorambucil plus ofatumumab; or chlorambucil plus rituximab; or ibrutinib monotherapy	Ibrutinib or idelalisib plus rituximab or venetoclax (if ibrutinib is not suitable because of comorbidities or comedication)

Table 2: **First-line treatment of chronic lymphocytic leukaemia in physically fit and physically unfit patients**

	Standard therapy	Alternative therapies
Refractory or progression within 3 years		
Physically fit	Ibrutinib possibly followed by allogeneic haemopoietic stem-cell transplant	Idelalisib plus rituximab; venetoclax; lenalidomide
Physically unfit	Change therapy	Ibrutinib; idelalisib plus rituximab; venetoclax; lenalidomide; CD20 antibody alone
Progression after 3 years		
All fitness levels	Repeat front-line therapy	Change to another chemoimmunotherapy; ibrutinib; idelalisib plus rituximab

Table 3: **Second-line treatment of chronic lymphocytic leukaemia, by response to first-line treatment and fitness**

should be carefully considered before indication of idelalisib plus CD20 antibody because severe viral and pneumocystis infections have been observed with this drug regimen.[102]

Treatment of relapse

The choice of an optimal second-line therapy should be guided by the intensity and side-effects of previous therapies and the duration of the previous response in addition to the parameters used for first-line treatment selection (table 2, table 3). Genetic defects should also be reassessed to identify genetic evolution (eg, acquisition of *TP53* aberration).

Patients with an early relapse after first-line chemotherapy or chemoimmunotherapy have a poor prognosis.[103–105] This poor outcome might be related to clonal evolution with an enrichment of adverse genetic alterations, such as a genetic *TP53* aberration, resulting from selection pressure and DNA damage during chemotherapy.[106–108] The kinase inhibitors ibrutinib[95,109] or idelalisib[96] are promising salvage therapies for patients with or without *TP53* aberration despite extensive pretreatment. With continuous ibrutinib treatment, 69% of patients with relapsed chronic lymphocytic leukaemia are still in remission at 30 months.[110] Notably, in the RESONATE-17 study,[63] promising duration of response to ibrutinib was seen in patients in relapse who carry del(17p), with a median progression-free survival of about 29 months. In a phase 3 trial[95] comparing ibrutinib with ofatumumab in relapsed patients, ibrutinib had superior efficacy with respect to response, progression-free survival, and overall survival. In another phase 3 trial[96] of idelalisib plus rituximab versus rituximab plus placebo in relapsed patients (42% of the study population carried a *TP53* aberration), progression-free survival and overall survival were significantly longer in the idelalisib group than in the placebo group.

Venetoclax has remarkable activity in chronic lymphocytic leukaemia. In a phase 2 trial[64] of venetoclax for patients with substantial pretreatment, the overall response rate was 79% and the complete response rate was 20%. Notably, 5% of these patients achieved MRD-negative remission. In another trial[65] of venetoclax in 107 patients with del(17p) and relapsed or refractory chronic lymphocytic leukaemia, the overall response rate was 79%, and the complete response rate was 8%. In subsequent trials combining venetoclax with rituximab in patients who had previously been treated, the overall response rate was 86%, and the complete response rate was 41%.[111] Findings from similar combination studies combining venetoclax with obinutuzumab[112] showed an overall response in 100% of patients and a complete response in 24% of patients. Notably, these venetoclax–antibody combinations also resulted in MRD-negative remissions, with about 50% of patients achieving an MRD-negative response in the bone marrow. Tumour lysis syndrome might occur during the initial phase of venetoclax treatment in patients with increased lymphocyte count or bulky lymphadenopathy. Patients at risk therefore need appropriate prophylaxis in addition to a slow-dose escalation. Venetoclax has been approved for patients with *TP53* aberration who were previously treated for chronic lymphocytic leukaemia. In Europe, venetoclax is also approved for patients relapsing after previous chemoimmunotherapy, for patients who progress on kinase inhibitors, and as first-line therapy for patients with *TP53* aberration not suitable for kinase inhibitors.

Repetition of the previous treatment or alternative second-line chemoimmunotherapy can be considered in patients without high-risk genetic features who have a long duration of remission after first-line treatment (>36 months after chemoimmunotherapy). The combination of venetoclax in first relapse of chronic lymphocytic leukaemia will soon be approved on the basis of results from the MURANO trial, in which venetoclax plus rituximab was compared with bendamustin plus rituximab.[66]

An allogeneic stem-cell transplant can be a curative option for selected patients with refractory or relapsing chronic lymphocytic leukaemia. However, this option is only feasible in a few young and physically fit patients with a matching donor.[113] Since allogeneic stem-cell transplants are associated with serious mortality and morbidity, the indication and timing of transplantation has been redefined in the era of targeted signalling inhibitors.[114] Genetically high-risk patients are recommended first-line treatment with kinase inhibitors, and allogeneic stem-cell transplantation is deferred until first or second relapse.[114] When evaluating the possibility of an allogeneic stem-cell transplant, the risks associated with the procedure should be carefully discussed with the patient.

Maintenance and consolidation

The fact that most patients eventually relapse after chemoimmunotherapy has generated interest in consolidation or maintenance strategies to improve the depth and duration of remission. Data from several trials show that an alemtuzumab-based consolidation can increase the rate of MRD-negative remissions and prolong progression-free survival.[115,116] However, this approach was associated with life-threatening infections in a sizeable proportion of patients. Consolidation or maintenance with the anti-CD20 monoclonal antibodies ofatumumab or rituximab has been tested in more recent trials.[117–119] In a phase 3 trial,[120] ofatumumab maintenance therapy prolonged progression-free survival by about 14 months in 474 patients completing second-line or third-line treatment for relapsed chronic lymphocytic leukaemia. Although this trial led to approval of ofatumumab maintenance in relapsed patients, this strategy is not approved after first-line

therapy. Findings from pilot trials[121] and a phase 3 trial[122] on lenalidomide maintenance therapy versus a watch-and-wait approach after frontline chemoimmunotherapy with FCR or bendamustine plus rituximab showed a significant difference in progression-free survival (13·3 months *vs* not reached). However, because no difference in overall survival was observed and lenaldomide was associated with toxicities, maintenance treatment with this drug should only be considered in some patients.

Response assessment, follow-up, and outcomes

Guidelines by the International Workshop on Chronic Lymphocytic Leukemia define criteria for the assessment of the clinical response to treatment and propose five response categories: complete remission, partial remission, stable disease, progression, or refractory disease.[17] In general practice, blood counts, a physical examination, and imaging studies are sufficient to assess the response. In clinical trials, the assessment of MRD has become an important endpoint and has been approved by the European Medicines Agency as an endpoint in clinical trials.[123,124] The presence of detectable MRD at completion of therapy is predictive of shorter progression-free survival and overall survival. Results of a quantitative assessment of MRD in 471 patients in the CLL8 trial[125] showed that that MRD negativity (as defined by the detection of less than one chronic lymphocytic leukaemia cell per 10 000 leukocytes) correlated with longer progression-free survival, and median MRD levels were lower with the FCR regimen than with FC. In patients who achieved partial remissions but were MRD negative, the outcome was similar to complete remissions.[126] MRD assessment is therefore recommended in clinical trials using standardised protocols of either four-colour flow cytometry or allele-specific oligonucleotide PCR (with a sensitivity of one chronic lymphocytic leukaemia cell per 10 000 leukocytes).[127]

Complications

Several complications are typical for chronic lymphocytic leukaemia: infections, autoimmune cytopenias, and transformation to high-grade lymphoma. Transformation of chronic lymphocytic leukaemia to a diffuse large B-cell lymphoma or Hodgkin's lymphoma occurs in about 1% of patients with chronic lymphocytic leukaemia per year and might thus affect up to 16% of patients during the course of the disease.[128,129] The transformation to diffuse large B-cell lymphoma is called Richter's transformation and usually has a very poor prognosis when the diffuse large B-cell lymphoma is clonally related to the underlying chronic lymphocytic leukaemia. The clonal relation of the Richter's transformation to the original chronic lymphocytic leukaemia clone (or clones) should be investigated to rule out the de-novo occurrence of lymphoma, which might trigger a different treatment strategy.[130] The presence of *NOTCH1* mutations in patients with chronic lymphocytic leukaemia increases the risk of Richter's transformation.[131] Suspected Richter's transformation must be confirmed by a histopathology examination of a lymph node or other involved organ, and treatment includes therapies used for diffuse large B-cell lymphoma, such as rituximab plus CHOP (cyclophosphamide, vincristine, doxorubicin, prednisolone), or more intense treatment regimens such as rituximab plus hyper CVAD/MA (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine), R-EPOCH (R-etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), or OFAR (oxaliplatin, fludarabine, cytarabine, rituximab).[132–134] The duration of treatment response in Richter's transformation is typically short, and an allogeneic haematopoietic stem-cell transplant should be considered in all responding patients with an available donor and sufficient fitness.[135] An autologous stem-cell transplant in patients without a donor or in patients who are ineligible for allogeneic transplant usually fails to prevent disease progression.[135] The transformation of chronic lymphocytic leukaemia into Hodgkin's disease is a separate and rare entity, where conventional chemotherapy against Hodgkin's lymphoma often achieves long-lasting remissions of Hodgkin's lymphoma.[129]

Patients with chronic lymphocytic leukaemia are also at increased risk of developing secondary cancers.[136–138] This risk is highest in elderly patients and in patients with comorbidities and increases with each round of therapy.[136] Chemoimmunotherapy increases the risk of secondary myelodysplastic syndromes or acute myeloblastic leukaemia. The incidence of secondary myelodysplastic syndromes and acute myeloblastic leukaemia after FCR treatment is 2–5% depending on age and exposure to growth factors.[69,139,140] Chemoimmunotherapy using bendamustine as a backbone might be associated with a lower risk secondary myeloid malignancies than fludarabine plus cyclophosphamide.[79]

Patients with chronic lymphocytic leukaemia are also at risk of developing autoimmune cytopenias such as autoimmune haemolytic anaemia (incidence of 2–4%), immune thrombocytopenic purpura (2–5%), pure red blood cell aplasia (0·5–1%), and autoimmune granulocytopenia (<1%). Autoimmune cytopenias, particularly haemolytic anaemia, can also be triggered by exposure to purine nucleoside analogues. The treatment of autoimmune cytopenias depends on the type of autoimmune cytopenia and whether the patient also needs treatment for the underlying chronic lymphocytic leukaemia.[17]

With an impaired immune system, often transiently aggravated by anti-leukaemic therapies, patients with chronic lymphocytic leukaemia often develop infectious complications. Until recently, infections were among

the most frequent causes of death in patients with chronic lymphocytic leukaemia, and severe bloodstream infections still occur when treating with new drugs.[141] The type of infection depends on the type of anti-leukaemic therapy: immunosuppressive therapies such as purine analogues or alemtuzumab, kinase inhibitors, and BCL-2 inhibitors might reactivate opportunistic infections such as *Pneumocystis jirovecii*, cytomegalovirus, or Herpesviridae;[142] rituximab (or anti-CD20 antibodies) might reactivate hepatitis B virus;[143] and myelosuppressive chemotherapies or chemo-immunotherapies might increase the risk for bacterial infections. Patients under distinct anti-leukaemic therapies should therefore receive appropriate prophylaxis such as cotrimoxazole, antiviral therapies, or growth factor support to prevent sustained neutropenia.

Controversies and uncertainties

First-line chemoimmunotherapy improves overall survival for patients with chronic lymphocytic leukaemia.[59,60] First-line use of ibrutinib improves survival in elderly and physically unfit patients,[87] and the combined use of idelalisib and rituximab confers a survival benefit in elderly high-risk patients with relapsed chronic lymphocytic leukaemia.[96]

These observations have raised the question of whether combinations of novel drugs with or without chemoimmunotherapy might achieve longer remissions or even cure some patients. The German CLL Study Group tested the so-called tailored and targeted treatment aiming for a total MRD eradication (sequential triple-T concept),[144] which consists of an optional debulking treatment with up to two cycles of a single drug (eg, bendamustine) followed by 6 months of induction therapy using combinations of monoclonal antibodies with kinase inhibitors or BCL-2-antagonists, or both, followed by MRD-tailored maintenance.[144] This concept aims for a more individualised treatment with an optional debulking for patients with a high tumour load, and with a tailored treatment duration based on the molecular response to therapy. This approach has generated promising early results.[145]

The optimal first-line treatment approach in elderly or physically unfit patients is unclear. In principle, at least three options exist: ibrutinib monotherapy, chemo-immunotherapy with chlorambucil and anti-CD20 antibodies, and, for some patients, bendamustine plus anti-CD20 antibodies. Head-to-head comparisons between the three therapeutic approaches are not available. Since chemoimmunotherapies are less effective in patients with unmutated *IGHV*[60,69,70,86] and ibrutinib seems more efficient in this group of patients, these patients might derive greatest benefit from kinase inhibitor-based approaches. This supposition, however, needs to be formally tested in clinical trials, particularly in young or fit patients.

Outstanding research questions

Which set of prognostic and predictive factors respectively will have greatest utility in the future?

The introduction of highly effective, novel therapies is expected to change the natural history of chronic lymphocytic leukaemia. Since several new drugs show very good efficacy in patients with *TP53* aberration and in patients with unmutated *IGHV*, the effect of these treatment advances might be largest for this subset of patients who historically have had a very poor prognosis. Consequently, the importance and implications of some specific prognostic markers in therapy selection might evolve as new therapies become available. To date, the poor outcome associated with some predictive markers, such as complex karyotype and *TP53* aberration, persists even with the novel drugs.

Should we treat patients with high-risk chronic lymphocytic leukaemia earlier?

Solid evidence suggests that early treatment with chemotherapy or chemoimmunotherapy does not improve the long-term outcome of chronic lymphocytic leukaemia.[49] However, with the advent of highly effective, targeted, and less toxic therapies it is possible that very high-risk patients, such as those with *TP53* aberration, would benefit from early therapeutic intervention. Early treatment of these patients remains a research question, and a watch-and-wait strategy remains the standard of care for asymptomatic early-stage patients.

How important is the elimination of MRD?

MRD is a robust predictor of progression-free survival and overall survival in patients treated with chemotherapy or chemoimmunotherapy[123,125] and has become a relevant endpoint for clinical trials. The clinical importance of MRD in patients treated with novel targeted therapies, however, is unclear. Drugs like ibrutinib show sustained disease control despite the absence of complete response or MRD-negative remission in most patients. This observation has raised the question whether achieving deep responses remains a meaningful endpoint with these therapy approaches. Although combinations of ibrutinib or idelalisib with anti-CD20 antibodies or even chemotherapy might improve the rate of MRD-negative remissions,[146,147] whether such treatment intensifications improve progression-free survival or overall survival compared with ibrutinib or idelalisib alone is unclear.

By contrast with other novel therapies, venetoclax-based treatments frequently induce MRD-negative remissions and might be amenable to a response evaluation strategy similar to that used for chemotherapy and chemo-immunotherapy. These nuances indicate that the optimal approach to response evaluation and the role of MRD status might need to be tailored to the treatment strategy used.

How long should patients continue on novel therapies?

Treatment with ibrutinib or idelalisib alone rarely induces complete remissions. These drugs are therefore often administered chronically until patients show substantial side-effects or until disease progression.[87,109] Whether the small subset of patients who achieve a MRD-negative remission with these drugs can discontinue treatment is unknown. Even for venetoclax, which seems more potent and induces MRD-negative remissions, the optimal duration of therapy is yet to be determined.

How can we prevent disease-related complications?

The reason for an increased risk for secondary primary cancers in patients with chronic lymphocytic leukaemia is unclear. This could be caused by shared risk factors (eg, genetic risk factors or exposure to toxic drugs), disease-related immunosuppression, or the side-effects of chronic lymphocytic leukaemia therapies. Chronic lymphocytic leukaemia also appears to contribute to inferior cancer-specific survival once a second cancer occurs.[148] Age-adapted screening of common cancers (ie, skin, breast, colon, cervical cancer) is highly recommended to facilitate early detection and treatment.[149]

Prevention of infections is another concern, since patients often have severe and sometimes fatal infections. Influenza and pneumococcal vaccines might be useful, particularly in elderly untreated patients.[150] In patients receiving immunosuppressive or myelosuppressive therapies, prophylaxis against *P jirovecii*, viral diseases, or bacterial infections might be helpful.

Novel immunotherapies

A variety of efforts have been undertaken to enhance the adoptive immune response against chronic lymphocytic leukemic B cells in patients with unfavourable genetic features. Approaches such as immune checkpoint inhibitors and genetic manipulation of T cells with chimeric antigen receptors[151] hold the promise of providing an alternative to allogeneic transplants in the future.[152]

Conclusion

Tremendous progress has been made in the management of chronic lymphocytic leukaemia in the past decade. These advances have led to a number of new questions about the optimal management of chronic lymphocytic leukaemia. Accordingly, patients should be encouraged to participate in well designed clinical trials. Clinical research has substantially improved outcomes for patients, and further progress will only be achieved by continuing these efforts systematically.

Contributors

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