

Early Intervention in Asymptomatic Chronic Lymphocytic Leukemia

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Abstract: Of the estimated 21,000 patients who will receive a new diagnosis of chronic lymphocytic leukemia (CLL) this year in the United States, approximately 80% will have early-stage disease. Patients with early-stage disease do not meet the criteria in the 2018 International Workshop on CLL guidelines for the initiation of therapy, and therefore they are not routinely offered treatment. The current management of these patients follows a “watch-and-wait” paradigm, which entails a regular follow-up every 3 to 6 months that includes a physical examination and relevant laboratory testing to evaluate for disease progression. These recommendations are based on decades of careful observations showing that treatment in early-stage CLL does not improve overall survival. With the advent of better prognostic tools to identify patients at high risk, in addition to the recent approval of several novel oral agents with impressive efficacy, the time is ripe to re-examine this question. This review (1) summarizes the results of studies of early intervention in CLL that led to the current consensus for “watch and wait” in early-stage CLL, (2) discusses the role of contemporary risk stratification in early-stage CLL, (3) describes the adverse clinical complications of untreated CLL, and (4) presents the results of ongoing clinical trials of novel agents used in patients with early-stage CLL.

Introduction

Chronic lymphocytic leukemia (CLL) is a low-grade B-cell lymphoproliferative neoplasm. It is estimated that 21,000 new cases will be diagnosed in the United States in 2021,¹ and in the majority of patients, the diagnosis will be discovered incidentally on the basis of lymphocytosis noted in a complete blood cell count. CLL is considered incurable, and most patients ultimately experience significant disease-related morbidity and die of the disease or its complications.^{2,3} In the past 4 decades, as the result of significant advances that have been made, the armamentarium of treatments for CLL has expanded tremendously. The treatment of CLL has evolved from single-agent alkylator therapy with an agent such as chlorambucil (Leukeran, Aspen Global), to combination therapy with a purine nucleoside analogue and an alkylating agent (eg, fludarabine and

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Novel agents, prediction, risk, time to first therapy

Table 1. Indications for the Initiation of Anti-CLL Therapy

B symptoms
- Fever (unexplained temperature >38°C [100.4°F])
- Drenching night sweats
- Weight loss (unintentional weight loss of >10% of body weight over a period of ≤6 mo)
Marrow failure
- Anemia (Hgb <10 g/dL)
- Thrombocytopenia (platelet count <100 × 10 ⁹ /L)
Massive/progressive splenomegaly
Massive/progressive lymphadenopathy
LDT of <6 mo or ≥50% increase in ALC in 2 mo
Autoimmune complications (eg, AIHA, ITP) not responsive to corticosteroids
Symptomatic extranodal involvement (skin, CNS, kidneys)

AIHA, autoimmune hemolytic anemia; ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukemia; CNS, central nervous system; Hgb, hemoglobin; ITP, immune thrombocytopenia purpura; LDT, lymphocyte doubling time; mo, months.

Source: Adapted from Hallek M et al. *Blood*. 2018;131(25):2745-2760.⁴

cyclophosphamide), and then to combination chemoimmunotherapy (eg, fludarabine, cyclophosphamide, and rituximab [FCR], or bendamustine and rituximab [BR]). Recombinant genetically based approaches to enhance the cytotoxicity of anti-CD20 monoclonal antibodies led to the approval of ofatumumab (Arzerra, Novartis) and obinutuzumab (Gazyva, Genentech), which have contributed to impressive strides in the management of CLL. In the past decade, several novel oral agents have been approved for the treatment of CLL. These include the Bruton tyrosine kinase (BTK) inhibitors ibrutinib (Imbruvica, Pharmacyclics/Janssen) and acalabrutinib (Calquence, AstraZeneca); the phosphoinositide 3-kinase (PI3K) inhibitors idelalisib (Zydelig, Gilead) and duvelisib (Copiktra, Verastem); and the B-cell lymphoma 2 (BCL2) inhibitor venetoclax (Venclexta, AbbVie). Collectively, these therapies represent a paradigm shift in our approach to the management of patients with CLL.

The 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines are consensus recommendations that provide widely accepted indications for the initiation of anti-CLL therapy (Table 1).⁴ Approximately 80% of patients with CLL have early-stage asymptomatic disease at the time of diagnosis and do not meet any of the 2018 iwCLL criteria for the initiation of therapy. A “watch-and-wait” approach is typically favored for these patients if they are not enrolled in a clinical trial. However, in the era of novel agents with greater effectiveness and more favorable side effect profiles (such as less marrow toxicity), and with the development of robust

prognostic models, discussed below, we believe that an evaluation of the benefits of early treatment intervention in patients with asymptomatic CLL is timely. In this review, we highlight past efforts to conduct treatment in early-stage CLL, describe how prognostic models permit the detection of high-risk early-stage CLL, and summarize the emerging data from recent clinical trials, based on novel agents, that assessed the efficacy and safety of early intervention in CLL.

Historical Overview of Early Intervention in CLL

Early intervention refers to the administration of anti-CLL therapy to patients who otherwise would be under observation alone owing to a lack of symptoms related to CLL. This situation typically applies to patients with a new diagnosis who do not meet the 2018 iwCLL criteria for the initiation of therapy. A number of studies have been conducted in the past 4 decades to determine if early intervention in patients with asymptomatic CLL can improve outcomes. In a small phase 3 study of interferon alfa (n=21) vs observation (n=23), the use of interferon alfa did not improve progression-free survival (PFS) and overall survival (OS) in patients with Binet stage A CLL.⁵ In 2 randomized phase 3 studies that enrolled a total of 1535 patients, the French Cooperative Group on Chronic Lymphocytic Leukemia reported that continuous chlorambucil therapy (administered orally as a single agent at a daily dose of 0.1 mg/kg) or intermittent chlorambucil therapy (administered with prednisone: chlorambucil dosed at 0.3 mg/kg daily for 5 days each month, and prednisone dosed at 40 mg/m² daily for 5 days each month) for a total of 3 years improved disease control compared with no treatment.⁶ Similar results were published by Shustik and colleagues in a Cancer and Leukemia Group B (CALGB) study comparing treatment with chlorambucil (administered at a dose of 0.5 mg/kg orally on day 1 of each month, with subsequent monthly dose increases of 0.1 mg/kg until clinical improvement or toxicity) in 48 patients who had early-stage CLL vs no treatment.⁷ Neither study showed an OS benefit when chlorambucil was compared with no treatment. A meta-analysis of chlorambucil-based treatments by the CLL Trialists’ Collaborative Group also demonstrated no improvement in OS for immediate vs deferred chlorambucil-based treatments.⁸ Given the lack of an OS benefit with these approaches, chlorambucil-based treatments for early-stage asymptomatic CLL have not been incorporated into routine practice.

With the availability of the purine nucleoside fludarabine for the management of CLL in the 2000s, the German CLL Study Group (GCLLSG) conducted the CLL1 trial, which compared fludarabine (25 mg/m² intravenously daily for 5 days, repeated every 28 days for

a maximum of 6 cycles) with observation in patients who had early-stage CLL. To be eligible for trial participation, all patients were required to have 2 of the following 4 adverse characteristics: diffuse bone marrow infiltration, rapid lymphocyte doubling time (LDT), serum β_2 -microglobulin level above 4.35 mg/dL, and serum thymidine kinase level above 10 IU/L (the latter being a marker for the proliferation rate in CLL, with a higher value predicting a more aggressive course). Among the 189 patients enrolled in the study, fludarabine therapy led to a significant improvement in PFS (30 vs 13 months; $P < .01$) and in treatment-free survival (74 vs 41 months; $P = .04$). Nonetheless, improvement in OS did not occur (127 months vs not reached; $P = .75$).⁹ The subsequent CLL7 study intensified the treatment regimen to 6 cycles of standard FCR vs observation in 201 patients with asymptomatic CLL. Patients in this study had at least 2 of the following 4 adverse characteristics: rapid LDT, serum thymidine kinase level above 10 IU/L, unmutated immunoglobulin heavy chain variable (*IGHV*) genes, and high-risk fluorescence in situ hybridization (FISH) results, including del(11q), del(17p), and trisomy 12. After approximately 5 years of follow-up, the median event-free survival (EFS) was significantly better with FCR than with observation (median not reached vs 18.5 months; $P < .001$); however, the 5-year OS rate did not differ between the 2 arms (82.9% vs 79.9%, respectively; $P = .86$).¹⁰ Given the excessive toxicities associated with FCR (mainly hematologic toxicities and infections) and the lack of a difference in OS, fludarabine-based therapies are not recommended in patients with early-stage asymptomatic CLL.

Several studies have tested the use of anti-CD20 monoclonal antibody treatments such as rituximab, which provide a far less toxic treatment platform than cytotoxic chemotherapy for early-intervention trials. These approaches used rituximab either as a single agent or in combination with other monoclonal antibodies, such as alemtuzumab (Campath, Genzyme).¹¹⁻¹³ The studies demonstrated response rates of 80% to 95%, a response duration of approximately 18 months, and an improvement in time to the initiation of cytotoxic therapy in comparisons with historical controls who had high-risk disease. However, these approaches have not been adopted into routine practice, given the small numbers of patients and lack of long-term outcome data.

Contemporary Risk Models for CLL Progression Among Patients With Newly Diagnosed Disease

The risk for progression to symptomatic disease in CLL is variable. Some patients live for decades without therapy, whereas others die within a few years after diagnosis

owing to disease progression despite treatment.¹⁴ Therefore, one of the essential components for successful early treatment in asymptomatic patients is rigorous patient selection. The importance of patient selection was well demonstrated in a recent phase 3 clinical study of patients with smoldering multiple myeloma, another example of a relatively indolent hematologic malignancy. Smoldering multiple myeloma, like CLL, is observed until specific criteria for therapy are met. In this study, treatment with lenalidomide (Revlimid, Celgene) was compared with observation and was found to be superior in reducing the risk for progression to symptomatic disease, with a favorable risk-to-benefit ratio seen mainly in patients at high risk for disease progression.¹⁵ Therefore, given that patients at higher risk for progression to symptomatic disease are more likely to benefit from early intervention than are those at lower risk for disease progression, appropriate patient selection is an essential component of efforts to assess the benefits of early treatment in CLL.

Prognostic models for risk stratification in CLL have evolved from the early Rai and Binet staging systems^{16,17} to contemporary models integrating clinical, biological, and genomic characteristics. These novel models improve prognostic accuracy and thus serve as a better guide for clinicians and patients alike.¹⁸ Such prognostic models were developed primarily to predict OS, the most robust endpoint in cancer. However, in the context of appropriate patient selection for early intervention, the optimal risk model is one that accurately predicts time to first therapy (TTFT). Four such models exist and are listed in Table 2. The best validated and most widely accepted model is the CLL International Prognostic Index (CLL-IPI),¹⁹ which is based on 5 readily available factors and categorizes patients with CLL into 4 risk groups. It was originally developed to predict OS among treatment-naïve patients with CLL enrolled in several phase 3 studies. However, by applying this model to patients with untreated CLL, investigators were able to predict TTFT in 2 cohorts of untreated patients, one from the Mayo Clinic and the other a Scandinavian population-based cohort.

The CLL1 study researchers recently published their own independent prediction model for TTFT among 539 patients with CLL who were enrolled into the observation arm of the study.²⁰ Their CLL prognostic model, CLL1-PM, is a 6-factor model and has considerable overlap with the CLL-IPI score. However, the former model includes a del(11q) abnormality on FISH and an LDT of less than 12 months, neither of which is part of the CLL-IPI model, whereas Rai stage I to IV is included in the CLL-IPI model but not in the CLL1-PM model.

A head-to-head comparison of these 2 models conducted by the CLL1 investigators from the GCLLSG revealed similar performances, although the C-statistic score (a measure of model prediction accuracy in which

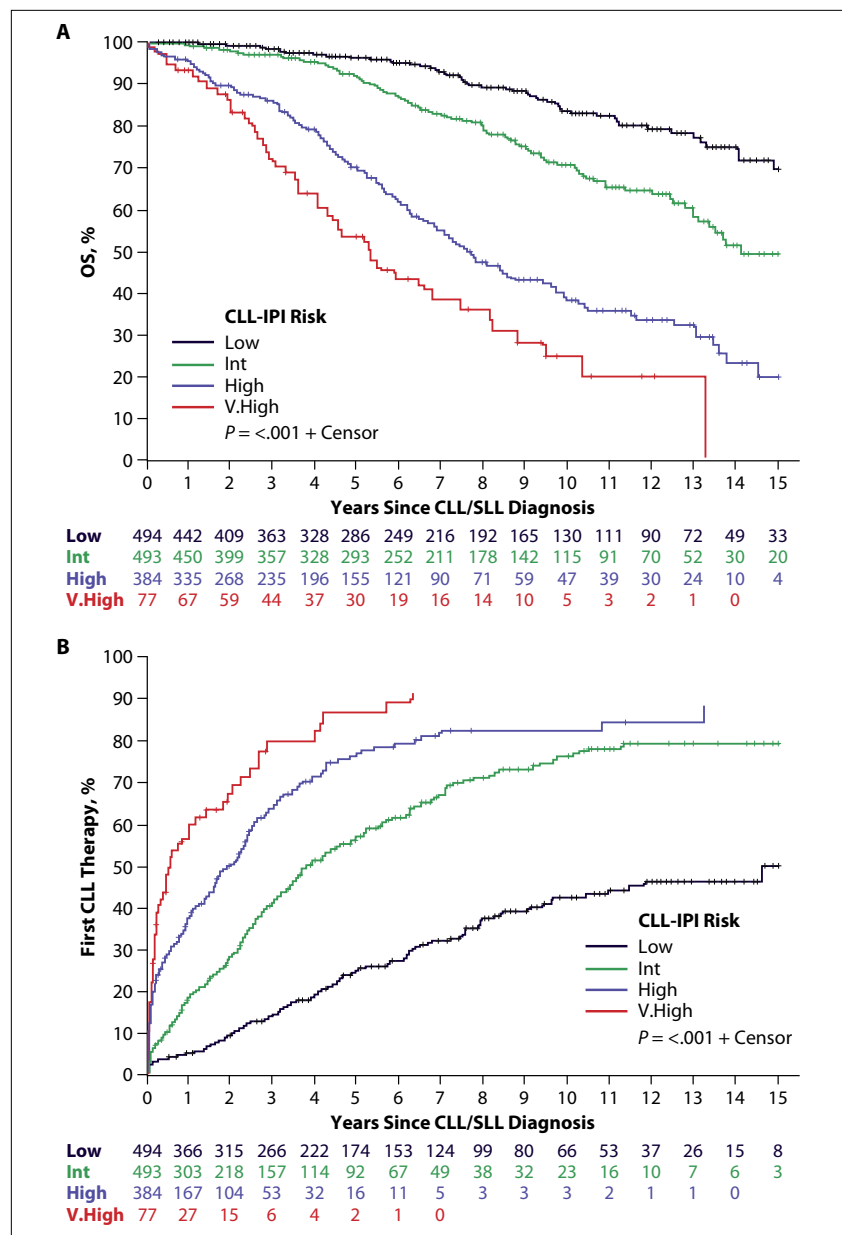
Table 2. Models Predicting Time to First Therapy

Model / N / Median Follow-up	Prognostic Factors (Points Where Applicable)	Model Prediction Outcomes (Points Where Applicable)	Pros, Cons / Comments
MDACC ²¹ 930 26 mo	1. Unmutated <i>IGHV</i> (1.065) 2. Diameter in centimeters of largest palpated cervical lymph node (diameter × 4.172) 3. FISH 17p- (11.285) or 11q- (9.312) 4. >3 involved lymph node sites (7.37) 5. LDH (LDH [U/L]/100 × 5 if <i>IGHV</i> mutated; LDH [U/L]/100 × 1.065 if <i>IGHV</i> unmutated) Total score: sum of above + 35.467	Nomogram with point score ranging from 0 to 87.4 (median, 21.0) 20 points: ~95% 2-y TTFT; ~90% 4-y TTFT 50 points: ~65% 2-y TTFT; ~40% 4-y TTFT	Pros: Clinical accessible parameters Cons: Nomogram-based score, not readily calculated; short follow-up First modern model to assess TTFT
GCLLSG ²² 1948 in the GCLLSG cohort; 676 in the Mayo validation cohort 63.4 mo	1. FISH 17p- (6) 2. FISH 11q- (1) 3. Thymidine kinase level >10 U/L (2) 4. B2M >3.5 mg/L (2), >1.7 and ≤3.5 mg/L (1) 5. Unmutated <i>IGHV</i> (1) 6. ECOG PS >0 (1) 7. Male sex (1) 8. Age >60 y (1)	Low risk (0-2): 5-y TFS 80% Intermediate risk (3-5): 5-y TFS 60% High risk (6-10): 5-y TFS 25% Very high risk (11-14): 5-y TFS 0%	Pros: Mostly accessible parameters; validated model with external cohort; model predicts OS Cons: Model developed primarily for OS prediction and extrapolated for TFS; model does not account for comorbidities; TK not available in many laboratories; younger patient population than in typical CLL cohort Validated with external cohort from Mayo Clinic; TFS the primary measured outcome rather than TTFT
CLL-IPI ¹⁹ 3472 in the main cohort; 838 in the Mayo validation cohort; 416 in the SCAN validation cohort 79.9 mo	1. FISH 17p- or <i>TP53</i> mutation (4) 2. <i>IGHV</i> mutation (2) 3. B2M >3.5 mg/L (2) 4. Rai stage I-IV (1) 5. Age >65 y (1)	Low risk (0-1): 5-y TTFT 78% Intermediate risk (2-3): 5-y TTFT 54% High risk (4-6): 5-y TTFT 32% Very high risk (7-10): 5-y TTFT 0%	Pros: Mostly accessible parameters; simple model to be calculated with patient Cons: Model developed primarily for OS prediction and extrapolated for TFS; model does not account for comorbidities Originally designed for survival prediction among treatment-naïve patients with CLL, but prediction of TTFT was tested in validation untreated cohorts (Mayo and SCAN); most frequently used model for prediction of survival and time to next therapy
CLL1-PM ²⁰ 539 8.5 y	1. FISH 17p- (3.5) 2. Unmutated <i>IGHV</i> (2.5) 3. FISH 11q- (2.5) 4. B2M >3.5 mg/L (2.5) 5. LDT <12 mo (1.5) 6. Age >60 y (1.5)	Very low risk (0-1.5): 5-y TTFT 85.9% Low risk (2-4): 5-y TTFT 51.8% High risk (4.5-6.5): 5-y TTFT 27.6% Very high risk (7-14): 5-y TTFT 11.3%	Pros: In head-to-head comparison has slightly better C-statistics vs CLL-IPI model Cons: Not validated externally

B2M, β_2 -microglobulin; CLL-IPI, chronic lymphocytic leukemia International Prognostic Index; CLL1-PM, chronic lymphocytic leukemia prognostic model; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; GCLLSG, German Chronic Lymphocytic Leukemia Study Group; *IGHV*, immunoglobulin heavy chain variable gene; LDH, lactate dehydrogenase; LDT, lymphocyte doubling time; MDACC, MD Anderson Cancer Center; mo, months; OS, overall survival; PS, performance status; SCAN, Scandinavian population-based case-control study; TFS, treatment-free survival; *TP53*, tumor protein p53 gene; TTFT, time to first therapy; y, years.

Figure A, Overall survival in patients with early-stage CLL seen at the Mayo Clinic from 1995 to 2019, according to CLL-IPI group assignment. **B,** Time to first therapy in the same patient population according to CLL-IPI group assignment.

CLL, chronic lymphocytic leukemia; CLL-IPI, CLL International Prognostic Index; OS, overall survival; SLL, small lymphocytic lymphoma.



a score of 1.0 indicates a perfect predictor) marginally favored the CLL1-PM over the CLL-IPI (0.74 vs 0.71, respectively).²⁰ However, the observation arm in the CLL1 study had a higher proportion of favorable-risk patients (62% very low-risk patients compared with 46% low-risk patients in the Mayo validation cohort of the CLL-IPI). This finding suggests selection bias, which likely affected model performance. The 2 other notable prognostic models for TTFT are the MD Anderson Cancer Center (MDACC) nomogram²¹ and the GCLLSG model.²² The MDACC nomogram, the first model to predict TTFT, utilizes 5 readily available parameters. The nomogram is based on a complex formula, however, and its application

in the clinic is challenging. The GCLLSG model is limited by the incorporation of the thymidine kinase level, a measurement that is not widely available in the United States. In our clinical practice, we use the CLL-IPI model to predict the TTFT, given its ease of clinical applicability and its multicenter design and validation across several studies.²³⁻²⁵

With the emergence of models to predict TTFT, the next question that comes up is, which risk group(s) would be considered suitable for assessing the effect of early intervention vs the traditional “watch-and-wait” approach in asymptomatic patients? The OS and TTFT among patients with newly diagnosed CLL seen at Mayo Clinic

from January 1995 through December 2019 are shown in the Figure. Among 1448 patients, the median TTFT values in the very high-risk and high-risk groups were 0.5 and 1.9 years, respectively, compared with 3.8 and 14.6 years in the intermediate-risk and low-risk groups, respectively. To maximize proof of efficacy for early intervention, the risk for disease progression in selected patients should be higher than the rate of treatment failure owing to toxicity or resistance. If we assume that (1) the response rate in patients with asymptomatic CLL is similar to the rate in those with symptomatic CLL and (2) the rate of treatment failure at 3 years with the use of contemporary therapies in patients with symptomatic CLL is 10% to 25%,²⁶⁻²⁹ then patients in the CLL-IPI high-risk and very high-risk groups (who have 3-year TTFT rates of 50% and 75%, respectively) are likely the ones most suitable to provide evidence for the efficacy of early intervention.

Adverse Clinical Consequences of Untreated CLL

Data about the adverse clinical consequences of a “watch-and-wait” management strategy are slowly emerging. In a study of 1475 patients with newly diagnosed CLL seen at Mayo Clinic in Rochester, Minnesota, approximately 25% of the patients had hypogammaglobulinemia at the time of diagnosis, and among the patients with a normal serum level of immunoglobulin G at the time of diagnosis, hypogammaglobulinemia developed in approximately 25% over time (even in the absence of treatment), suggesting that immune dysfunction may occur as a consequence of expansion of the malignant B-cell clone.³⁰ In a recent study of 2905 patients from the Danish National CLL Registry with newly diagnosed CLL, the cumulative incidence of infection (the proportion of individuals who had blood cultures drawn was used as a proxy for infection, regardless of whether infection was identified) was 12% in the first year among untreated patients with CLL.³¹ Older age, male sex, advanced Binet stage, unmutated *IGHV* genes, serum β_2 -microglobulin level above 4 mg/dL, and hypogammaglobulinemia were predictors of an increased risk for infection in these patients. Using a competing-risk model, the authors demonstrated that the cumulative risk for needing therapy at 1 year after diagnosis was 11% and the risk for death at 1 year was 1%, suggesting that infectious complications are an important source of morbidity in patients with untreated CLL. The authors extended these findings in a larger cohort of patients and with the use of machine learning developed the CLL Treatment Infection Model (CLL-TIM), which identified patients at risk for infection or CLL treatment within 2 years of diagnosis.³²

In addition to infections, patients with CLL are at

increased risk for the development of nonhematologic malignancies in comparison with age- and sex-matched healthy controls.³³⁻³⁸ The risk for nonhematologic malignancies, particularly nonmelanoma skin cancers, was significantly increased in patients who had a high-risk or very high-risk CLL-IPI score compared with patients who had a low-risk or intermediate-risk CLL-IPI score (4-year risk: 30% vs 10%, respectively).³⁹ Finally, the occurrence of clonal evolution in patients with untreated CLL during the watch-and-wait phase of disease management is being increasingly recognized. Studies have demonstrated the acquisition of novel genetic aberrations before the administration of therapy that are distinct from the original clonal genetic features, even among individuals with favorable-risk markers such as mutated *IGHV* genes and del(13q) by FISH. This finding suggests that the accumulation of novel somatic mutations is not restricted to the post-therapy setting.^{40,41} It is important to note that despite these observations, no evidence available to date indicates that early intervention to treat CLL will reverse many of these immune deficits or genomic aberrations and lead to improved outcomes. Carefully conducted clinical trials specifically examining such biological outcomes of interest, as well as clinical benefits, are critical if we are to acquire a full understanding of the long-term implications of early therapy.

Selection of Endpoints for Early-Intervention Studies in CLL

The choice of endpoint(s) for early intervention in studies of patients with asymptomatic CLL is an important design question. The possible clinical endpoints, and details of the pros and cons of each, are listed in Table 3. OS is the gold standard as a primary endpoint but requires a long follow-up, which makes it a problematic choice. Moreover, OS benefit may be “diluted” by the ongoing emergence of therapeutic options that gradually improve OS in this disease.⁴²⁻⁴⁵ Indeed, the US Food and Drug Administration (FDA) accelerated approvals of drugs to treat hematologic cancers were based mostly on surrogate endpoints, such as response rate and PFS.^{46,47} Therefore, PFS is the current leading endpoint for drug approval, including in studies of early intervention in other hematologic malignancies, as discussed earlier.¹⁵ Studies relying on PFS as the primary endpoint are still expected to require a long follow-up, although the sample size is generally smaller than with an OS endpoint. Critics of PFS as an endpoint in early-intervention studies note that the results of comparing a drug that is approved for a particular indication with placebo are a foregone conclusion, and therefore such studies generally do not truly inform practice. In addition, “progression”

Table 3. Choice of Endpoints for Clinical Trials Assessing Early Intervention in CLL

Endpoint	Pros	Cons	Comments
OS	Highest level of evidence of clinical benefit Easily measured	Large studies and long follow-up needed to assess for survival difference	Less likely to be primary endpoint in most studies because of time and resources needed
PFS	Shorter follow-up and smaller cohort to detect difference between intervention arm and control arm	Definition may vary from study to study Concept of PFS not readily intuitive to patients May not be surrogate marker for OS	Most common primary endpoint for drug approval
EFS	Likely a better measure for capturing clinical progression with clinical relevance in early-stage CLL	Symptomatic progression of disease can be subjective; therefore, important to use this endpoint in the context of randomized trials to avoid bias	Likely will be important endpoint for most early-stage CLL trials
MRD	Surrogate marker for PFS/OS in CLL and can be assessed at shorter follow-up	Not yet established as valid test for drug approval in CLL Optimal timing of MRD assessment not established Difference in sensitivity between bone marrow and peripheral blood samples	Several methods exist (PCR-based, flow cytometry-based, next-generation sequencing)
QoL	Can be assessed at regular intervals to detect changes over time Clinically applicable and requires limited resources Timely measurement of treatment efficacy and toxicity	Not yet validated as endpoint in clinical studies Semiquantitative measure Interpatient variability	Increasingly incorporated into clinical trials
Infections and second cancers	Novel endpoint Explores effect of CLL-mediated immunosuppression on rate of infections and second cancers, endpoints that are often overlooked	Therapy may affect risk for infections and second cancers, an issue that may be best addressed in randomized trials comparing therapy against placebo Long follow-up required to assess effects	Likely to be increasingly incorporated into clinical trials

CLL, chronic lymphocytic leukemia; EFS, event-free survival; MRD, minimal residual disease; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; QoL, quality of life.

Table 4. Early Intervention Clinical Studies in the Era of Novel Agent Therapies

Study	N	Study Design	Study Population	Primary Endpoint	Intervention
CLL12 (NCT02863718)	515	Ran-domized double-blind phase 3	Patients with untreated Binet stage A CLL and no need for treatment	EFS	Subjects with intermediate-, high-, or very high-risk CLL according to GCLLSG risk model randomized to ibrutinib 420 mg daily or placebo; treatment continued until disease progression and no later than 60 mo after randomization; low-risk patients observed
OSU (NCT02518555)	44	Ran-domized phase 2	Patients with untreated asymptomatic CLL/SLL and ≥ 1 of following high-risk genomic features: - FISH del(17p) - FISH del(11q) - Complex karyotype (≥ 3 cytogenetic abnormalities on stimulated karyotype) - Unmutated <i>IGVH</i>	2-y PFS	Ibrutinib 420 mg daily for up to 24 cycles (28-d cycle) concurrently with vaccination (PCV13, trivalent influenza, and DTaP) or sequentially after vaccination (starting from cycle 4)
MDACC (NCT03207555)	50	Phase 2	Patients with untreated asymptomatic CLL and estimated TTFT of ≤ 3 y, according to MDACC nomogram	CR; CRi	Ibrutinib 420 mg daily for up to 24 cycles (28-d cycle)
Mayo Clinic (NCT03516617)	120	Phase 2	Patients with untreated CLL/SLL and high- or very high-risk CLL-IPI score to be randomized into 2 treatment arms (A and B); patients with low-intermediate CLL-IPI score to be observed (arm C)	Rate of uMRD CR in arms A and B; TTFT in arm C	Arm A: acalabrutinib 100 mg BID for 24 mo Arm B: acalabrutinib 100 mg BID for 24 mo plus IV obinutuzumab d 1, 2, 8, 15 in cycle 1 and d 1 in cycles 2-6 Arm C: observation alone
Moffitt Cancer Center (NCT03514017)	25	Phase 2	High-risk patients with untreated CLL	ORR and TTR	Pembrolizumab (anti-PD-1 monoclonal antibody) in combination with ibrutinib
PreVent-ACaLL (NCT03868722)	212	Phase 3	Patients with untreated CLL at high ($>65\%$) risk for infection and/or in need of CLL treatment within 2 y of diagnosis	Grade ≥ 3 infection-free survival at 24 wk	Acalabrutinib (100 mg BID from cycle 1 d 1 for 12 wk) and venetoclax, with ramp-up during first 5 wk starting at cycle 1 d 1; thereafter, 400 mg once daily for total of 12 wk counted from cycle 1 d 1; or observation
EVOLVE (SWOG; NCT04269902)	247	Phase 3	Patients with untreated CLL who have high- or very high-risk CLL-IPI score at diagnosis or complex karyotype	OS at 6 y	Immediate treatment with venetoclax, weekly ramp-up of dose to 400 mg daily \times 12 mo, and with IV obinutuzumab d 1, 2, 8, 15 in cycle 1 and d 1 in cycles 2-6; or observation initially and then delayed treatment with venetoclax and obinutuzumab as in immediate-treatment arm when patients meet 2018 iwCLL criteria for therapy

BID, twice a day; CLL, chronic lymphocytic leukemia; CLL-IPI, chronic lymphocytic leukemia International Prognostic Index; CR, complete response; CRi, complete remission with incomplete count recovery; d, day(s); DTaP, diphtheria, tetanus, pertussis; EFS, event-free survival; FISH, fluorescence in situ hybridization; GCLLSG, German Chronic Lymphocytic Leukemia Study Group; IV, intravenous; iwCLL, International Workshop on CLL; MDACC, MD Anderson Cancer Center; mo, months; ORR, overall response rate; OS, overall survival; OSU, Ohio State University Comprehensive Cancer Center; PCV13, pneumococcal conjugate vaccine; PD-1, programmed death 1; PFS, progression-free survival; SLL, small lymphocytic lymphoma; SWOG, Southwest Oncology Group; TTFT, time to first therapy; TTR, time to response; uMRD, undetectable minimal residual disease; wk, weeks.

in CLL typically manifests as worsening lymphocytosis or asymptomatic lymph node enlargement. Neither of these meets the 2018 iwCLL criteria for the initiation of therapy, so that PFS is a particularly challenging endpoint to include in trials of early-stage CLL. In contrast, EFS, which is defined as the interval before the occurrence of symptomatic progression, the initiation of CLL therapy, or death for any reason, is a better endpoint for trials of early-stage CLL.

The response rate served as a surrogate marker for disease control in the chemotherapy era. However, the attainment of a response in the era of novel agents is frequent (>90%) and is expected to be similar in the population of patients with asymptomatic early-stage CLL. For this reason, it is challenging to use the response rate as a primary measure of effectiveness when comparing an FDA-approved medication with placebo, just as it is to use a PFS endpoint. Moreover, the traditional response criteria are challenged in the current treatment era by the typical rapid reduction of lymphadenopathy with BTK inhibitors but paradoxical rise in peripheral blood lymphocytosis, a phenomenon also known as partial response with lymphocytosis.⁴⁸

The surrogate endpoint of minimal residual disease (MRD) is attractive in many hematologic cancers.⁴⁹ MRD assessment has the advantage of early measurement of outcome, shortening the duration of a clinical trial. Various methods are available for MRD measurement, including multiparameter flow cytometry, allele-specific polymerase chain reaction, and next-generation sequencing.⁴ The presence of less than 1 CLL cell per 10,000 leukocytes is the accepted definition for undetectable MRD (uMRD), and the European Research Initiative on CLL (ERIC) has recently made attempts to harmonize MRD assessment across multiple centers.^{50,51} MRD has been established as a prognostic marker for survival in patients who have CLL treated with chemoimmunotherapy (CIT).⁵²⁻⁵⁶ CIT is no longer the standard of care, however, and the role of MRD in response evaluation and its prognostic role in CLL should undergo reassessment in the era of novel agents. The prognostic significance of uMRD may depend on the specific novel agent used; with venetoclax, a significant proportion of patients with CLL achieve uMRD in both bone marrow and blood, in both the frontline²⁷ and relapsed settings.^{57,58} Although uMRD has not been fully validated as a surrogate endpoint in CLL in the United States, the European Medicines Agency has determined that it may be used as an intermediate endpoint in randomized trials, with subsequent confirmation of efficacy on longer-term follow-up.⁵⁹

Quality-of-life (QoL) measurements are an increasingly important endpoint in cancer therapy. Although results are not consistent across trials, patients with CLL

report functional impairment in physical well-being, emotional strength, energy, sleep quality, and other QoL domains.^{28,60-63} These impairments in QoL measures appear during early-stage disease, when patients are observed without active treatment, and generally increase with disease stage. Patients treated with ibrutinib had better social functioning, less fatigue, and less loss of appetite than did patients on CIT,⁶³ illustrating the more favorable toxicity profiles of novel agents. This is an important finding because it increases the chances of successful early intervention in the novel-agent era compared with the previous unsuccessful CIT approaches.

Unique endpoints measuring other complications related to CLL, such as nonhematologic cancers and infections, may also be of interest in patients with untreated CLL because these can lead to significant morbidity during the “wait-and-watch” phase of disease management. The challenges of incorporating novel agents such as BTK inhibitors and BCL2 inhibitors in such situations are that these treatments may themselves increase the risk for infections^{27,64} and nonhematologic malignancies.^{65,66} Early-intervention studies with a randomized design platform can provide the best evidence regarding whether the risk for nonhematologic cancers and serious infections is related to underlying CLL vs CLL therapy.

Studies of Early Intervention in Patients With Asymptomatic CLL in the Novel-Agent Era

The key studies of early intervention in CLL that use novel oral agents are summarized in Table 4. The largest and first study of novel agents in patients with asymptomatic CLL was CLL12. In this placebo-controlled, double-blind, randomized phase 3 study, patients who had Binet stage A CLL without an indication for therapy were risk stratified according to the GCLLSG model.²² Patients with low-risk disease were observed, whereas patients with intermediate-, high-, or very high-risk disease were randomly assigned to ibrutinib at 420 mg daily or placebo. Treatment was continued until symptomatic disease progression (but no later than 60 months after randomization). The study recruited 515 patients. A total of 363 patients were randomized to receive ibrutinib (n=182) or placebo (n=181). Patients with low-risk disease by the model (n=152) were not included in the primary efficacy endpoint.⁶⁷ After a median follow-up of 31 months, the median EFS was not reached in the ibrutinib arm and was 47.8 months in the placebo arm (hazard ratio, 0.25; 95% CI, 0.14-0.43; $P<.0001$). Twelve deaths occurred in the study, and the data are still immature for OS analysis. Any-grade adverse events (AEs) occurred at similar rates in the ibrutinib arm (82.2%) and the placebo arm (84.8%). The most commonly reported AEs leading

to interruption in the ibrutinib arm vs the placebo arm included arrhythmias (18 vs 0 patients), bleeding (8 vs 1 patient), diarrhea (4 vs 3 patients), and neoplasia (4 vs 3 patients). Treatment was discontinued by 34.1% of the ibrutinib-treated patients vs 45.9% of the patients who received placebo. AEs (n=53) were the primary cause of discontinuation in the ibrutinib arm, whereas disease progression (n=45) was more common in the placebo arm.

Several phase 2 studies that are exploring novel agents for early-stage CLL are looking at BTK inhibitors alone or in combination. A phase 2 study from The Ohio State University randomly assigned 44 patients with high-risk genomics (unmutated *IGHV* genes, high-risk results by FISH, or complex karyotype) to receive ibrutinib concurrently with or sequentially after vaccine administration.⁶⁸ Therapy with ibrutinib was reported to be safe, with no grade 4 toxicities and no grade 3/4 hematologic AEs. Grade 3 atrial fibrillation developed in 2 patients. Early treatment was associated with improvement in QoL measures of cancer-related stress: anxiety and loss of sleep. Three phase 2 studies of patients with high-risk asymptomatic early-stage CLL assessing the efficacy and safety of ibrutinib, acalabrutinib with or without obinutuzumab, and ibrutinib in combination with pembrolizumab (Keytruda, Merck) are ongoing, with no outcome results reported to date.

EVOLVE is a phase 3 North American Intergroup Study that is expected to open enrollment this year to patients with previously untreated early-stage CLL who are at high or very high risk for disease progression according to the CLL-IPI. Patients will be randomly assigned to therapy with venetoclax and obinutuzumab at diagnosis or to delayed therapy with venetoclax and obinutuzumab when disease progression occurs and they meet 2018 iwCLL criteria for the initiation of therapy. The primary endpoint of this study is OS in the immediate-therapy vs the delayed-therapy arm (NCT04269902). Another study, PreVent-ACaLL (NCT03868722), will randomly assign 212 patients at high risk for infection and/or needing therapy, according to the CLL-TIM algorithm,³² in a 1:1 ratio to combination therapy with acalabrutinib and venetoclax vs placebo for a fixed duration of 12 weeks. The primary endpoint of this study is survival free of grade 3 or higher infection in the treatment arm vs the observation arm after 24 weeks (12 weeks after the end of treatment).⁶⁹

Summary

The current paradigm of “watch and wait” in early-stage CLL can quickly morph into “wait and worry” for many patients who do not need therapy at the time of diagnosis. Previous clinical trials of treatments for patients with

early-stage CLL did not extend into routine clinical practice owing to the excessive toxicity and/or ineffectiveness of the treatments and a lack of robust prognostic models for appropriate patient selection. We have now reached an exciting era in which a plethora of effective anti-CLL therapies are available that have fewer toxic effects on bone marrow reserve and immune status than did past therapies. The parallel improvement in prognostic tools for disease progression has created a new opportunity to reassess the role of early treatment in patients with asymptomatic (or minimally symptomatic) disease who are at high risk for disease progression. Several ongoing clinical trials will ultimately pave the way for the adoption of an early-treatment approach in patients with high-risk asymptomatic CLL, and we strongly support enrolling appropriate patients with early-stage CLL in rationally designed trials. However, until the mature results of such trials become available, we continue to follow the 2018 iwCLL guidelines for starting therapy in patients with newly diagnosed, early-stage CLL.

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